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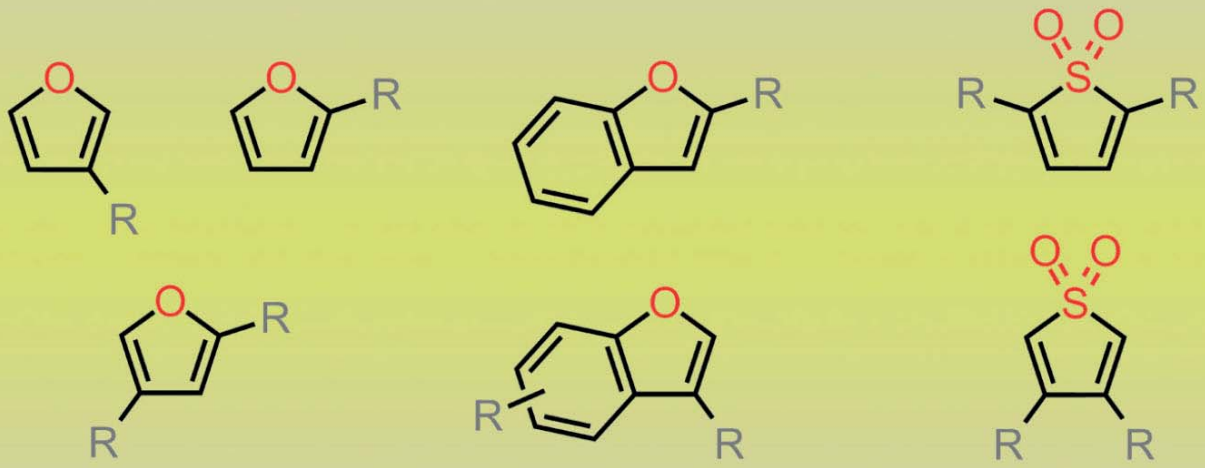
Iridium-Catalyzed Asymmetric Hydrogenation of Furan Derivatives and Thiophene 1,1-Dioxides



Larissa Pauli

Iridium-Catalyzed Asymmetric Hydrogenation of Furan Derivatives and Thiophene 1,1-Dioxides

Iridium-Catalyzed Asymmetric Hydrogenation of Furan Derivatives and Thiophene 1,1-Dioxides

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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]

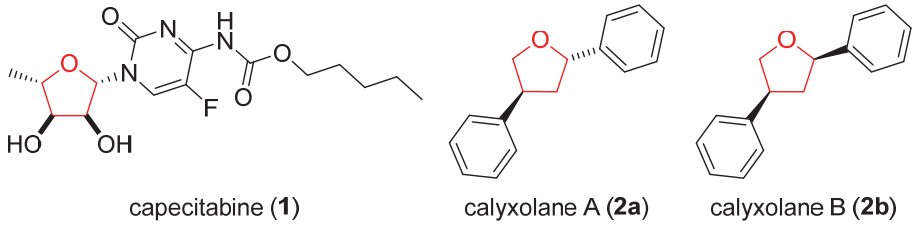


Figure 1.1 Structures of natural and man-made chiral tetrahydrofurans.

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]

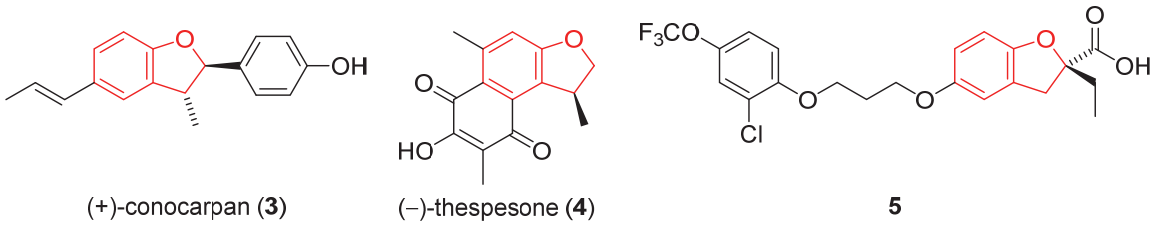


Figure 1.2 Structures of biologically active benzodihydrofurans.

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]

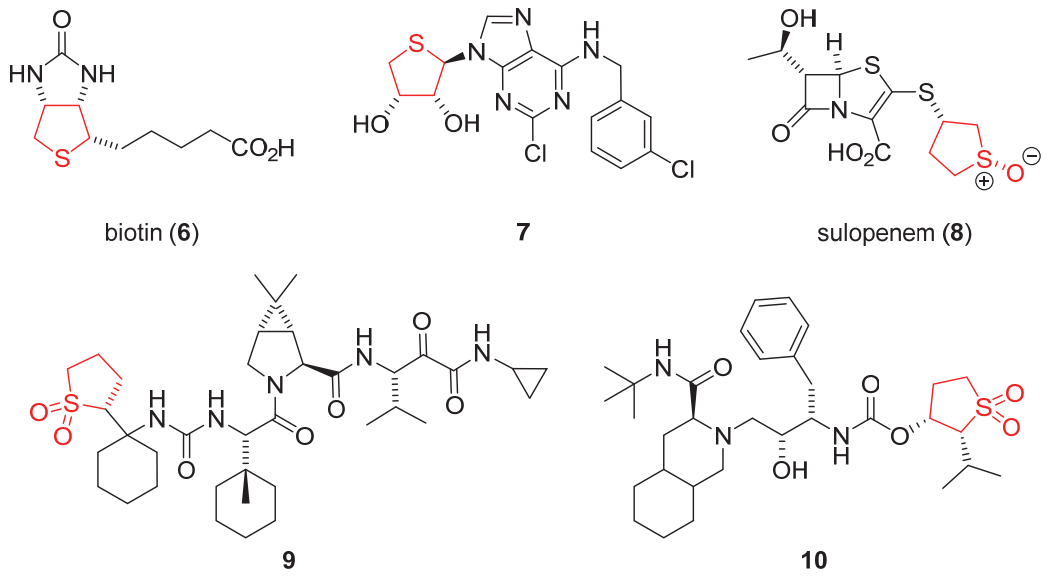
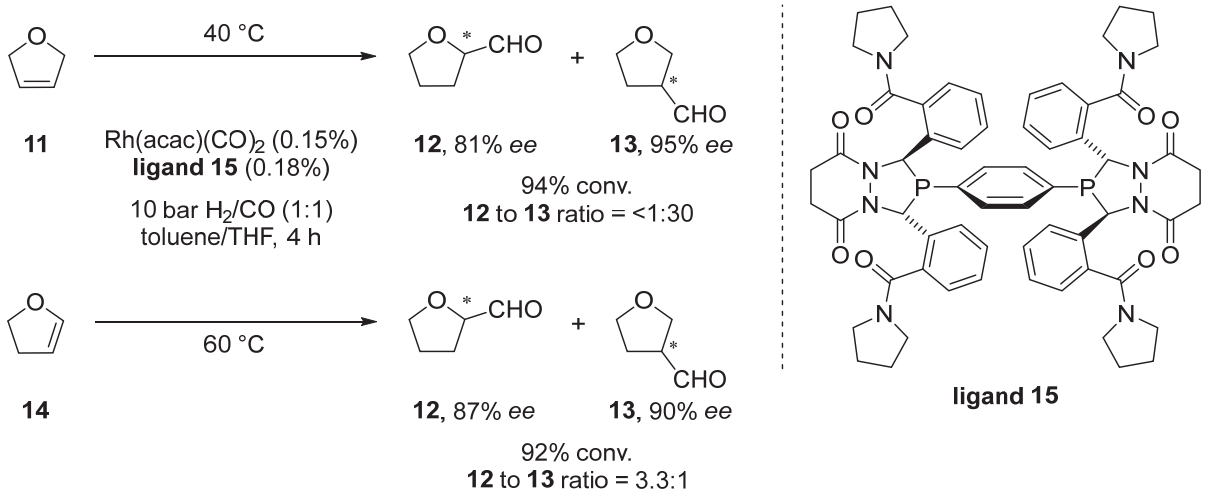


Figure 1.3 Structures of chiral tetrahydrothiophenes and oxidized analogs.

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

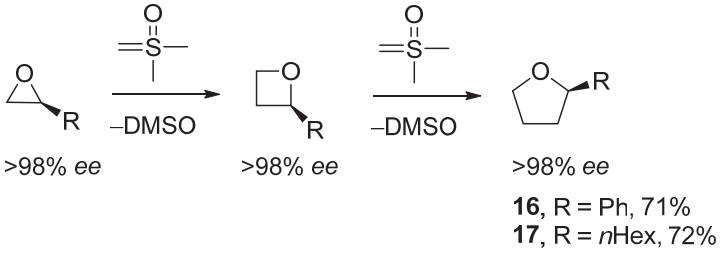
The hydroformylation reaction, discovered by ROELEN in 1938, emerged as an important industrial process for the synthesis of aldehydes from olefins.[12] An asymmetric version of this reaction involving a homogeneous catalyst was recently applied to the synthesis of 2- and 3-substituted tetrahydrofuran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

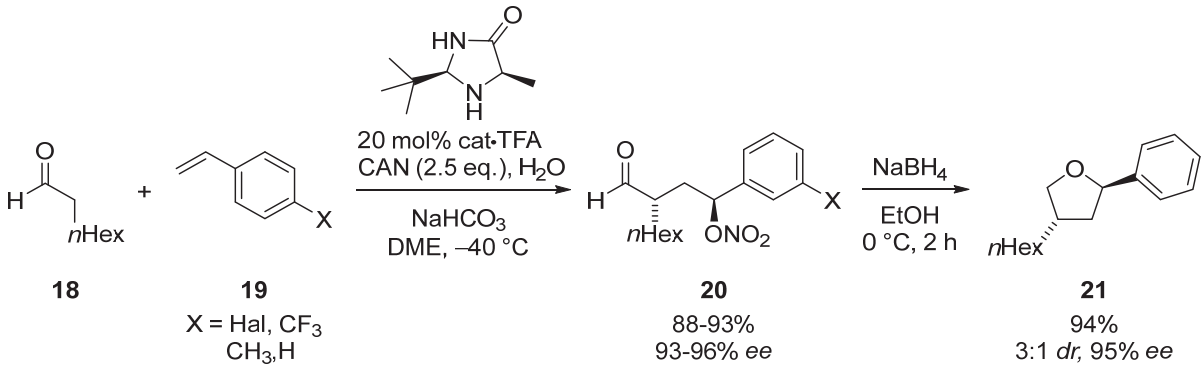
A more broadly applicable transformation is shown in *Scheme 1.2*. The consecutive ring-expansion reaction of epoxides with dimethylsulfonium methylide, gives access to both 2-aryl and 2-alkyl substituted tetrahydrofurans depending on the substitution of the epoxide.[14]



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.

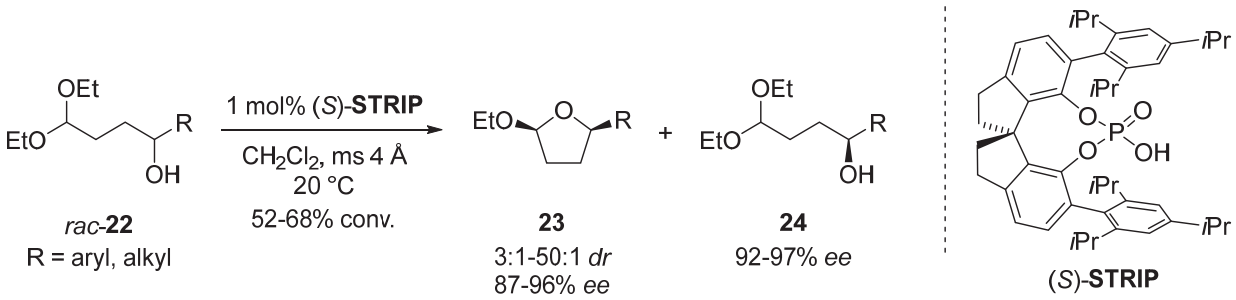
The preparation of 2,4-disubstituted tetrahydrofurans from enantioenriched intermediates can be accomplished by a reduction-cyclization sequence in one step, as shown in the application of enatiopure γ-nitro-aldehydes **20** described by MACMILLAN in the context of the organocatalyzed carbo-oxidation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

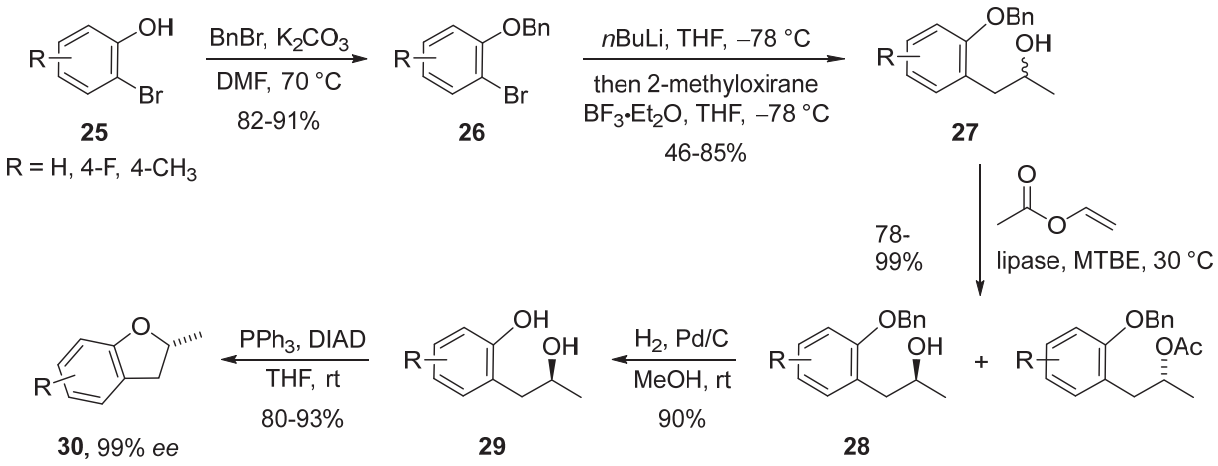
Starting from racemic compounds, as in the kinetic resolution of homoaldols *via* catalytic asymmetric transacetalization, enantioenriched 2,5-disubstituted tetrahydrofurans **23** can be obtained (*Scheme 1.4*).[18]



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.

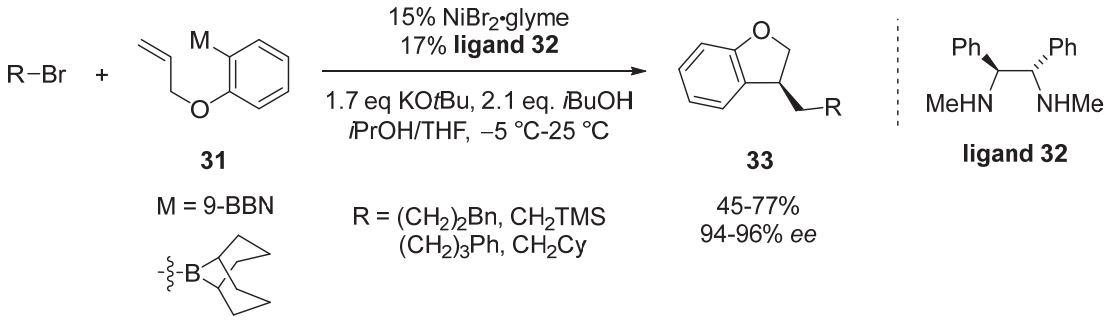
A chemoenzymatic strategy was applied to the asymmetric synthesis of 2,3-dihydrobenzofurans (*Scheme 1.5*).[19] Protection of commercially available phenols **25** followed by reaction with *n*BuLi and 2-methyloxirane resulted in racemic alcohols **27**. The alcohols were enzymatically resolved to deliver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

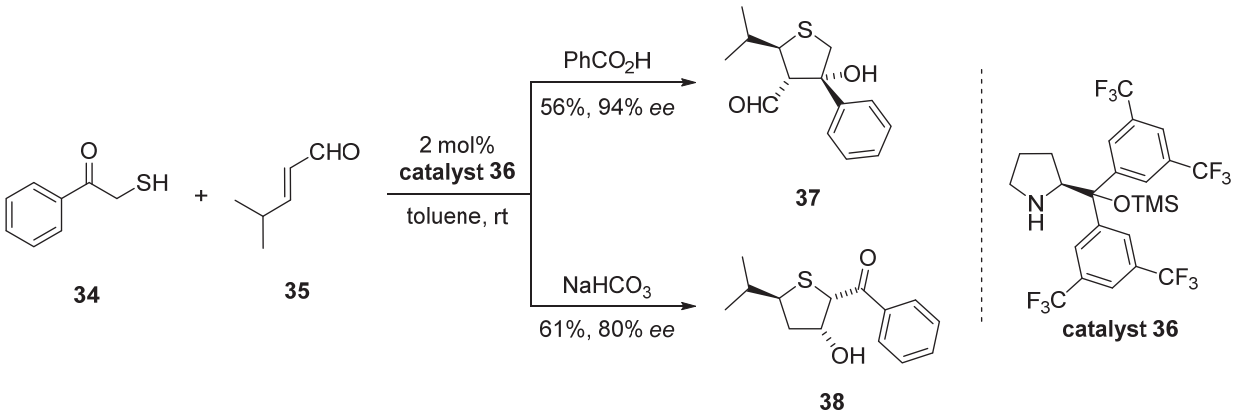
Product **30** was obtained in enantiomerically pure fashion, but with the limitation of a maximum yield of 50% and the drawback of a lengthy synthesis.

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.

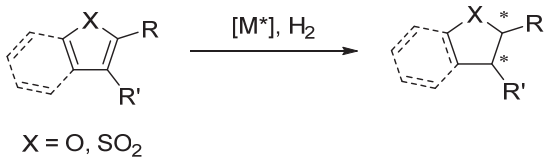
Domino reactions have also been successfully utilized in the asymmetric synthesis of tetrahydrothiophene derivatives, such as the Michael-aldol reaction sequence.[21] Depending on the use of acidic or basic additives in the organocatalytic system, tetrahydrothiophene carbaldehydes **37** or (tetrahydrothiophen-2-yl)phenyl 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*).

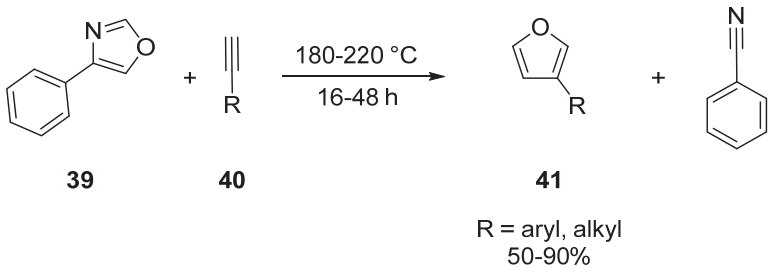
Finally, investigations on the iridium-catalyzed hydrogenation of oxazoles and thiazoles are reported in *Chapter 6*.

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]

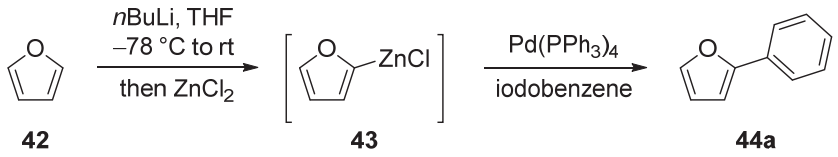


Scheme 2.1 Synthesis of 3-substituted furans *via* tandem DIELS–ALDER/ retro DIELS–ALDER sequence.

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*.

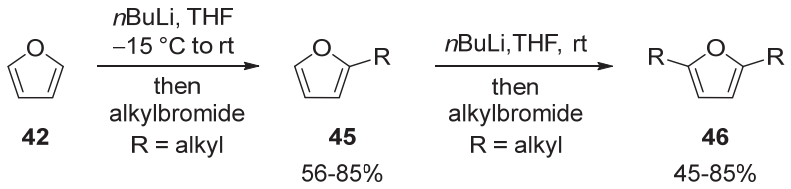
Preparation of 2-substituted furans can be achieved either by electrophilic aromatic substitution or metallation. The latter approach takes advantage of the inductive effect of the oxygen atom, allowing functionalization at the C2/C5 position. The commercially, readily available and relatively cheap 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]



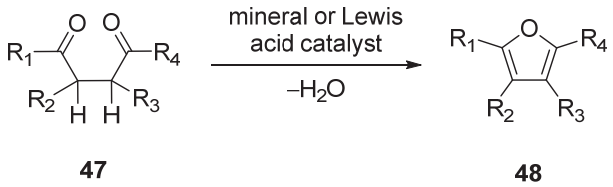
Scheme 2.2 Synthesis of 2-phenylfuran (**44a**) *via* NEGISHI cross-coupling.

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*).

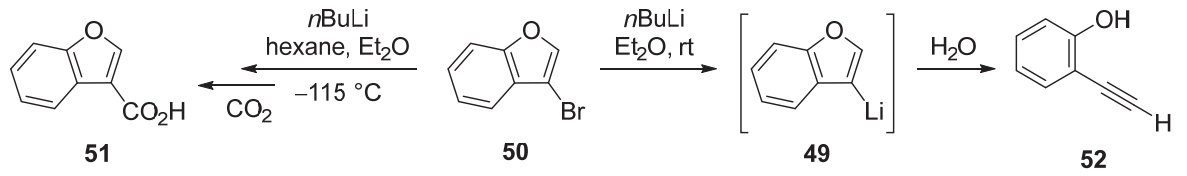


Scheme 2.4 Synthesis of substituted furans *via* PAAL–KNORR furan synthesis.

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

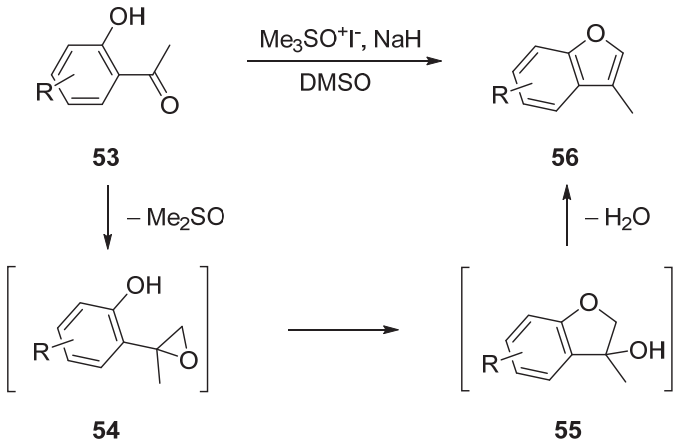
conditions. The synthesis of 2,4-disubstituted furans can be achieved from acyclic, readily available starting materials in a multi-step synthesis. As such synthetic protocols were applied to the synthesis of some substrates, their discussion will follow in *Section 2.4*.

3-Substituted benzofurans can be accessed by lithium-halogen exchange using 3-bromobenzofuran (**50**) at low temperature to avoid ring-opening of 3-lithiobenzofuran (**49**) to give 2-hydroxyphenylacetylene (**52**) (*Scheme 2.5*).[30]



Scheme 2.5 Generation of 3-lithiobenzofuran (**49**).

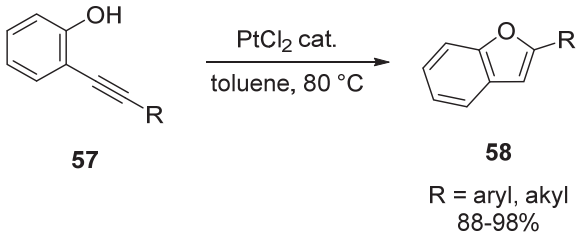
More often though ring construction represents a more practical alternative to metallation. An example of how 3-substituted benzofurans can easily be generated by ring formation is shown in *Scheme 2.6*.[31] One possible reaction pathway involves initial formation of the hydroxy-epoxide **54** *via* COREY–CHAYKOVSKY reaction followed by intramolecular ring opening to give the 3-hydroxydihydrobenzofuran **55**, that finally undergoes water elimination promoted by elevated temperature or acid to furnish the desired 3-methylbenzofuran **56**. Although this series of steps appears to be likely, the hydroxy-epoxide intermediate **54** was not detected in this reaction.



Scheme 2.6 Synthesis of 3-substituted benzofurans **56** *via* COREY–CHAYKOVSKY reaction.

Benzofurans with substitution at C2 can be prepared either by direct metallation, analogous to 2-substituted furans, or by application of cross-coupling reactions, such as SUZUKI[32] or NEGISHI[33] coupling (*Section 2.6*). Platinum-catalyzed intramolecular

carboalkoxylation provides 2-aryl-substituted as well as 2-alkyl substituted benzofurans in a single step (*Scheme 2.7*).[34]



57 **58**

R = aryl, akyl
88-98%

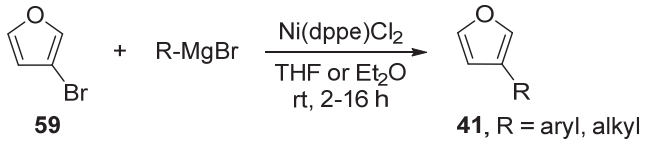
Scheme 2.7 Synthesis of 2-substituted benzofurans **55**.

Catalytic amounts of $PtCl_2$ activate the alkyne towards nucleophilic attack. Hence, phenol derivative **57** bearing an alkyne at the *ortho*-position smoothly cyclizes to benzofuran **58**.

2.2 Synthesis of 3-Substituted Furans

2.2.1 Aromatic Substituents

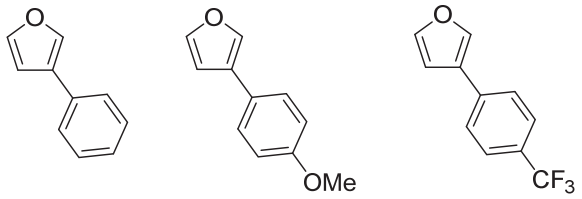
The synthesis of 3-substituted furans can be achieved in many different ways. A cross-coupling reaction was chosen to substitute the furan with both aryl and alkyl substituents at the C3 position in one step. Thus starting from the commercially available 3-bromofuran (**59**) the corresponding alkyl or aryl substituent could be introduced *via* a nickel-catalyzed KUMADA coupling[26] with the appropriate Grignard reagent (*Scheme 2.8*).



59 **41**, R = aryl, alkyl

Scheme 2.8 Synthesis of 3-aryl-substituted furans.

To investigate the electronic effects of the substituents on the iridium-catalyzed hydrogenation of furans, three different aromatic substituents bearing electron neutral **41a**, electron donating **41b** and electron withdrawing **41c** groups were successfully attached to the heterocycle using the above mentioned cross-coupling (*Figure 2.1*).



41a, 60% **41b**, 77% **41c**, 52%

Figure 2.1 Structures of aryl 3-substituted furans with corresponding yields.

A first attempt to synthesize furan **41a** from commercially available 3-bromofuran (**59**) succeeded in moderate yield overnight (37%) (*Table 2.1*, entry 1). While nickel salts could be removed by distillation, the homocoupling product which was formed during the reaction had to be separated by flash chromatography.

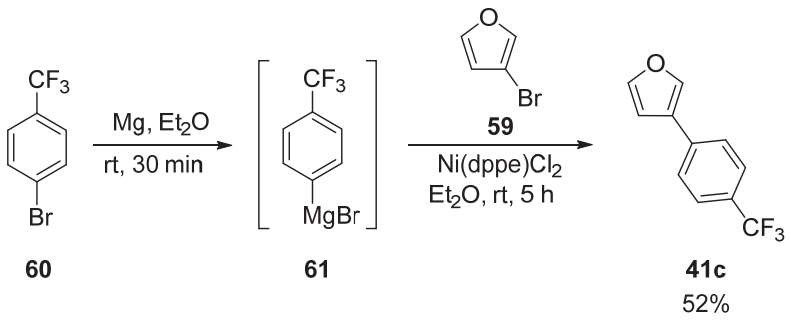
Table 2.1 Influence of the reaction parameters on the yield of 3-phenylfuran (**41a**).

entry	time (h)	PhMgBr (eq.)	scale (mmol)	yield (%)[a]
1	16	1.20	3.35	37
2	2	1.05	4.21	37
3	3	1.10	7.52	60

[a] Yield after distillation and flash chromatography.

To reduce the amount of the undesired by-product a smaller excess of the Grignard compound was used in the second run (*Table 2.1*, entry 2). After a reaction time of two hours 3-bromofuran (**59**) was completely consumed. However, this modification did not improve the yield. Only after the reaction was performed on a twice bigger scale with the same concentration, the yield increased to 60% (*Table 2.1*, entry 3).

3-(4-Methoxyphenyl)furan (**41b**) was synthesized in the same manner as furan **41a** using commercially available 4-methoxyphenylmagnesium bromide and was obtained 77% yield. The synthesis of 3-((4-trifluoromethyl)phenyl)furan (**41c**) was achieved by using freshly prepared Grignard compound from 4-bromobenzotrifluoride (**60**) and 3-bromofuran (**59**) through metal-catalyzed cross-coupling reaction (*Scheme 2.9*).



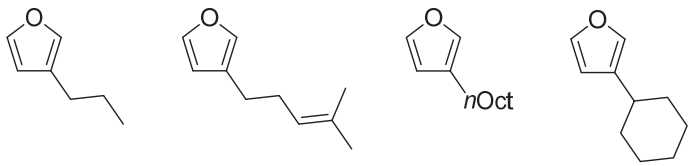
Scheme 2.9 Synthesis of 3-(4-(trifluoromethyl)phenyl)furan (**41c**) *via* Grignard reaction and subsequent KUMADA coupling.

The yield of the 3-aryl-substituted furans varied with the electronic properties of the substituents. While the highest yield was obtained for the substrate with an electron donating methoxy group (77%), the yield was lower when an electron withdrawing moiety (CF_3) was introduced. It should be noticed that also in the case of compounds **41b** and **41c** the undesired homocoupling by-products had to be removed by flash chromatography.

2.2.2 *Aliphatic Substituents*

To broaden the scope and to investigate the different influences of alkyl and aryl substituents on the iridium-catalyzed hydrogenation of furans, linear and branched alkyl chains were also considered.

The sequence of a Grignard reaction and KUMADA coupling described above was applied to prepare 3-alkyl substituted furans. However, 3-propylfuran (**62**) could not be isolated. This can be attributed to the volatility of furans with short alkyl chains, as in case of 3-propylfuran (**62**) and 3-(4-methylpent-3-en-1-yl)furan (**63**) (*Figure 2.2*).



62, 0% **63**, 2% **64**, 14% **65**, 40%

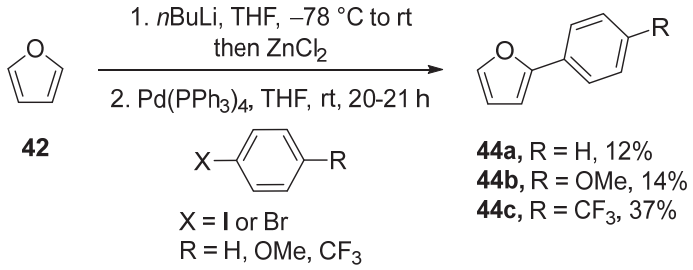
Figure 2.2 Structures of alkyl 3-substituted furans with corresponding yields.

Compound **63**, also called perillen, was found to be the characteristic flowery odor in many essential oils.[35] Perillen (**63**) was synthesized from the freshly prepared Grignard compound from 5-bromo-2-methyl-2-pentene and 3-bromofuran (**59**). The product was detected by GC-MS in the crude reaction mixture and by proton NMR analysis after flash chromatography together with *n*pentane. After letting the combined fractions standing over night the product **63** evaporated almost completely. When longer alkyl chains were introduced, like in 3-octylfuran (**64**), the desired furan could be prepared through the aforementioned nickel-catalyzed cross-coupling reaction in 14% yield. Substitution of the furan at the 3-position was also possible with branched alkyl moieties as for 3-cyclohexylfuran (**65**) although with moderate yield (40%). The low yield was not optimized and is a result of tedious product purification to remove the homocoupling by-product by flash chromatography and metal traces by distillation.

2.3 Synthesis of 2-Substituted Furans

The synthesis of 2-substituted furans is even more straightforward. Because of the inductive effect of the oxygen atom direct α-lithiation is possible.[30] After deprotonation of furan (**39**), the lithiated intermediate can be either transmetallated or directly reacted with electrophiles.

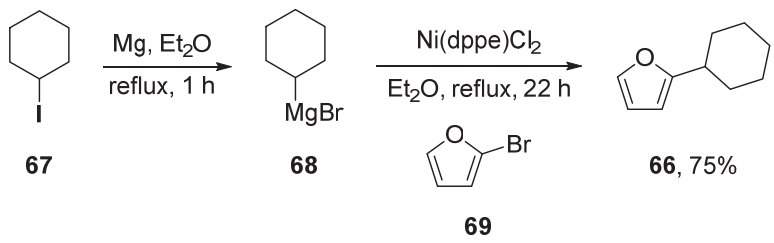
Aryl substituted furans were successfully synthesized by initial lithiation followed by transmetallation with zinc, since the heteroaryl zinc compounds are usually compatible with many functional groups.[27] The zinc derivative was then subjected to NEGISHI cross-coupling reaction conditions (*Scheme 2.10*).



Scheme 2.10 Synthesis of 2-substituted aryl furans by cross-coupling.

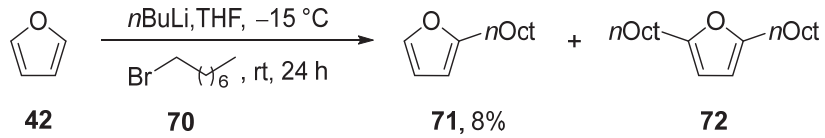
The electronic properties of the aryl halides used as cross-coupling partners had a great influence on the yield of the products. When an electron withdrawing group was present, the product was obtained in higher yield than with aryl halides bearing an electron donating substituent. Since the main emphasis of the research presented in this thesis was the investigation of the asymmetric hydrogenation of furans, the synthesis of the substrates was not extensively optimized.

Both cyclic and acyclic alkyl substituted furans were investigated. The method of choice to prepare 2-cyclohexylfuran (**66**) was the KUMADA cross-coupling.[36] After chromatographic separation of the homocoupling by-product, the pure product **66** was obtained in good yield (*Scheme 2.11*).



Scheme 2.11 Synthesis of 2-cyclohexylfuran (**66**) by KUMADA coupling.

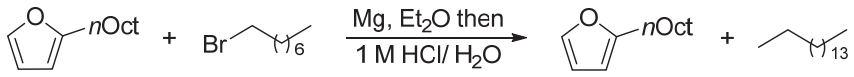
Direct lithiation in THF, followed by electrophilic substitution was chosen to prepare 2-octylfuran (**71**) (*Scheme 2.12*). Even though furan is readily deprotonated, the reaction proceeded only slowly. After 24 hours, starting material **70** was still detected together with the desired product **71** and the disubstituted by-product **72**.



42 **70** **71**, 8% **72**

Scheme 2.12 Synthesis of 2-octylfuran (**71**).

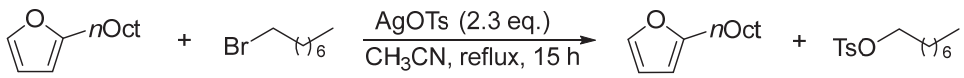
Separation of the three components by flash chromatography with pure *n*pentane was not possible. However, the desired product **71** and the 2,5-disubstituted furan **72** were separated by "Kugelrohr" distillation. The low yield is a direct consequence of the difficult separation from the starting material. Therefore several methods were tried to convert the unreacted starting material into a compound that is easier to remove. Fractions from the distillation were used for these investigations. One possibility was to transform 1-bromooctane (**70**) into the corresponding Grignard compound with subsequent hydrolysis to give highly volatile alkane **73**, which can be simply removed by evaporation (*Scheme 2.13*).



71 **70** **71** **73**

Scheme 2.13 Formation of a Grignard compound from 1-bromooctane (**70**) with subsequent hydrolysis.

After formation of the alkyl Grignard reagent from a mixture of product **71** and starting material **70** (1:0.7, ^{1}H-NMR), the reaction mixture was quenched. But instead of the expected octane, the dimer **73** was detected by ^{1}H-NMR and GC-MS. The separation of hexadecane **73** from product **71** was performed by flash chromatography to deliver the latter in quantitative recovery. Another fraction with a lower content of bromo alkane **70** (9%, by ^{1}H-NMR) was converted using silver tosylate into the corresponding tosylated compound **74**, *via* S_N2 reaction (*Scheme 2.14*).



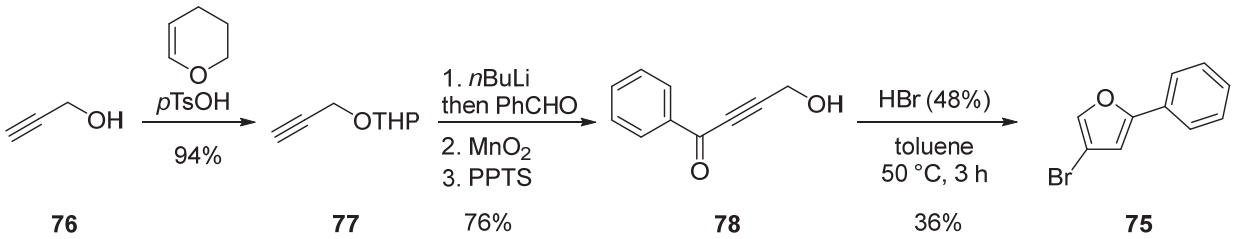
71 **70** **71** **74**

Scheme 2.14 Transformation of 1-bromooctane (**70**) into the corresponding tosylate **74**.

By-product **74** has not only a different retention factor on the thin layer chromatography, but is also UV active and therefore even easier to be removed by flash chromatography. Indeed separation was straightforward with an almost quantitative product recovery from the mixture (96%).

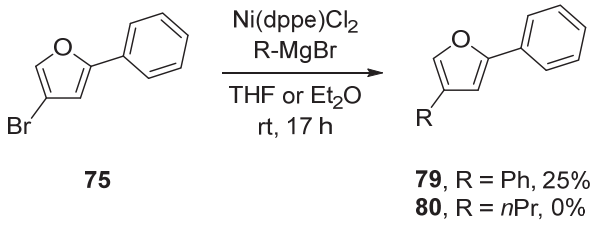
2.4 Synthesis of 2,4-Disubstituted Furans

The preparation of 2,4-disubstituted furans required a different strategy. A multi-step synthesis starting from commercially available propargyl alcohol was chosen, which gives direct access to 4-bromo-2-phenylfuran (**75**) (*Scheme 2.15*).[37]



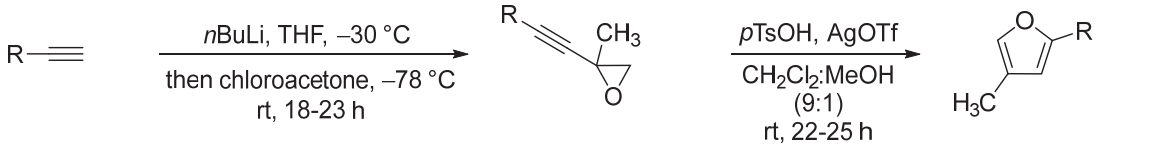
Scheme 2.15 Synthesis of 4-bromo-2-phenylfuran (**75**) in five steps.

The relatively cheap propargyl alcohol (**76**) was protected as a THP ether **77** and, after lithiation, the chain was elongated by reaction with benzaldehyde. Oxidation to the ketone with manganese dioxide and acid catalyzed deprotection afforded the alcohol **78**. These three reactions were performed in a stepwise manner, although a one pot procedure was also reported with lower yield (68%).[37] Alcohol **78** reacted in the presence of hydrobromic acid to give product **75**. As for the mono-substituted furans, the brominated precursor **75** was subjected to the KUMADA cross-coupling conditions (*Scheme 2.16*).



Scheme 2.16 Synthesis of 2,4-disubstituted furans.

After successful introduction of a phenyl substituent to yield 2,4-diphenylfuran (**79**), aliphatic moieties were attached. Therefore, furan **75** was reacted with the Grignard reagent, obtained from 1-bromopropane, in the cross-coupling. In this case, not only conversion was incomplete, but additional dehalogenation of the starting material **75** hampered the isolation of 2-phenyl-4-propylfuran (**80**). Thus another procedure was considered for the preparation of mixed aryl-alkyl and purely alkyl substituted 2,4-disubstituted furans, that required only two steps to obtain two different substituted furans with moderate yield (*Scheme 2.17*).[38]



81, R = Ph
82, R = *n*Hex

83, R = Ph, 71%
84, R = *n*Hex, 57%

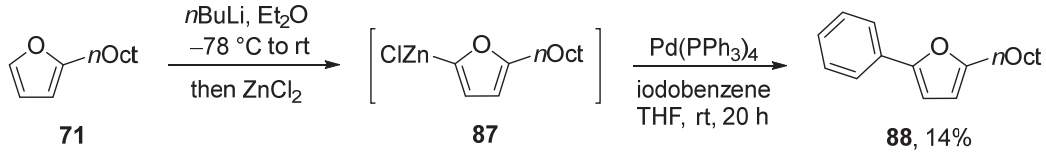
85, R = Ph, 51%
86, R = *n*Hex, 49%

Scheme 2.17 Two-step synthesis of 4-methyl-2-phenylfuran (**85**) and 2-hexyl-4-methylfuran (**86**).

Starting with either phenyl acetylene (**81**) or 1-octyne (**82**), lithiation and addition of chloroacetone resulted in the corresponding epoxides **83** and **84**. In the second step the epoxide underwent an acid-catalyzed rearrangement in the presence of methanol. The synthesis of 2-hexyl-4-methylfuran (**86**) was accomplished with a moderate overall yield (30%) after flash chromatography and distillation. In the case of 4-methyl-2-phenylfuran (**85**) both reaction steps proceeded very well, but purification was challenging. According to the literature,[39] the compound should form colorless needles with a melting point of 37–39 °C. However, it was not possible to crystallize it, because it readily dissolves in *n*pentane at room temperature. After purification with flash chromatography and distillation furan **85** was either obtained as pale yellow hygroscopic crystals or as colorless oil.

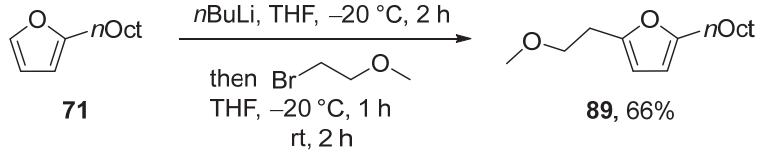
2.5 Synthesis of 2,5-Disubstituted Furans

Previous investigations on the iridium-catalyzed hydrogenation of symmetrical 2,5-disubstituted furans showed mainly the formation of the achiral *meso* form,[40] therefore this substitution pattern was not further studied. However, unsymmetrical 2,5-disubstituted furans were investigated, since their hydrogenation could not lead to the formation of *meso* species. The 2,5-dialkyl and 2-aryl-5-alkyl substituted furans were prepared from the 2-substituted furans already synthesized as described in *Section 2.3*. After deprotonation of 2-octylfuran (**71**) with *n*BuLi and transmetallation with zinc, the organozinc compound **87** was reacted with iodobenzene in a palladium-catalyzed NEGISHI coupling (*Scheme 2.18*).



Scheme 2.18 Synthesis of 2-phenyl-5-octylfuran (**88**) *via* NEGISHI cross-coupling.

Because of incomplete conversion (80%, by GC-MS) and several purifications needed (flash chromatography twice and a distillation) the product was isolated in low yield (14%). The pure 2,5-alkyl substituted furan **89** was also obtained in a one-step procedure starting from the same precursor **71** (*Scheme 2.19*).

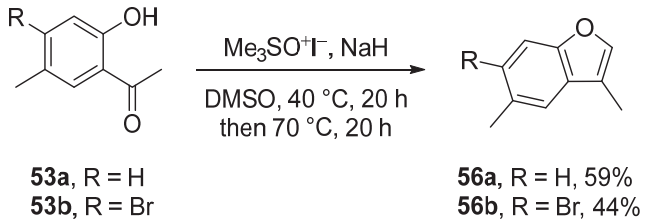


Scheme 2.19 Synthesis of (2-(2-methoxyethyl)-5-octylfuran) (**89**) by direct metallation.

Although the starting furan **71** was not completely consumed (77%, by GC-MS), the purification of the crude mixture was straightforward because of the different polarities of the product and the starting material **71**. As a result the product 2-(2-methoxyethyl)-5-octylfuran (**89**) was obtained in good yield (66%).

2.6 Synthesis of 3-Substituted and 2-Substituted Benzofurans

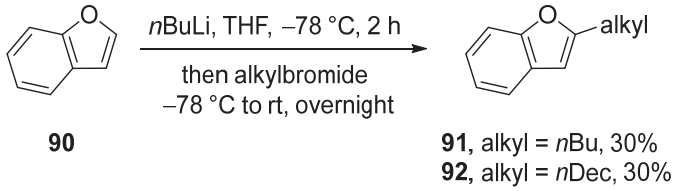
Substituted benzofurans can be obtained either by cyclization reaction of acyclic precursors or by substitution of a prefunctionalized or a simple benzofuran. For the synthesis of the 3-substituted benzofurans shown in this work, a cyclization reaction was chosen (*Scheme 2.20*).[41]



Scheme 2.20 Synthesis of 3-substituted benzofurans by COREY–CHAYKOVSKY reaction.

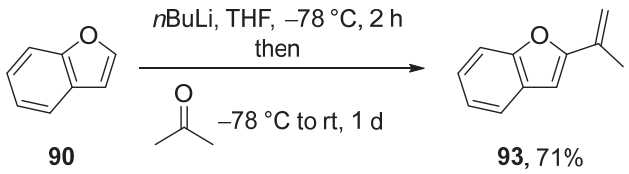
The commercially available acetophenone derivatives **53a** and **53b** were transformed to the corresponding benzofurans **56a** and **56b** *via* COREY–CHAYKOVSKY reaction. To prevent *O*-methylation, the epoxidation reaction had to be performed at 40 °C. After consumption of the starting material the temperature could be increased to obtain full conversion of the tertiary alcohols into benzofurans **56a** and **56b**.[42]

Benzofurans substituted with an alkyl moiety at the 2-position were prepared by direct metallation with subsequent nucleophilic substitution (*Scheme 2.21*).[33]



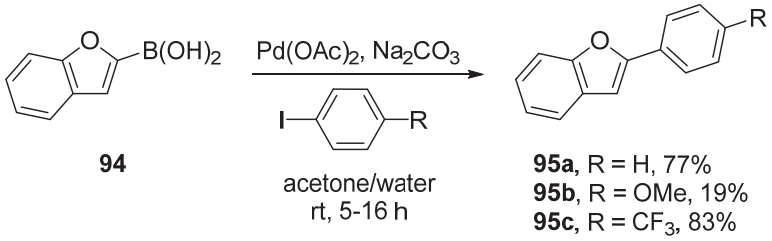
Scheme 2.21 Synthesis of 2-alkyl substituted benzofurans.

For both substrates it was necessary to purify the corresponding product by flash chromatography with subsequent bulb to bulb distillation. In this way the starting material, bromo alkane and/or benzofuran, could be removed. When the reaction was performed with *t*BuLi and isopropyl iodide, only 5% of the product was detected by proton NMR with the rest being benzofuran. Even a second treatment of this mixture with *t*BuLi and phenantroline, as indicator for lithiation of the heterocycle, did not improve the yield. Nevertheless, a similar substituted 2-alkenyl benzofuran **93** was synthesized by electrophilic addition of acetone to the lithiated benzofuran followed by water elimination (*Scheme 2.22*).



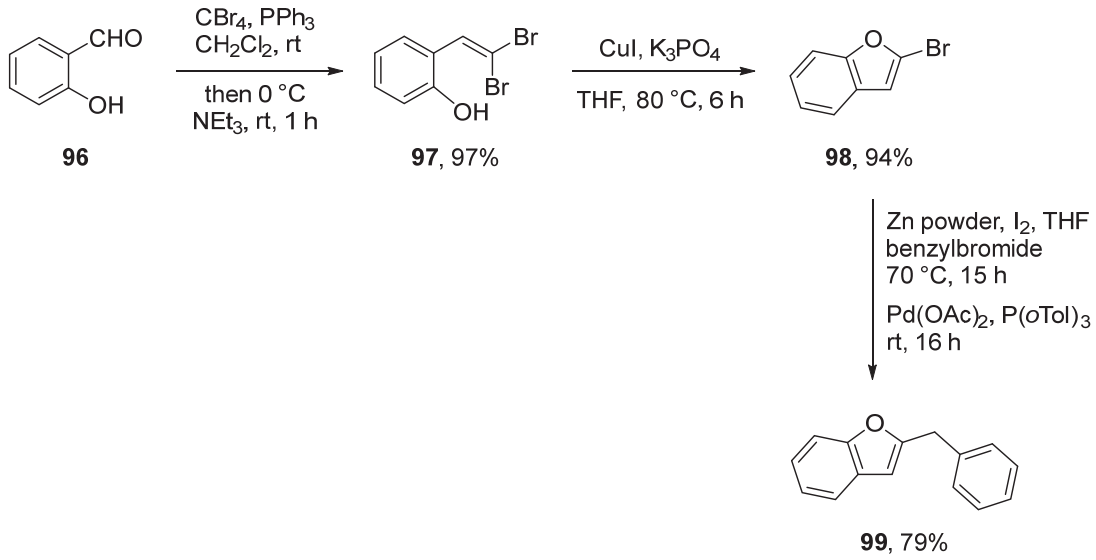
Scheme 2.22 Synthesis of 2-(prop-1-en-2-yl)benzofuran (**93**).

In addition to alkyl substituted benzofuran substrates several aryl substituted analogs were prepared. To this end, SUZUKI cross-coupling was selected as the reaction of choice (*Scheme 2.23*).[33]



Scheme 2.23 Synthesis of 2-substituted aryl benzofurans *via* SUZUKI coupling.

The reaction of 2-benzofuranboronic acid (**94**) with iodobenzene and 4-iodobenzotrifluoride proceeded with high yield. Only the benzofuran substituted with an electron-donating group **95b** was obtained in lower yield. The benzyl substituted analog was synthesized from a brominated precursor in a multiple-step synthesis (*Scheme 2.24*).[33, 43]



Scheme 2.24 Synthesis of 2-benzylbenzofuran (**99**).

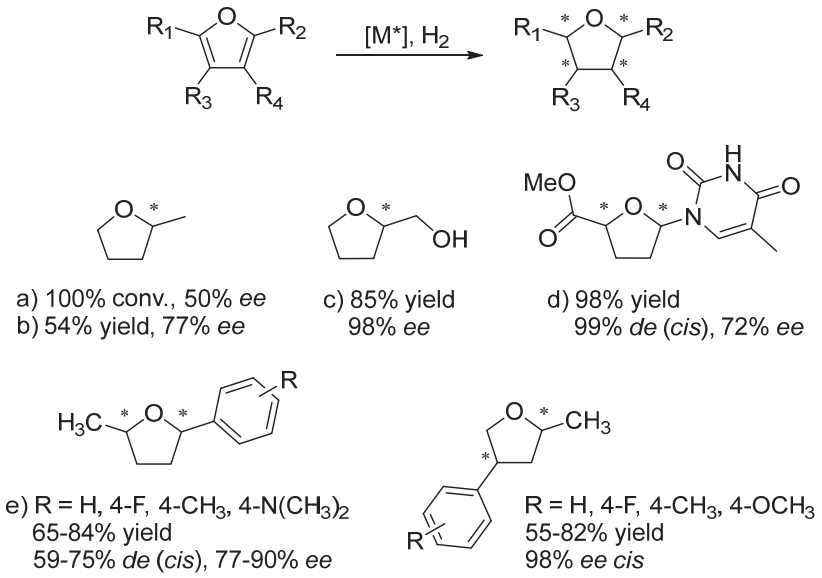
Without the need for protecting groups the aldehyde **96** was converted into *gem*-dibromoolefin **97** *via* RAMIREZ–COREY–FUCHS olefination reaction. To the preformed PPh_3=CBr_2 ylide NEt_3 was added followed by salicyladehyde **96** to provide the

gem-dibromoolefin **97** in quantitative yield. The latter was then converted into 2-bromobenzofuran (**98**) in high yield through an intramolecular cyclization in the presence of copper iodide and potassium phosphate. NEGISHI cross-coupling of 2-bromobenzofuran (**98**) with benzylbromide resulted in 2-benzylbenzofuran (**99**) in good yield.

3 Iridium-Catalyzed Asymmetric Hydrogenation of Furans and Benzofurans

3.1 Introduction

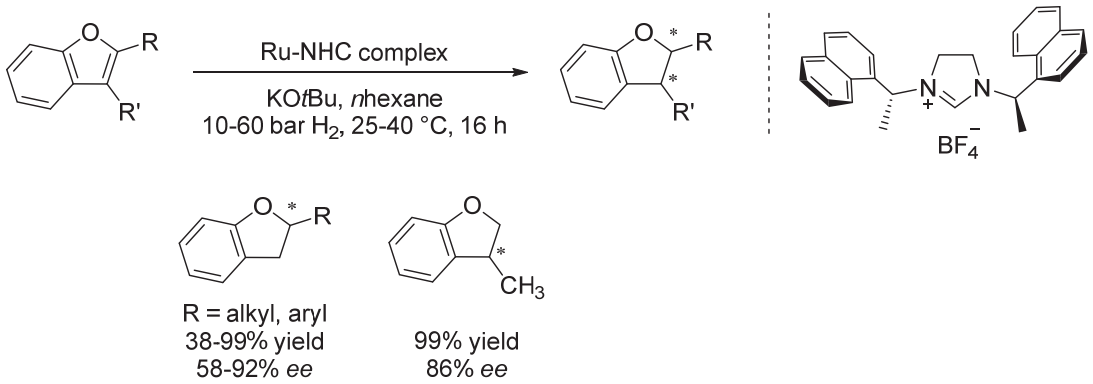
Stereoselective hydrogenation of heterocycles is a promising method to prepare chiral heterocyclic compounds, which are abundant in biological active molecules (see *Chapter 1*). Although optically active tetrahydrofuran and dihydrofuran units are present in numerous pharmaceutically relevant molecules, general methods for their asymmetric synthesis are rather scarce. After the pioneering work of the TAKAYA group in 1995 reporting an enantiomeric excess of 50% for the asymmetric hydrogenation of 2-methylfuran with a Ru(binap) catalyst (*Scheme 3.1,* example a),[23k] further progress was rather slow. In 2003 two heterogeneous catalytic systems were reported that gave 77% *ee* in the hydrogenation of 2-methylfuran (rhodium on wool, *Scheme 3.1,* example b)[23j] and 98% *ee* in the hydrogenation of furfural (using a Pt-biopolymer complex, *Scheme 3.1,* example c).[23g] However, these systems are not well defined and the scope of the hydrogenation was not investigated.



Scheme 3.1 Progress in the asymmetric hydrogenation of substituted furans.

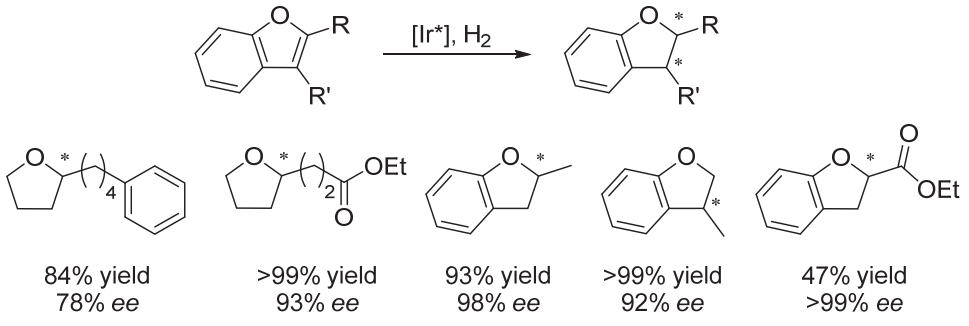
In 2006, SPINDLER and co-workers published a rhodium(diphosphine)-catalyzed hydrogenation of a 2,5-disubstituted furan leading to the corresponding enantiomerically enriched tetrahydrofuran with perfect *cis* selectivity and 72% *ee* (*Scheme 3.1,* example d).[23f] Recently after completion of the experimental work for this thesis,

GLORIUS and co-workers reported a ruthenium catalyst based on a chiral *N*-heterocyclic carbene ligand for the reduction of an array of 2,5- and 2,4-disubstituted furans (*Scheme 3.1*, example e).[23l] Electron-donating groups on the phenyl ring gave 2,5-tetrahydrobenzofurans with lower conversion, but higher *ee*, whereas no general trend was observed for the diastereomeric ratio. The 2,4-disubstituted *cis* products were selectively obtained with moderate yield, but excellent enantiomeric excess. Also 2-substituted benzofurans were investigated using the same catalytic system (*Scheme 3.2*). While benzofuran substrates carrying alkyl substituents were reported to give inferior results, high enantiomeric excess was reported for heterocycles bearing an aryl moiety.[23b] The authors demonstrated the applicability of their protocol to aryl-substituted benzofurans in the enantioselective total synthesis of corsifuran A.[23c]



Scheme 3.2 Recent progress in the asymmetric hydrogenation of substituted benzofurans.

A systematic study of the asymmetric hydrogenation of heteroaryl-aryl alkenes, carried out in the group of PFALTZ, showed that certain N,P ligand-based iridium catalysts reduce not only the olefinic C=C bond, but also the adjacent furyl substituent.[23h] In a subsequent catalyst screening for the asymmetric hydrogenation of furan and benzofuran derivatives, bicyclic pyridine-phosphinite complexes such as **L1** and **L2** (see *Figure 3.1*) with bulky electron-rich (*t*Bu)$_2$P groups showed superior activity and enantioselectivity (*Scheme 3.3*).



Scheme 3.3 Results of initial studies performed in the PFALTZ group.

In view of the fact that a widely applicable hydrogenation system for the reduction of structurally diverse furans and benzofurans is still not available, a more thorough investigation of the iridium-catalyzed hydrogenation of furan and benzofuran derivatives was carried out. The results of this study are described in this chapter.

3.2 Iridium Complexes Used for the Hydrogenation of Furans and Benzofurans

The substituted furans synthesized during this work (see *Chapter 2*) were investigated as substrates for the iridium-catalyzed asymmetric hydrogenation, using a range of catalysts based on the N,P ligands shown in *Figure 3.1*.

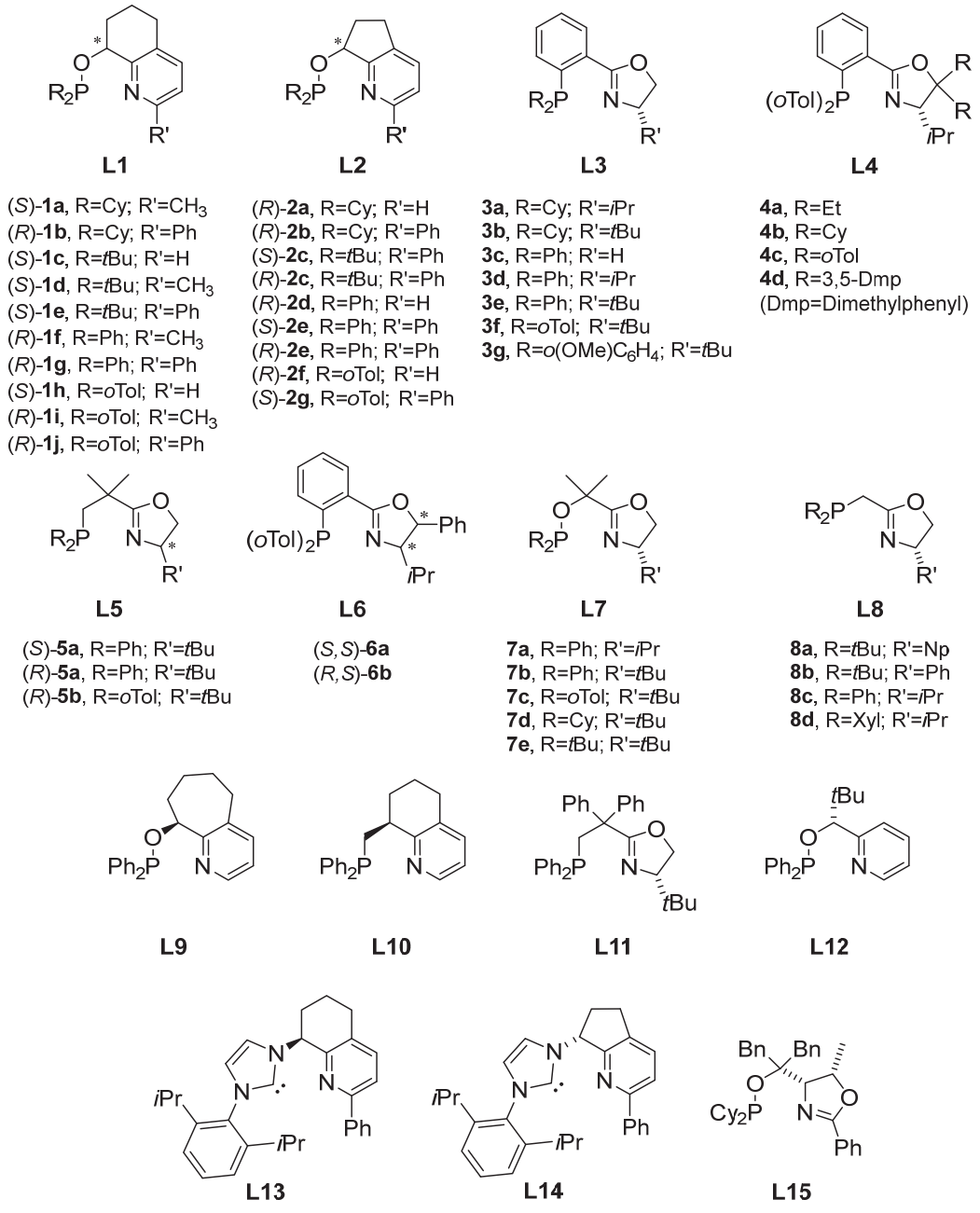
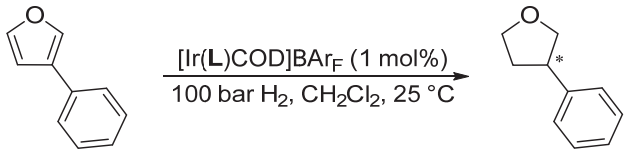


Figure 3.1 Ligand structures of [Ir(**L**)COD]BAr$_F$ complexes used in this work.

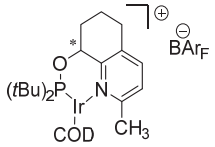
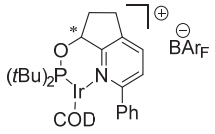
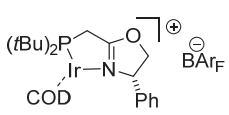
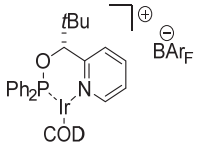
3.3 Enantioselective Hydrogenation of 3-Substituted Furans

Hydrogenation experiments were first performed with 3-phenylfuran (**41a**). For the initial investigation four different catalytic systems were chosen (*Table 3.1*).

Table 3.1 Iridium-catalyzed hydrogenation of 3-phenylfuran (**41a**).



41a **100**

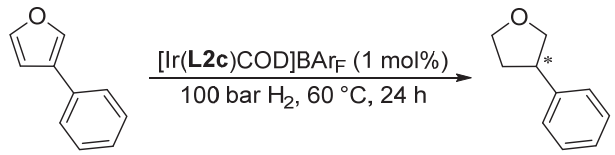
entry	catalyst structure	ligand	*t* (h)	conv. (%)[a]	*ee* (%)[a]
1		(*S*)-**L1d**	4	3	9 (–)
2		(*S*)-**L1d**	24	5	17 (–)
3		(*S*)-**L1d**	24	1	n.d.[b]
4		(*S*)-**L2c**	4	36	>**98** (–)
5		(*S*)-**L2c**	24	74	>**99** (–)
6		(*S*)-**L2c**	24	86	**99** (–)[b]
7		**L8b**	4	3	46 (–)
8		**L8b**	24	21	51 (–)
9		**L8b**	24	30	63 (–)[b]
10		**L12**	4	<1	n.d.
11		**L12**	24	<1	n.d.
12		**L12**	24	<1	n.d.[b]

[a] Determined by GC analysis on a chiral stationary phase. [b] Reaction carried out at 40 °C.

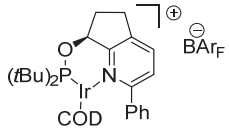
With the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1d** substrate **41a** was reduced with very low conversion and low enantiomeric excess (entries 1-3). The five-membered ring analog of ligand, **L2c**, afforded after four hours 3-phenyltetrahydrofuran (**100**) with good *ee* although with low conversion (entry 4). Prolonged reaction time combined with higher temperature resulted in increased conversion without affecting the excellent enantioselectivity (entries 5 and 6). The low conversion obtained with the phosphino-methyl-oxazoline ligand **L8b** could be improved together with the enantiomeric excess by increasing both the temperature and the reaction time (entries 8 and 9). In contrast, for the hydrogenation of furan **41a** with the complex based on ligand **L12** an increase in temperature and reaction time did not improve the performance of the catalyst, which failed to provide the desired

tetrahydrofuran **100** in detectable amount (entries 10-12). To further increase the conversion the reaction parameters of the enantioselective hydrogenation with ligand **L2c** were scrutinized (*Table 3.2*).

Table 3.2 Optimization of the reaction parameters for the hydrogenation of furan **41a**.



41a **100**

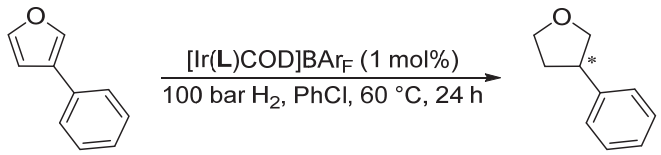
entry	catalyst structure	cat. load. (mol%)	solvent	conv. (%)[a]	*ee* (%)[a]
1		1	CH_2Cl_2	94	99 (–)
2		2	CH_2Cl_2	96	99 (–)
3		0.5	PhCl	77	98 (–)
4		1	PhCl	94	98 (–)
5		2	PhCl	99	**98** (–)
6		1	PhCl	99	**98** (+)[b]

[a] Determined by GC analysis on a chiral stationary phase. [b] Reaction carried out with (*R*)-enantiomer of **L2c**.

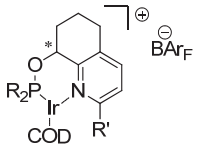
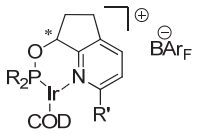
The increased reaction temperature of 60 °C had the most noticeable influence on the conversion (94% *vs.* 74% and 86% at 25 °C and 40 °C, respectively). Higher catalyst loading resulted in slightly higher conversion (entry 2). When the solvent was changed to chlorobenzene the hydrogenation reaction gave with similar results (entry 4). With 2 mol% catalyst loading the yield was almost quantitative (entry 5). High enantioselectivity was also obtained with lower catalyst loading, but at the expense of conversion (entry 3). With the (*R*)-enantiomer of the pyridine-phosphinite ligand **L2c** using 1 mol% catalyst loading, tetrahydrofuran **100** was obtained with excellent conversion and enantiomeric excess (entry 6).

With optimized reaction conditions in hand, other available iridium-complexes previously developed in our group were tested. The results of the hydrogenation of 3-phenylfuran (**41a**) with different bicyclic pyridine-phosphinite ligand complexes containing five or six-membered carbocyclic rings are presented in *Table 3.3*.

Table 3.3 Iridium-catalyzed hydrogenation of furan **41a** using ligands **L1** and **L2**.



41a **100**

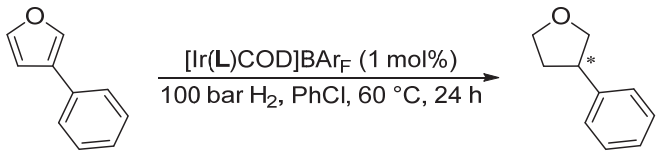
entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[a]
1		Cy	CH_3	(*S*)-**L1a**	18	19 (–)
2		Cy	Ph	(*R*)-**L1b**	<1	n.d.
3		*t*Bu	Ph	(*S*)-**L1e**	33	**79** (–)
4		Ph	CH_3	(*R*)-**L1f**	<1	n.d.
5		Ph	Ph	(*R*)-**L1g**	–[b]	–
6		*o*Tol	H	(*S*)-**L1h**	6	7 (+)
7		*o*Tol	CH_3	(*R*)-**L1i**	2	n.d.
8		Cy	H	(*R*)-**L2a**	<1	n.d.
9		Cy	Ph	(*R*)-**L2b**	61	**73** (+)
10		Ph	H	(*R*)-**L2d**	<1	n.d.
11		*o*Tol	H	(*R*)-**L2f**	<1	n.d.
12		*o*Tol	Ph	(*S*)-**L2g**	20	51 (–)

[a] Determined by GC analysis on a chiral stationary phase. [b] Starting material was recovered.

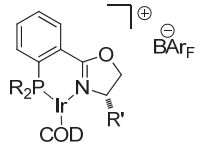
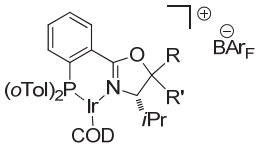
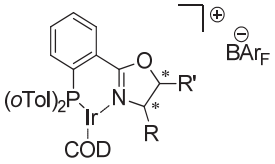
Among the cyclohexane-annulated bicyclic pyridine-phosphinite ligands **L1**, **L1e** having the same substituents as **L2c**, gave the highest enantioselectivity with 79% *ee* (entry 3). This combination of an alkyl group at the phosphorus atom and a phenyl substituent on the pyridine ring also gave the best results for the five-membered ring analogs (entry 9). However, the enantioselectivities were significantly lower than those induced by ligand **L2c** (see *Table 3.2*).

Chiral phosphino-oxazoline ligands **L3**, **L4** and **L6** were also investigated in the hydrogenation of 3-phenylfuran (**41a**) (*Table 3.4*).

Table 3.4 Iridium-catalyzed hydrogenation of substrate **41a** with phosphino-oxazoline ligands.



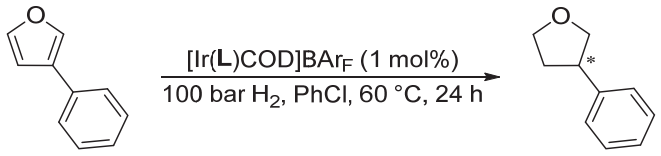
41a **100**

entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[a]
1		Cy	*i*Pr	**L3a**	15	38 (+)
2		Cy	*t*Bu	**L3b**	31	30 (+)
3		Ph	*i*Pr	**L3d**	–[b]	–
4		Ph	*t*Bu	**L3e**	–[b]	–
5		*o*Tol	*t*Bu	**L3f**	74	7 (–)
6		*o*(OMe)C$_6$H$_4$	*t*Bu	**L3g**	<1	n.d.
7		Et	Et	**L4a**	45	7 (+)
8		Cy	Cy	**L4b**	<1	n.d.
9		*o*Tol	*o*Tol	**L4c**	56	28 (–)
10		3,5-Dmp[c]	3,5-Dmp[c]	**L4d**	91	56 (+)
11		*i*Pr	Ph	(*S*,*S*)-**L6a**	60	6 (+)
12		*i*Pr	Ph	(*R*,*S*)-**L6b**	80	8 (–)

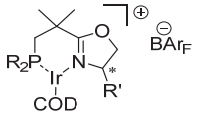
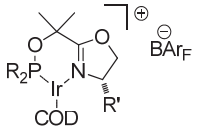
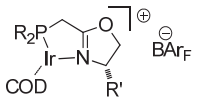
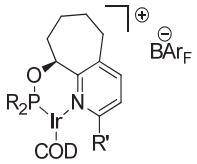
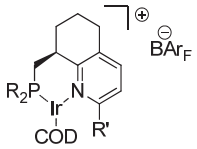
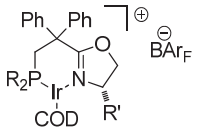
[a] Determined by GC analysis on a chiral stationary phase. [b] Starting material was recovered.
[c] Dmp: Dimethylphenyl.

The hydrogenation of 3-phenylfuran (**41a**) using chiral phosphino-oxazoline ligand **L3** under the optimized reaction conditions gave no or only low enantiomeric excess (entries 1-6). The decrease of the *ee* correlates with increasing steric bulk on the ligand. Moreover, the conversion varied strongly (0-74%). With ligand **L4** higher enantioselectivity (56% *ee*) was obtained with moderate to good conversion (entries 7-10). On the other hand, ligand class **L6** emerged to be less selective in the hydrogenation of furan **41a**. Even though 3-phenyltetrahydrofuran (**100**) could be obtained with moderate conversion, the enantiomeric excess turned out to be very low (entries 11 and 12). Other classes of iridium-catalysts were investigated with 3-phenylfuran (**41a**) (*Table 3.5*).

Table 3.5 Iridium-catalyzed hydrogenation of furan **41a** with selected ligand classes.



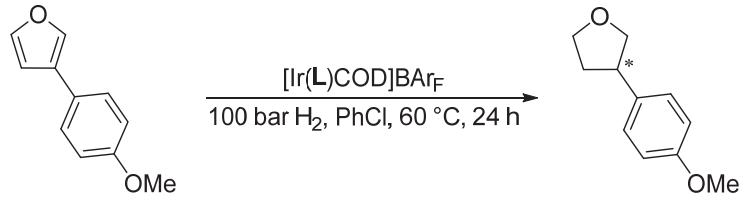
41a **100**

entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[a]
1		Ph	*t*Bu	(*R*)-**L5a**	<1	n.d.
2		*o*Tol	*t*Bu	(*R*)-**L5b**	22	8 (+)
3		Ph	*i*Pr	**L7a**	2	n.d.
4		Ph	*t*Bu	**L7b**	3	n.d.
5		*o*Tol	*t*Bu	**L7c**	–[b]	–
6		*t*Bu	Np	**L8a**	47	**77** (+)
7		Ph	*i*Pr	**L8c**	<1	n.d.
8		Xyl	*i*Pr	**L8d**	<1	n.d.
9		Ph	H	**L9**	6	18 (+)
10		Ph	H	**L10**	22	42 (–)
11		Ph	*t*Bu	**L11**	30	*rac*

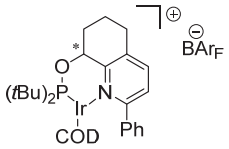
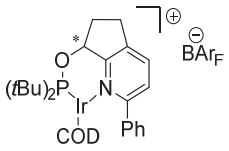
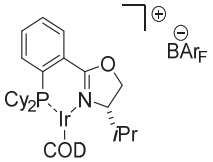
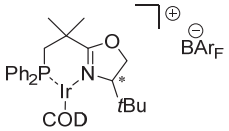
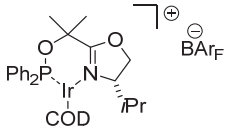
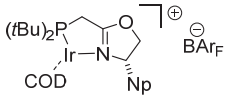
[a] Determined by GC analysis on a chiral stationary phase. [b] Starting material was recovered.

The iridium catalyst based on Neo-PHOX ligand **L5** suffered from low conversion and very low *ee* (entries 1 and 2). Higher enantiomeric excess, but lower conversion was induced by Simple-PHOX ligands **L7a-b** (entries 3 and 4). Phosphino-methyl-oxazoline ligand **L8a** gave the highest enantioselectivity (77% *ee*) among the ligand classes shown in *Table 3.5*. Also here the alkyl substituent on the phosphorus atom was crucial for the activity of the catalytic system, since replacement of the alkyl by a phenyl or xylyl group resulted in almost no conversion (entry 6 *vs.* entries 7 and 8).
Some of the ligands that had been already tested for the hydrogenation of furan **41a**, were also investigated for the reduction of 3-(4-methoxyphenyl)furan (**41b**) (*Table 3.6*).

Table 3.6 Selected iridium catalysts in the hydrogenation of furan **41b**.



41b **101**

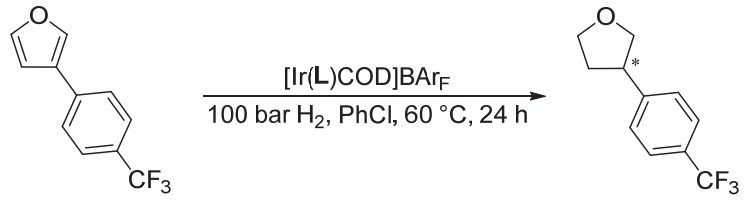
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1e**	4	65 (–)[e]
2		(*S*)-**L2c**	77	93 (–)[c]
3			83	**95** (–)
4			97	94 (–)[d]
5			98	91 (–)[e]
6		(*R*)-**L2c**	85	**95** (+)
7			96	94 (+)[d]
8			99	92 (+)[e]
9		**L3a**	40	21 (+)
10		(*R*)-**L5a**	9	20 (–)
11		**L7a**	23	34 (–)
12		**L8a**	47	71 (+)

[a] Determined by GC analysis on a chiral stationary phase. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction carried out at 40 °C in CH_2Cl_2. [d] Reaction time 63 h. [e] 2 mol% catalyst loading.

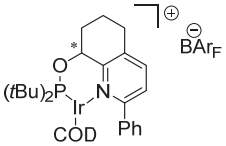
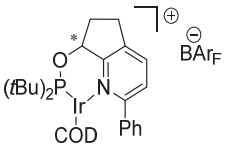
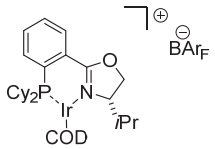
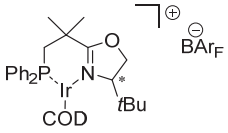
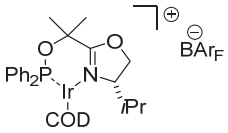
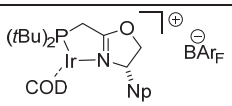
This substrate was also reduced with high enantioselectivity up to 95% *ee* when using the bicyclic pyridine-phosphinite ligand **L2c**. The conversion could be enhanced by increasing the catalyst loading to 2 mol% at the expense of the enantiomeric excess (entry 3 *vs.* entry 5). However, longer reaction times resulted in high conversion while

retaining the enantioselectivity (entries 4 and 7). With the phosphino-methyl-oxazoline ligand **L8a** similar results were obtained as for 3-phenylfuran (**41a**) (see *Table 3.5*) (47%, 71% *ee vs.* 47%, 77% *ee*). Furthermore, the hydrogenation of 3-(4-(trifluoromethyl)phenyl)furan (**41c**) was studied (*Table 3.7*).

Table 3.7 Selected iridium catalysts in the hydrogenation of furan **41c**.



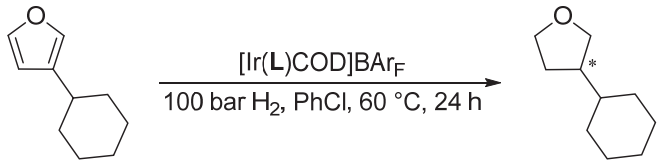
41c **102**

entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[a]
1		(*S*)-**L1e**	17	88 (–)[d]
2		(*S*)-**L2c**	81	97 (–)[b]
3			64	97 (–)
4			70	97 (–)[c]
5			88	**97** (–)[d]
6		(*R*)-**L2c**	69	96 (+)
7			64	96 (+)[c]
8			89	**96** (+)[d]
9		**L3a**	1	n.d.
10		(*R*)-**L5a**	<1	n.d.
11		**L7a**	<1	n.d.
12		**L8a**	13	53 (+)

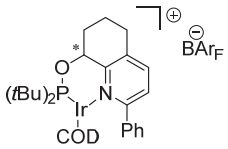
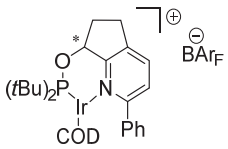
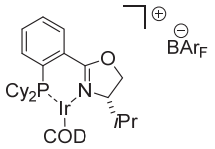
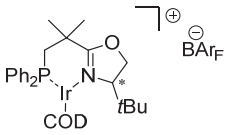
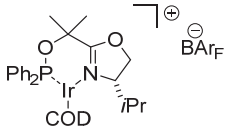
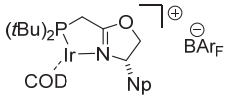
[a] Determined by GC analysis on a chiral stationary phase. [b] Reaction carried out at 40 °C in CH_2Cl_2. [c] Reaction time 63 h. [d] 2 mol% catalyst loading.

The hydrogenation of furan **41c** with the complex based on ligand **L2c** proceeded with higher enantioselectivity (97% *ee*), however with lower conversion compared to reaction of 3-(4-methoxyphenyl)furan (**41b**). Surprisingly, a decrease of the reaction temperature had a positive effect on the conversion (entry 2). Increased catalyst loading led to higher conversion using both enantiomers of ligand **L2** (entries 5 and 8).

Table 3.8 Selected iridium catalysts in the hydrogenation of 3-cyclohexylfuran (**65**).



65 **103**

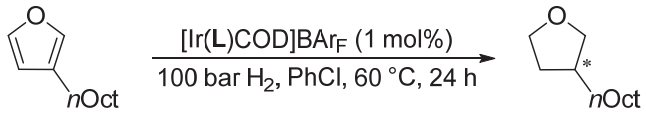
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[a]
1		(*S*)-**L1e**	28	75 (–)[d]
2		(*S*)-**L2c**	31	>98 (–)[b]
3			76	98 (–)
4			71	98 (–)[c]
5			**>99**	**98** (–)[d]
6		(*R*)-**L2c**	49	98 (+)
7			57	97 (+)[c]
8			77	98 (+)[d]
9		**L3a**	41	54 (+)
10		(*R*)-**L5a**	2	n.d.
11		**L7a**	29	2 (+)
12		**L8a**	29	50 (+)

[a] Determined by GC analysis on a chiral stationary phase. [b] Reaction carried out at 40 °C in CH_2Cl_2. [c] Reaction time 63 h. [d] 2 mol% catalyst loading.

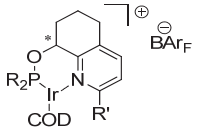
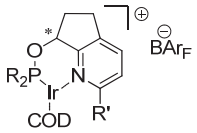
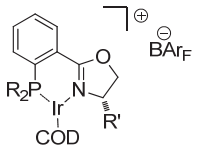
In order to directly compare the hydrogenation results for 3-aryl substituted furans with those for alkyl substituted ones, the hydrogenation of 3-cyclohexylfuran (**65**) was performed with the same ligands (*Table 3.8*). A similar level of enantioselectivity as for the hydrogenation of 3-phenylfuran (**41a**) was obtained for 3-cyclohexylfuran (**65**) with the iridium complex based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c**, but with lower conversion (entry 3). Paralleling what observed for 3-phenylfuran (**41a**), an increased catalyst loading gave higher conversion with no erosion of the enantiomeric excess (entry 5). Prolonged reaction time did not drive the reaction to completion (entries 4 and 7).

A substrate bearing a linear alkyl chain, 3-octylfuran (**64**), was also tested under the optimized reaction conditions (*Table 3.9*).

Table 3.9 Iridium-catalyzed hydrogenation of furan **64** with selected complexes.



64 **104**

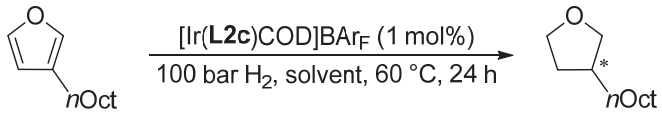
entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[a]
1		*t*Bu	Ph	(*S*)-**L1e**	4	81 (–)
2		*t*Bu	Ph	(*S*)-**L1e**	–[b]	–
3		*t*Bu	Ph	(*S*)-**L2c**	13	94 (–)
4		*t*Bu	Ph	(*S*)-**L2c**	–[b]	–
5		Ph	Ph	(*S*)-**L2e**	1	n.d.
6		Ph	Ph	(*S*)-**L2e**	–[b]	–
7		Ph	*t*Bu	**L3e**	1	n.d.
8		Ph	*t*Bu	**L3e**	–[b]	–

[a] Determined by GC analysis on a chiral stationary phase. [b] Reaction carried out at 110 bar H_2 pressure and 100 °C, starting material was recovered.

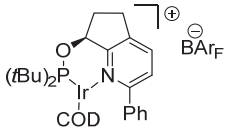
Although 3-octylfuran (**64**) was hydrogenated with low conversion in the presence of the highly active catalyst complex based on **L2c**, it was reduced with high enantio-selectivity (entry 3). Forcing hydrogenation conditions, such as increased reaction temperature and hydrogen pressure, resulted in no conversion at all (entries 2, 4, 6, 8).

To increase the conversion different solvents were tested using the iridium catalyst based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c** (*Table 3.10*).

Table 3.10 Solvent screening for the hydrogenation of 3-octylfuran (**64**).



64 **104**

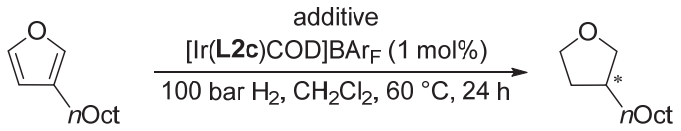
entry	catalyst structure	solvent	conv. (%)[a]	*ee* (%)[a]
1		toluene	–[b]	–
2		benzene	–[b]	–
3		*i*PrOH	–[b]	–
4		EtOAc	–[b]	–
5		MeOH	–[b]	–
6		EtOH	–[b]	–
7		CH_2Cl_2	20	95 (–)

[a] Determined by GC analysis on a chiral stationary phase. [b] Starting material was recovered.

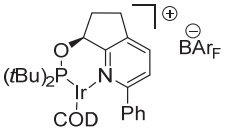
The only medium in which the hydrogenation gave product **104** was CH_2Cl_2, the standard solvent used in iridium-catalyzed hydrogenation.[44]

Apart from the loss of aromaticity during hydrogenation, one explanation for the observed low reactivity of furan **64** might be the coordination of the oxygen atom to the metal center of the catalyst. Lewis acids could facilitate the hydrogenation by coordination to the oxygen atom of the substrate. In addition, complexation of the O-atom of the furan by the Lewis acid could prevent catalyst deactivation by coordination of the substrate or the hydrogenated product to the iridium atom. In this case stoichiometric amounts of the Lewis acid should be used. Both strong and weak Lewis acids were tested in the iridium-catalyzed asymmetric hydrogenation of 3-octylfuran (**64**) with the four ligands shown in *Table 3.9*. In this study the catalyst based on **L2c** behaved as well as the most active and selective one, so in the further investigation only this catalytic system was tested. The results obtained upon addition of additives are summarized in *Table 3.11*.

Table 3.11 Hydrogenation of 3-octylfuran (**64**) with additives.



64 **104**

entry	catalyst structure	additive	amount (eq.)	conv. (%)[a]	*ee* (%)[a]
1		none	–	20	95 (–)
2		$B(OCH_3)_3$	1.74	21	95 (–)
3		$BF_3{\cdot}O(C_2H_5)_2$	1.01	>99	59 (+)
4		$B(C_6F_5)_3$	1.01	>99	41 (+)
5		CF_3CH_2OH	2.75	17	93 (–)
6		CF_3CH_2OH	5.51	36	95 (–)
7		CF_3CH_2OH	11	44	95 (–)
8		CF_3CH_2OH	22	51	95 (–)
9		CF_3CH_2OH	70	69	97 (–)[b]
10		CF_3CH_2OH	70	94	95 (–)[b,c]

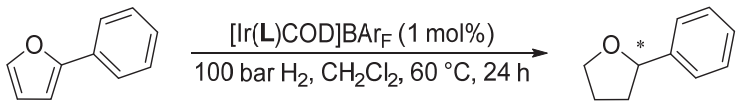
[a] Determined by GC analysis on a chiral stationary phase. [b] CF_3CH_2OH as solvent.
[c] 2 mol% catalyst loading.

Similar conversion was induced upon the addition of trimethyl borate without affecting the enantiomeric excess (entry 1). A stronger influence on the conversion was observed in the presence of stronger Lewis acids, BF_3 etherate and tris(pentafluorophenyl)borane, however, at the expense of a substantial loss of enantioselectivity and unexpected inversion of the product configuration (entries 2 and 3). In contrast, the addition of the Brønsted acidic trifluoroethanol resulted in similar low conversion when used as additive, but in high conversion and perfect enantiomeric purity when utilized as a solvent (entries 5-8 *vs.* entries 9 and 10). The role of this additive is not fully understood; it could form hydrogen bonds to the furan O-atom and prevent its coordination to the iridium atom. At the same time trifluoroethanol is a non-nucleophilic solvent providing a very weakly coordinating environment, which is necessary for high catalytic activity. In any case, the strong rate-enhancing effect of trifluoroethanol offered a practically useful solution to overcome reactivity problems in the hydrogenation of 3-octylfuran (**64**).

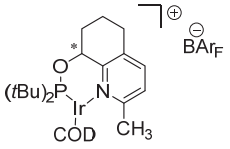
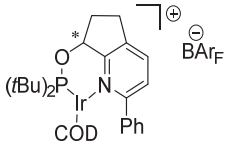
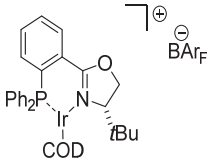
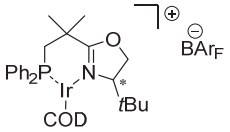
3.4 Enantioselective Hydrogenation of 2-Substituted Furans

Next, the previously synthesized 2-substituted furans were tested in the iridium-catalyzed hydrogenation. The hydrogenation results for 2-phenylfuran (**44a**) are summarized in *Table 3.12*.

Table 3.12 Iridium-catalyzed hydrogenation of 2-phenylfuran (**44a**) with selected complexes.



44a **105**

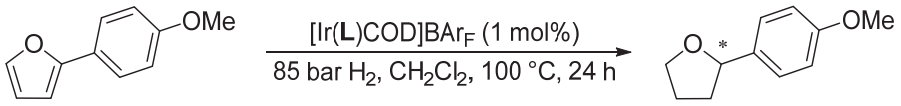
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1d**	11	6
2		(*S*)-**L2c**	15	2
3		**L3e**	15	3
4		(*S*)-**L5a**	2	8

[a] Determined by GC analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

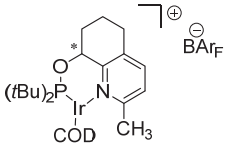
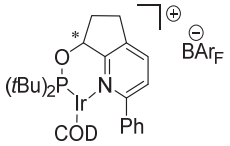
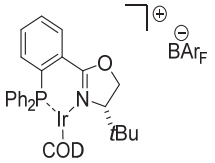
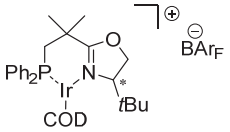
With all four selected iridium complexes the hydrogenation reaction of 2-phenylfuran (**44a**) proceeded only sluggishly. Surprisingly, only low conversion and almost racemic product **105** was obtained. Therefore, the hydrogenation of this substrate was not further studied.

Instead, 2-(4-methoxyphenyl)furan (**44b**) was investigated and the results of this study are summarized in *Table 3.13*.

Table 3.13 Iridium-catalyzed hydrogenation of furan **44b** with selected complexes.



44b **106**

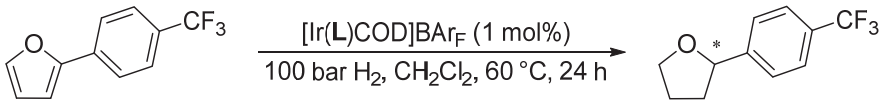
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1d**	–[c]	–
2		(*S*)-**L2c**	–[c]	–
3		*rac*-**L2c**	–[c,d]	–
4		**L3e**	–[c]	–
5		(*S*)-**L5a**	–[c]	–

[a] Determined by GC analysis. [b] Determined by HPLC analysis on chiral stationary phase.
[c] Starting material was recovered. [d] Reaction carried out at 60 °C and 100 bar H_2 pressure.

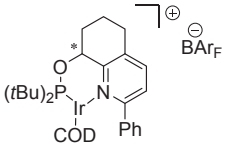
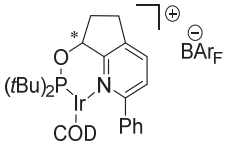
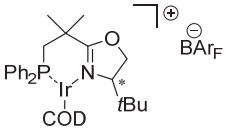
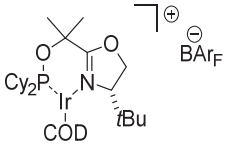
Paralleling the results observed in the case of 2-phenylfuran (**44a**), also 2-(4-methoxyphenyl)furan) (**44b**) was not reactive at all under standard reaction conditions (entry 3). Electron donating groups on the phenyl substituent made the furan even less reactive than the phenyl substituted furan **44a**, therefore the reaction temperature was increased to 100 °C. However, even at this temperature no reaction took place.

The substrate with an electron withdrawing group on the 2-substituted furan **44c** was also tested (*Table 3.14*).

Table 3.14 Iridium-catalyzed hydrogenation of furan **44c** with selected complexes.



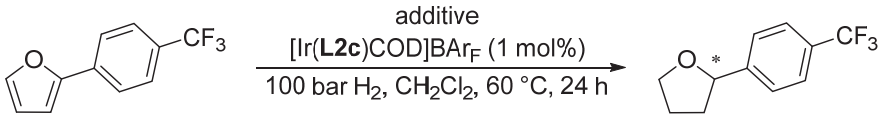
44c **107**

entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1e**	9	18 (+)
2		(*S*)-**L2c**	**80**	**69** (+)
3		*rac*-**L2c**	52	–
4		(*S*)-**L5a**	1	n.d.
5		**L7d**	1	n.d.

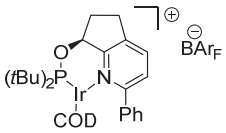
[a] Determined by GC analysis. [b] Determined by HPLC analysis on chiral stationary phase.
[c] Starting material was recovered. [d] Reaction carried out at 60 °C and 100 bar H_2 pressure.

The results show that the electronic properties of the furan substrate have a great influence on the outcome of the hydrogenation reaction. With an electron withdrawing substituent on the 2-substituted furan **44c**, the hydrogenation proceeded under standard conditions with good conversion, but moderate enantioselectivity. Encouraged by these findings some additives were investigated in the hydrogenation of this substrate (*Table 3.15*).

Table 3.15 Iridium-catalyzed hydrogenation of furan **44c** with additives.



44c **107**

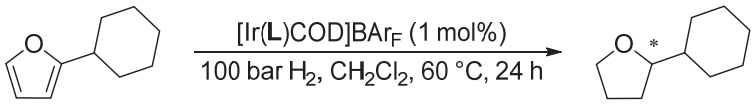
entry	catalyst structure	additive	amount (eq.)	conv. (%)[a]	*ee* (%)[a]
1		none	–	80	69 (+)
2		$B(OCH_3)_3$	1.74	29	48 (+)
3		$BF_3{\cdot}O(C_2H_5)_2$	1.01	63	31 (+)
4		$B(C_6F_5)_3$	1.01	82	19 (+)
5		CF_3CH_2OH	42	62	14 (−)

[a] Determined by GC analysis on a chiral stationary phase.

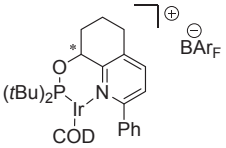
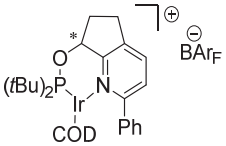
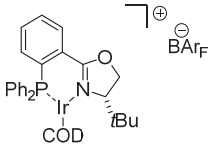
Both the enantiomeric excess and the conversion during hydrogenation of 2-(4-(trifluoro-methyl)phenyl)furan (**44c**) were lower than without additives. Only with tris(pentafluorophenyl)borane the furan **44c** was converted with comparable conversion, but with lower enantioselectivity (19% *ee vs.* 69% *ee*). When trifluoro-ethanol was added to the hydrogenation reaction, the reduced compound **107** was obtained with moderate conversion and low enantiomeric excess (entry 4).

The influence of an alkyl substituent at the 2-position of furan was also investigated in the hydrogenation of 2-cyclohexylfuran (**66**) (*Table 3.16*).

Table 3.16 Iridium-catalyzed hydrogenation of furan **66** with selected complexes.



66 **108**

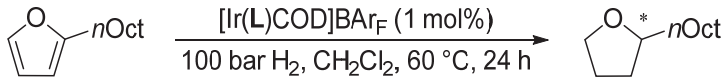
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[a]
1		(*S*)-**L1e**	54	63 (+)
2		(*S*)-**L2c**	65	80 (+)
3			**96**	**82** (+)[b]
4		**L3e**	1	n.d.

[a] Determined by GC analysis on a chiral stationary phase. [b] 2 mol% catalyst loading.

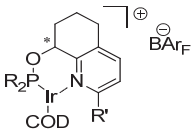
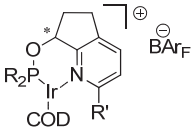
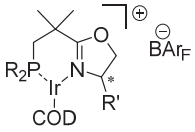
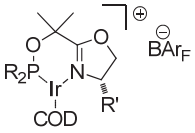
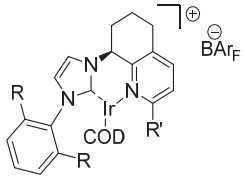
Hydrogenation of 2-cyclohexylfuran (**66**) with the catalyst based on the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1e** proceeded with moderate conversion and enantioselectivity (entry 1). The five-membered ring analog of ligand **L2c** promoted the hydrogenation reaction of furan **66** with both higher conversion and slightly better enantiomeric excess (entry 2). By increasing the catalyst loading to 2 mol%, the conversion improved to 96% without affecting the *ee* (entry 3). The catalyst based on the PHOX ligand **L3e** showed only little activity and low enantiomeric excess (entry 4).

The sterically less hindered 2-alkyl substituted furan **71** was also tested in the hydrogenation with various catalysts (*Table 3.17*).

Table 3.17 Iridium-catalyzed hydrogenation of 2-octylfuran (**71**) with various complexes.



71 **109**

entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[a]
1		*t*Bu	Ph	(*S*)-**L1e**	36	**75**
2		*t*Bu	Ph	(*S*)-**L2c**	**86**	58
3		Ph	Ph	(*S*)-**L2e**	6	19
4		Ph	*t*Bu	(*S*)-**L5a**	3	45
5		*o*Tol	*t*Bu	**L7c**	2	19
6		*i*Pr	Ph	**L13**	56	12

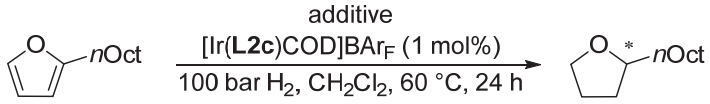
[a] Determined by GC analysis on a chiral stationary phase.

The hydrogenation of 3-octylfuran (**71**) proved very challenging, too. The reaction suffers from low activity and only moderate enantiomeric excess with the ligands shown in *Table 3.17*. The cyclohexane-annulated pyridine-phosphinite complex

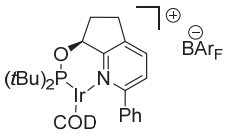
derived from ligand **L1e** gave higher enantiomeric excess (75% *ee*), whereas the complex based on the five-membered ring analog **L2c** reduced the furan to higher extent (86%) (entries 1 and 2). The importance of an alkyl group on the phosphorus atom is demonstrated by ligand **L2e**. When the *t*Bu group was exchanged to a phenyl group, the activity was strongly reduced (entry 2 *vs.* entry 3). The phosphino-oxazoline derived ligands, Neo-PHOX **L5a** and Simple-PHOX **L7c** gave only little conversion with moderate to low enantioselectivity (entries 4 and 5). The NHC ligand **L13** was tested in the hydrogenation of furans for the first time and resulted in moderate conversion, but low enantiomeric excess (entry 6).

An extensive screening of additives was carried out to increase the conversion in the hydrogenation of 2-octylfuran (**71**). The catalyst complex based on ligand **L2c**, which gave the highest conversion with this substrate was investigated using trifluoroethanol as additive or solvent (*Table 3.18*).

Table 3.18 Iridium-catalyzed hydrogenation of furan **71** with CF_3CH_2OH.



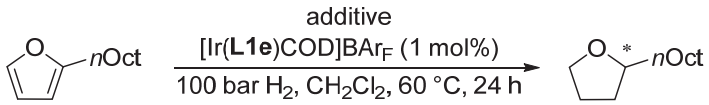
71 **109**

entry	catalyst structure	additive	amount (eq.)	conv. (%)[a]	*ee* (%)[a]
1		CF_3CH_2OH	11	87	69 (+)
2		CF_3CH_2OH	22	83	64 (+)
3		CF_3CH_2OH	44	78	68 (+)
4		CF_3CH_2OH	70	**97**	**65** (+)[b]

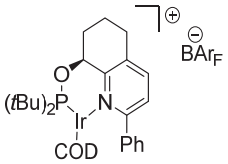
[a] Determined by GC analysis on a chiral stationary phase. [b] CF_3CH_2OH as solvent.

The effect on the conversion of the hydrogenation reaction of substrate **71** upon addition of the weakly Brønsted acidic trifluoroethanol was contradictory. When used as an additive, lower conversion was obtained, but when it was applied as the solvent the hydrogenation proceeded almost to completion (97%). The enantiomeric excess remained almost constant. Also in case of the catalyst based on the cyclohexane-annulated bicyclic pyridine-phosphinite **L1e** an additive screening was performed (*Table 3.19*).

Table 3.19 Iridium-catalyzed hydrogenation of 2-octylfuran (**71**) with additives.



71 **109**

entry	catalyst structure	additive	amount (eq.)	conv. (%)[a]	*ee* (%)[a]
1		$B(OCH_3)_3$	1.74	31	65 (+)
2		$BF_3{\cdot}O(C_2H_5)_2$	1.01	>99	23 (+)
3		$B(C_6F_5)_3$	1.01	>99	20 (−)
4		CF_3CH_2OH	70	18	20 (+)[b]

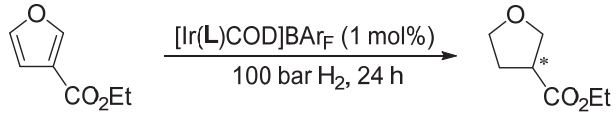
[a] Determined by GC analysis on a chiral stationary phase. [b] CF_3CH_2OH as solvent.

A much larger increase of reactivity was observed when using the stronger Lewis acids BF_3 etherate and tris(pentafluorophenyl)borane, however, at the expense of a substantial loss of enantioselectivity (entries 2 and 3).

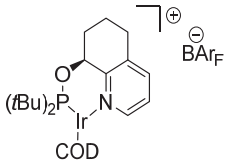
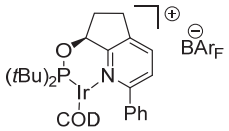
3.5 Enantioselective Hydrogenation of 3- and 2-Furancarboxylic acid ethyl ester

Optimized conditions for 3-substituted furans were applied to the hydrogenation of ethyl 3-substituted furan **110** and 2-substituted furan **111** using the most active and selective cyclopentane-annulated bicyclic pyridine-phosphinite catalyst **L2c**. 3-Furancarboxylic acid ethyl ester (**110**) was reduced, but with low conversion and only moderate enantioselectivity (*Table 3.20*).

Table 3.20 Iridium-catalyzed hydrogenation of furan **110**.

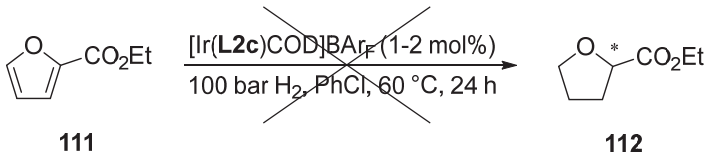


110 **110a**

entry	catalyst structure	ligand	solvent	T (°C)	conv. (%)[a]	*ee* (%)[a]
1		(*S*)-**L1c**	CH_2Cl_2	40	11	71 (–)[b]
2		(*S*)-**L2c**	CH_2Cl_2	40	2	59 (–)
3			CH_2Cl_2	40	<1	n.d.[b]
4			PhCl	60	<1	n.d.
5			PhCl	60	10	42 (–)[b]

[a] Determined by HPLC analysis on a chiral stationary phase. [b] 2 mol% catalyst loading.

The catalyst based on the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1c** promoted the hydrogenation of 3-furancarboxylic acid ethyl ester (**110**) with higher enantioselectivity (71% *ee*) than the five-membered ring counterpart **L2c**, shown by KAISER (entry 1 *vs.* entry 2).[40]



111 **112**

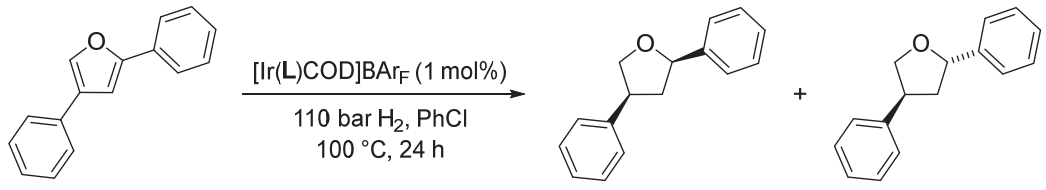
Scheme 3.4 Iridium-catalyzed hydrogenation of furan **111**.

The reduction of 2-furancarboxylic acid ethyl ester (**111**) in contrast did not give the desired reduced product **112**, even after increasing the catalyst loading to 2 mol% (*Scheme 3.4*).

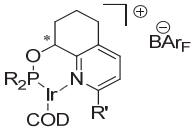
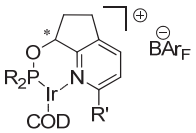
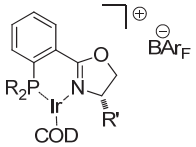
3.6 Enantioselective Hydrogenation of 2,4-Disubstituted Furans

The advantage of the hydrogenation of disubstituted furans is represented by the potential selective generation of two new stereogenic centers in one reaction step. When 2,4-diphenylfuran (**79**) was reduced under standard conditions with palladium on charcoal to give the racemate, both diastereomers calyxolane A **2a** and calyxolane B **2b** were obtained in a ratio of 75:25 (*cis*:*trans*). The natural products were separated by flash chromatography, analyzed and identified by proton NMR. As for the mono-substituted furans, also for substrate **79** standard hydrogenation conditions were applied first. With catalyst complex bearing ligand **L2c** very low conversion was obtained (1%) with moderate *cis*:*trans* ratio (64:36). Therefore more forcing reaction conditions were applied (*Table 3.21*).

Table 3.21 Iridium-catalyzed hydrogenation of 2,4-diphenylfuran (**79**).



79 **2b** **2a**

entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*dr* (*cis*:*trans*)[a]
1		*t*Bu	H	(*S*)-**L1c**	2	72:28
2		*t*Bu	Ph	(*S*)-**L1e**	41	79:21
3		*o*Tol	Ph	(*R*)-**L1j**	21	73:27
4		*t*Bu	Ph	(*S*)-**L2c**	52	80:20
5		*t*Bu	Ph	(*S*)-**L2c**	55	74:26[b]
6		Ph	Ph	(*S*)-**L2e**	60	81:19
7		Cy	*t*Bu	**L3b**	1	n.d.
8		Ph	*t*Bu	**L3e**	2	80:20

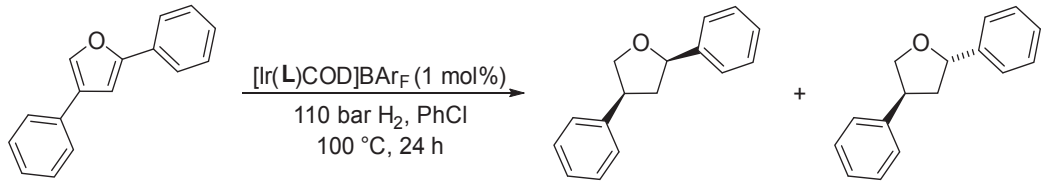
[a] Determined by GC analysis. [b] 2 mol% catalyst loading.

Higher temperature as well as higher hydrogen pressure had a positive effect on the hydrogenation reaction of 2,4-diphenylfuran (**79**). However, the conversion was moderate and the hydrogenation of substrate **79** was performed without the determination of the enantiomeric purity, because no suitable conditions for determination of the enantiomeric excess by HPLC were found.

Others determined the optical purity by ^{1}H-NMR in the presence of the lanthanide chiral shift reagent Pr(hfc)$_3$ (praseodymium(III) tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorate])[45] in cases where selectively the *cis* diastereomer of tetrahydrofuran **2b** was formed during the reaction.

The hydrogenation reaction of disubstituted furan **79**, which led to moderate conversion (60%) could not be reproduced. Additional purification of the substrate **79** by flash chromatography did not improve the conversion. Therefore, the enantiomeric excess of the hydrogenation mixture was determined by ^{1}H-NMR analysis and Pr(hfc)$_3$ as the shift reagent of choice (*Table 3.22,* entry 1).

Table 3.22 Iridium-catalyzed hydrogenation of 2,4-diphenylfuran (**79**).



79 **2b** **2a**

entry	catalyst structure	ligand	conv. (%)[a]	*dr* (*cis*:*trans*)[a]	*cis* *ee* (%)	*trans* *ee* (%)
1		(*R*)-**L2e**	35	67:33	39[b]	n.d.
2		(*S*)-**L2e**	19	74:26	38[c]	68[d]
3		(*S*)-**L2e**	16	71:29		

[a] Determined by GC analysis. [b] ^{1}H-NMR analysis with 0.17 eq. Pr(hfc)$_3$. [c] ^{1}H-NMR analysis with 0.21 eq. Pr(hfc)$_3$. [d] ^{1}H-NMR analysis with 0.19 eq. Pr(hfc)$_3$.

The following signal splitting of the hydrogenation mixture was obtained after addition of 0.17 equivalents of the shift reagent. Unfortunately due to overlap of some signals, only the enantiomeric excess of the *cis* isomer could be determined (*Figure 3.2*).

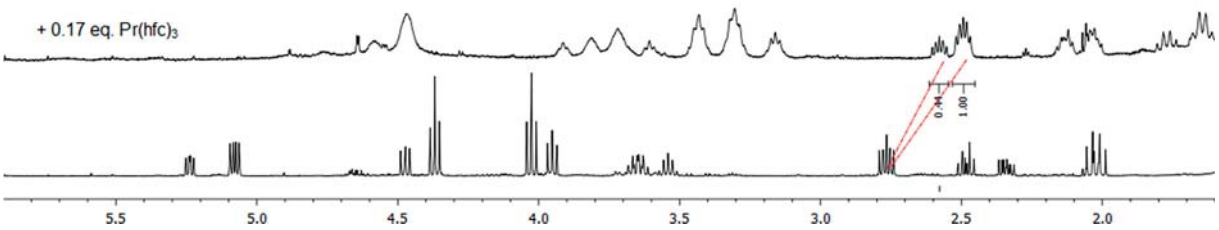


Figure 3.2 Signal splitting of a hydrogenation mixture of tetrahydrofurans **2b** and **2a** (*cis*:*trans*) upon addition of Pr(hfc)$_3$.

Combined reaction mixtures with similar *cis*/*trans* and substrate/product ratios were purified by flash chromatography and then the shift reagent was added (entry 2 and 3). The signals of both diastereoisomers were split and the enantiomeric excess of each could be determined (*Figure 3.3*).

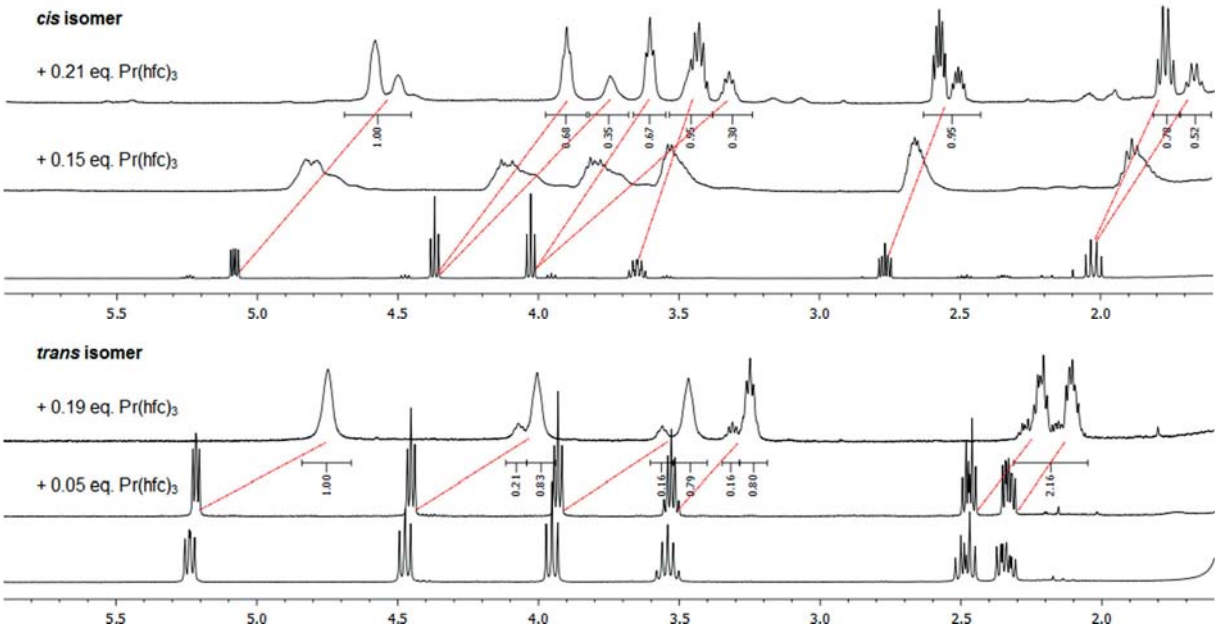


Figure 3.3 Signal splitting of pure *cis* (top) and *trans* (bottom) diastereoisomers upon addition of $Pr(hfc)_3$.

Although the enantiomeric excess remained the same after column chromatography for the *cis* isomer **2b**, the difficulty in reliably measuring the enantiomeric excess by ^{1}H-NMR analysis while both diastereoisomers are present is displayed *Figure 3.4*.

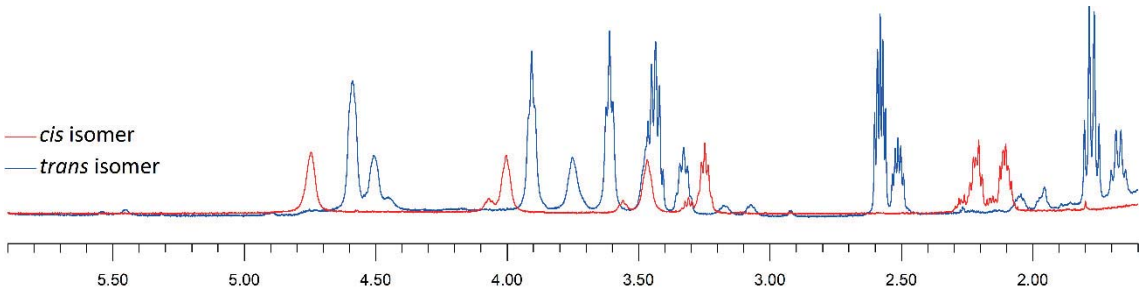


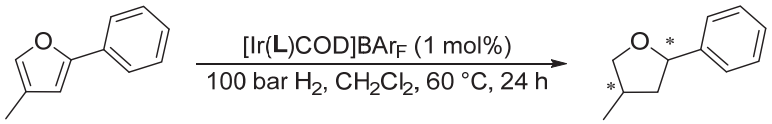
Figure 3.4 Overlapping spectra of *cis* and *trans* diastereoisomers of tetrahydrofurans **2b** and **2a**.

The spectra shows the overlap of the significant section of the proton NMR spectrum of both purified diastereoisomers of tetrahydrofurans **2b** and **2a**, recorded under the same conditions.

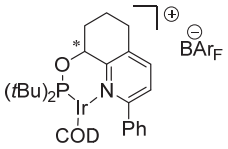
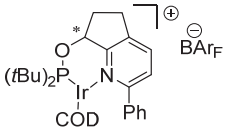
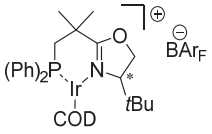
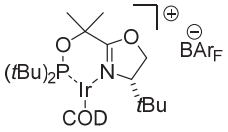
The influence of an alkyl substituent on the 2,4-disubstituted furan was investigated in the asymmetric hydrogenation of 4-methyl-2-phenylfuran (**85**). The

hydrogenation of this substrate **85** with palladium on charcoal gave only the corresponding alcohol. When the BAr_F analog of the CRABTREE catalyst was applied, only very low conversion was obtained (1%). Subsequently, different iridium catalysts were tested in the hydrogenation of this substrate (*Table 3.23*).

Table 3.23 Iridium-catalyzed hydrogenation of 4-methyl-2-phenylfuran (**85**).



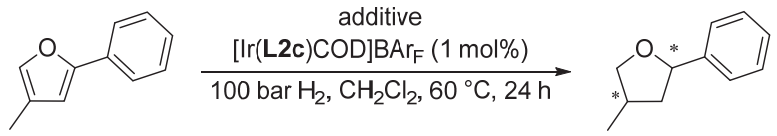
85 **103**

entry	catalyst structure	ligand	conv. (%)[a]	*dr* (*cis*:*trans*)[b,c]	*cis* *ee* (%)[b]	*trans* *ee* (%)[b]
1		(*S*)-**L1e**	32	86:14	5	77
2		(*S*)-**L2c**	**60**	**92:8**	28	82
3		(*R*)-**L2c**	31	72:28	*rac*	97
4		(*R*)-**L5a**	1	82:18	n.d.	*rac*
5		**L7e**	2	73:27	18	50

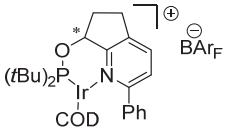
[a] Determined by GC analysis. [b] Determined by GC analysis on a chiral stationary phase. [c] Assignment of diastereomers by comparison of ^{1}H-NMR spectra with literature values.[46]

The highest conversion and good diastereoselectivity among the iridium-based catalysts tested were obtained with the catalyst based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c** (entry 2). Other iridium catalysts gave similar diastereomeric ratios, but suffered from low conversion. Unfortunately the enantiomeric excess for the major diastereomer (*cis*) did not exceed 28% *ee*. Additives were also investigated to improve the conversion (*Table 3.24*).

Table 3.24 Iridium-catalyzed hydrogenation of furan **85** with additives.



85 **113**

entry	catalyst structure[a]	additive	amount (eq.)	conv. (%)[b]
1		$B(OCH_3)_3$	1.74	88
2		$BF_3{\cdot}O(C_2H_5)_2$	1.01	–[c]
3		$B(C_6F_5)_3$	1.00	–[c]
4		CF_3CH_2OH	70	66

[a] Racemic mixture of [Ir(**L2c**)COD]BAr_F. [b] Determined by GC analysis. [c] Only by-products formed.

Hydrogenation with additives was only performed with the racemic catalyst based on ligand **L2c** to give the racemic product **113**. Conversion was improved when the reaction was performed in trifluoroethanol (entry 4), whereas the highest conversion was obtained with trimethyl borate as an additive (entry 1). With BF_3 etherate or tris(pentafluorophenyl)borane as additive the starting material **85** was consumed, but only a mixture of unidentified products was formed (entries 2 and 3).

The reactivity of the purely dialkyl substituted furan, 2-hexyl-4-methylfuran (**86**) was also tested. Under standard reaction conditions (100 bar H_2, PhCl, 60 °C) the hydrogenation with different catalysts bearing N,P ligands gave only low conversion (17%). Therefore, the general reactivity of substrate **86** was investigated with the CRABTREE catalyst. Only after the solvent was exchanged to dichloromethane, the hydrogenation with the BAr_F analog of the CRABTREE catalyst (2 mol%) resulted in the reduced product **114** with 81% conversion.

The strong solvent dependence of the hydrogenation of 2-hexyl-4-methylfuran (**86**) was investigated with a control experiment. The iridium catalyst based on PHOX ligand **L3e** was submitted to the same hydrogenation reaction conditions optimized for furans in chlorobenzene. After removal of the solvent and subsequent flash chromatography the catalytically inactive trinuclear iridium complex **115**[47] was obtained, as clearly shown by ^{1}H-NMR spectra (*Figure 3.5*). This observation could also explain the low conversion of other unreactive furans in chlorobenzene.

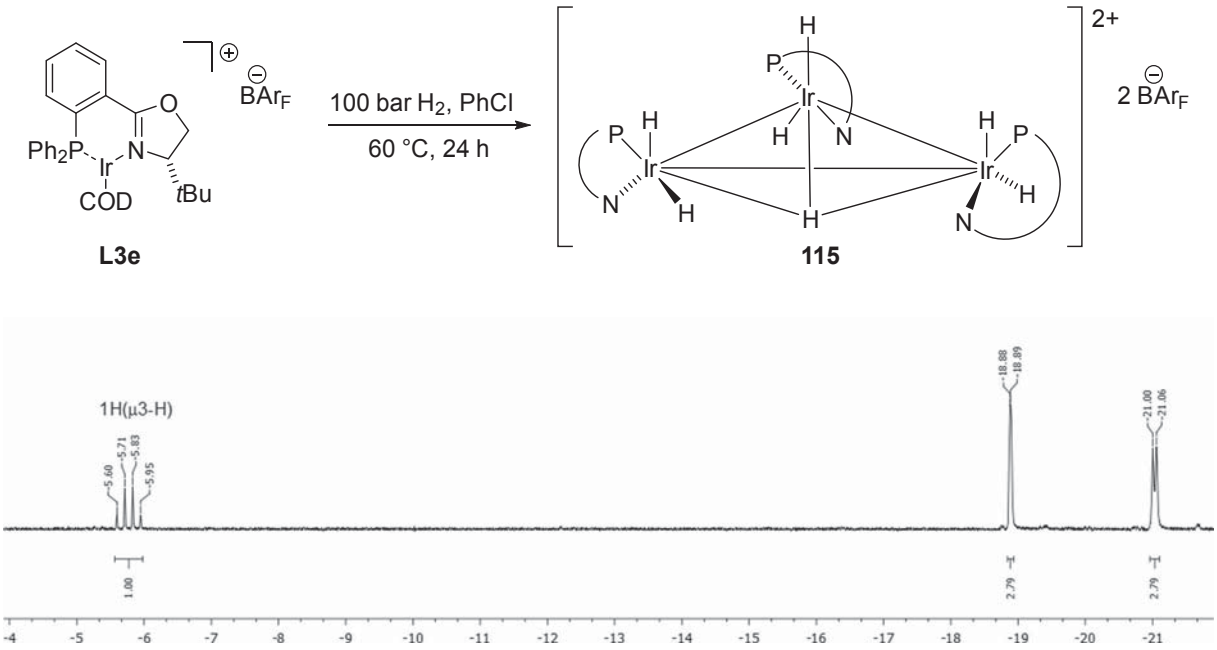
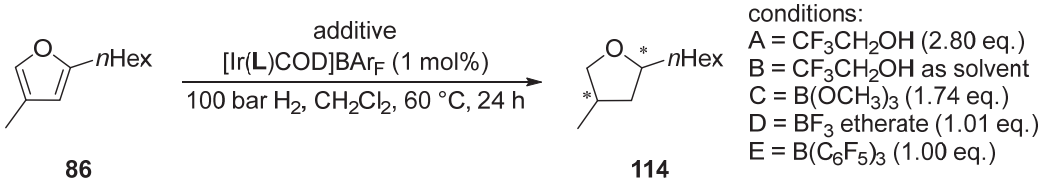


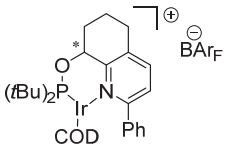
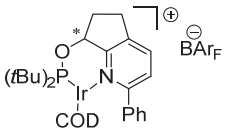
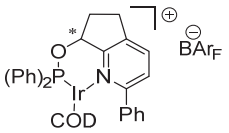
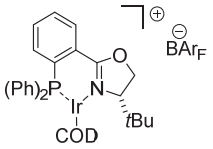
Figure 3.5 Detail of the hydride region in the proton NMR of the unreactive trimer iridium species **115**.

When dichloromethane was utilized as the solvent in the hydrogenation of 2-hexyl-4-methylfuran (**86**), the conversion remained still a challenge (6%). Therefore, additives were tested such as trifluoroethanol and trimethyl borate (*Table 3.25*).

Table 3.25 Iridium-catalyzed hydrogenation of furan **86** with additives.



86 **114**

entry	catalyst structure	ligand	conditions	conv. (%)[b]	*dr* (*cis*:*trans*)[b]	*cis* *ee* (%)[c]
1		(*S*)-**L1e**	A	77	82:18	10
2			B	59	76:24	11
3			C	39	77:23	10
4		(*S*)-**L2c**	A	>99	84:16	13
5			B	>99	83:17	18
6			C	68	87:13	13
7			D	>99	**93:7**	41
8			E	>99	86:14	**55**
9		(*S*)-**L2e**	A	95	80:20	35
10			B	>99	76:24	41
11			C	99	81:19	44
12		**L3e**	A	5	83:17	15
13			B	8	82:18	4
14			C	3	83:17	n.d.

[a] Determined by GC analysis. [c] Determined by GC analysis on a chiral stationary phase.

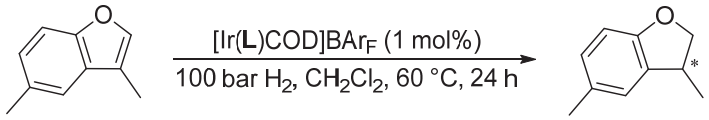
The cyclopentane-annulated bicyclic complexes bearing ligands **L2c** and **L2e** proved to be highly active in the hydrogenation of furan **86**. Depending on the substituents on the ligand full conversion was reached with trifluoroethanol as additive or as solvent, but also with trimethylborate high conversion could be obtained. The catalyst based on the cyclohexane-annulated pyridine-phosphinite complex **L1e** reduced the substrate **86** with lower enantioselectivity and reactivity (entries 1-3). With the catalyst bearing PHOX ligand **L3e** almost no product and low *ee* were observed (entries 12-14). The highest diastereomeric ratio was obtained with the catalyst based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c** and the Lewis acidic BF_3 etherate (entry 7), while the use of tris(pentafluorophenyl)borane resulted in enhanced enantioselectivity but lower diastereoselectivity (entries 8).

A 2,5-disubstituted analog, 2-octyl-5-phenylfuran, was also tested. However, only very low conversion (7%) was achieved using complex [Ir(**L2c**)COD]BAr_F under standard conditions.

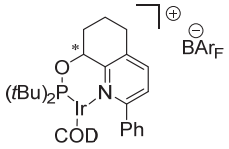
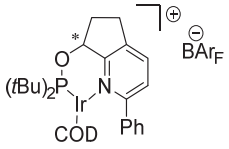
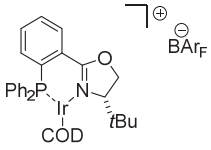
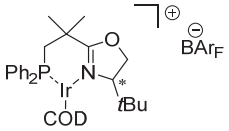
3.7 Enantioselective Hydrogenation of 3-Substituted Benzofurans

The iridium-catalyzed hydrogenation of 3,5-dimethylbenzofuran (**56a**) was performed using the standard conditions applied for substituted furans (*Table 3.26*).

Table 3.26 Iridium-catalyzed hydrogenation of benzofuran **56a**.



56a **116**

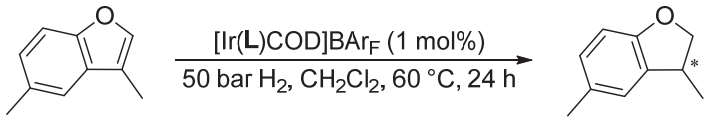
entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1e**	22	51 (+)
2		(*S*)-**L2c**	77	51 (+)
3		**L3e**	3	51 (–)
4		(*R*)-**L5a**	14	36 (+)

[a] Determined by GC analysis. [b] Determined by HPLC analysis on a chiral stationary phase.
[c] Autoclave leaking resulted in 60 bar H_2 pressure after 24 h.

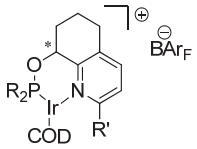
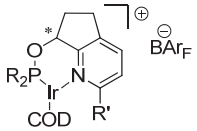
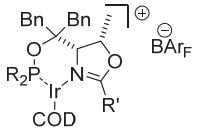
The catalysts bearing the cyclopentane and cyclohexane-annulated bicyclic pyridine-phosphinite ligands **L1e** and **L2c** reduced substrate **56a** with moderate enantioselectivity. Whereas, when the cyclopentane-annulated ligand **L2c** was employed the hydrogenation proceeded to a higher extent than in the case of the six-membered ring analog **L1e** (entry 2 *vs.* entry 1). Phosphino-oxazoline derived ligands **L3e** and **L5a** gave only low conversion and moderate enantioselectivity (entries 3 and 4).

Optimization of the hydrogenation conditions for 3-substituted benzofurans by SCHEIL has shown that 50 bar hydrogen pressure are sufficient to achieve high conversion at 60 °C, whereas higher temperature reduces the conversion.[48] The results of the iridium-catalyzed hydrogenation of 3,5-dimethylbenzofuran (**56a**) using the same conditions are shown in *Table 3.27*.

Table 3.27 Iridium-catalyzed hydrogenation of 3,5-dimethylbenzofuran (**56a**).



56a **116**

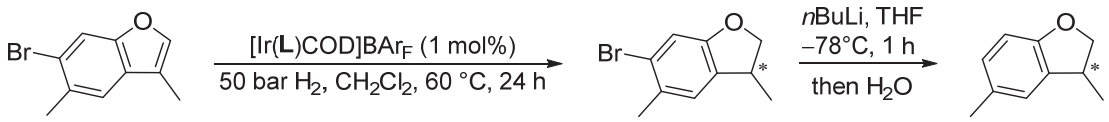
entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[b]
1		*t*Bu	H	(*S*)-**L1c**	16	74 (+)
2		*t*Bu	CH_3	(*S*)-**L1d**	**89**	**92** (+)
3		Cy	Ph	(*R*)-**L2b**	76	62 (−)
4		Cy	Ph	**L15**	66	75 (−)

[a] Determined by GC analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

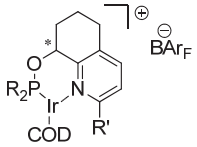
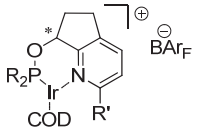
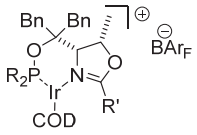
In case of the cyclohexane-annulated bicyclic pyridine-phosphinite complex **L1d** the highest activity and enantioselectivity in the reduction of 3,5-dimethyl-benzofuran (**56a**) were achieved under these conditions (entry 2). The substituent on the pyridine ring had a dramatic influence on the conversion. With a proton on this site the conversion dropped significantly (entries 1 *vs.* 2). Another catalyst based on the five-membered ring analog **L2b** converted benzofuran **56a** into compound **116** with moderate conversion and enantiomeric excess (entry 3). The Thre-PHOX complex [Ir(**L15**)COD]BAr_F, which was shown to give superior results in the hydrogenation of unfunctionalized trisubstituted arylalkenes,[49] afforded the reduced product **116** also with moderate levels of conversion and enantioselectivity (entry 4).

A brominated derivative of benzofuran **56a**, 6-bromo-3,5-dimethylbenzofuran (**56b**), was tested with the same catalysts (*Table 3.28*).

Table 3.28 Iridium-catalyzed hydrogenation of 6-bromo-3,5-dimethylbenzofuran (**56b**).



56b **117** **116**

entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[b]
1		*t*Bu	H	(*S*)-**L1c**	3	52 (+)
2		*t*Bu	CH_3	(*S*)-**L1d**	65	**93** (+)
3					**75**	91 (+)[c]
4		Cy	Ph	(*R*)-**L2b**	54	63 (–)
5		Cy	Ph	**L15**	26	59 (–)

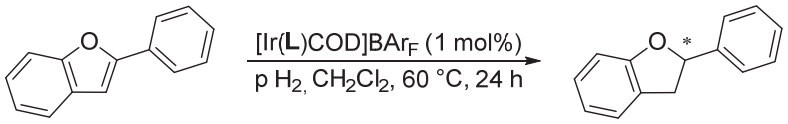
[a] Determined by GC analysis. [b] Determined by HPLC analysis on a chiral stationary phase.
[c] 2 mol% catalyst loading.

The hydrogenation mixture of dihydrobenzofuran **117** was analyzed after debromination with *n*BuLi and subsequent hydrolysis to dihydrobenzofuran **116**. The brominated benzofuran **56b** seems to be less reactive than the alkyl substituted benzofuran **56a**. Under the same reaction conditions the catalyst based on ligand **L1d** provided product **116** with lower conversion than in the reduction of the non-brominated substrate (65% *vs.* 89%). However, the conversion could be further increased to 75% with a higher catalyst loading (2 mol%, entry 3).

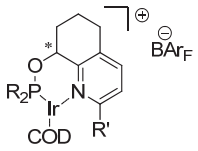
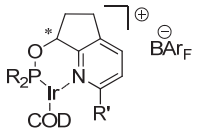
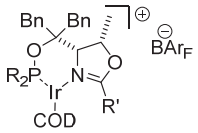
3.8 Enantioselective Hydrogenation of 2-Substituted Benzofurans

The synthesized 2-aryl substituted benzofurans were also tested in the iridium-catalyzed hydrogenation reaction with several catalyst complexes, which showed already high activity for 3-substituted benzofurans. For the hydrogenation of 2-phenylbenzofuran (**95a**) four different ligands were selected (*Table 3.29*).

Table 3.29 Iridium-catalyzed hydrogenation of 2-phenylbenzofuran (**95a**).

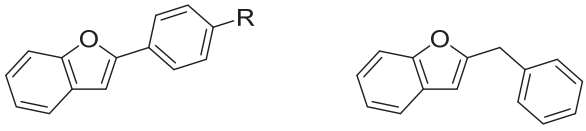


95a **118**

entry	catalyst structure	R	R'	ligand	p H_2 (bar)	conv. (%)[a]
1		*t*Bu	H	(*S*)-**L1c**	50	–
2					100	–
3		*t*Bu	CH_3	(*S*)-**L1d**	50	–
4					100	–
5		*t*Bu	Ph	(*S*)-**L2c**	50	2
6					100	4
7					100	–[b]
8		Cy	Ph	**L15**	50	–
9					100	1

[a] Determined by ^{1}H-NMR analysis. [b] CF_3CH_2OH as solvent.

2-Phenylbenzofuran (**95a**) proved to be an extremely challenging substrate for hydrogenation, giving no or negligible conversion regardless of the catalyst used. Only very low conversion was obtained with the cyclopentane-annulated bicyclic pyridine-phosphinite catalyst complex [Ir(**L2c**)COD]BAr_F (entry 5) under previously utilized hydrogenation conditions for 3-substituted benzofurans. Even at 100 bar hydrogen pressure, the conversion did not exceed 4% (entry 6). Also trifluoroethanol did not promote the hydrogenation reaction (entry 7).



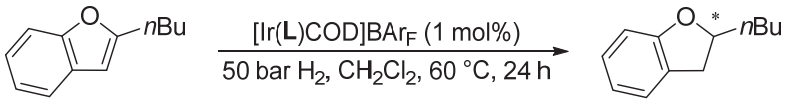
95b, R = OMe, 0%
95c, R = CF_3, 2% (PhCl)

99, 0%

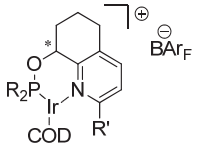
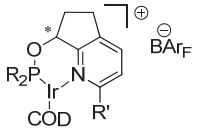
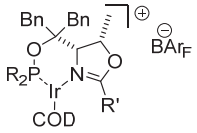
Figure 3.6 Selected hydrogenation results for 2-substituted benzofurans with the catalyst based on ligand **L2c**. Reaction conditions: 1 mol% catalyst, 100 bar H_2, CH_2Cl_2, 60 °C, 24 h.

Also the hydrogenation of other 2-aryl substituted benzofurans or 2-benzylbenzofuran (**99**) proceeded with no or only very low conversion (*Figure 3.6*). The electronic properties of the aryl substituent had only little influence on the reactivity of the substrates. Next 2-alkyl substituted benzofurans were tested as substrates. The results observed for the reduction of 2-butylbenzofuran (**91**) are outlined in *Table 3.30*.

Table 3.30 Iridium-catalyzed hydrogenation of 2-butylbenzofuran (**91**).



91 **119**

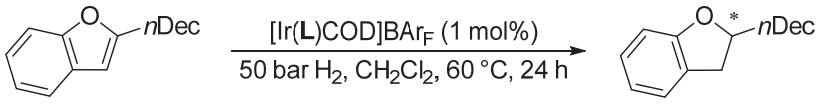
entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[b]
1		*t*Bu	CH_3	(*S*)-**L1d**	31	18 (+)
2		Cy	Ph	(*R*)-**L2b**	75	94 (−)
3		*t*Bu	Ph	(*S*)-**L2c**	**>99**	**99** (+)
4		Cy	Ph	**L15**	96	42 (−)

[a] Determined by ^{1}H-NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

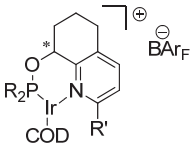
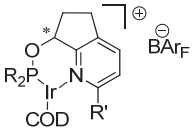
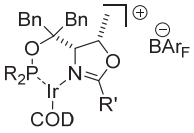
With the complex based on the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1d** low conversion and enantiomeric excess were obtained (entry 1). Much higher activity, but also enhanced enantioselectivity, was observed with the five-membered ring analog **L2** (entry 2 and 3). Depending on the substituents on the P-atom, moderate or very high conversion was achieved. With the catalyst bearing the Thre-PHOX ligand **L15** the substrate **91** was converted to dihydrobenzofuran **119** a high extent, but with moderate *ee* (entry 4).

Another 2-substituted benzofuran **92** with a linear alkyl chain as substituent was also investigated (*Table 3.31*).

Table 3.31 Iridium-catalyzed hydrogenation of 2-decylbenzofuran (**92**).



92 **120**

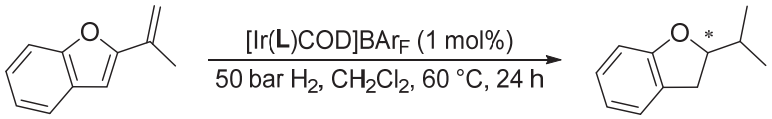
entry	catalyst structure	R	R'	ligand	conv. (%)[a]	*ee* (%)[b]
1		*t*Bu	H	(*S*)-**L1c**	69	10 (+)
2		*t*Bu	CH_3	(*S*)-**L1d**	23	20 (+)
3		*t*Bu	Ph	(*S*)-**L2c**	**>99**	**99** (+)
4		Cy	Ph	**L15**	98	42 (−)

[a] Determined by ^{1}H-NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

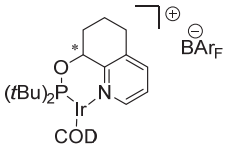
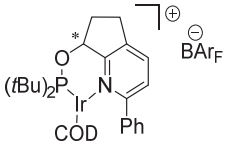
A similar trend of reactivity to that of benzofuran **91** was observed for 2-decylbenzofuran (**92**). Moderate conversion was obtained employing the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1c**, whereas *ortho* substitution on the pyridine ring gave lower conversion (entry 1 *vs.* 2). The highest activity was achieved with the cyclopentane-annulated ligand **L2c** giving dihydrobenzofuran **120** with perfect enantioselectivity in a quantitative manner (entry 3). With the catalyst based on the Thre-PHOX ligand **L15** the hydrogenation of benzofuran **92** proceeded with similar results as the hydrogenation of substrate **91** (see *Table 3.30*).

A branched alkyl substituent at the 2-position of a benzofuran was also investigated in the hydrogenation reaction of compound **93** with two selected catalysts (*Table 3.32*).

Table 3.32 Iridium-catalyzed hydrogenation of 2-(prop-1-en-2-yl)benzofuran (**93**).



93 **121**

entry	catalyst structure	ligand	conv. (%)[a]	*ee* (%)[b]
1		(*S*)-**L1c**	75	24 (+)
2		(*S*)-**L2c**	**99**	**97** (+)

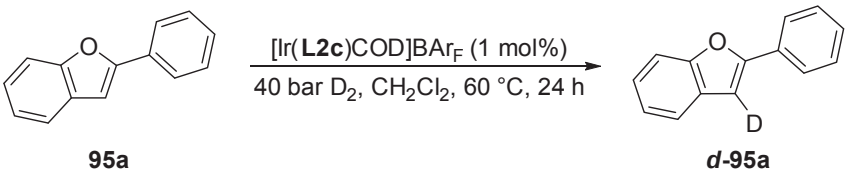
[a] Determined by ^{1}H-NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

Moderate conversion was obtained with the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1c** along with low enantiomeric excess (entry 1), whereas the catalyst bearing the five-membered ring analog **L2c** converted substrate **93** completely to the reduced dihydrobenzofuran **121** with excellent enantioselectivity (entry 2).

3.9 Investigations on the Deactivating Effect of Aromatic Substituents at the C2

Hydrogenation of 2-alkyl substituted benzofurans proceeded with high conversions and very good enantiomeric excesses, in contrast to 2-aryl substituted analogs which showed poor or no reactivity. The same trend had already been observed for 2-alkyl substituted furans and 2-phenylfuran (**44a**) (*Table 3.12*). Conjugation between the aryl and the furan π-system as the deactivating effect can be ruled out, since 2-benzylbenzofuran (**99**) as well is resistant to hydrogenation. However, formation of a catalytically inactive cyclometallated complex by coordination of catalyst to the furan O-atom and subsequent insertion of the iridium atom into adjacent C-H bond of the aryl or benzyl substituent could provide an explanation.

Cyclometallation induced by coordination to a heteroatom is a facile process,[50] which in case of N,P ligands containing an 2-phenylpyridine unit has been observed to cause catalyst deactivation.[51] To obtain evidence for such a process, the hydrogenation of 2-phenylbenzofuran (**95a**) was performed with deuterium gas under standard conditions using the catalyst based on ligand **L2c**.



95a **d-95a**

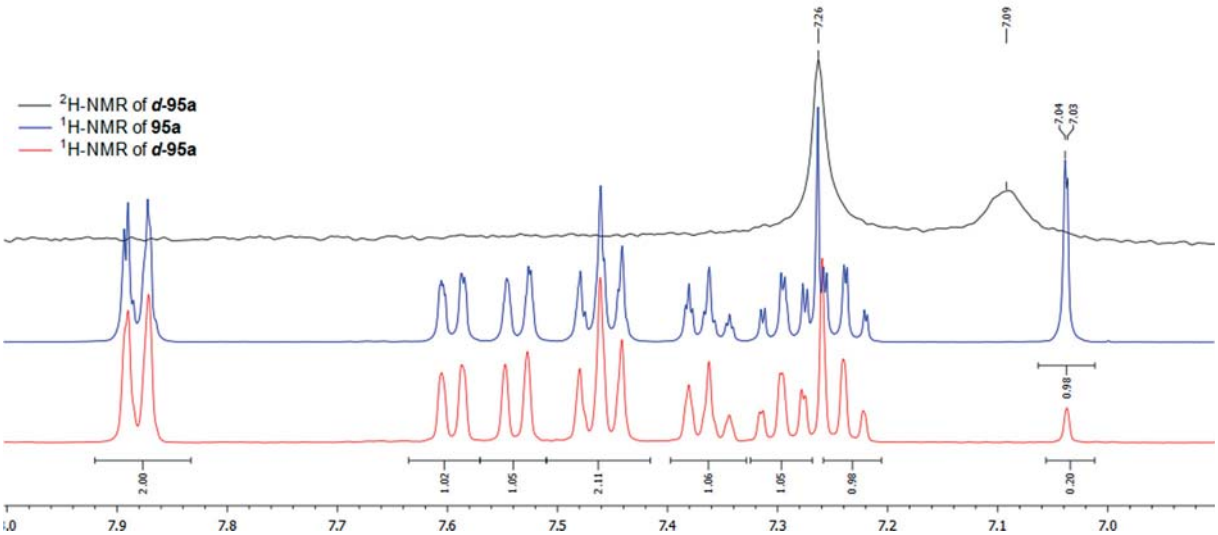


Figure 3.7 ^{2}H-NMR of ***d*-95a** (top) in $CHCl_3$ with $CDCl_3$, ^{1}H-NMR of **95a** (middle) and ^{1}H-NMR of ***d*-95a** (bottom) in $CDCl_3$.

At 40 bar of D_2 pressure high deuterium incorporation (80%) at C3 was obtained according to ^{1}H-NMR and GC-MS analyses performed after catalyst removal. However, no deuterium incorporation at the phenyl substituent was observed. In *Figure 3.7* a section of the proton NMR spectrum of the deuterated product ***d*-95a**, the starting material **95a** and the deuterium NMR spectrum of ***d*-95a** are shown. The unexpected deuteration of 2-phenylbenzofuran (**95a**) at C3 raised the question of the behavior of alkyl substituted analogs under the same conditions. Therefore, 2-decylbenzofuran (**92**) was submitted to similar conditions using the same catalyst (30 bar D_2, 60 °C, 4 h). The obtained mixture of the reduced deuterated benzodihydrofuran ***d*-120** and deutarated benzofuran ***d*-92** (71:29, GC-MS) was chromatographically separated. The proton NMR spectrum of the deuterated product ***d*-92**, the starting material **92** and the deuterium NMR spectrum of ***d*-92** shows an incorporation of deuterium at the C3 (89%), but also on the alkyl substituent (74%) (*Figure 3.8*).

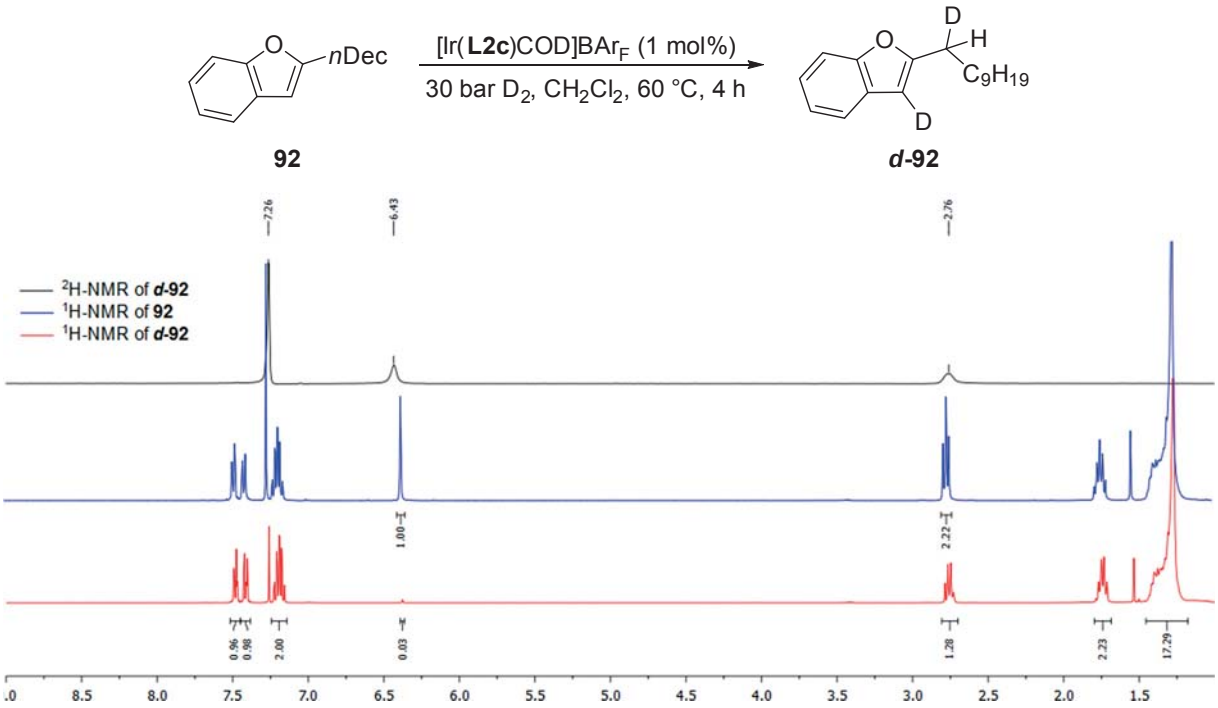


Figure 3.8 ^{2}H-NMR of ***d*-92** (top) in $CHCl_3$ with $CDCl_3$, ^{1}H-NMR of **92** (middle) and ^{1}H-NMR of ***d*-92** (bottom) in $CDCl_3$.

Since deuteration experiments with D_2 did not provide any evidence for the formation of an iridacycle stemming from cyclometallation, further studies are necessary to clarify the deactivating factor in the hydrogenation of 2-aryl substituted furans and benzofurans.

3.10 Summary

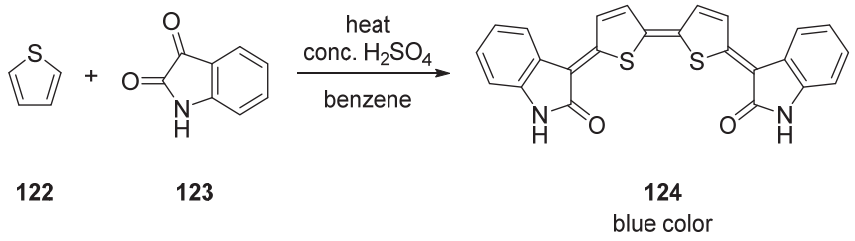
In conclusion, the best results in the iridium-catalyzed hydrogenation of 3-substituted furans were obtained with the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c**. Thereby, both high enantiomeric excess and conversion were achieved for five substrates. For furans that are substituted with a linear alkyl chain, trifluoro-ethanol was required to induce high levels of activity and enantioselectivity. The corresponding 2-substituted furans proved to be less reactive than their 3-substituted counterparts. Although high conversions were achievable with 2-alkyl furans, the enantioselectivity was lower compared to reactions of 3-substituted furans. Asymmetric hydrogenation of 2,4-disubstituted furans turned out to be very challenging for several reasons, not least because of the problem of controlling *cis*/*trans* selectivity.

Surprisingly, in the iridium-catalyzed hydrogenation of 3-substituted benzofurans only the catalyst based on the cyclohexane-annulated pyridine-phosphinite ligand **L1d** showed high activity and enatioselectivity, whereas the five-membered ring analog, bearing ligand **L2c**, suffered from moderate activity and enantioselectivity. In contrast, the 2-alkyl substituted benzofurans gave superior results. With the iridium catalyst based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c** these substrates reacted with higher enantiomeric excess than with the NHC ruthenium catalyst system developed by GLORIUS. Unfortunately, 2-aryl substituted benzofurans could not be reduced by utilization of the iridium catalysts.

4 Synthesis of Thiophene 1,1-Dioxides as Substrates for Iridium-Catalyzed Asymmetric Hydrogenation

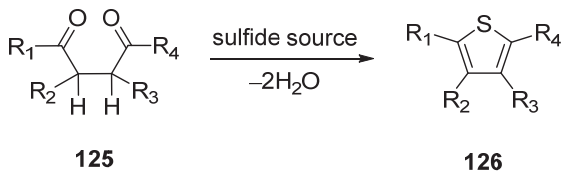
4.1 Introduction

The discovery of thiophene (**122**), which occurs in coal-tar distillates, is one of the classic anecdotes in organic chemistry. An important evidence for the presence of benzene, in the early days, was the blue color produced after reaction with isatin (**123**) and concentrated sulfuric acid upon heating (*Scheme 4.1*). In 1882, when VIKTOR MEYER failed to demonstrate this test during his lecture, because his assistant, after he ran out of commercial benzene, replaced it with a sample he had prepared from benzoic acid, it became clear that a contaminant in commercially available benzene rather benzene itself was responsible for the color. In fact the blue color could be attributed to the thiophene derivative **124**. In further investigations, MEYER isolated the impurity and characterized it as its sulfonic acid derivative.[30]



Scheme 4.1 Historically important reaction of thiophene (**122**) with isatin (**123**).

Since its discovery many different protocols to synthesize substituted thiophenes were reported. In general, such heterocycles can be prepared using similar methods as for the synthesis of substituted furans. While mono-substituted thiophenes are usually generated by functionalization of the ring, the di- or multisubstituted ones are often obtained by cyclization reactions, such as the PAAL-KNORR reaction (*Scheme 4.2*).

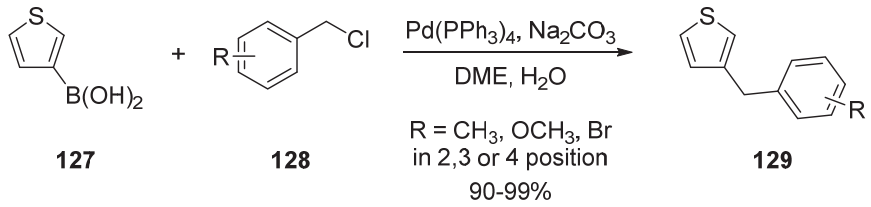


Scheme 4.2 Synthesis of thiophenes *via* cyclization reactions.

During this ring-closure, a 1,4-dicarbonyl compound **125** reacts with a source of sulfide such as LAWESSON'S reagent or phosphorous pentasulfide to give substituted thiophenes **126**. By applying this procedure various substitution patterns of thiophene

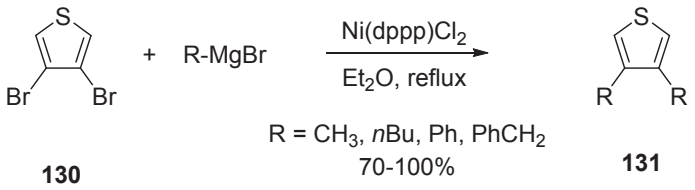
can be obtained. However, this procedure is limited by the synthetic accessibility of the required 1,4-dicarbonyl compounds.

Direct lithiation of mono-substituted thiophenes takes place at the 2-position, while two equivalents of lithiating agent can easily produce 2,5-dilithiothiophene from thiophene (**122**).[52] Prefunctionalized thiophenes such as the corresponding boronic acids or brominated precursors can be submitted to various cross-coupling reactions as shown in *Scheme 4.3* and *Scheme 4.4*.



Scheme 4.3 Synthesis of 3-substituted thiophenes *via* SUZUKI-MIYAURA cross-coupling.

Mono-substituted benzyl-thiophenes are generated by coupling of commercially available thiophene-3-boronic acid (**127**) with benzyl chloride derivatives **128**.[53] Neither electronic properties nor the position of the substituents on the benzyl chloride **128** have an effect on the efficiency of the cross-coupling reaction. Although only one example of a coupling between thiophene-2-boronic acid and benzylchloride was reported, the high yield lies in the same range as for the reaction with thiophene-3-boronic acid (**127**). Even more versatile is the KUMADA coupling of 3,4-dibromothiophene (**130**) with either alkyl or aryl Grignard reagents to generate the corresponding 3,4-disubstituted thiophenes **131** in high yields (*Scheme 4.4*).[54]

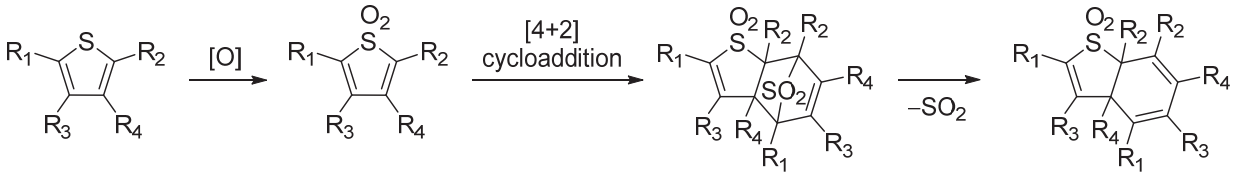


Scheme 4.4 Synthesis of 3,4-disubstituted thiophenes *via* KUMADA cross-coupling.

The reaction of simple alkyl Grignard reagents can have a different outcome depending on the position of the bromine on the thiophene ring. While 3,4-dibromo- and 3-bromothiophene react smoothly with butylmagnesium bromide to afford the corresponding product in high yield, 2-bromo and 2,5-dibromothiophene formed thiophene (**122**) as a major or sole product instead of the desired coupling product 2,5-dibutylthiophene, that is not formed at all. The authors assume a rapid metal-halogen exchange between reactive alkyl Grignard reagents and the thiophene

halides leading to the predominant formation of thiophene (**122**), whereas more stabilized Grignard reagents reacted faster to give the cross-coupling product.[54]

The corresponding thiophene 1,1-dioxides can easily be obtained by oxidation reaction of substituted thiophenes.[55] Since, the *S*,*S*-dioxides are no longer aromatic they are relatively reactive and can undergo self-dimerization *via* [4+2] cycloaddition followed by SO_2 elimination, depending on the substitution pattern (*Scheme 4.5*).[56]

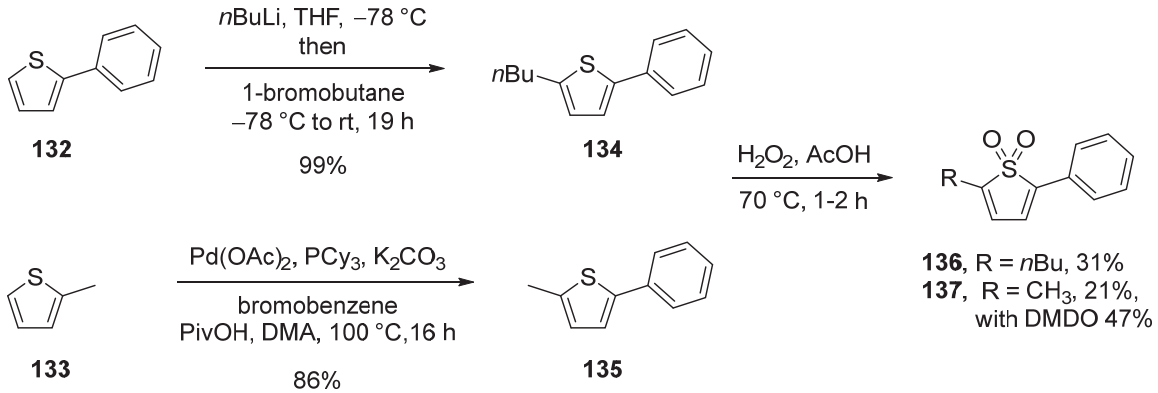


Scheme 4.5 Synthesis and reaction of substituted thiophene 1,1-dioxides.

Therefore stable regioisomers, such as 2,5-disubstituted and also 3,4-disubstituted thiophene 1,1-dioxides[57] were chosen as substrates for the iridium-catalyzed asymmetric hydrogenation reaction, and their synthesis is described in the sections below.

4.2 Synthesis of 2,5-Disubstituted Thiophene 1,1-Dioxides

Unsymmetrical 2,5-disubstituted thiophenes were synthesized from commercially available mono-substituted precursors such as 2-phenylthiophene (**132**) and 2-methyl-thiophene (**133**) by either metallation or direct arylation of the heterocycle (*Scheme 4.6*).

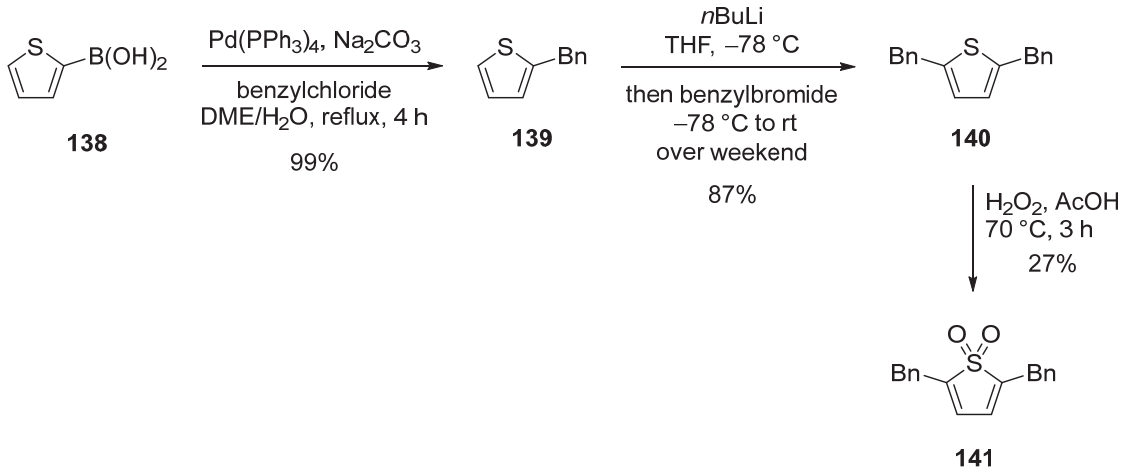


Scheme 4.6 Synthesis of asymmetrical 2,5-disubstituted thiophene 1,1-dioxides.

Lithiation and subsequent trapping with 1-bromobutane gave 2-butyl-5-phenyl-thiophene (**134**) in quantitative yield. Palladium-catalyzed direct arylation with pivalic acid (*in situ* generated potassium pivalate) as accelerator was used to synthesize 2-methyl-5-phenylthiophene (**135**) in good yield.[58] Both thiophenes were oxidized to the corresponding 1,1-dioxides **136** and **137** using hydrogen peroxide in acetic acid.

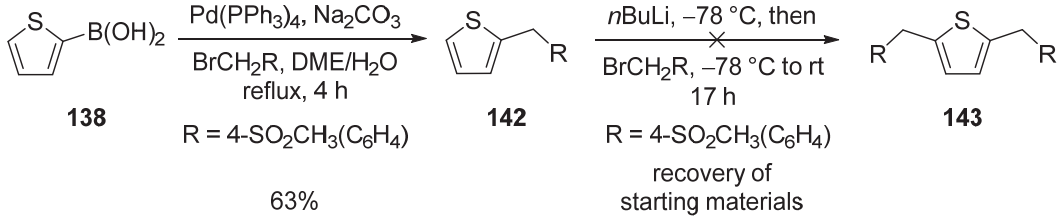
Although, both substrates were oxidized with full conversion, only moderate yields could be achieved after chromatographic purification with subsequent crystallization. When thiophene **135** was oxidized using freshly prepared DMDO (dimethyldioxirane) from acetone, sodium bicarbonate and Oxone® only 80% conversion was reached but with higher yield after purification (47% *vs.* 21%).

Symmetrically 2,5-disubstituted thiophene 1,1-dioxides were also prepared as test substrates. 2,5-Dibenzylthiophene 1,1-dioxide (**141**) was synthesized in three steps (*Scheme 4.7*). First thiophene-2-boronic acid (**138**) reacted in a SUZUKI-MIYAURA cross-coupling with benzylchloride to give 2-benzylthiophene (**139**) in quantitative yield.[53] This compound was subjected to deprotonation with *n*BuLi and S_N2 reaction with benzylbromide to give 2,5-dibenzylthiophene (**140**) also in good yield and subsequent oxidation resulted in the corresponding 1,1-dioxide **141**.



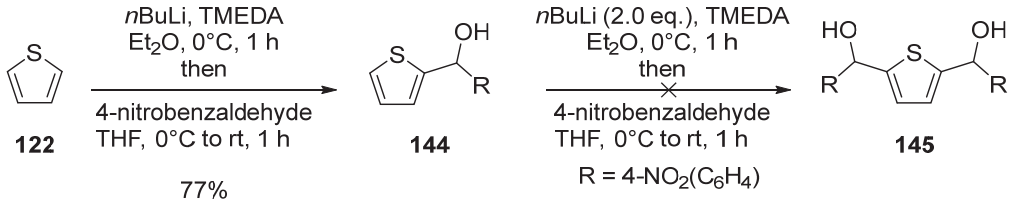
Scheme 4.7 Synthesis of 2,5-dibenzylthiophene 1,1-dioxide (**141**).

Substitution on the benzyl ring was also investigated by using a similar approach for the synthesis of 2,5-bis(4-(methylsulfonyl)benzyl)thiophene (**143**) (*Scheme 4.8*). Palladium-catalyzed coupling yielded the 2-substituted thiophene **142**, but this could not be further converted into the disubstituted thiophene **143** by metallation and alkylation with the corresponding benzylbromide.



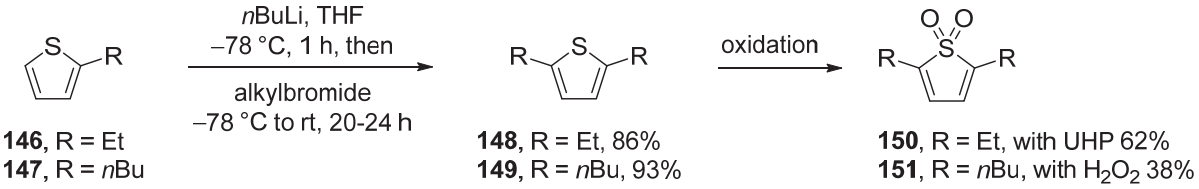
Scheme 4.8 Synthesis plan for 2,5-bis(4-(methylsulfonyl)benzyl)thiophene (**143**).

One possible explanation for the unsuccessful transformation in the second step could be the lithiation of the methylsulfonyl group in *para* position of benzylbromide. Therefore, a substituent without acidic protons was chosen. Literature known mono-substitution of thiophene (**122**) with 4-nitrobenzaldehyde delivered the 2-substituted thiophene **144** in 77% yield, but did not give any disubstituted product **145**, although two equivalents of *n*BuLi were used (*Scheme 4.9*).



Scheme 4.9 Synthesis plan for 2,5-disubstituted thiophene **145**.

Alkyl substituted thiophene 1,1-dioxides were also prepared and investigated as potential substrates for asymmetric hydrogenation. Their synthesis was performed in a straightforward direct metallation of 2-alkyl substituted thiophenes **146** and **147** and the corresponding 2,5-disubstituted thiophenes **148** and **149** were obtained in high yield (*Scheme 4.10*). The oxidation of 2,5-dibutylthiophene (**149**) with hydrogen peroxide in acetic acid gave the product in only moderate yield, while the ethyl substituted thiophene **148** could be transformed using the urea-hydrogen peroxide (UHP) complex in trifluoroacetic anhydride in good yield at room temperature in just one hour.[55b]



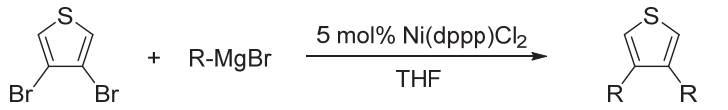
Scheme 4.10 Synthesis of 2,5-dialkyl substituted thiophene 1,1-dioxides **150** and **151**.

This procedure using the stable, inexpensive and easily handled reagent UHP was also applied to the oxidation of 3,4-disubstituted thiophenes as described in *Section 4.3*.

4.3 Synthesis of 3,4-Disubstituted Thiophene 1,1-Dioxides

First attempts at synthesizing aryl disubstituted 3,4-thiophenes were based on a nickel-catalyzed cross-coupling reaction (see *Scheme 4.4*).[59] Therefore, 3,4-dibromothiophene (**130**) was mixed with Ni(dppp)Cl_2 in dry THF and the corresponding Grignard reagent was added (*Table 4.1*). After 18 hours only 10% conversion was observed in the synthesis of 3,4-diphenylthiophene (**131a**). Heating the reaction mixture to reflux for two hours did not improve the conversion (entry 1). Also when the temperature during the addition of the Grignard reagent was decreased to 0 °C the same level of conversion was observed. Only after using a freshly opened bottle of phenylmagnesium bromide solution the conversion rose to 27% along with formation of the homo-coupling by-product (entries 2 and 3).

Table 4.1 Variation of reaction parameters in the synthesis of 3,4-disubstituted thiophenes **131a** and **131b**.



130 **131a**, R = Ph; **131b**, R = Bn

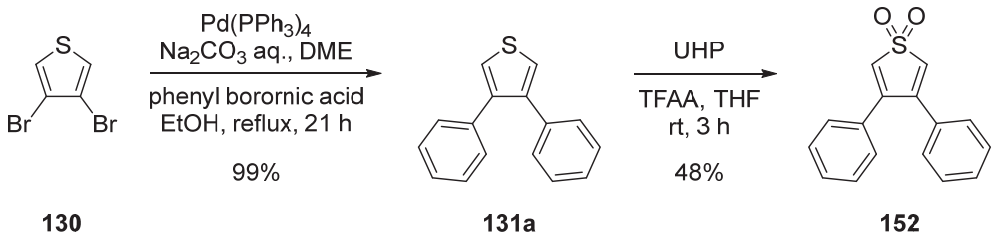
entry	Grignard reagent	addition of RMgBr at	reaction conditions	conv. to **131** (%)[a]
1	PhMgBr 3.8 M in Et_2O	rt	18 h at rt then 2 h reflux	10 11
2	PhMgBr 3.8 M in Et_2O	0 °C	12 h reflux	10
3	PhMgBr 3.0 M in Et_2O[d]	0 °C	16 h reflux	27[b]
4	BnMgBr 2.0 M in THF	0 °C	20 h reflux	–[c]
5	BnMgBr 2.0 M in THF[d]	0 °C	20 h reflux	–[c]

[a] Determined by GC-MS analysis. [b] Formation of 47% biphenyl. [c] 1:1 ratio of 2-benzylthiophene and bibenzyl determined by ^{1}H-NMR analysis. [d] Freshly opened bottle of Grignard reagent was used.

The 3,4-dibenzyl substituted thiophene **131b** could not be obtained following this procedure. While in the reaction with phenyl magnesium bromide some product **131a** was formed, benzyl magnesium bromide and 3,4-dibromothiophene (**130**) gave only

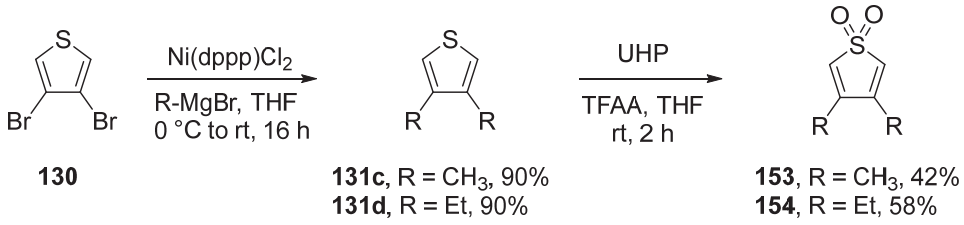
2-benzylthiophene and the homo-coupling by-product from the Grignard reagent, regardless of the quality of the Grignard reagent (entry 4 and 5).

However, 3,4-diphenthiophene (**131a**) could be prepared in a efficient manner *via* SUZUKI coupling from 3,4-dibromothiophene (**130**) and phenyl boronic acid.[60] During this cross-coupling reaction no major by-products were formed and the product **131a** was isolated after purification in quantitative yield (99%). Oxidation of 3,4-diphenylthiophene (**131a**) with urea-hydrogen peroxide complex delivered the corresponding *S*,*S*-dioxide (**152**) in moderate yield (*Scheme 4.11*).



Scheme 4.11 Synthesis of 3,4-diphenylthiophene 1,1-dioxide (**152**).

Alkyl substituted 3,4-thiophenes in contrast, were synthesized *via* the above described KUMADA coupling (*Table 4.1*) using 5 mol% of the nickel catalyst and 3,4-dibromothiophene (**130**) in THF under reflux for 16 hours.[59] The addition of the alkyl Grignard reagent was conducted at 0 °C, yielding both thiophenes **131c** and **131d** in 90% yield and were used without further purification (*Scheme 4.12*).



Scheme 4.12 Synthesis of 3,4-dialkyl thiophene 1,1-dioxides **153** and **154**.

Oxidation of thiophenes **131c** and **131d** with UHP proceeded with yields that were comparable to the yield registered for 3,4-diphenylthiophene 1,1-dioxide (**152**). The highest yield (58%) was obtained for the ethyl substituted 3,4-thiophene **154**.

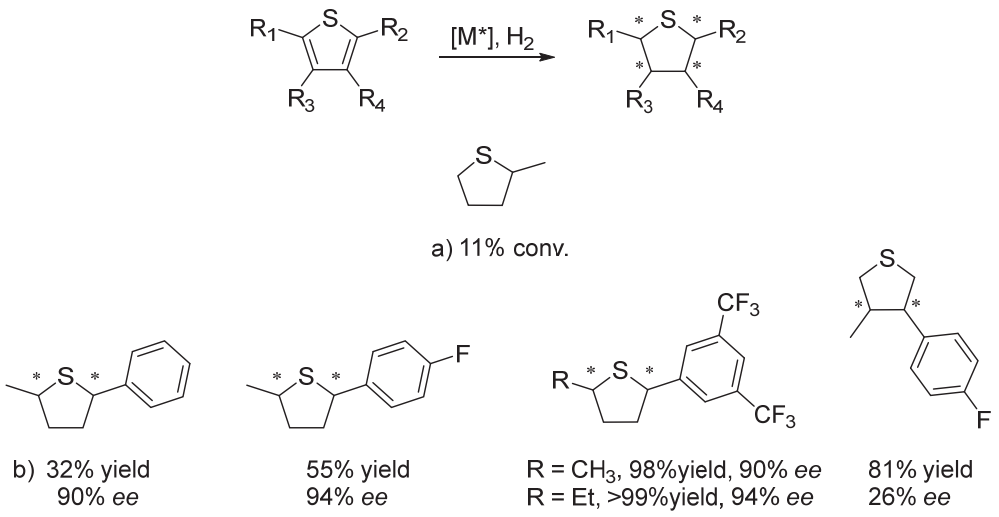
With these new substrates in hand, investigations on the iridium-catalyzed asymmetric hydrogenation using different catalysts based on N,P ligands were made that are summarized in the following chapter.

5 Iridium-Catalyzed Asymmetric Hydrogenation of Thiophene 1,1-Dioxides

5.1 Introduction

The wide occurrence of optically active tetrahydrothiophenes in biological and medicinal chemistry makes them interesting core structures for synthetic organic chemists. The hydrogenation of thiophenes provides a straightforward synthetic approach to obtain the saturated analogs. In general, the hydrogenation of sulfur containing substrates remains still a challenge, although the hydrogenation of unsubstituted thiophenes and benzothiophenes has been extensively studied by many groups due to its industrial importance for hydrodesulfurization (HDS).[61] This process is employed to remove sulfur containing molecules as H_2S from petroleum and other fossil fuel feedstock through reaction with hydrogen, typically catalyzed by transition metals. While most of the sulfur containing compounds are susceptible to HDS, substituted thiophene or benzothiophene rings are resistant to desulfurization.

Direct hydrogenation of thiophenes is not only difficult due to their aromaticity, but also to the catalyst poisoning ability of sulfur containing compounds, which also explains why only two examples of hydrogenation procedures were reported using a homogeneous catalyst up to date (*Scheme 5.1*).[23a, 62]



Scheme 5.1 Examples of hydrogenation of thiophenes by BOROWSKI (a) and GLORIUS (b).

The first example of hydrogenation of thiophenes was reported in 2003 by BOROWSKI, who described the reduction of 2-methylthiophene to the corresponding racemic tetrahydrothiophene using a ruthenium (bis)dihydrogen complex, but only with low

conversion (example a).[62] Enantioselective reduction with a broader scope was recently demonstrated by GLORIUS (example b).[23a] Using a ruthenium catalyst with a monodentate *N*-heterocyclic carbene, 2,5-disubstituted thiophenes were reduced in moderate to perfect yield and high enantioselectivity. Electron withdrawing substituents on the phenyl ring resulted in higher yield. A 3,4-disubstituted thiophene was also reduced with good yield but low enantiomeric excess, while mono-substituted tetrahydrothiophenes were quantitatively obtained as racemates.

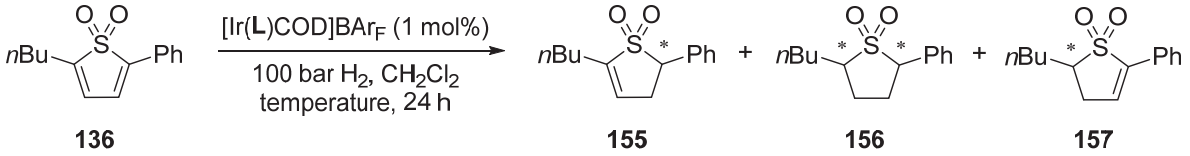
Although the examples discussed above represent important advances in the hydrogenation of substituted thiophenes, the substrate scope that they cover is still very limited. Especially in the case of asymmetric hydrogenation, only two compounds with a particular substitution pattern could be reduced with synthetically useful levels of yields and enantiomeric excess. Therefore, methods that broaden the applicability of this reaction would certainly be of high value.

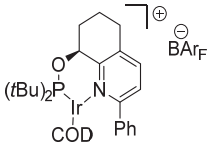
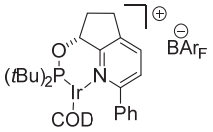
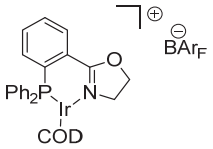
5.2 Enantioselective Hydrogenation of 2,5-Disubstituted Thiophene 1,1-Dioxides

The two asymmetrically substituted thiophenes **134** and **135** were subjected to hydrogenation after they were synthesized as described in *Section 4.2*. The asymmetric hydrogenation was performed with both catalysts bearing ligand **L1e** and **L2c** in CH_2Cl_2 at 60 °C and 100 bar hydrogen pressure for 24 hours. Since no reduction occurred, it was envisaged that a way to improve the reactivity of thiophenes towards hydrogenation could be based on reducing or removing their aromaticity. To this end, it was decided to employ thiophene 1,1-dioxides as non-aromatic thiophene surrogates. Upon hydrogenation, the resulting cyclic sulfones could be further reduced to afford the desired tetrahydrothiophenes.

From the hydrogenation of furans and benzofurans it is known that the catalysts based on the cyclopentane- and cyclohexane-annulated bicyclic pyridine-phosphinite ligands **L1** and **L2** perform best in terms of enantioselectivity and activity (*Section 3.10*), therefore these two catalysts were tested in the hydrogenation of the sulfur containing substrates **136** and **137** as shown in *Table 5.1* and *Table 5.2*.

Table 5.1 Iridium-catalyzed hydrogenation of 2-butyl-5-phenylthiophene 1,1-dioxide (**136**).[a]



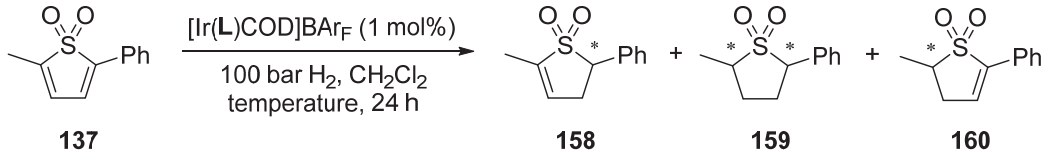
entry	catalyst structure	ligand	T (°C)	**155** (%)[b]	**156** (%)[b]	**157** (%)[b]
1		(*S*)-**L1e**	60	68	14	18
2		(*R*)-**L2c**	60	51	18	31
3			rt	51	18	31[c]
4		**L3c**	60	–	20	24[d]

[a] Conversion was determined by ^{1}H-NMR analysis and was complete unless noted. [b] Determined by GC-MS analysis. [c] Reaction performed on 0.2 mmol scale. [d] Reaction performed at 85 bar H_2 pressure with 40% conversion.

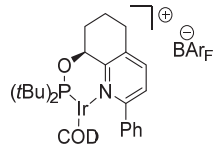
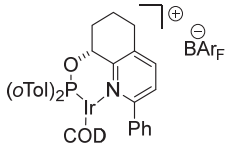
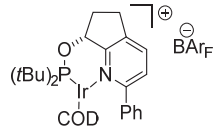
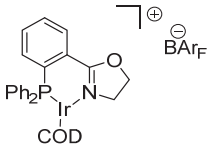
Hydrogenation of thiophene 1,1-dioxide **136** proceeded with full conversion at 60 °C with both catalysts based on pyridine-phosphinite ligands **L1** and **L2** (entries 1 and 2). Even at room temperature substrate **136** was completely converted without affecting the ratio of the products (entry 2 *vs.* 3). When the achiral catalyst bearing the PHOX ligand **L3c** was used, only moderate conversion was achieved (entry 4). Asymmetric hydrogenation on a 0.2 mmolar scale was performed with catalyst bearing ligand **L2c** (entry 3), the products were separated on a semi-preparative HPLC with a chiral stationary phase and the product ratio was determined. Unfortunately, only one of the two mono-reduced products was obtained in its pure form. From the multiplicity and the chemical shift of significant signals in the proton NMR spectrum, such as the olefinic proton (ddt, 6.39 ppm) and the proton at the stereogenic center (dd, 4.42 ppm), this compound was identified as 2-butyl-5-phenyl-4,5-dihydrothiophene (**155**) and its structure was confirmed by 2D-NMR analysis. This leads to the assumption that the double bond in conjugation to the phenyl ring is hydrogenated first. However, the enantiomeric excess could not be determined by HPLC analysis on a chiral stationary phase, due to peak overlap with the corresponding tetrahydrothiophene **156**.

Hydrogenation of 2-methyl-5-phenylthiophene 1,1-dioxide (**137**) was performed using the same catalysts as used for substrate **136** (*Table 5.2*).

Table 5.2 Iridium-catalyzed hydrogenation of 2-methyl-5-phenylthiophene 1,1-dioxide (**137**).[a]



137 **158** **159** **160**

entry	catalyst structure	ligand	T (°C)	**158** (%)[b]	**159** (%)[b]	**160** (%)[b]
1		(*S*)-**L1e**	60	58	35	7
2			rt	72	8	20
3			rt	71	–	29[c]
4			rt	55	12	33
5		(*R*)-**L1j**	rt	30	17	53
6		(*R*)-**L2c**	60	32	49	19
7			rt	42	15	43
8		**L3c**	60	9	15	42[d]

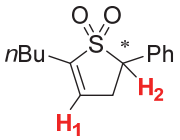
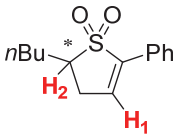
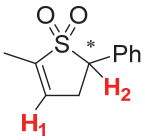
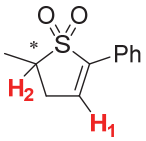
[a] Conversion was determined by ^{1}H-NMR analysis and was complete unless noted. [b] Determined by GC-MS analysis. [c] Reaction performed on 0.2 mmol scale. [d] Reaction performed at 85 bar H_2 pressure with 66% conversion.

The hydrogenation reaction of 2-methyl-5-phenylthiophene 1,1-dioxide (**137**) was also not particularly selective. The use of the catalysts shown in *Table 5.2* resulted in all three possible reduction products, except for one hydrogenation performed with the catalyst bearing ligand **L1e** at room temperature (entry 3). This experiment was performed on a larger scale (0.2 mmol) to subsequently perform a semi-preparative separation. Both mono-reduced products **158** and **160** were obtained in pure form and identified by ^{1}H-NMR analysis (*Table 5.3*). The *ee* values for both products **158** and **160** were found to be >99%. Since this hydrogenation could not be reproduced (entry 4), the high enantiomeric excesses could not be confirmed due to peak overlap. The catalysts based on ligands **L1j** and **L2c** reduced the substrate completely, but not very selectively (entries 5 and 6). The reaction temperature had no influence on the product

distribution (entry 6 *vs.* 7). In analogy to thiophene 1,1-dioxide **136**, only moderate conversion was obtained upon the reduction of 2-methyl-5-phenylthiophene 1,1-dioxide (**137**) with the achiral catalyst based on PHOX ligand **L3c**. For the other reactions (entries 5-8) the *ee* value again could not be determined due to peak overlap of the signals corresponding to 2,3-dihydrothiophene 1,1-dioxides **158**, **160** and tetrahydrothiophene 1,1-dioxide **159**.

The comparison of the chemical shifts of protons H_1 and H_2 for both 4,5-dihydrothiophene 1,1-dioxides **155** and **158** and both 2,3-dihydrothiophene 1,1-dioxides **157** and **160** shows a high degree of similarity (*Table 5.3*). Based on the structure of dihydrothiophene **155**, which was confirmed by two-dimensional NMR analysis, the assignment of the ^{1}H-NMR spectra of purified dihydrothiophenes **158** and **160** was made by analogy.

Table 5.3 Comparison of the ^{1}H-NMR shifts of H_1 and H_2 of **155** and **157** with those of **156** and **158**.

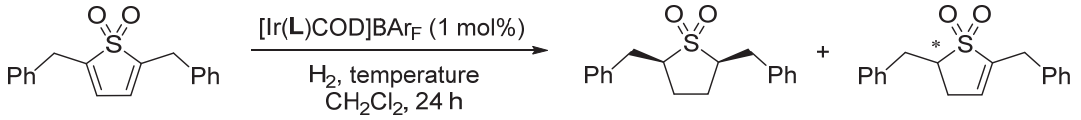
compound / ^{1}H-NMR shift [ppm]	 **155**	 **157**	 **158**	 **160**
H_1 (multiplicity)	6.39 (ddt)	6.71 (dd)	6.41 (m_c)	6.72 (dd)
H_2 (multiplicity)	4.42 (dd)	3.35 (m_c)	4.42 (dd)	3.46 (dq)

^{1}H-NMR in $CDCl_3$.

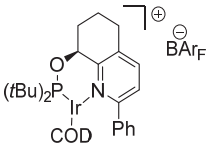
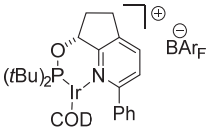
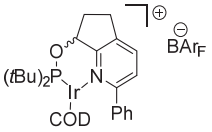
The fully hydrogenated compounds **156** and **159** are assumed to be the *meso* compounds based on the hydrogenation results for 2,5-dibenzylthiophene 1,1-dioxide (**141**), 2,5-dibutylthiophene 1,1-dioxide (**151**) and 2,5-diethylthiophene 1,1-dioxide (**150**) (see below).

To facilitate the analysis of the product mixtures symmetrical 2,5-disubstituted substrates were considered for further investigations, in order to reduce the number of possible products. While 2,5-diphenylthiophene 1,1-dioxide, as well as 2,5-dimethylthiophene 1,1-dioxide were not particularly reactive in the iridium-catalyzed hydrogenation reaction as shown by TOSATTI, they were not further investigated.[42] Instead, 2,5-dibenzylthiophene 1,1-dioxide (**141**) was tested with catalysts based on the annulated pyridine-phosphinite ligands **L1e** and **L2c** (*Table 5.4*).

Table 5.4 Iridium-catalyzed hydrogenation of 2,5-dibenzylthiophene 1,1-dioxide (**141**).



141 *meso*-**161** **162**

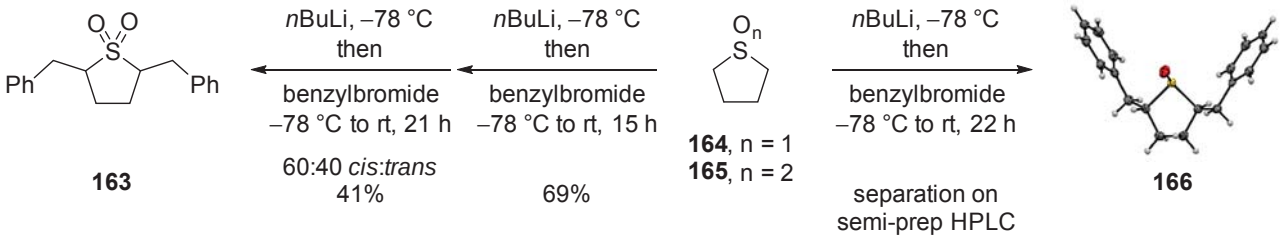
entry	catalyst structure	T (°C)	p H_2 (bar)	*meso*-**161** (%)[a]	**162** (%)[a]	*ee* (%) of **162**[b]
1		60	100	89	8	>99
2		rt	100	87	9	>99
3		rt	50	89	7	>99
4		60	100	78	19	>99
5		rt	100	71	23	>99
6		rt	50	78	18	>99
7		rt[c]	50	78	19	>99
8		rt[d]	50	72	22	>99
9		rt[e]	50	86	8	–
10		rt[e]	50	79	12	–

[a] Determined by ^{1}H-NMR analysis, conversion was complete unless noted. [b] Determined by HPLC on a chiral stationary phase. [c] Reaction time 6 h. [d] Reaction was performed with the (*S*)-enantiomer. [e] 2 mol% of a mixture of both enantiomers of catalyst bearing ligand **L2c** was used.

Asymmetric hydrogenation of 2,5-dibenzylthiophene 1,1-dioxide (**141**) proceeded with full conversion with both selected catalysts. In general, a higher amount of the fully reduced *meso*-**161** product was obtained with the catalyst bearing the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L1e** (entries 1-3). For the reduction with the five membered ring analog based on ligand **L2c** no or only little effect was observed upon variation of the reaction temperature (entry 4 *vs.* 5), hydrogen pressure (entry 5 *vs.* 6) or reaction time (entry 6 *vs.* 7). Although, high enantiomeric excess could be achieved for the mono-hydrogenated product **162**, it was only formed in 23% regardless of the reaction conditions (entry 5).

Tetrahydrothiophene 1,1-dioxide *meso*-**161** was identified by ^{1}H-NMR analysis and the two reference compounds, 2,5-diphenyltetrahydrothiophene 1,1-dioxide (**163**) and 2,5-diphenyltetrahydrothiophene 1-oxide (**166**) that were prepared by stepwise deprotonation and substitution of tetrahydrothiophene 1,1-dioxide (**165**) and tetrahydrothiophene 1-oxide (**164**), respectively (*Scheme 5.2*). While the reaction of

tetrahydrothiophene 1,1-dioxide (**165**) gave the product **163** as a mixture of both diastereomers (60:40, *cis*:*trans*), tetrahydrothiophene 1-oxide (**164**) reacted with *n*BuLi and benzylbromide to selectively form the corresponding *cis* isomer of compound **166**, due to site selective coordination and attack from the back by benzylbromide together with mono-substituted product, which was separated by semi-preparative HPLC on an achiral stationary phase. Suitable crystals for X-ray analysis of both fully reduced compounds **163** and **166** were obtained, the structure of the latter is shown in *Scheme 5.2*.



Scheme 5.2 Synthesis of reference compounds **163** and **166**.

Analysis of the reaction mixture resulting from asymmetric hydrogenation (*Table 5.4*) revealed a by-product **167** in small amounts (3-7%, ^{1}H-NMR). This [2+2] cycloaddition product **167** was isolated, analyzed by two-dimensional NMR and its structure was confirmed by X-ray analysis (*Figure 5.1*).

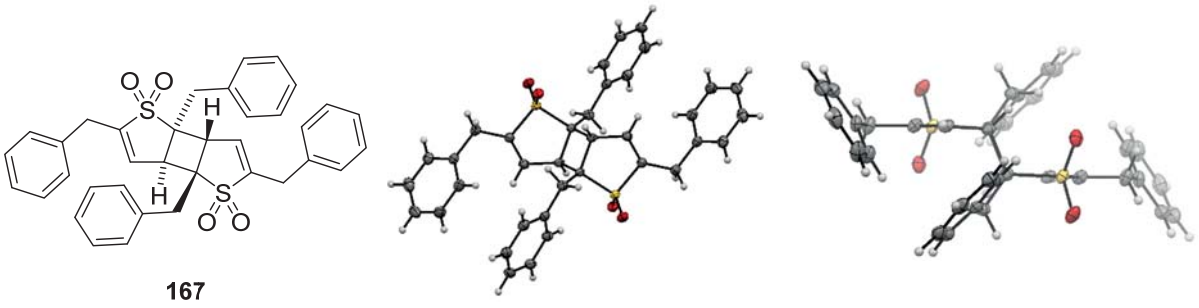


Figure 5.1 Structure of [2+2] cycloaddition product **167**.

The by-product **167** was not formed during the hydrogenation as initially assumed, but was already present in the starting material **141** in amounts ranging from 4% to 59% depending on the age of the substrate. The sample containing 59% of the [2+2] cycloaddition product had been stored on the benchtop in a glass bottle for three months. Formation of the cyclized product **167** by thermal cycloaddition could be excluded, since the amount did not increase upon heating of 2,5-dibenzylthiophene 1,1-dioxide (**141**) either neat or in CD_3CN to 80-90 °C for 17 to 19 hours. This reaction could also be light-induced by sunlight as it is known for unsubstituted and

mono-substituted benzothiophene 1-oxides[63] and 1,1-dioxides[64] and for 3,4-dichloro-thiophene 1,1-dioxide[65] when exposed to sunlight or irradiation with a mercury arc lamp (313 or 356 nm). Therefore, the photodimerization reaction was investigated in collaboration with Prof. Wenger (University of Basel). A sample of 2,5-dibenzyl-thiophene 1,1-dioxide (**141**) in acetonitrile ($c = 5\times10^{-4}$ M), containing 4% of the cyclized product **167**, was irradiated with a xenon lamp for the indicated time and the absorption of this solution was recorded subsequently (*Figure 5.2*). In orange the absorption of the sample before irradiation is shown and in black the absorption of the pure dimer **167**.

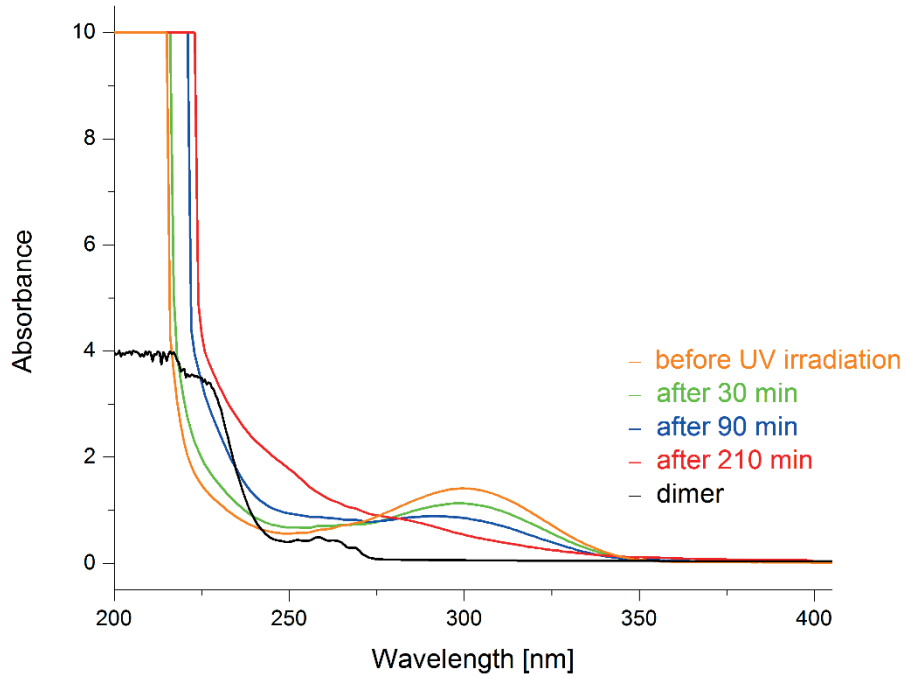
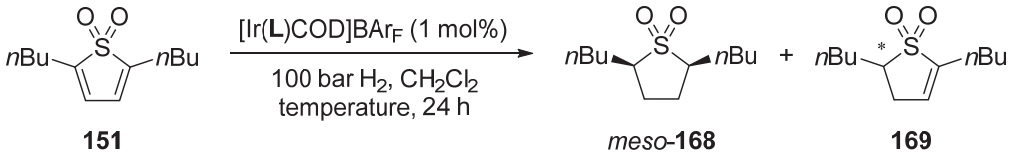


Figure 5.2 Irradiation of 2,5-dibenzylthiophene 1,1-dioxide (**141**) with a Xe lamp in CH_3CN.

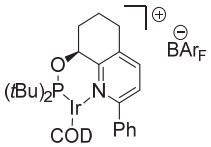
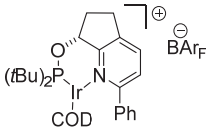
While the absorption spectrum after irradiation for 30 minutes (green) does not change dramatically, the significant maximum value for 2,5-dibenzylthiophene 1,1-dioxide (**141**) at around 300 nm disappears after irradiating for 210 minutes. Evaporation of the solvent with subsequent proton NMR analysis of this irradiated sample showed an increased formation of the dimer **167** (mono:dimer, 1.0:1.4). Experiments at higher concentration ($c = 3\times10^{-2}$ M) using a 300 W xenon arc light source did not result in higher yield. Since no adequate apparatus was available the investigations were terminated at this point.

Alkyl 2,5-disubstituted substrates such as 2,5-dibutylthiophene 1,1-dioxide (**151**) and 2,5-diethylthiophene 1,1-dioxide (**150**) were also investigated in the asymmetric iridium-catalyzed hydrogenation. The results obtained for substrate **151** with selected catalysts are shown in *Table 5.5*.

Table 5.5 Iridium-catalyzed hydrogenation of 2,5-dibutylthiophene 1,1-dioxide (**151**).[a]



151 *meso*-**168** **169**

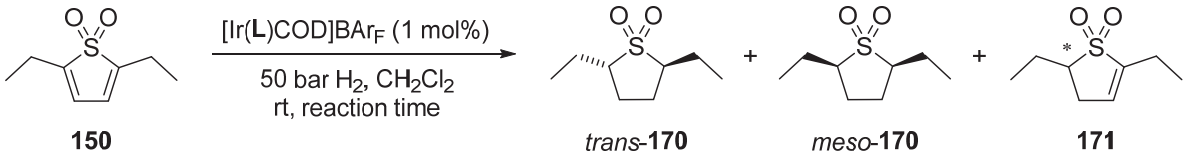
entry	catalyst structure	ligand	T (°C)	*meso*-**168** (%)[b]	**169** (%)[b]
1		(*S*)-**L1e**	60	86	14
2			rt	80	20
3		(*R*)-**L2c**	60	86	14
4			rt	84	16

[a] Conversion was determined by ^{1}H-NMR analysis and was complete unless noted. [b] Determined by GC-MS.

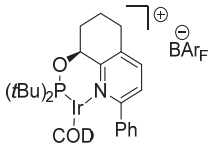
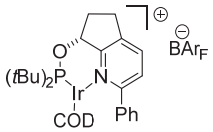
The hydrogenation proceeds to completion at elevated and also at room temperature to give the *meso* compound **168** as the main product. Unfortunately, the enantiomeric excess of the mono-reduced product **169** could not be determined, since the enantiomers could not be separated by GC analysis with a chiral stationary phase. In order to reduce the molar weight and thereby shorten the retention time of the compound, a reduction of the sulfone **169** to the corresponding sulfide was envisioned. Lithium aluminum hydride was used in large excess (10 eq.), but the product was only formed as the minor component (up to 35%) together with unidentified by-products, which could not be separated.

As an alternative substrate, 2,5-diethylthiophene 1,1-dioxide (**150**), having a lower molecular mass than **151**, was synthesized (see *Section 4.2*) and submitted to the same hydrogenation conditions (*Table 5.6*).

Table 5.6 Iridium-catalyzed hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**).



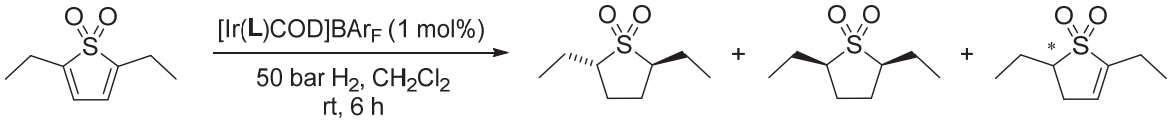
150 *trans*-**170** *meso*-**170** **171**

entry	catalyst structure	reaction time (h)	*trans*-**170** (%)[a]	*meso*-**170** (%)[a]	**171** (%)[a]	*ee* (%) of **171**[b]
1		24	0.3	60	40	99 (–)
2		6	–	41	59	98 (–)
3		24	2	30	70	>99 (+)
4		6	–	**16**	**84**	**>99** (+)

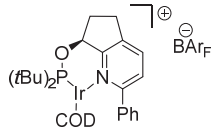
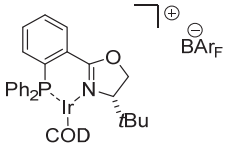
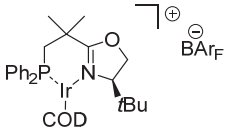
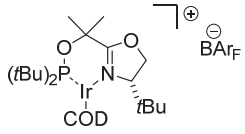
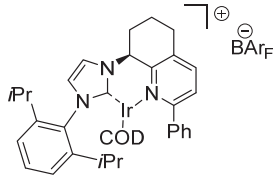
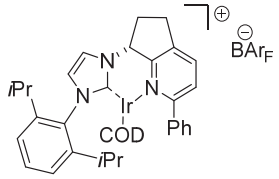
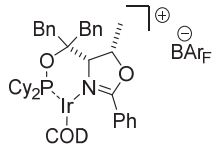
[a] Determined by GC analysis, conversion was complete unless noted. [b] Determined by GC analysis on a chiral stationary phase.

Asymmetric hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**) proceeded with complete conversion to afford both fully hydrogenated products *trans*-**170** and *meso*-**170** together with the mono-reduced product **171**. For substrate **150** the reaction time had some impact on the product ratio. When the hydrogenation was carried out for a prolonged reaction time (24 h) with the catalyst bearing ligand **L1e**, the *meso*-**170** isomer was formed as the major product, whereas after a reaction time of only six hours the mono-hydrogenated product **171** was the main product (entry 1 *vs.* 2). The product distribution resulting from the hydrogenation of substrate **150** with the catalyst based on **L2c** was not very much affected by the reaction time, as in both cases the main product was 2,3-dihydrothiophene **171** (entries 3 and 4). Although the hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**) required still some optimization, the enantiomeric excess determined for 2,3-dihydrothiophene **171** was very high with the catalyst based on the cyclohexane-annulated pyridine-phosphinite ligand **L1e** (entry 2) and even higher with the complex based on ligand **L2c** (entries 3 and 4). As the amount of both undesired fully reduced product *trans*-**170** and *meso*-**170** was reduced by shorter reaction time, further catalyst screening was performed under these conditions (50 bar H_2, 6 h) (*Table 5.7*).

Table 5.7 Catalyst screening for the hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**).



150 *trans*-**170** *meso*-**170** **171**

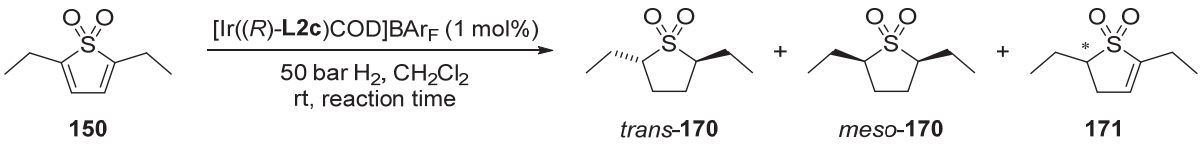
entry	catalyst structure	ligand	conv. (%)[a]	*meso*-**170** (%)[a]	**171** (%)[a]	*ee* (%) of **171**[b]
1		(*S*)-**L2c**	**>99.9**[c]	**15**	**85**	**>99** (–)
2		**L3e**	6	52	48	41 (+)
3		(*S*)-**L5a**	13	74	26	58 (–)
4		**L7e**	25	37	63	46 (+)
5		**L13**	>99.9[d]	23	76	89 (–)
6		**L14**	>99.9[e]	45	55	32 (+)
7		**L15**	3	–	3	36 (+)

[a] Determined by GC analysis. [b] Determined by GC analysis on a chiral stationary phase. [c] 0.2% of *trans*-**170** product was formed. [d] 1% of *trans*-**170** product was formed. [e] 0.1% of *trans*-**170** product was formed.

In general low conversion was obtained for the hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**) with the tested oxazoline based N,P ligands, only pyridine-based catalysts bearing ligands **L2c**, **L13** and **L14** brought the reaction to its completion (entries 1, 5 and 6). Both the selectivity and the enantiomeric excess were moderate for

all catalytic systems, except for the catalysts bearing the cyclohexane-annulated bicyclic pyridine-phosphinite ligand **L2c** (entry 1) and the *N*-heterocyclic carbene ligand **L13** (entry 5). Having found the most active and selective catalyst, the asymmetric hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**) was further optimized. First, the reaction time was varied in the hydrogenation using the catalyst bearing ligand **L2c** (*Table 5.8*).

Table 5.8 Catalyst screening for the hydrogenation of 2,5-diethylthiophene 1,1-dioxide (**150**).

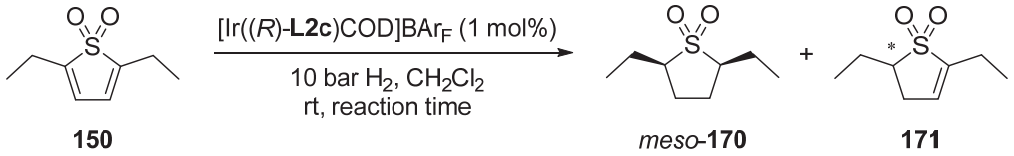


entry	reaction time (h)	*trans*-**170** (%)[a]	*meso*-**170** (%)[a]	**171** (%)[a]	*ee* (%) of **171**[b]
1	3	0.2	14	86	>99 (+)
2	1	0.1	13	87	>99 (+)
3	0.5	–	12	88	>99 (+)

[a] Determined by GC analysis, conversion was complete unless noted. [b] Determined by GC analysis on a chiral stationary phase.

This reaction parameter had essentially no impact on the amount of undesired fully reduced products *trans*-**170** and *meso*-**170**. Surprisingly, only 30 minutes were needed to drive the hydrogenation reaction to completion without any formation of the *trans*-**170** product (entry 3). Furthermore, the effect of hydrogen pressure in the hydrogenation of thiophene 1,1-dioxide **150** with the same catalyst was investigated (*Table 5.9*).

Table 5.9 Optimization of the hydrogenation conditions for 2,5-diethylthiophene 1,1-dioxide (**150**).

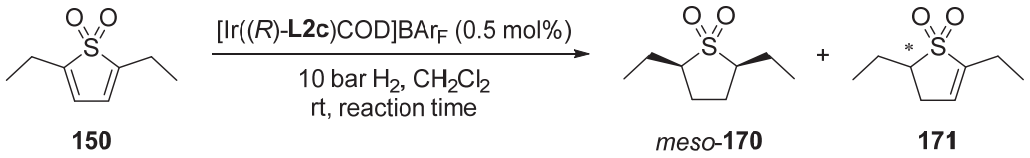


entry	reaction time (min)	conv. (%)[a]	*meso*-**170** (%)[a]	**171** (%)[a]	*ee* (%) of **171**[b]
1	60	>99.9	15	85	>99 (+)
2	60[c]	>99.9	9	91	>99 (+)
3	30	>99.9	5	95	>99 (+)
4	20	**>99.9**	**4**	**96**	**>99** (+)
5	15	99.6	3	97	>99 (+)
6	10	96	2	98	>99 (+)
7	10[d]	86	1	99	>99 (+)

[a] Determined by GC analysis, no *trans*-**170** product was formed. [b] Determined by GC analysis on a chiral stationary phase. [c] Reaction performed at 0 °C. [d] Reaction performed on a 0.1 mmol scale.

Under a reduced hydrogen pressure of no *trans*-**170** product was detected. By decreasing the reaction temperature to 0 °C the formation of the undesired fully reduced product *meso*-**170** was reduced (entry 2). Shorter reaction time had the same beneficial effect on the product distribution (entry 3-6), but to reach full conversion the reaction had to be run for a minimum of 20 minutes (entry 4). Variation of reaction parameters, such as temperature, time or hydrogen pressure did not have any effect on the excellent enantiomeric excess observed for mono-hydrogenated product **171**. The efficiency of this catalytic system was then tested by reducing the catalyst loading (*Table 5.10*).

Table 5.10 Iridium-catalyzed hydrogenation of substrate **150** using 0.5 mol% catalyst loading.

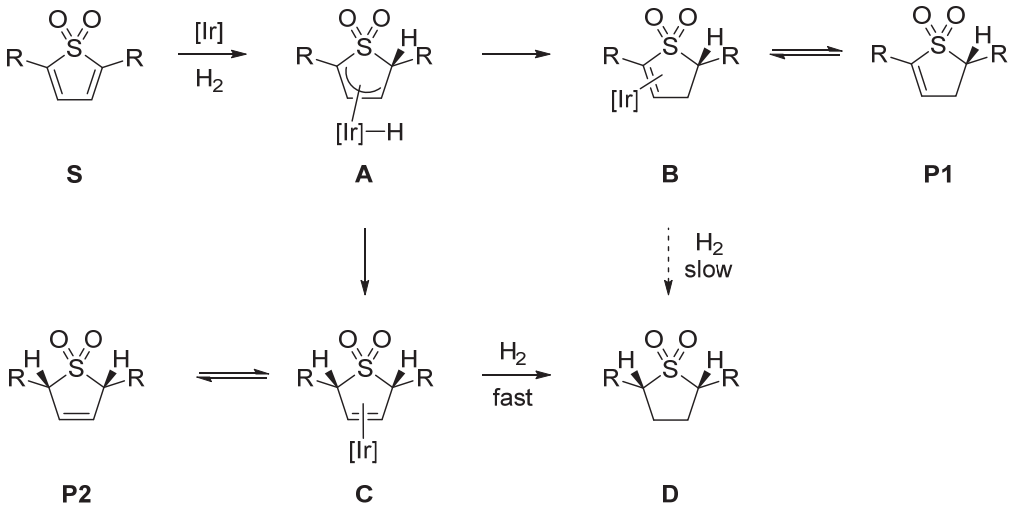


entry	reaction time (min)	conv. (%)[a]	*meso*-**170** (%)[a]	**171** (%)[a]	*ee* (%) of **171**[b]
1	60	75	2	98	>99 (+)
2	90	91	2	98	>99 (+)
3	120	**>99.9**	**6**	**94**	**>99** (+)
4	180	>99.9	12	88	>99 (+)

[a] Determined by GC analysis, no *trans*-**170** product was formed. [b] Determined by GC analysis on a chiral stationary phase.

With lower catalyst loading (0.5 mol%) the amount of the *meso*-**170** product also decreased, but at expense of conversion (entry 1). Prolonged reaction time of 90 minutes resulted in the same ratio of products *meso*-**170** and mono-hydrogenated product **171**, but still no full conversion was achieved (entry 2). Although, after two hours the reaction proceeded in a quantitative manner, the proportion of product *meso*-**170** increased (entry 3) and doubled upon prolongation of the reaction time for another hour (entry 4).

The mono-hydrogenated sulfone **171** stemming from a hydrogenation with the catalyst bearing ligand **L2c** (50 bar H_2, rt, 1 h) was re-submitted after catalyst removal to identical hydrogenation conditions. Surprisingly, the remaining double bond was not reduced carrying out the reaction for one hour at 50 bar hydrogen pressure. This observation may be explained by the following reaction pathway (*Scheme 5.3*).



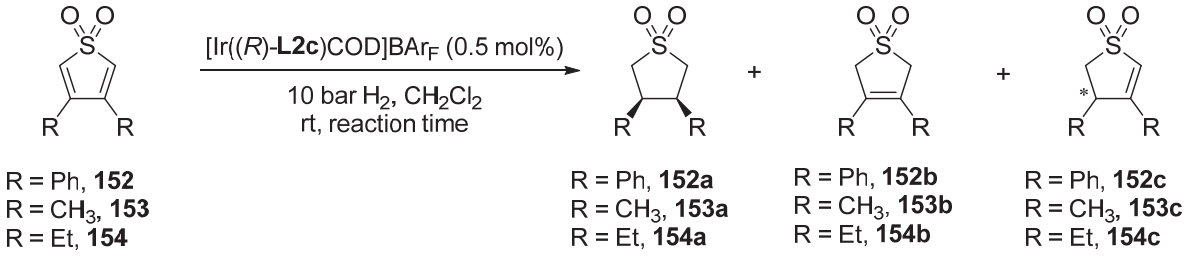
Scheme 5.3 Possible reaction pathway for iridium-catalyzed hydrogenation of 2,5-disubstituted thiophene 1,1-dioxides.

Upon hydrogenation of the first C=C bond the iridium center remains bound to the heterocycle forming an allyl-complex **A**. This complex can undergo reductive elimination to give either the p complex B, which upon decomplexation furnishes the mono-hydrogenated product **P1** or the iridium complex **C**. Further reduction of complex **B** is presumably very slow or does not proceed at all, while hydrogenation of the disubstituted double bond in complex **C** is faster to give the *meso* compound **D**.

5.3 Enantioselective Hydrogenation of 3,4-Disubstituted Thiophene 1,1-Dioxides

3,4-Diaryl and dialkylsubstituted thiophene 1,1-dioxides were also investigated as substrates (*Table 5.11*).

Table 5.11 Iridium-catalyzed hydrogenation of 3,4-disubstituted substrates.



entry	R	T (°C)	p H_2 (bar)	conv. (%)[a]	**a** (%)[a]	**b** (%)[a]	**c** (%)[a]	*ee* of **c** (%)[b]
1	Ph	60	100	89	–	17	83	18
2	CH_3	60	100	48	36	21	48	39
3	CH_3	60	50	50	–	50	50	42
4	CH_3	rt[c]	50	7	–	–	99	*rac*
5	Et	60	100	75	16	32	52	n.d.[d]
6	Et	60	50	41	–	36	64	n.d.[d]
7	Et	rt[c]	50	16	–	–	99	n.d.[d]

[a] Determined by ^{1}H-NMR analysis. [b] Determined by GC or HPLC analysis on a chiral stationary phase. [c] Reaction performed with racemic catalyst bearing ligand **L2c** for 4 h. [d] Enantiomeric excess could not be determined, due to peak overlap of thiophene 1,1-dioxide **154** with mono-hydrogenated product **154c**.

Unfortunately, 3,4-disubstituted thiophene 1,1-dioxides **152**, **153** and **154** proved to be less reactive than their 2,5-disubstituted counterparts (*Section 5.2*). In addition to the 4,5-dihydrothiophene 1,1-dioxides **152c**, **153c** and **154c**, the isomers 2,5-dihydro-thiophene 1,1-dioxides **152b**, **153b** and **154b** were observed. All products shown above, were identified by proton NMR analysis and their structures confirmed by two-dimensional NMR spectroscopy. 3,4-Diphenylthiophene 1,1-dioxide (**152**) was reduced only to 89%, the major product being the mono-hydrogenated compound **152c**. Unfortunately, the observed enantiomeric excess reached only 18% (entry 1). Although higher *ee* was obtained in the hydrogenation of 3,4-dimethylthiophene 1,1-dioxide (**153**) it was still moderate (entries 2 and 3). While the reduction of substrate

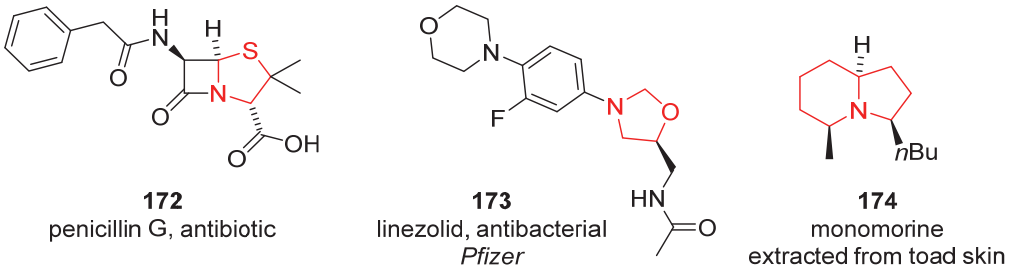
153 at higher hydrogen pressure resulted in additional formation of the undesired fully reduced compound **153a**, lowering the hydrogen pressure gave a 1:1 mixture of dihydrothiophene 1,1-dioxides **153b** and **153c** (entry 2 *vs.* entry 3). Although the hydrogenation of 3,4-diethylthiophene 1,1-dioxide (**154**) proceeded with higher conversion at higher hydrogen pressure in higher conversion, those conditions fostered the formation of the *meso* compound **154a** (entry 5). At 50 bar hydrogen pressure only the two dihydrothiophene 1,1-dioxides **154b** and **154c** were formed. The enantiomeric excess of 2,5-dihydrothiophene 1,1-dioxide could not be determined, due to peak overlap with the starting material **154**. Both 3,4-dialkyl substituted substrates **153** and **154** were transformed only with low levels of conversion at room temperature with the racemic catalyst based on ligand **L2c** (entries 4 and 7).

Overall, the results obtained with 3,4-disubstituted thiophene 1,1-dioxides are inferior to those obtained with their 2,5-disubstituted counterparts.

6 Iridium-Catalyzed Asymmetric Hydrogenation of Other Heterocycles

6.1 Introduction

To broaden the substrate scope of asymmetric iridium-catalyzed hydrogenation of heterocycles, the hydrogenation protocols developed for furans, benzofurans and thiophene 1,1-dioxides were applied to substituted thiazoles, oxazoles and indolizines. Reduced heterocycles of this type occur in many bioactive natural products and pharmaceuticals as shown by some examples in *Figure 6.1*.



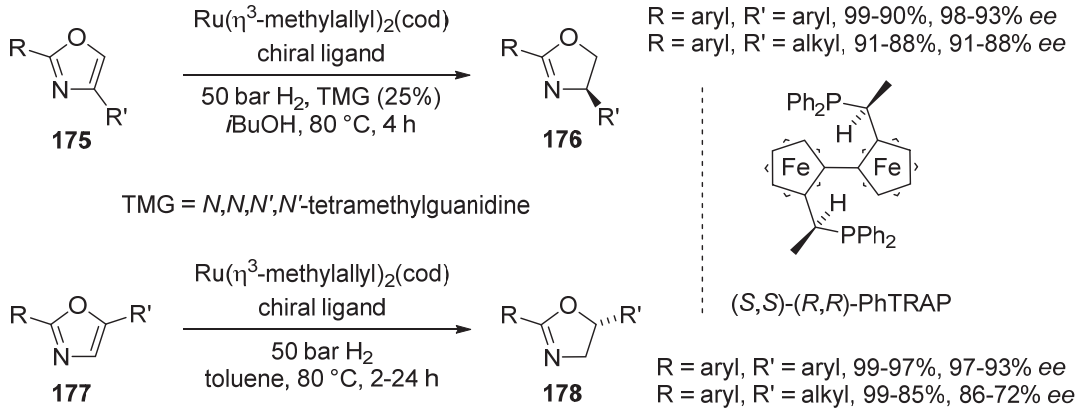
172
penicillin G, antibiotic

173
linezolid, antibacterial
Pfizer

174
monomorine
extracted from toad skin

Figure 6.1 Structure motifs of reduced heterocycles in drugs or natural products.

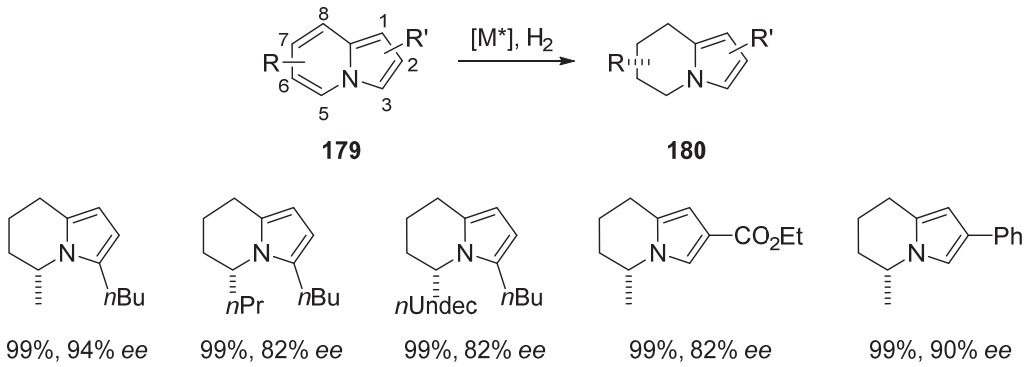
Penicillin G (**172**) is a naturally occurring substance with antibiotic properties produced by the mold fungus *Penicillium notatum*. It was discovered by ALEXANDER FLEMING, who was awarded with the Nobel Prize in 1945. Linezolid (**173**) is a synthetic antibiotic which is active against most Gram-positive bacteria, that are resistant to other antibiotics.[66] Monomorine (**174**) is a natural alkaloid extracted from ants or toad skin,[67] which is probably used as defense agent against predators. An efficient way to access these kinds of core structures is the asymmetric reduction of the corresponding unsaturated compounds. While the asymmetric hydrogenation of substituted thiazoles has not been reported to date, 2,4- and 2,5-disubstituted oxazoles were reduced with a chiral ruthenium catalyst to give the enantioenriched products **176** and **178** (*Scheme 6.1*).[68]



Scheme 6.1 Asymmetric hydrogenation of 2,4- and 2,5-disubstituted oxazoles.

To obtain high conversion for the hydrogenation of 2,4-disubstituted oxazoles **175** the addition of TMG was crucial. Higher enantiomeric excess was induced in the asymmetric reduction of 2,5-disubstituted oxazoles **177** when changing the solvent to toluene. Diaryl and mixed alkyl/aryl substituted 4,5-dihydrooxazoles were obtained in high yield with excellent enantiomeric excess, whereas the hydrogenation of alkyl/aryl substituted oxazoles resulted in lower levels of enantiomeric excess for both substitution patterns.

Asymmetric hydrogenation of indolizine with a ruthenium catalyst based on an *N*-heterocyclic carbene ligand was realized in the research group of GLORIUS (*Scheme 6.3*).[69]

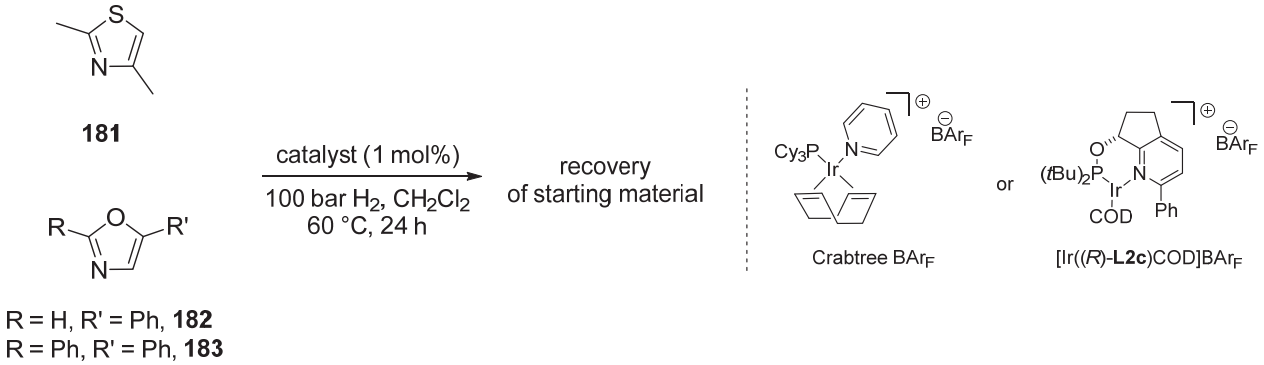


Scheme 6.2 Asymmetric hydrogenation of disubstituted indolizines.

Differently substituted indolizines were reduced enantioselectively in high yield. Simultaneously with elongation of the alkyl substituent at the 5-position the *ee* dropped for 3,5-substituted indolizines. Although functional group tolerance was shown by means of one substrate, the substrate scope is still limited, since hydrogenation of derivatives with other substitution patterns resulted in moderate or no enantioselectivity at all.

6.2 Attempted Enantioselective Hydrogenation of Thiazoles and Oxazoles

The commercially available heterocycles **181**, **182** and **183** were tested as substrates using the conditions and the catalysts shown in *Scheme 6.3*.

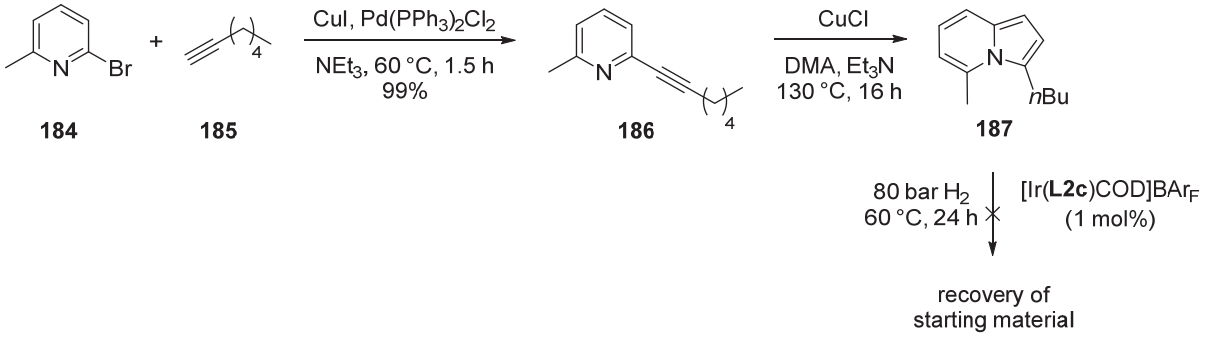


Scheme 6.3 Hydrogenation of thiazole **181** and oxazoles **182** and **183**.

Only starting materials were recovered after applying the hydrogenation conditions successfully used for the reduction of furans and thiophene 1,1-dioxides. Neither the BAr_F analog of the CRABTREE catalyst could promote the reduction even under harsh conditions, nor the iridium catalyst based on the cyclopentane-annulated bicyclic pyridine-phosphinite ligand **L2c**. The reactivity of these substrates must be very low perhaps due to inhibition of the catalyst as a result of coordination of the N-atom with the metal center.

6.3 Attempted Enantioselective Hydrogenation of Indolizines

In a two-step synthesis starting from 2-bromo-6-methylpyridine (**184**) and 1-heptyne (**185**) 2-(hept-1-yn-1-yl)-6-methylpyridine (**186**) was obtained in a quantitative manner (*Scheme 6.4*).[69] Alkynyl pyridine **186** underwent a copper assisted cycloisomerization to give the light sensitive 3-butyl-5-methylindolizine (**187**). Indolizine **187** was weighted in the glove box to perform the hydrogenation reaction using the catalyst bearing ligand **L2c**.



Scheme 6.4 Synthesis and hydrogenation of 3-butyl-5-methylindolizine (**187**).

Again no reaction was observed even under forcing hydrogenation conditions and therefore this scaffold was not further investigated.

7 Experimental Section

7.1 Working Techniques

The synthesis of air- and moisture-sensitive compounds was carried out using dried glassware under argon and standard Schlenk techniques. Flash chromatographic purifications were performed on Merck silica gel 60 (40-63 mm particle size). The eluents were of technical grade and distilled prior to use. Solvents were collected from a purification column system (PureSolv, Innovative Technology Inc.) or purchased from Aldrich or Fluka in sure/sealed bottles over molecular sieves. The hydrogenation experiments were set up under air, unless otherwise noted.

7.2 Analytical Methods

NMR Spectroscopy: NMR spectra were recorded on a Bruker Advance 400 (400 MHz) instrument. The chemical shift δ value is given in ppm and referenced to the residual solvent peaks: 7.26 ppm (^{1}H-NMR) and 77.16 ppm (^{13}C-NMR) for $CHCl_3$, and 2.50 ppm (^{1}H-NMR) and 39.43 ppm (^{13}C-NMR) for DMSO. Multiplets were assigned with s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) or br (broad).

Mass Spectrometry (MS): Mass spectra were recorded by Dr. H. Nadig (Department of Chemistry, University of Basel) on a VG70-250 (electron ionization, EI) or a MAR 312 (fast atom bombardment, FAB) mass spectrometer. FAB was performed using 3-nitrobenzyl alcohol as a matrix. GC-MS spectra were measured on a 5890 Series II with Macherey-Nagel OPTIMA1 Me_2Si column (25 m × 0.2 mm × 0.35 μm) and a HP6890 gas chromatograph with a HP5970A detector equipped with a Macherey-Nagel OPTIMA5 5% polyphenylmethylsiloxane column (30 m × 0.25 mm × 0.25 μm) using a mass selective detector (EI). The signals are given in mass to charge ratio (m/z). The fragmentation pattern and intensities are given in brackets. All values are rounded to the nearest whole number.

High Resolution Mass Spectrometry (HRMS): High resolution mass spectra were recorded by O. Greter (Mass Spectrometry Service Facility at LOC, ETH Zürich) on a Waters Micromass AutoSpec Ultima MassLynx 4.0 Micromass (electron ionization, EI) mass spectrometer with an EBE-triSector mass analyzer. The signals are given in mass to charge ratio (m/z). The fragmentation pattern and intensities are given in brackets.

Infrared Spectroscopy (IR): Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrometer. Absorption bands are given in wave numbers $\tilde{\nu}$ [cm^{-1}]. The peak intensity is assigned with s (strong), m (medium) and w (weak).

Melting Point (m.p.): Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected.

Optical Rotation ($[\alpha]_D^{20}$): Optical rotations were measured on a Perkin Elmer Polarimeter 341 in a 1 dm cuvette at 20 °C. The mass concentration (c) is given in g/100 mL.

Gas Chromatography (GC): Gas chromatograms were recorded on a Carlo Erba HRGC Mega2 Series 800 (HRGS Mega2) instrument. Separations on achiral phases were performed on a Restek Rtx-1701 column (30 m × 0.25 mm × 0.25 μm). For GC on chiral phases β- and γ-cyclodextrin columns (30 m × 0.25 mm × 0.25 μm) were used.

High Performance Liquid Chromatography (HPLC): HPLC analyses were performed on Shimadzu systems with SCL-10A system controller, CTO-10AC column oven, LC10-AD pump system, DGU-14a degasser and SPD-M10A diode array or UV/VIS detector. For *ee* determination columns from Daicel Chemical Industries Ltd. were used.

Thin Layer Chromatography (TLC): TLC plates were purchased from Macherey-Nagel (Polygram SIL G/UV_{254}, 0.2 mm silica with fluorescence indicator, 40 × 80 mm).

Elemental Analysis (EA): Elemental analyses were measured at the Department of Chemistry, University of Basel, Microanalytical Laboratory by W. Kirsch and S. Mittelheiser on a Leco CHN-900 analyzer or a Vario Micro Cube by Elementar (C-, H, N-detection). The data are indicated in mass percent.

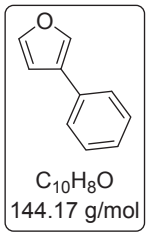
7.3 General Hydrogenation Procedures

General Hydrogenation Procedure with Pd/C: A high pressure steel autoclave (Premex Reactor AG, HMP-005) with glass insert and a magnetic stirring bar was charged with Pd/C (10 mol%), 0.2 mmol of substrate and 1.0 mL EtOAc. The sealed hydrogenation vessel was attached to a high pressure hydrogen line and purged with H_2. At 50 bar hydrogen pressure the mixture was stirred for 4 hours at room temperature. After H_2 was released, the solution was filtered over a Chromafil O-20/15 organic solvent stable filter (0.2 µm pore size) and the solution was analyzed after removal of the solvent.

General Hydrogenation Procedure with Iridium Catalysts: A high pressure steel autoclave (Premex Reactor AG, HMP-005) with glass insert and a magnetic stirring bar was charged with catalyst (0.001 mmol), substrate (0.1 mmol) and 0.25 mL of degased solvent. The sealed hydrogenation vessel was attached to a high pressure hydrogen line and purged with H_2. At specified hydrogen pressure the mixture was stirred for indicated time at the corresponding temperature. After H_2 was released, the solution was concentrated and diluted with 0.2 mL of *n*hexane:MTBE (4:1) and filtered over a plug of silica gel in a pasteur pipette. The solution was analyzed after removal of the solvent.

7.4 Synthesis and Characterization of Substituted Furans and Benzofurans

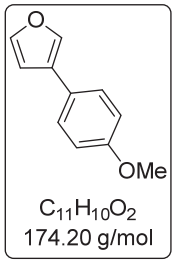
3-Phenylfuran (41a)



Following a modified procedure of PRIDGEN *et al.*,[26] Ni(dppe)Cl$_2$ (41.3 mg, 0.08 mmol, 1.04 mol%) was dissolved under slightly positive argon flow in dry THF (30 mL) in a 250 mL two-necked flask equipped with a reflux condenser. First 3-bromofuran (1.14 g, 7.52 mmol, 1.00 eq.) then phenyl magnesium bromide (1.0 M in THF, 8.30 mL, 8.30 mmol, 1.10 eq.) was added dropwise *via* syringe, the latter over a period of 20 min. The reaction mixture was stirred for three hours, quenched with an aqueous saturated NH$_4$Cl solution (50 mL) and was transferred to a separation funnel. After separation of the phases, the aqueous phase was extracted with MTBE (3×100 mL) and the combined organic phases were dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure. The obtained orange crystals were purified first by bulb to bulb distillation (1.0 torr, 120 °C) and subsequent flash chromatography (silica gel, 40×4 cm, *n*pentane) to give the title compound **41a** as colorless crystals (651 mg, 4.51 mmol, 60%).

m.p. 56–58 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.77 (dd, $^4J_{HH}$ = 1.6, 0.9 Hz, 1H, OC*H*), 7.51–7.48 (m, 3H, 2 *H*C$_{ar}$, OC*H*CH), 7.49–7.48 (m, 2H, *H*C$_{ar}$), 7.41 (tt, $^{3,4}J_{HH}$ = 7.4, 1.7 Hz, 2H, *H*C$_{ar}$), 7.30 (tt, $^{3,4}J_{HH}$ = 7.4, 1.3 Hz, 1H, *H*C$_{ar}$), 6.74 (dd, $^{3,4}J_{HH}$ = 1.8, 0.8 Hz, 1H, OCHC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 143.8 (OCHCH), 138.6 (OCH), 132.6 (*C*$_{furan}$), 128.9 (2 HC$_{ar}$), 127.1 (HC$_{ar}$), 126.6 (*C*$_{ar}$), 126.0 (2 HC$_{ar}$), 109.0 (OCHCH); **MS** (EI), *m*/*z* (%) 144 (M^+, 100), 115 (80); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3147w, 3127w, 3079w, 3061w, 3021w, 2022w, 1948w, 1888w, 1816w, 1701w, 1653w, 1587w, 1512m, 1491w, 1448m, 1367w, 1302w, 1238w, 1184w, 1161s, 1099w, 1075m, 1052m, 1026w, 1015s, 922m, 907m, 871s, 795m, 750s, 690s, 674s, 668s; **EA:** calculated for $C_{10}H_8O$: C = 83.31, H = 5.59; measured: C = 82.53, H = 5.75; R_f = 0.46 (silica gel, *n*hexane:EtOAc, 2:1); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 60 kPa H_2, 95 °C, 32 min, 5.0 K/min, 160 °C, 5 min): t_R = 17.5 min. The NMR spectra were consistent with the literature data.[70]

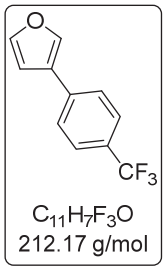
3-(4-Methoxyphenyl)furan (41b)



Compound **41b** was synthesized following the procedure described for the synthesis of 3-phenylfuran (**41a**) using Ni(dppe)Cl_2 (23.1 mg, 0.04 mmol, 0.94 mol%), 3-bromofuran (647 mg, 4.27 mmol, 1.00 eq.) in THF (30 mL) and 4-methoxyphenylmagnesium bromide (1.0 M in THF, 4.80 mL, 4.80 mmol, 1.12 eq.). The obtained orange crystals were purified first by bulb to bulb distillation (1.0 torr, 170 °C) and subsequent flash chromatography (silica gel, 40×4 cm, *n*pentane:EtOAc, 50:1) to give the title compound **41b** as colorless crystals (570 mg, 3.27 mmol, 77%).

m.p. 107–108 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.66 (dd, $^4J_{HH}$ = 1.4, 1.1 Hz, 1H, OC*H*), 7.46 (t, $^3J_{HH}$ = 1.7 Hz, 1H, OC*H*CH), 7.41 (t, $^3J_{HH}$ = 8.9 Hz, 2H, *H*C$_{ar}$), 6.92 (d, $^3J_{HH}$ = 8.8 Hz, 2H, *H*C$_{ar}$), 6.66 (dd, $^{3,4}J_{HH}$ = 1.8, 0.9 Hz, 1H, OCHC*H*), 3.83 (s, 3H, C*H*$_3$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 158.9 (*C*$_{ar}$), 143.6 (O*C*HCH), 137.8 (O*C*H), 127.2 (2 HC$_{ar}$), 126.2 (*C*$_q$), 125.2 (*C*$_q$), 114.4 (2 HC$_{ar}$), 109.0 (OCH*C*H), 55.5 (*C*H$_3$); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 9.8 min), *m*/*z* (%) 174 (M^+, 100), 159 (80), 131 (48), 103 (12), 102 (18), 77 (31), 76 (10), 63 (10), 51 (13); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3145w, 3125w, 3020w, 2964w, 2839w, 2051w, 1700w, 1611w, 1585m, 1571m, 1517s, 1500w, 1492w, 1466w, 1452w, 1443w, 1428w, 1419w, 1360w, 1310m, 1296s, 1246s, 1236s, 1182m, 1158s, 1112m, 1097w, 1051w, 1024s, 1016s, 922m, 874s, 834s, 782s, 737m, 730m, 721m, 695w, 636m; **EA:** calculated for $C_{10}H_8O$: C = 75.85, H = 5.79; measured: C = 75.83, H = 6.03; R_f = 0.18 (silica gel, *n*pentane:EtOAc, 50:1); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 80 kPa H_2, 95 min, 30 min, 5.0 K/min, 160 °C, 10 min): t_R = 41.0 min. The NMR spectra were consistent with the literature data.[70]

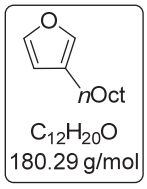
3-(4-Trifluoromethyl)phenyl)furan (41c)



Compound **41c** was synthesized following the procedure described for the synthesis of 3-phenylfuran (**41a**). The Grignard reagent was freshly prepared from magnesium (117 mg, 4.81 mmol, 1.11 eq.) and 4-bromobenzotrifluoride (0.62 mL, 4.35 mmol, 1.00 eq.) in Et_2O (5 mL). The solution was added to Ni(dppe)Cl_2 (30.2 mg, 0.06 mmol, 1.22 mol%) and 3-bromofuran (0.44 mL, 4.70 mmol, 1.08 eq.) in Et_2O (15 mL). The obtained dark red crystals were purified first by bulb to bulb distillation (0.2 torr, 150 °C) and subsequent flash chromatography (silica gel, 40×4 cm, *n*pentane) to give the title compound as colorless crystals (682 mg, 3.22 mmol, 52%).

m.p. 55–56 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.80 (s_{br}, 1H, OC*H*), 7.63 (d, $^3J_{HH}$ = 8.2 Hz, 2H, *H*C$_{ar}$), 7.58 (d, $^3J_{HH}$ = 8.2 Hz, 2H, *H*C$_{ar}$), 7.51 (t, $^3J_{HH}$ = 1.5 Hz, 1H, OC*H*CH), 6.73 (dd, $^{3,4}J_{HH}$ = 1.9, 0.9 Hz, 1H, OCHC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.3 (OCHCH), 139.5 (OCH), 136.2 (*C*$_{furan}$), 129.1 (q, $^2J_{CF}$ = 33 Hz, *C*$_{ar}$), 126.1 (2 HC$_{ar}$), 125.9 (q, $^3J_{CF}$ = 3.8 Hz, 2 HC$_{ar}$), 125.5 (*C*$_{ar}$), 124.3 (q, $^1J_{CF}$ = 271 Hz, *C*F_3), 108.8 (OCHCH); **^{19}F{^{1}H}-NMR** (376.5 MHz, $CDCl_3$, 300 K): δ (ppm) −62.7 (C*F*$_3$); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 6.3 min), *m*/*z* (%) 212 (M^+, 100), 193 (13), 183 (34), 164 (13), 133 (22), 115 (55), 63 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3167w, 3132w, 2358w, 2323w, 1696w, 1617m, 1594w, 1523w, 1497w, 1421w, 1318s, 1291m, 1238w, 1230m, 1177w, 1161s, 1123s, 1108s, 1102s, 1067s, 1053s, 1016s, 1010m, 957w, 922w, 872m, 844s, 789s, 773m, 741m, 731m; **EA:** calculated for $C_{11}H_7F_3O$: C = 62.27, H = 3.33; measured: C = 61.94, H = 3.39; R_f = 0.22 (silica gel, *n*pentane); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 60 kPa H_2, 95 min, 32 min, 5.0 K/min, 160 °C, 5 min): t_R = 21.3 min. The NMR spectra were consistent with the literature data.[70]

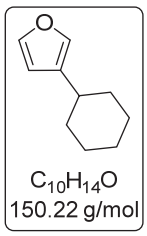
3-Octylfuran (64)



Compound **64** was synthesized following the procedure described for the synthesis of 3-phenylfuran (**41a**). The Grignard reagent was freshly prepared from magnesium (629 mg, 25.9 mmol, 1.20 eq.) and 1-bromooctane (4.40 mL, 24.8 mmol, 1.15 eq.) in Et_2O (10 mL). The solution was added to 3-bromofuran (2.00 mL, 21.6 mmol, 1.00 eq.) and Ni(dppe)Cl_2 (139 mg, 0.26 mmol, 1.22 mol) in Et_2O (30 mL). The brown oil was purified by flash chromatography (silica gel, 40×4 cm, *n*pentane) and bulb to bulb distillation (0.3 torr, 60 °C), yielding the product as a pale yellow oil (537 mg, 2.98 mmol, 14%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.34 (t, $^3J_{HH}$ = 1.7 Hz, 1H, OC*H*CH), 7.20 (dq, $^4J_{HH}$ = 1.9, 1.0 Hz, 1H, OC*H*), 6.27 (dd, $^{3,4}J_{HH}$ = 1.9, 0.9 Hz, 1H, OCHC*H*), 2.40 (t, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2), 1.55 (m$_c$, 2H, CH_2), 1.31 (m, 10H, CH_2), 0.89 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.7 (OCHCH), 138.9 (OCH), 125.5 (C_{furan}), 111.2 (OCHCH), 32.0 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 11.4 min), *m*/*z* (%) 180 (M^+, 13), 95 (28), 82 (100), 81 (52), 53 (18), 41 (21); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2955m, 2924s, 2854s, 1502w, 1466w, 1379w, 1161w, 1065w, 1026w, 874s, 777s, 721w; **EA:** calculated for $C_{12}H_{20}O$: C = 79.94, H = 11.18; measured: C = 79.28, H = 10.99; R_f = 0.39 (silica gel, *n*pentane); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 95 °C, 50 min, 0.1 °C/min, 96 °C, 0 min, 10 °C/min, 180 °C, 10 min): t_R = 24.4 min. The NMR spectra were consistent with the literature data.[71]

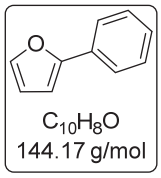
3-Cyclohexylfuran (65)



Compound **65** was synthesized following the procedure described for the synthesis of 3-phenylfuran (**41a**). The Grignard reagent was freshly prepared from magnesium (204 mg, 8.41 mmol, 1.81 eq.) and cyclohexylbromide (1.03 mL, 8.25 mmol, 1.77 eq.) in Et_2O (5 mL). The solution was added to Ni(dppe)Cl_2 (28.8 mg, 0.05 mmol, 1.17 mol%) and 3-bromofuran (0.43 mL, 4.65 mmol, 1.00 eq.) in Et_2O (15 mL). The obtained dark red crystals were purified first by bulb to bulb distillation (0.2 torr, 25 °C) and subsequent flash chromatography (silica gel, 30×2 cm, *n*pentane) to give the title compound as colorless oil (276 mg, 1.84 mmol, 40%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.34 (t, $^3J_{HH}$ = 1.6 Hz, 1H, OC*H*), 7.19 (d, $^4J_{HH}$ = 0.7 Hz, 1H, OCHC*H*), 6.30 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OCHC*H*), 2.42 (tt, $^{2,3}J_{HH}$ = 11.0, 3.6 Hz, 1H, C*H*), 1.93 (d, $^2J_{HH}$ = 11.6 Hz, 2H, CH_2), 1.82–1.67 (m, 3H, CH_2), 1.42–1.17 (m, 5H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.6 (O*C*HCH), 137.7 (O*C*H), 131.5 (C_{furan}), 109.8 (OCH*C*H), 34.7 (*C*H), 33.8 (2 *C*H_2), 26.5 (2 *C*H_2), 26.3 (*C*H_2); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 5.2 min), *m*/*z* (%) 150 (M^+, 58), 121 (22), 109 (14), 108 (24), 107 (42), 95 (52), 94 (55), 93 (14), 91 (23), 82 (100), 81 (50), 79 (61), 78 (10), 77 (48), 67 (19), 66 (16), 65 (26), 55 (11), 53 (28), 51 (20), 41 (33); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2922w, 2851m, 2666w, 2365w, 2323w, 1700w, 1560w, 1500w, 1447w, 1385w, 1358w, 1300w, 1259w, 1245w, 1213w, 1178w, 1160m, 1067w, 1030m, 1010w, 963w, 890w, 874s, 777s, 735s, 721w; **EA:** calculated for $C_{10}H_{14}O$: C = 79.96, H = 9.39; measured: C = 79.56, H = 9.54; R_f = 0.37 (silica gel, *n*pentane); **GC** (6-Methyl-2,3-pentyl-γ-cyclodextrin (60% in polysiloxane PS086), 30 m × 0.25 mm × 0.125 µm, 60 kPa H_2, 60 min, 30 min, 1.0 K/min, 100 °C, 5 min, 10.0 K/min, 180 °C, 5 min): t_R = 41.2 min. The NMR spectra were consistent with the literature data.[72]

2-Phenylfuran (44a)

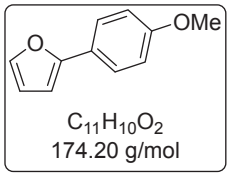


Following a modified procedure of NEGISHI *et al.*,[27] in a 100 mL three-necked flask furan (0.59 mL, 8.03 mmol, 1.20 eq.) was dissolved in dry THF (10 mL) under argon and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol, 2.40 eq.) was added *via* syringe over a period of 10 min. The reaction mixture was stirred at this temperature for additional hour and another hour at room temperature. In a 25 mL Schlenk tube $ZnCl_2$ (1.35 g, 9.69 mmol, 1.45 eq.) was dried by heating under vacuum. After cooling down to room temperature, zinc chloride was dissolved in 5 mL THF and the lithiated furan in Et_2O was added and stirred for one hour at room temperature. In a 250 mL three-necked flask $Pd(PPh_3)_4$ (86.0 mg, 0.07 mmol, 1.11 mol%) was dissolved in THF (20 mL) and iodobenzene (0.75 mL, 6.66 mmol, 1.00 eq.) was added. Then the zinc chloride solution was added and the resulting mixture stirred at room temperature for 21 h. The reaction mixture was poured in a separation funnel onto ice cold aqueous 3 M HCl (20 mL) and Et_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were washed with aqueous saturated $NaHCO_3$ solution (75 mL) and with brine (75 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was

purified by flash chromatography (silica gel, 25×4 cm, *n*pentane) yielding the product **44a** as a colorless oil (123 mg, 0.78 mmol, 12%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.66–7.68 (m, 2H, *H*C$_{ar}$), 7.46 (m, 1H, OC*H*), 7.36–7.40 (m, 2H, *H*C$_{ar}$), 7.23–7.27 (m, 1H, *H*C$_{ar}$), 6.65 (d, $^3J_{HH}$ = 3.3 Hz, 1H, OCHCHC*H*), 6.47 (dd, $^3J_{HH}$ = 3.3, 1.8 Hz, 1H, OCHC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 154.2 (*C*$_{furan}$), 142.2 (OCH), 131.0 (*C*$_{ar}$), 128.8 (2 HC$_{ar}$), 127.5 (HC$_{ar}$), 123.9 (2 HC$_{ar}$), 111.8 (OCHCHCH), 105.1 (OCHC*H*); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 7.0 min), *m*/*z* (%) 144 (M^+, 100), 116 (24), 115 (93), 89 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3063w, 3026w, 1769w, 1726w, 1683m, 1597w, 1506m, 1476m, 1447m, 1279w, 1218m, 1256m, 1068m, 1023m, 1009s, 903s, 885m, 805w, 758s, 735s, 691s, 680m, 664s, 593m, 518s, 511s, 502s; R_f = 0.17 (silica gel, *n*pentane); **HPLC** (IC, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 220 nm): t_R = 7.9 min, enantiomers: t_{R1} = 19.8 min, t_{R2} = 23.2 min. The NMR spectra were consistent with the literature data.[73]

2-(4-Methoxyphenyl)furan (44b)

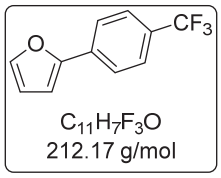


Compound **44b** was synthesized following the procedure described for the synthesis of 2-phenylfuran (**44a**) using furan (0.59 mL, 8.03 mmol, 1.20 eq.), *n*BuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol, 2.38 eq.), $ZnCl_2$ (1.15 g, 8.28 mmol, 1.23 eq.), $Pd(PPh_3)_4$ (84.0 mg, 0.07 mmol, 1.07 mol%) and 4-iodoanisole (1.60 mL, 6.70 mmol, 1.00 eq.). The crude material was purified by flash chromatography (silica gel, 27×4 cm, cyclohexane:EtOAc, 20:1) and bulb to bulb distillation (0.2 torr, 100 °C) yielding **44b** as a colorless solid (167 mg, 0.96 mmol, 14%).

m.p. 51–53 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.61 (d, $^3J_{HH}$ = 8.9 Hz, 2H, *H*C$_{ar}$), 7.43 (dd, $^{3,4}J_{HH}$ = 1.8, 0.7 Hz, 1H, OC*H*), 6.92 (d, $^3J_{HH}$ = 8.9 Hz, 2H, *H*C$_{ar}$), 6.52 (dd, $^{3,4}J_{HH}$ = 3.3, 0.7 Hz, 1H, OCHCHC*H*), 6.45 (dd, $^3J_{HH}$ = 3.3, 1.8 Hz, 1H, OCHC*H*), 3.84 (s, 3H, C*H*$_3$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.1 (*C*$_{ar}$OCH$_3$), 154.2 (*C*$_{furan}$), 141.5 (OCH), 125.4 (2 HC$_{ar}$), 124.2 (*C*$_{ar}$), 114.3 (2 HC$_{ar}$), 111.7 (OCHCHCH), 103.5 (OCHCH), 55.5 (OCH$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 12.0 min), *m*/*z* (%) 174 (M^+, 100), 159 (81), 145 (11), 131 (36), 103 (15), 102 (12), 77 (18); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3119w, 3005w, 2961w, 2936w, 2835w, 1610m, 1585m, 1570m, 1508m, 1481m, 1466m, 1441m, 1300m, 1242m, 1178m,

1005s, 1013s, 903m, 833s, 793s, 729s, 665m, 596s; R_f = 0.33 (silica gel, cyclohexane:EtOAc, 20:1). The NMR spectra were consistent with the literature data.[74]

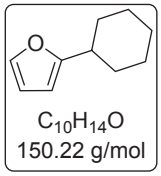
2-(4-Trifluoromethyl)phenylfuran (44c)



Compound **44c** was synthesized following the procedure described for the synthesis of 2-phenylfuran (**44a**) using furan (0.59 mL, 8.03 mmol, 1.19 eq.), *n*BuLi (1.6 M in hexanes, 10.0 mL, 16.0 mmol, 2.38 eq.), $ZnCl_2$ (1.15 g, 8.28 mmol, 1.23 eq.), $Pd(PPh_3)_4$ (78.5 mg, 0.07 mmol, 1.00 mol%) and 4-bromobenzotrifluoride (0.94 mL, 6.72 mmol, 1.00 eq.). The crude material was purified by flash chromatography (silica gel, 27×4 cm, *n*pentane, material immobilized on silica gel) yielding the product as a colorless solid (534 mg, 2.52 mmol, 37%).

m.p. 82–83 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.77 (d, $^3J_{HH}$ = 8.1 Hz, 2H, *H*C$_{ar}$), 7.63 (d, $^3J_{HH}$ = 8.2 Hz, 2H, *H*C$_{ar}$), 7.52 (d, $^3J_{HH}$ = 1.3 Hz, 1H, OC*H*), 6.77 (d, $^3J_{HH}$ = 3.4 Hz, 1H, OCHCHC*H*), 6.51 (dd, $^3J_{HH}$ = 3.4, 1.8 Hz, 1H, OCHC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 152.7 (*C*$_{furan}$), 143.2 (OCH), 134.1 (*C*$_{ar}$), 129.1 (q, $^2J_{CF}$ = 32.4 Hz, *C*$_{ar}$), 127.8 (*C*$_{ar}$), 125.9 (q, $^3J_{CF}$ = 3.8 Hz, 2 HC$_{ar}$), 124.3 (q, $^1J_{CF}$ = 272 Hz, *C*F$_3$), 123.9 (2 HC$_{ar}$), 112.1 (OCHCHCH), 107.1 (OCHCH); **^{19}F{^{1}H}-NMR** (376.5 MHz, $CDCl_3$, 300 K): δ (ppm) −62.5 (C*F*$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 7.2 min), *m*/*z* (%) 212 (M^+, 100), 183 (47), 133 (17), 115 (55), 81 (10); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2362w, 1617m, 1480m, 1419m, 1321s, 1285m, 1154w, 1109s, 1069s, 1010s, 903m, 884m, 846s, 809s, 745s; R_f = 0.30 (silica gel, *n*pentane); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min): t_R = 12.3 min; **HPLC** (IC, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 220 nm): t_R = 7.3 min. The NMR spectra were consistent with the literature data.[74]

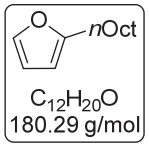
2-Cyclohexylfuran (66)



Following a modified procedure of POLITIS *et al.*,[36] freshly pestled magnesium (316 mg, 13.0 mmol, 2.62 eq.) was added with a grain of iodine in a 50 mL three-necked flask equipped with a dropping funnel and a reflux condenser, in dry Et_2O (1 mL). Iodocyclohexane (1.60 mL, 12.1 mmol, 2.44 eq.) in Et_2O (5 mL) was added over a period of 30 min. The flask was rinsed with Et_2O (5 mL) and the mixture was refluxed for one hour. In a 100 mL three-necked flask equipped with a thermometer, $Ni(dppe)Cl_2$ (68.4 mg, 0.13 mmol, 2.61 mol%) and 2-bromofuran (0.46 mL, 4.96 mmol, 1.00 eq.) were dissolved in Et_2O (15 mL) and the resulting solution was cooled to −2 °C. Over a period of 10 min the freshly prepared Grignard compound was added. After complete addition the reaction mixture was refluxed for 22 hours. It was quenched carefully with an aqueous 5% HCl solution (40 mL) and the flask was rinsed with Et_2O (20 mL). The phases were separated, the aqueous phase was extracted with Et_2O (50 mL), the organic phases were washed with water (2×40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (silica gel, 22×4 cm, *n*pentane) yielding the product **66** as a colorless oil (558 mg, 3.71 mmol, 75%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.29 (d, $^3J_{HH}$ = 1.1 Hz, 1H, OC*H*), 6.27 (dd, $^3J_{HH}$ = 3.1, 1.9 Hz, 1H, OCHC*H*), 5.94 (d, $^3J_{HH}$ = 3.1 Hz, 1H, OCHCHC*H*), 2.66–2.56 (m, 1H, CH_2), 2.07–1.95 (m, 2H, CH_2), 1.85–1.65 (m, 3H, CH_2), 1.43–1.20 (m, 5H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 161.2 (C_{furan}), 140.5 (OCH), 110.0 (OCHCH), 102.7 (OCHCHCH), 37.4 (*C*H), 31.7 (2 *C*H_2), 26.3 (*C*H_2), 26.1 (2 *C*H_2); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 5.5 min), *m*/*z* (%) 150 (M^+, 44), 135 (10), 121 (13), 108 (13), 107 (100), 94 (56), 81 (27), 79 (21), 77 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2926m, 2853w, 1589w, 1448w, 1011w, 934w, 881w, 795w, 723s, 598m; **EA:** calculated for $C_{10}H_{14}O$: C = 79.96, H = 9.39; measured: C = 79.51, H = 9.25; R_f = 0.36 (silica gel, *n*pentane); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 60 °C, 1 °C/min, 120 °C, 10 °C/min, 180 °C, 10 min): t_R = 27.8 min. The NMR spectra were consistent with the literature data.[75]

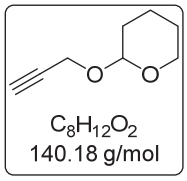
2-Octylfuran (71)



In a 100 mL three-necked flask equipped with a thermometer, *n*BuLi (1.6 M in hexanes, 19.0 mL, 30.4 mmol, 1.02 eq.) was dissolved in dry THF (20 mL) and cooled to −15 °C. The furan (2.20 mL, 29.9 mmol, 1.00 eq.) was added dropwise over a period of 5 min. The reaction mixture was stirred for additional 10 min at −15 °C, was then allowed to warm up to room temperature and stirred for 1 d. To the orange mixture 1-bromooctane (5.91 g, 30.0 mmol, 1.00 eq.) was added dropwise over a period of 10 min. The mixture was stirred for 1 d and quenched with ice. After separating the phases, the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were washed with aqueous saturated $NaHSO_3$ solution (40 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The yellow oil was purified first by flash chromatography (silica gel, 27×4 cm, *n*pentane) and subsequent bulb to bulb distillation (0.3 torr, 65 °C), yielding the product **71** as a colorless oil (437 mg, 2.42 mmol, 8%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.29 (dd, $^{3,4}J_{HH}$ = 1.8, 0.7 Hz, 1H, OC*H*), 6.27 (dd, $^3J_{HH}$ = 3.1, 1.9 Hz, 1H, OCHC*H*), 5.97 (dd, $^{3,4}J_{HH}$ = 3.1, 0.8 Hz, 1H, $OC_{18}H_{17}CH$), 2.61 (t, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2), 1.63 (m_c, 2H, CH_2CH_2), 1.39–1.21 (m, 10H, CH_2), 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 156.8 (C_{furan}), 140.8 (O*C*H), 110.2 (OCH*C*H), 104.7 (OC(C_8H_{17})*C*H), 32.0 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2), 29.4 (*C*H_2), 28.2 (*C*H_2), 28.1 (*C*H_2), 22.8 (*C*H_2), 14.3 (*C*H_3); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 7.9 min), *m*/*z* (%) 180 (M^+, 14), 95 (25), 82 (31), 81 (100), 53 (19), 41 (20); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2951m, 2923s, 2853m, 1507m, 1465w, 1147w, 1074w, 1006w, 885w, 722s, 668s; **EA:** calculated for $C_{12}H_{20}O$: C = 79.94, H = 11.18; measured: C = 79.88, H = 11.02; R_f = 0.45 (silica gel, *n*pentane); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 95 °C, 45 min, 10 °C/min, 180 °C, 10 min): t_R = 20.2 min. The NMR spectra were consistent with the literature data.[76]

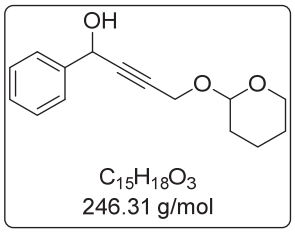
2-(Prop-2-yn-1-yloxy)tetrahydro-2H-pyran (77)



Following a modified procedure of EARL *et al.*,[77] in a 100 mL three-necked flask equipped with a thermometer and a reflux condenser, *p*TsOH·H_2O (2.30 g, 0.01 mmol, 0.002 mol%) was added to 3,4-dihydro-2Hpyran (45.9 g, 0.53 mol, 1.06 eq.) and heated to 60 °C. Propargyl alcohol (28.3 g, 0.50 mol, 1.00 eq.) was added *via* dropping funnel over a period of 35 min, while the inner temperature was kept at 60-65 °C. After complete addition, the reaction mixture was stirred at 60 °C for two more hours. Finally the mixture was neutralized with solid Na_2CO_3 (850 mg) and stirred for one hour at room temperature. The pale yellow mixture was filtered and distilled (1.0 torr, 54–57 °C) to give the product as a colorless oil (65.8 g, 0.47 mol, 94%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 4.81 (t, $^3J_{HH}$ = 3.4 Hz, 1H, C*H*), 4.25 (dq, $^{2,4}J_{HH}$ = 16.0, 2.4 Hz, 2H, CH_2), 3.83 (m$_c$, 1H, CH_2), 3.55–3.50 (m, 1H, CH_2), 2.40 (t, $^4J_{HH}$ = 2.4 Hz, 1H, C*H*), 1.88–1.69 (m, 2H, CH_2), 1.66–1.47 (m, 4H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 97.0 (*C*H), 79.9 (*C*$_q$), 74.1 (*C*H), 62.1 (*C*H_2), 54.1 (*C*H_2), 30.3 (*C*H_2), 25.5 (*C*H_2), 19.1 (*C*H_2); **GC-MS** (EI, 70 eV, Me_2Si, 80 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 4.9 min), *m*/*z* (%) 139 (11), 85 (100), 83 (13), 82 (15), 81 (12), 69 (12), 67 (14), 57 (36), 56 (47), 55 (50), 54 (16), 53 (23), 43 (23), 42 (16), 41 (79); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3286w, 2942m, 2927m, 2879w, 2852w, 1454w, 1441w, 1390w, 1345w, 1264w, 1202m, 1183w, 1119s, 1079m, 1057m, 1023s, 975w, 947m, 901s, 870s, 816m, 621m, 607m, 602w, 509s, 506s; ***R**$_f$* = 0.43 (silica gel, cyclohexane:EtOAc, 10:1). The NMR spectra were consistent with the literature data.[77]

1-Phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol (77a)

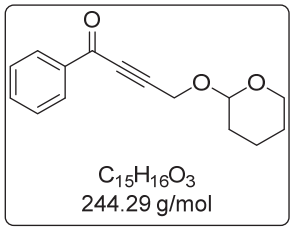


Following a modified procedure of OBRECHT *et al.*,[37] in a 100 mL three-necked flask 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (1.57 g, 11.2 mmol, 1.00 eq.) was dissolved in THF (30 mL) and cooled to −78 °C. Then *n*BuLi (1.6 M in hexanes, 7.70 mL, 12.3 mmol, 1.10 eq.) was added dropwise over a period of 15 min. After the addition was completed, the pale yellow reaction mixture was warmed to −30 °C and stirred for 30 min at this temperature. Then, benzaldehyde (1.36 g, 12.7 mmol, 1.13 eq.) was added at −78 °C and the resulting reaction mixture was stirred for 30 min. Finally the mixture was warmed to 0 °C, stirred for 30 min and transferred to a separation funnel containing a mixture of Et_2O (50 mL), aqueous

saturated NH_4Cl solution (30 mL) and ice. After phase separation, the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phases were washed with brine (2×50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The yellow oil was purified by flash chromatography (silica gel, 40×4 cm, cyclohexane:EtOAc, 5:1) to give the product as a yellow oil (2.67 g, 10.8 mmol, 96%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.54 (d, $^3J_{HH}$ = 6.9 Hz, 2H, HC_{ar}), 7.40–7.31 (m, 3H, 3 HC_{ar}), 5.52 (dt, $^{3,4}J_{HH}$ = 6.2, 1.8 Hz, 1H, CH), 4.82 (t, $^3J_{HH}$ = 3.4 Hz, 1H, CH), 4.36 (qt, $^{2,4}J_{HH}$ = 16.0, 1.7 Hz, 2H, CH_2), 3.84 (m_c, 1H, CH_2), 3.55–3.50 (m, 1H, CH_2), 2.33 (d, $^3J_{HH}$ = 6.1 Hz, 1H, OH), 1.89–1.69 (m, 2H, CH_2), 1.67–1.48 (m, 4H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 140.5 (C_{ar}), 128.8 (2 HC_{ar}), 128.6 (HC_{ar}), 126.8 (2 HC_{ar}), 97.0 (*C*H), 85.8 (C_q), 82.9 (C_q), 64.8 (*C*H), 62.2 (CH_2), 54.5 (CH_2), 30.4 (CH_2), 25.5 (CH_2), 19.2 (CH_2); **MS** (FAB), *m*/*z* (%) 229 (14), 145 (37), 128 (10), 117 (19), 85 (100); **IR** ($\tilde{\nu}$[cm^{-1}]) 3403w, 2944m, 2870w, 2852w, 2228m, 1716m, 1643s, 1597s, 1580s, 1450s, 1443m, 1391w, 1353w, 1313s, 1259s, 1202m, 1176m, 1102s, 1070m, 1057m, 1031s, 1023s, 955m, 901s, 872m, 815m; **EA:** calculated for $C_{15}H_{18}O_3$: C = 73.15, H = 7.37; measured: C = 72.34, H = 7.59; R_f = 0.40 (silica gel, cyclohexane:EtOAc, 1:1). The NMR spectra were consistent with the literature data.[78]

1-Phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-one (77b)

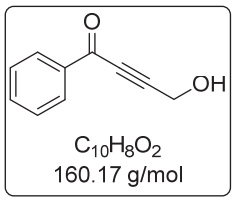


Following a modified procedure of OBRECHT *et al.*,[37] in a 250 mL two-necked flask 1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)-but-2-yn-1-ol (1.60 g, 6.51 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (100 mL) and MnO_2 (6.61 g, 66.9 mol, 10.3 eq.) was added. The suspension was stirred at room temperature for five hours and then filtered over a pad of celite. After removing the solvent under reduced pressure, the crude product was filtered over a pad of silica gel (1×5 cm) and washed with cyclohexane:EtOAc (10:1). The solvent was removed and the product was obtained as a yellow oil (1.54 g, 6.31 mmol, 97%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 8.14 (d, $^3J_{HH}$ = 7.1 Hz, 2H, HC_{ar}), 7.62 (tt, $^{3,4}J_{HH}$ = 7.4, 1.5 Hz, 1H, HC_{ar}), 7.50 (t, $^3J_{HH}$ = 7.7 Hz, 2H, HC_{ar}), 4.90 (t, $^3J_{HH}$ = 3.4 Hz, 1H, CH), 4.55 (s, 2H, CH_2), 3.88 (m_c, 1H, CH_2), 3.60–3.55 (m, 1H, CH_2), 1.91–1.74 (m, 2H, CH_2), 1.72–1.50 (m, 4H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 177.7

(*C*=O), 136.6 (*C*$_{ar}$), 134.4 (H*C*$_{ar}$), 129.8 (2 H*C*$_{ar}$), 128.7 (2 H*C*$_{ar}$), 97.5 (*C*H), 90.6 (*C*$_q$), 83.7 (*C*$_q$), 62.3 (*C*H$_2$), 54.2 (*C*H$_2$), 30.3 (*C*H$_2$), 25.4 (*C*H$_2$), 19.1 (*C*H$_2$); **GC-MS** (EI, 70 eV, Me$_2$Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 16.4 min), *m*/*z* (%) 159 (14), 144 (55), 131 (15), 116 (15), 115 (100), 114 (13), 105 (32), 89 (14), 85 (15), 77 (46), 66 (22), 63 (10), 55 (19), 53 (11), 51 (32), 50 (16), 41 (34); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2942m, 2869w, 2851w, 2360w, 2228m, 1723w, 1643s, 1597s, 1581s, 1449s, 1390w, 1344m, 1313s, 1260s, 1202s, 1175m, 1120s, 1099m, 1027s, 901s; R_f = 0.15 (silica gel, cyclohexane:EtOAc, 10:1). The NMR spectra were consistent with the literature data.[78]

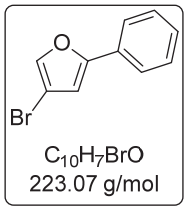
4-Hydroxy-1-phenylbut-2-yn-1-one (78)



Following a modified procedure of OBRECHT *et al.*,[37] in a 100 mL three-necked flask equipped with a reflux condenser, 1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-one (1.54 g, 6.31 mmol, 1.00 eq.) was dissolved in EtOH (30 mL) and PPTS[79] (323 mg, 1.29 mol, 20.4 mol%) was added. The reaction mixture was stirred at 60 °C for two hours and then quenched with water (60 mL). After separation of the phases, the aqueous phase was extracted with EtOAc (2×60 mL) and the combined organic phases were washed with brine (2×60 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, cyclohexane:EtOAc, 10:1) to give the product as a brown oil (827 mg, 5.16 mmol, 82%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 8.14 (d, $^3J_{HH}$ = 7.1 Hz, 2H, *H*C$_{ar}$), 7.62 (tt, $^{2,3}J_{HH}$ = 7.4, 1.5 Hz, 1H, *H*C$_{ar}$), 7.49 (t, $^3J_{HH}$ = 7.7 Hz, 2H, *H*C$_{ar}$), 4.57 (s$_{br}$, 2H, C*H*$_2$), 2.19 (s$_{br}$, 1H, O*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 177.8 (*C*=O), 136.4 (*C*$_{ar}$), 134.5 (H*C*$_{ar}$), 129.8 (2 H*C*$_{ar}$), 128.8 (2 H*C*$_{ar}$), 92.2 (*C*$_q$), 83.5 (*C*$_q$), 51.2 (*C*H$_2$); **GC-MS** (EI, 70 eV, Me$_2$Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 11.9 min), *m*/*z* (%) 160 (M$^+$, 45), 131 (74), 104 (38), 77 (100), 51 (83), 50 (50); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3403w, 3061w, 2908w, 2857w, 2464w, 2230w, 1775w, 1639s, 1595s, 1579s, 1448s, 1312s, 1260s, 1175m, 1102m, 1095m, 1069m, 1023s, 1000m, 900m, 796w, 762w, 732m; R_f = 0.39 (silica gel, cyclohexane:EtOAc, 1:1). The NMR spectra were consistent with the literature data.[37]

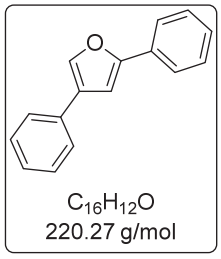
4-Bromo-2-phenylfuran (75)



Following a modified procedure of OBRECHT *et al.*,[37] in a 100 mL three-necked flask equipped with a thermometer and a reflux condenser, 4-hydroxy-1-phenylbut-2-yn-1-one (827 mg, 5.16 mmol, 1.00 eq.) was dissolved in dry toluene (60 mL) and 48% aqueous HBr solution (10.0 mL, 88.4 mmol, 17.1 eq.) was added dropwise. The reaction mixture was heated to 50 °C and stirred for three hours. After cooling to room temperature, it was diluted with EtOAc (200 mL) and poured onto ice. After separation of the phases, the aqueous phase was extracted with EtOAc (2×100 mL) and the combined organic phases were washed with brine (100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 40×4 cm, *n*pentane) to give the product as colorless crystals (417 mg, 1.87 mmol, 36%).

m.p. 43–44 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.64–7.61 (m, 2H, *H*C$_{ar}$), 7.47 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OC*H*), 7.42–7.37 (m, 2H, *H*C$_{ar}$), 7.30 (tt, $^{3,4}J_{HH}$ = 7.4, 1.5 Hz, 1H, *H*C$_{ar}$), 6.69 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OCC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 154.9 (O*C*(C_6H_5)), 140.3 (OCH), 129.9 (*C*$_{ar}$), 128.9 (2 H*C*$_{ar}$), 128.3 (H*C*$_{ar}$), 124.0 (2 H*C*$_{ar}$), 108.4 (OC*C*H), 101.6 (*C*Br); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 10.0 min), *m*/*z* (%) 224, 222 (M^+, 61), 143 (16), 116 (11), 115 (100), 114 (22), 113 (12), 89 (12), 77 (14), 63 (16), 62 (10), 51 (16), 50 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3146w, 3114w, 3075w, 3035w, 2360w, 2344w, 1971w, 1895w, 1773w, 1709w, 1608w, 1585m, 1568m, 1515m, 1476m, 1445m, 1350m, 1309w, 1284w, 1275m, 1202m, 1179w, 1145m, 1121m, 1070m, 1034m, 1015m, 1000w, 979w, 924s, 907s, 799m, 757s; R_f = 0.25 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[37]

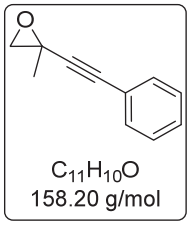
2,4-Diphenylfuran (79)



Compound **79** was synthesized following the procedure described for the synthesis of 3-phenylfuran (**41a**) using Ni(dppe)Cl_2 (24.3 mg, 0.05 mmol, 2.96 mol%), 4-bromo-2-phenylfuran (347 g, 1.55 mmol, 1.00 eq.) and phenylmagnesium bromide (1.0 M in THF, 1.71 mL, 1.71 mmol, 1.10 eq.). The crude crystals were purified by flash chromatography (silica gel, 40×4 cm, cyclohexane:EtOAc, 20:1) and subsequent bulb to bulb distillation (0.2 torr, 160 °C) to give the product as colorless crystals (84.2 mg, 0.38 mmol, 25%).

m.p. 108–109 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.76 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OC*H*), 7.74–7.72 (m, 2H, *H*C$_{ar}$), 7.56–7.53 (m, 2H, *H*C$_{ar}$), 7.44–7.39 (m, 4H, *H*C$_{ar}$), 7.31–7.27 (m, 2H, *H*C$_{ar}$), 6.97 (d, $^4J_{HH}$ = 0.9 Hz, 1H, OCC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 155.0 (O*C*(C$_6$H$_5$)), 138.0 (O*C*H), 132.5 (*C*$_{ar}$), 130.8 (*C*$_{ar}$), 129.0 (2 H*C*$_{ar}$), 128.9 (2 H*C*$_{ar}$), 128.5 (OCH*C*), 127.7 (H*C*$_{ar}$), 127.3 (H*C*$_{ar}$), 126.0 (2 H*C*$_{ar}$), 124.0 (2 H*C*$_{ar}$), 104.1 (OC*C*H); **MS** (EI), *m*/*z* (%) 220 (M^+, 100), 192 (20), 191 (81), 190 (14), 189 (36), 165 (28), 63 (10); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3035w, 2357m, 2342m, 1962w, 1946w, 1886w, 1743w, 1609m, 1538m, 1488m, 1452s, 1445m, 1363m, 1199m, 1185w, 1146m, 1102w, 1074m, 1059m, 1016s, 999m, 966m, 930s, 912s, 906s, 891m, 872m, 853w; ***R**$_f$* = 0.41 (silica gel, cyclohexane:EtOAc, 20:1); **GC** (6-Methyl-2,3-pentyl-γ-cyclodextrin, (60% in polysiloxane PS086), 30 m × 0.25 mm × 0.125 µm, 60 kPa H_2, 95 °C, 30 min, 5.0 K/min, 180 °C, 30 min): t_R = 65.4 min.

2-Methyl-2-(2-phenylethynyl)oxirane (83)

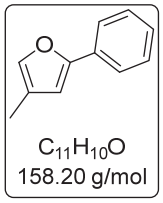


Following a modified procedure of LIGHTBURN *et al.*,[38b] in a 50 mL three-necked flask equipped with a thermometer phenyl acetylene (1.10 mL, 9.82 mmol, 1.00 eq.) was dissolved under argon in dry THF (25 mL) and cooled to −30° C. At this temperature *n*BuLi (1.6 M in hexanes, 6.60 mL, 10.6 mmol, 1.08 eq.) was added dropwise over a period of 30 min and the reaction mixture was then cooled to −78° C. Chloroacetone (0.85 mL, 10.2 mmol, 1.04 eq.) was added to the yellow solution over a period of 10 min, the cooling bath was removed and the dark red mixture was stirred at room temperature for 1 d. The reaction mixture was quenched with aqueous saturated NH_4Cl solution (50 mL) and ice, transferred to a separation funnel and rinsed with THF (25 mL). After the phases were separated, the aqueous phase was extracted with Et_2O (3×50 mL) and

the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash chromatography (silica gel, 40×4 cm, cyclohexane:EtOAc, 20:1) gave the product **83** as a pale yellow oil (1.10 g, 6.97 mmol, 71%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.45–7.41 (m, 2H, HC_{ar}), 7.35–7.28 (m, 3H, HC_{ar}), 3.13 (dq, $^{2,4}J_{HH}$ = 5.6, 0.8 Hz, 1H, CH_2), 2.85 (d, $^2J_{HH}$ = 5.6 Hz, 1H, CH_2), 1.66 (d, $^4J_{HH}$ = 0.5 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 132.0 (2 HC_{ar}), 128.8 (HC_{ar}), 128.4 (2 HC_{ar}), 122.3 (C_{ar}), 88.5 (C_q), 82.2 (C_q), 55.9 (CH_2), 47.8 (C_q), 23.2 (CH_3); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 12.3 min), *m*/*z* (%) 158 (M^+, 55), 130 (14), 129 (82), 128 (100), 127 (46), 115 (32), 103 (11), 102 (18), 77 (25), 74 (11), 63 (14), 51 (23), 50 (13); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3058w, 2988w, 1597w, 1491m, 1444w, 1380w, 1337m, 1292w, 1191w, 1066w, 907w, 813w, 757m, 694w; **EA:** calculated for $C_{11}H_{10}O$: C = 83.52, H = 6.37; measured: C = 83.34, H = 6.53; R_f = 0.17 (silica gel, cyclohexane:EtOAc, 20:1). The NMR spectra were consistent with the literature data.[80]

2-Phenyl-4-methylfuran (85)

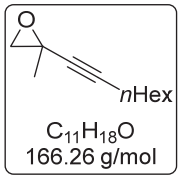


Following a modified procedure of BLANC *et al.*,[38a] in a 250 mL three-necked flask 2-methyl-2-(2-phenylethynyl)oxirane (**83**) (2.77 g, 17.5 mmol, 1.00 eq.) was dissolved in CH_2Cl_2/MeOH (100 mL, 9/1 v/v). To this mixture successively *p*TsOH (169 mg, 0.88 mmol, 5.01 mol%) and then AgOTf (230 mg, 0.88 mmol, 5.02 mol%) were added. The resulting mixture was stirred at room temperature for 1 d. The reaction mixture was filtered over a pad of silica gel (5×5 cm) and washed with CH_2Cl_2 (5×50 mL). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, 30×5 cm, *n*pentane) to give the title compound **85** as colorless oil (1.42 g, 8.98 mmol, 51%).

^{1}H-NMR (400.1 MHz, DMSO, 300 K): δ (ppm) 7.65 (dd, $^{3,4}J_{HH}$ = 8.3, 1.1 Hz, 2H, HC_{ar}), 7.50 (s, 1H, OCC*H*), 7.40 (t, $^3J_{HH}$ = 7.8 Hz, 2H, HC_{ar}), 7.27 (t, $^3J_{HH}$ = 7.4 Hz, 1H, HC_{ar}), 6.81 (s, 1H, OC*H*), 2.03 (d, $^4J_{HH}$ = 1.0 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, DMSO, 300 K): δ (ppm) 152.8 (O*C*(C_6H_5)), 139.3 (OCH), 130.4 (OCH*C*), 128.7 (2 HC_{ar}), 127.2 (HC_{ar}), 123.1 (2 HC_{ar}), 121.6 (C_{ar}), 108.3 (OC(C_6H_5)CH), 9.48 (CH_3); **MS** (EI), *m*/*z* (%) 158 (M^+, 100), 129 (51), 128 (25), 127 (11), 115 (23); **IR** ($\tilde{\nu}$ [cm^{-1}]) 1756s, 1701m, 1597m, 1580w, 1448m, 1351w, 1225w, 1058m, 982m, 914m, 752s, 725m, 694s; **EA:** calculated for

$C_{11}H_{10}O$: C = 83.52, H = 6.37; measured: C = 82.65, H = 6.31; R_f = 0.28 (silica gel, *n*pentane); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min): t_R = 14.7 min; **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 40 kPa H_2, 90 °C, 10 min, 0.1 °C/min, 92 °C, 10 °C/min, 180 °C, 10 min): t_R = 36.4 min. The NMR spectra were consistent with the literature data.[81]

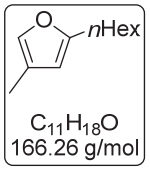
2-Methyl-2-(oct-1-yn-1-yl)oxirane (84)



Compound **84** was synthesized following the procedure described for the preparation of 2-methyl-2-(2-phenylethynyl)oxirane (**83**) using 1-octyne (1.50 mL, 9.97 mmol, 1.00 eq.), *n*BuLi (1.6 M in hexanes, 6.50 mL, 10.4 mmol, 1.04 eq.) and chloroacetone (0.85 mL, 10.2 mmol, 1.03 eq.). The crude product was distilled (20 mbar, 120 °C) and chromatographed (silica gel, 40×4 cm, cyclohexane:EtOAc, 20:1) to give the pure compound **84** as a pale yellow oil (949 mg, 5.71 mmol, 57%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 2.96 (dd, $^{2,4}J_{HH}$ = 5.6, 0.5 Hz, 1H, CH_2), 2.72 (d, $^2J_{HH}$ = 5.6 Hz, 1H, CH_2), 2.17 (t, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.48 (dd, $^{2,3}J_{HH}$ = 14.9, 7.4 Hz, 2H, CH_2), 1.39–1.26 (m, 6H, CH_2), 0.88 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 83.4 (C_q), 79.5 (C_q), 55.8 (CH_2), 47.7 (C_q), 31.4 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 18.8 (CH_2), 14.2 (CH_3); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 7.2 min), *m*/*z* (%) 109 (13), 97 (16), 96 (29), 93 (100), 91 (11), 82 (11), 81 (31), 79 (32), 77 (27), 68 (34), 67 (85), 66 (21), 65 (30), 55 (24), 53 (37), 52 (11), 51 (22), 43 (20), 41 (81); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2955m, 2932m, 2858m, 2355m, 1684w, 1466w, 1379w, 1339w; **EA:** calculated for $C_{11}H_{18}O$: C = 79.47, H = 10.91; measured: C = 79.40, H = 10.77; R_f = 0.21 (silica gel, cyclohexane:EtOAc, 20:1).

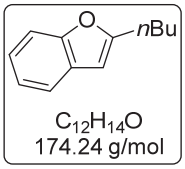
2-Hexyl-4-methylfuran (86)



Compound **86** was synthesized following the procedure described for the preparation of 2-phenyl-4-methylfuran (**85**) using 2-methyl-2-(oct-1-yn-1-yl)oxirane (**84**) (830 mg, 4.99 mmol, 1.00 eq.), *p*TsOH (48.7 mg, 0.25 mmol, 5.05 mol%) and AgOTf (69.6 mg, 0.27 mmol, 5.32 mol%). The crude residue was purified by flash chromatography (silica gel, 40×4 cm, *n*pentane) to give the title compound (403 mg, 2.43 mmol, 49%) as a colorless liquid.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.05 (t, $^4J_{HH}$ = 0.9 Hz, 1H, OC*H*), 5.84 (s, 1H, C*H*), 2.56 (t, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2), 1.99 (d, $^4J_{HH}$ = 0.9 Hz, 3H, CH_3), 1.61 (m_c, 2H, CH_2), 1.36–1.26 (m, 6H, CH_2), 0.89 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 156.8 (O*C*(C_6H_{13})), 137.3 (O*C*H), 120.5 (OCH*C*), 107.5 (OC(C_6H_{13})*C*H), 31.8 (*C*H_2), 29.1 (*C*H_2), 28.2 (*C*H_2), 28.1 (*C*H_2), 22.7 (*C*H_2), 14.2 (*C*H_3), 10.0 (*C*H_3); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 9.6 min), *m*/*z* (%) 166 (M^+, 23), 109 (22), 95 (100), 67 (21), 41 (27); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2955m, 2924m, 2858m, 2358w, 1618w, 1553w, 1458w, 1377w, 1122w, 935w, 798w, 737w; **EA:** calculated for $C_{11}H_{18}O$: C = 79.47, H = 10.91; measured: C = 79.67, H = 10.78; R_f = 0.33 (silica gel, *n*pentane); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 90 °C, 32 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 250 °C, 10 min): t_R = 27.2 min; **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 40 kPa H_2, 90 °C, 10 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 180 °C, 10 min): t_R = 21.4 min.

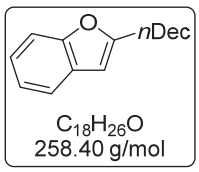
2-Butylbenzofuran (91)



Following a modified procedure of ORTEGA *et al.*,[33] in an 10 mL Schlenk tube benzofuran (0.22 mL, 2.02 mmol, 1.00 eq.) was dissolved in THF (4 mL) under argon and cooled to −78 °C. Then *n*BuLi (1.6 M in hexanes, 1.50 mL, 2.40 mmol, 1.19 eq.) was added *via* syringe, the mixture was stirred for another two hours at this temperature and then 1-bromobutane (0.32 mL, 2.94 mmol, 1.45 eq.) was added. The reaction was stirred at room temperature for 1 d, quenched with 10 mL water and transferred to a separation funnel. After extraction with MTBE (3×10 mL), the combined organic phases were dried over $MgSO_4$, filtered and concentrated to give the crude product. Flash chromatography (silica gel, 24×4 cm, *n*pentane) and subsequent bulb to bulb distillation (20 mbar, 100 °C) gave the desired product (106 mg, 0.61 mmol, 30%) as a colorless liquid.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.49–7.47 (m, 1H, HC_{ar}), 7.42–7.40 (m, 1H, HC_{ar}), 7.23–7.15 (m, 2H, HC_{ar}), 6.38 (d, $^4J_{HH}$ = 0.6 Hz, 1H, OCC*H*), 2.78 (t, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2), 1.74 (m_c, 2H, CH_2), 1.44 (m_c, 2H, CH_2), 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.9 (O*C*), 154.8 (O*C*), 129.2 (C_{ar}), 123.1 (HC_{ar}), 122.5 (HC_{ar}), 120.3 (HC_{ar}), 110.8 (HC_{ar}), 101.9 (OC*C*H), 30.1 (*C*H_2), 28.3 (*C*H_2), 22.4 (*C*H_2), 14.0 (*C*H_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 10.3 min), *m*/*z* (%) 174 (M^+, 24), 132 (35), 131 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2957m, 2930m, 2860w, 2330w, 1601m, 1587m, 1555m, 1452s, 1252m, 1169m, 1024m, 945m, 930m, 878m, 793m, 737s, 502s; $\boldsymbol{R_f}$ = 0.27 (silica gel, *n*pentane); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 210 and 240 nm): t_R = 8.1 min. The NMR spectra were consistent with the literature data.[33]

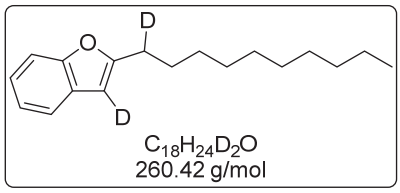
2-Decylbenzofuran (92)



Compound **92** was synthesized following the procedure decribed for the preparation of 2-butylbenzofuran (**91**) using benzofuran (**90**) (0.22 mL, 2.02 mmol, 1.00 eq.), *n*BuLi (1.6 M in hexanes, 1.70 mL, 2.72 mmol, 1.35 eq.) and 1-bromodecane (2.20 mL, 10.3 mmol, 5.11 eq.). Flash chromatography (silica gel, 19×2 cm, *n*pentane) and subsequent bulb to bulb distillation (0.1 torr, 80 °C) gave the desired product (177 mg, 0.60 mmol, 30%) as a colorless liquid.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.49–7.46 (m, 1H, HC_{ar}), 7.42–7.40 (m, 1H, HC_{ar}), 7.22–7.15 (m, 2H, HC_{ar}), 6.37 (d, $^4J_{HH}$ = 0.9 Hz, 1H, OCC*H*), 2.76 (t, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2), 1.74 (m_c, 2H, CH_2), 1.91–1.45 (m, 14H, CH_2), 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.9 (O*C*), 154.7 (O*C*), 129.2 (C_{ar}), 123.1 (HC_{ar}), 122.5 (HC_{ar}), 120.3 (HC_{ar}), 110.8 (HC_{ar}), 101.9 (OC*C*H), 32.1 (*C*H_2), 29.8 (*C*H_2), 29.7 (*C*H_2), 29.5 (*C*H_2), 29.5 (*C*H_2), 29.4 (*C*H_2), 28.6 (*C*H_2), 27.9 (*C*H_2), 22.8 (*C*H_2), 14.3 (*C*H_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 20.6 min), *m*/*z* (%) 258 (M^+, 25), 145 (10), 132 (52), 131 (100), 107 (10), 95 (25); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2922m, 2853w, 1603w, 1562s, 1556s, 1454m, 1252w, 1024w, 932w, 880w, 791w, 748m, 737m; $\boldsymbol{R_f}$ = 0.31 (silica gel, *n*pentane); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 210 and 240 nm): t_R = 7.8 min. The NMR spectra were consistent with the literature data.[33]

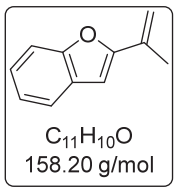
2-(Decyl-1-*d*)benzofuran-3-*d* (*d*-92)



In a 2 mL vial with a stirring bar, 2-decylbenzofuran (**92**) (25 mg, 0.1 mmol) and [Ir(**L2c**)COD]BAr_F (1 mol%) were dissolved in dry CH_2Cl_2 (0.5 mL) and the vial was placed in an autoclave. It was stirred at 30 bar of D_2 pressure and 60 °C for 4 h. The reaction mixture was concentrated, the residue redissolved in a *n*hexane/MTBE (4/1) mixture and filtered through a pasteur pipette filled with silica gel (ca. 5 cm). The filtrate was concentrated and the mixture of fully hydrogenated deuterated compound and ***d*-92** (71:29, GC-MS) was separated by flash chromatography (silica gel, *n*pentane). Benzofuran ***d*-92** was obtained as a colorless oil, which shows deuterium incorporation at C3 (89%) and on the alkyl chain (74%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.49–7.46 (m, 1H, HC_{ar}), 7.42–7.40 (m, 1H, HC_{ar}), 7.22–7.15 (m, 2H, HC_{ar}), 2.76 (t, $^3J_{HH}$ = 7.6 Hz, 1H, CH_2), 1.74 (m_c, 2H, CH_2), 1.91–1.45 (m, 14H, CH_2), 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{2}H-NMR** (76.8 MHz, $CDCl_3$ in $CHCl_3$, 300 K): δ (ppm) 6.43 (s, 1D), 2.76 (s, 0.8D); **^{13}C{^{1}H/^{2}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.6 (OC), 154.5 (OC), 128.9 (C_{ar}), 122.9 (HC_{ar}), 122.3 (HC_{ar}), 120.0 (HC_{ar}), 110.6 (HC_{ar}), 101.4 (OCCD), 31.8 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.0 (CHD), 27.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 10.2 min), *m*/*z* (%) 260 (M^+, 22), 146 (11), 134 (48), 133 (100), 132 (44), 96 (17), 95 (16), 81 (10), 41 (10).

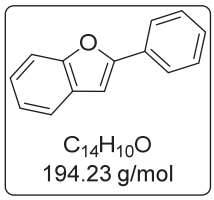
2-(Prop-1-en-2-yl)benzofuran (93)



In a 5 mL Schlenk tube benzofuran (0.20 mL, 1.84 mmol, 1.00 eq.) was dissolved in 4 mL THF under argon and cooled to −78 °C. Then *n*BuLi (1.6 M in hexanes, 1.70 mL, 2.72 mmol, 1.48 eq.) was added *via* syringe, the mixture was stirred for 2.5 hours at this temperature, then acetone (0.68 mL, 9.20 mmol, 5.01 eq.) was added. After stirring for 22 hours at room temperature, the reaction was quenched with aqueous 3 M HCl solution (10 mL) and transferred to a separation funnel. After phase separation, the organic phase was extracted with MTBE (2×20 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product. Flash chromatography (silica gel, 21×2 cm, *n*pentane) gave the desired product as a pale yellow oil (205 mg, 1.30 mmol, 71%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.46 (ddd, $^{3,4}J_{HH}$ = 7.6, 1.3, 0.6 Hz, 1H, *H*C$_{ar}$), 7.37 (dd, $^{3,4}J_{HH}$ = 8.0, 0.8 Hz, 1H, *H*C$_{ar}$), 7.21–7.17 (m, 1H, *H*C$_{ar}$), 7.12 (dt, $^{3}J_{HH}$ = 7.5, 1.0 Hz, 1H, *H*C$_{ar}$), 6.57 (s, 1H, OCC*H*), 5.72 (s, 1H, CH_2), 5.10 (m$_c$, 1H, CH_2), 2.06 (s, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 157.0 (*C*$_{ar}$), 154.9 (*C*$_{ar}$), 133.0 (*C*$_q$), 129.1 (*C*$_{ar}$), 124.7 (HC$_{ar}$), 122.8 (HC$_{ar}$), 121.1 (HC$_{ar}$), 113.4 (*C*H$_2$), 111.1 (HC$_{ar}$), 102.9 (O*C*H), 19.5 (*C*H$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 7.0 min), *m*/*z* (%) 159 (13), 158 (M$^+$, 100), 157 (15), 143 (35), 131 (10), 128 (11), 118 (12), 115 (23); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2946w, 2921m, 2852w, 1555m, 1473w, 1452s, 1439w, 1379w, 1337w, 1300m, 1257s, 1171s, 1146w, 1112m, 1096m, 1007w, 955m, 892m, 885m, 804s, 752m, 740s; ***R**$_f$* = 0.31 (silica gel, *n*pentane); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 24 °C, 230 nm): t_R = 8.1 min. The NMR spectra were consistent with the literature data.[82]

2-Phenylbenzofuran (95a)

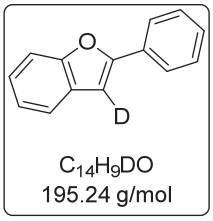


Following a modified procedure of SUZUKI *et al.*,[83] in a 25 mL Schlenk tube benzofuran-2-boronic acid (200 mg, 1.21 mmol, 1.05 eq.), $Pd(OAc)_2$ (24.7 mg, 0.11 mmol, 9.34 mol%), sodium carbonate (237 mg, 2.24 mmol, 1.94 eq.) and iodobenzene (0.13 mL, 1.15 mmol, 1.00 eq.) were dissolved in 6.5 mL acetone and 7.5 mL water. The black mixture was stirred at room temperature for five hours. Water (20 mL) was added to the reaction mixture and transferred to a separation funnel. After extraction with CH_2Cl_2 (3×20 mL), the combined organic phases were dried over $MgSO_4$, filtered and concentrated to give the crude product. Flash chromatography (silica gel, 21×3 cm, *n*pentane) gave the desired product as a colorless solid (180 mg, 0.93 mmol, 77%).

m.p. 117–118 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.88 (dd, $^{3,4}J_{HH}$ = 8.2, 1.0 Hz, 2H, *H*C$_{ar}$), 7.60–7.58 (m, 1H, *H*C$_{ar}$), 7.53 (dd, $^{3,4}J_{HH}$ = 8.1, 0.7 Hz, 1H, *H*C$_{ar}$), 7.46 (m$_c$, 2H, *H*C$_{ar}$), 7.36 (m$_c$, 1H, *H*C$_{ar}$), 7.29 (m$_c$, 1H, *H*C$_{ar}$), 7.26–7.22 (m, 1H, *H*C$_{ar}$), 7.04 (d, $^{4}J_{HH}$ = 0.8 Hz, 1H, OCC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 156.1 (O*C*), 155.0 (O*C*), 130.6 (*C*$_{ar}$), 129.4 (*C*$_{ar}$), 128.9 (2 HC$_{ar}$), 128.7 (HC$_{ar}$), 125.1 (2 HC$_{ar}$), 124.1 (HC$_{ar}$), 123.1 (HC$_{ar}$), 121.0 (HC$_{ar}$), 111.3 (HC$_{ar}$), 101.4 (OCCH); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 9.2 min), *m*/*z* (%) 195 (16), 194 (M$^+$, 100), 165 (42), 97 (12), 82 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3052w, 1564m, 1558m, 1471m, 1456s, 1442m, 1351m, 1305m, 1295m, 1272w, 1258m, 1208m, 1169m, 1146w, 1105m, 1074m, 1039s, 1020s, 1005m, 932m, 919s, 882m, 865w,

852w, 805s, 761s, 740s, 689s, 678s, 660s; R_f = 0.26 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[33]

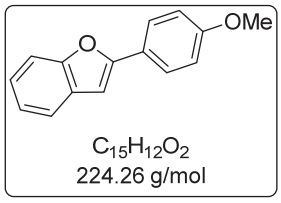
2-Phenylbenzofuran-3-*d* (*d*-95a)



In a 2 mL vial with a stirring bar, 2-phenylbenzofuran (**95a**) (11 mg, 0.05 mmol) and [Ir(**L2c**)COD]BAr_F (1 mol%) were dissolved in dry CH_2Cl_2 (0.25 mL) and the vial was placed in an autoclave. It was stirred at 40 bar of D_2 pressure and 60 °C for 24 h. The reaction mixture was concentrated, the residue redissolved in a *n*hexane/MTBE (4/1) mixture and filtered through a pasteur pipette filled with silica gel (ca. 5 cm). The filtrate was concentrated and compound ***d*-95a** was obatained as a colorless oil with deuterium incorporation at C3 (80%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.88 (dd, $^{3,4}J_{HH}$ = 8.2, 1.0 Hz, 2H, *H*C$_{ar}$), 7.60–7.58 (m, 1H, *H*C$_{ar}$), 7.53 (dd, $^{3,4}J_{HH}$ = 8.1, 0.7 Hz, 1H, *H*C$_{ar}$), 7.46 (m$_c$, 2H, *H*C$_{ar}$), 7.36 (m$_c$, 1H, *H*C$_{ar}$), 7.29 (m$_c$, 1H, *H*C$_{ar}$), 7.26–7.22 (m, 1H, *H*C$_{ar}$), 7.04 (d, $^4J_{HH}$ = 0.8 Hz, 0.2H, OCC*H*); **^{2}H-NMR** (76.8 MHz, $CDCl_3$ in $CHCl_3$, 300 K): δ (ppm) 7.09 (s, 1D); **^{13}C{^{1}H/^{2}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 156.0 (O*C*), 155.0 (O*C*), 130.6 (*C*$_{ar}$), 129.3 (*C*$_{ar}$), 128.9 (2 HC$_{ar}$), 128.7 (HC$_{ar}$), 125.1 (2 HC$_{ar}$), 124.4 (HC$_{ar}$), 123.1 (HC$_{ar}$), 121.0 (HC$_{ar}$), 111.3 (HC$_{ar}$), 101.2 (OC*C*D); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 9.2 min), *m*/*z* (%) 196 (18), 195 (M^+, 100), 194 (21), 166 (48), 165 (20), 98 (12), 83 (13).

2-(4-Methoxyphenyl)benzofuran (95b)

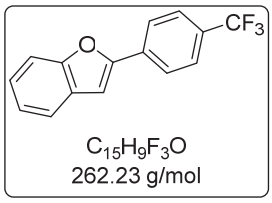


Compound **95b** was synthesized following the procedure for the preparation of 2-phenylbenzofuran (**95a**) using benzofuran-2-boronic acid (200 mg, 1.21 mmol, 1.08 eq.), $Pd(OAc)_2$ (24.8 mg, 0.11 mmol, 9.64 mol%), sodium carbonate (237 mg, 2.23 mmol, 1.99 eq.) and 4-iodoanisole (268 mg, 1.12 mmol, 1.00 eq.). Flash chromatography (silica gel, 25×3 cm, *n*pentane) gave the desired product as a colorless solid (48.3 mg, 0.21 mmol, 19%).

m.p. 134–135 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.80 (m$_c$, 2H, *H*C$_{ar}$), 7.57–7.49 (m, 2H, *H*C$_{ar}$), 7.25–7.19 (m, 2H, *H*C$_{ar}$), 6.98 (m$_c$, 2H, *H*C$_{ar}$), 6.89 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OCC*H*), 3.87 (s, 3H, C*H*$_3$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 160.1 (*C*$_{ar}$), 156.2 (*C*$_{ar}$), 155.4 (*C*$_{ar}$), 126.6 (2 HC$_{ar}$), 123.9 (HC$_{ar}$), 123.5 (*C*$_{ar}$), 123.0

(HCar), 120.7 (HCar), 114.4 (2 HCar), 111.1 (HCar), 99.8 (OCCH), 55.5 (CH_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 10.7 min), *m*/*z* (%) 225 (17), 224 (M^+, 100), 210 (11), 209 (71), 181 (33), 152 (20), 112 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2959w, 2931w, 2910w, 2898w, 2854w, 2837w, 1730m, 1722m, 1653w, 1608m, 1594m, 1587m, 1503s, 1465m, 1452s, 1440s, 1418s, 1322m, 1306m, 1297m, 1245s, 1210m, 1170m, 1111m, 1106m, 1040m, 1022s, 1006m, 933m, 919s, 885m, 834s, 819m, 803s, 798s, 780m, 749s, 741s, 637m, 623m, 611m, 534s, 523s, 519s, 515s, 504m; R_f = 0.30 (silica gel, *n*pentane:MTBE, 20:1). The NMR spectra were consistent with the literature data.[33]

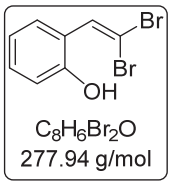
2-(4-(Trifluoromethyl))phenylbenzofuran (95c)



Compound **95c** was synthesized following the procedure for the preparation of 2-phenylbenzofuran (**95a**) using benzofuran-2-boronic acid (200 mg, 1.21 mmol, 1.08 eq.), $Pd(OAc)_2$ (25.3 mg, 0.11 mmol, 9.74 mol%), sodium carbonate (238 mg, 2.25 mmol, 1.98 eq.) and 4-iodobenzotrifluoride (315 mg, 1.13 mmol, 1.00 eq.). Flash chromatography (silica gel, 25×3 cm, *n*pentane) gave the desired product as a colorless solid (246 mg, 0.94 mmol, 83%).

m.p. 162–164 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.97 (d, $^3J_{HH}$ = 8.3 Hz, 2H, *H*Car), 7.70 (d, $^3J_{HH}$ = 8.4 Hz, 2H, *H*Car), 7.62 (d, $^3J_{HH}$ = 7.5 Hz, 1H, *H*Car), 7.55 (d, $^3J_{HH}$ = 8.2 Hz, 1H, *H*Car), 7.36–7.24 (m, 2H, *H*Car), 7.15 (s, 1H, OCC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 155.3 (*C*ar), 154.4 (*C*ar), 133.8 (*C*ar), 130.3 (q, $^2J_{CF}$ = 32.6 Hz, *C*CF_3), 129.0 (*C*ar), 125.9 (q, $^3J_{CF}$ = 3.8 Hz, 2 HCar), 125.3 (HCar), 125.1 (2 HCar), 124.2 (q, $^1J_{CF}$ = 271.8 Hz, *C*F_3), 123.4 (HCar), 121.5 (HCar), 111.5 (HCar), 103.4 (OCCH); **^{19}F{^{1}H}-NMR** (376.5 MHz, $CDCl_3$, 300 K): δ (ppm) −62.7 (C*F*$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 7.2 min), *m*/*z* (%) 263 (16), 262 (M^+, 100), 165 (25), 106 (14); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2922w, 2854w, 1615m, 1610w, 1566w, 1475w, 1450m, 1413m, 1320m, 1299m, 1277m, 1259m, 1189w, 1160s, 1148m, 1129w, 1103s, 1066m, 1043m, 1031m, 1012m, 976w, 961w, 937m, 920m, 885m, 856w, 848m, 841s, 803s, 770w, 745s, 725w, 708w, 689s, 657w, 635w, 612m, 577s; R_f = 0.26 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[33]

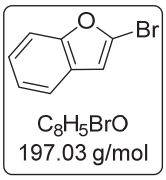
2-(2,2-Dibromovinyl)phenol (97)



Following a modified procedure of NEWMAN *et al.*,[84] in a 250 mL round bottom flask PPh_3 (9.79 g, 37.0 mmol, 6.01 eq.) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. Then CBr_4 (6.19 g, 18.5 mmol, 3.01 eq.) in CH_2Cl_2 (20 mL) was added. After 10 minutes NEt_3 (5.50 mL, 39.3 mmol, 6.39 eq.) was added followed by salicylaldehyde (0.60 mL, 6.15 mmol, 1.00 eq.) in CH_2Cl_2 (6 mL). The mixture was stirred for 30 min at 2 °C and then for two hours at room temperature. The reaction was quenched with aqueous saturated NH_4Cl solution (70 mL) and transferred to a separation funnel. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (2×70 mL) and the combined organic phases were concentrated to a total volume of 10 mL. Filtration of the crude product over a pad of silica gel (4×5 cm) and washing with CH_2Cl_2 (120 mL) and Et_2O (40 mL) gave a yellow oil which was chromatographed (silica gel, 22×4 cm, *n*pentane:EtOAc, 85:15) to give the product as a colorless solid (1.65 g, 5.94 mmol, 97%).

m.p. 58–60 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.56 (s, 1H, C*H*=CBr_2), 7.54 (dd, $^{3,4}J_{HH}$ = 7.8, 0.5 Hz, 1H, *H*C_{ar}), 7.26–7.22 (m, 1H, *H*C_{ar}), 6.96 (t, $^3J_{HH}$ = 7.6 Hz, 1H, *H*C_{ar}), 6.83 (dd, $^{3,4}J_{HH}$ = 8.1, 0.9 Hz, 1H, *H*C_{ar}), 4.96–4.92 (m, 1H, OH); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 152.6 (*C*$_{ar}$), 132.5 (*C*H=CBr_2), 130.2 (H*C*$_{ar}$), 129.4 (H*C*$_{ar}$), 123.0 (*C*$_{ar}$), 120.8 (H*C*$_{ar}$), 115.9 (H*C*$_{ar}$), 92.2 (CH=*C*Br_2); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 15.0 min), *m*/*z* (%) 278 (M^+, 20), 118 (100), 90 (19), 89 (25), 63 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 1556m, 1493w, 1445m, 1348w, 1339w, 1298w, 1232m, 1198w, 1178m, 1153w, 1091m, 1042m, 1001m, 914w, 878m, 835s, 824s, 756m, 745s, 719w, 600m, 571m, 507s; R_f = 0.31 (silica gel, *n*pentane:EtOAc, 85:15). The NMR spectra were consistent with the literature data.[84]

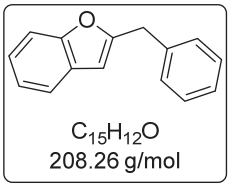
2-Bromobenzofuran (98)



Following a modified procedure of NEWMAN *et al.*,[84] in a 25 mL Young tube 2-(2,2-dibromovinyl)phenol (**97**) (991 mg, 3.57 mmol, 1.00 eq.), K_3PO_4 (1.55 g, 7.15 mmol, 2.00 eq.) and copper iodide (34.5 mg, 0.18 mmol, 5.00 mol%) were dissolved in THF (15 mL) and refluxed for six hours. The reaction mixture was then filtered over a pad of silica gel (2×5 cm), washed with MTBE (120 mL) and concentrated. The crude product was chromatographed (silica gel, 20×2 cm, *n*pentane) and the desired product was obtained as a colorless oil (660 mg, 3.35 mmol, 94%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.52–7.44 (m, 2H, *H*C$_{ar}$), 7.28–7.21 (m, 2H, *H*C$_{ar}$), 6.73 (d, $^4J_{HH}$ = 0.8 Hz, 1H, OCC*H*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 155.9 (*C*$_{ar}$), 128.9 (*C*$_{ar}$), 128.3 (*C*$_q$), 124.4 (HC$_{ar}$), 123.5 (HC$_{ar}$), 120.2 (HC$_{ar}$), 111.1 (HC$_{ar}$), 108.4 (OCBr*C*H); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 15.0 min), *m*/*z* (%) 197 (M^+, 60), 196 (60), 89 (100), 63 (20), 62 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2365w, 1616w, 1605w, 1537m, 1445s, 1250s, 1161s, 1088w, 1065s, 1024m, 930m, 918s, 880s, 789s, 735s, 602s; R_f = 0.41 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[84]

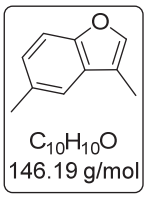
2-Benzylbenzofuran (99)



Following a modified procedure of ORTEGA *et al.*,[33] in a 10 mL Young tube zinc (571 mg, 8.51 mmol, 2.04 eq.) was heated with a heatgun for 15 minutes. After the flask had cooled to room temperature iodine (76.1 mg, 0.30 mmol, 7.19 mol%) and THF (4 mL) were added. As soon as the pale yellow color of the reaction mixture disappeared benzylbromide (0.73 mL, 5.98 mmol, 1.44 eq.) was added under argon and the resulting mixture was stirred at 70 °C overnight. In a 25 mL Young tube $Pd(OAc)_2$ (48.1 mg, 0.21 mmol, 5.04 mol%) and P(*o*Tol)$_3$ (124 mg, 0.40 mmol, 9.69 mol%) were dissolved in THF (12 mL). After 10 minutes 2-bromobenzofuran (829 mg, 4.17 mmol, 1.00 eq.) was added and the mixture was cooled to −10 °C. The previously prepared zinc compound was added over a period of 10 minutes at this temperature and the cooling bath was removed. The mixture was stirred for four hours, then filtered over a pad of silica gel (2×5 cm) and washed with EtOAc (2×50 mL). Flash chromatography (silica gel, 24×2 cm, *n*pentane) gave the desired product as a colorless oil (689 mg, 3.31 mmol, 79%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.49–7.40 (m, 2H, HC_{ar}), 7.36–7.26 (m, 5H, HC_{ar}), 7.19 (m_c, 2H, HC_{ar}), 6.38 (d, $^{4}J_{HH}$ = 0.8 Hz, 1H, OCC*H*), 4.12 (s, 2H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 157.9 (C_{ar}), 155.1 (C_{ar}), 137.4 (C_{ar}), 129.1 (2 HC_{ar}), 129.0 (C_{ar}), 128.8 (2 HC_{ar}), 126.9 (HC_{ar}), 123.6 (HC_{ar}), 122.7 (HC_{ar}), 120.5 (HC_{ar}), 111.1 (HC_{ar}), 103.5 (O*C*CH), 35.2 (CH_2); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 17.3 min), *m*/*z* (%) 209 (14), 208 (M^+, 95), 207 (100), 179 (10), 178 (20),131 (52), 89 (14), 77 (10); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3062w, 3029w, 2358w, 1740w, 1600w, 1584w, 1495w, 1472w, 1452s, 1420w, 1316w, 1252m, 1191w, 1164w, 1104w, 953m, 829w, 804w, 793w, 750m, 741m, 703m, 628m, 569m, 548m, 534s, 524s, 509m, 504s; R_f = 0.16 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[33]

3,5-Dimethylbenzofuran (56a)[85]

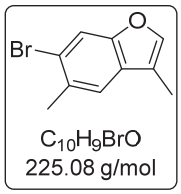


Following a modified procedure of COREY *et al.*,[41] a 250 mL three-necked round bottom flask equipped with a reflux condenser, was charged with sodium hydride (60% m/m; 252 mg, 6.30 mmol, 1.50 eq.), which was washed with *n*pentane (3×10 mL). Trimethyloxosulfonium iodide (1.40 g, 6.30 mmol, 1.50 eq.) was added and argon atmosphere was established in the reaction vessel. Absolute DMSO (50 mL) was slowly added and the resulting mixture was stirred for 45 min. After that a solution of 2-hydroxy-5-methylacetophenone (1.00 g, 4.20 mmol, 1.00 eq.) in absolute DMSO (25 mL) was added and the reaction mixture was stirred for 18 hours at 40 °C and then for 5.5 hours at 90 °C. It was extracted with Et_2O (3×30 mL), the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 17×2 cm, *n*pentane) to obtain the product as a colorless liquid (570 mg, 94% m/m, 3.90 mmol, 59%) containing traces of *n*pentane (6% m/m).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.37–7.31 (m, 3H, HC_{ar}), 7.10 (dd, $^{3,4}J_{HH}$ = 8.3, 1.3 Hz, 1H, OC*H*), 2.47 (s, 3H, CH_3), 2.23 (d, $^{4}J_{HH}$ = 1.3 Hz, 3H, OCHCCH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 153.8 (O*C*), 141.6 (OCH), 131.8 (OC*C*), 129.2 (*C*CH_3), 125.4 (HC_{ar}), 119.4 (HC_{ar}), 115.5 (OCH*C*CH_3), 110.9 (HC_{ar}), 21.5 (*C*H_3), 8.0 (*C*H_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 6.3 min), *m*/*z* (%) 146 (M^+, 100), 145 (99), 131 (21), 117 (23), 115 (24), 91 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2919w, 2862w, 2356w, 1456m, 1286m, 1186s, 1089s, 804m, 786m, 608m; **HRMS** (EI, 30 eV, 100 °C) calc. *m*/*z* for $C_{10}H_{10}O$: 146.0732,

found: 146.0731; R_f = 0.71 (silica gel, cyclohexane: EtOAc, 9:1); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 90 °C, 32 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 250 °C, 10 min): t_R = 55.3 min; **HPLC** (OJ, *n*heptane:*i*PrOH 100:0, 0.5 mL/min, 208 and 250 nm): t_R = 23.3 min.

6-Bromo-3,5-dimethylbenzofuran (56b)[85]

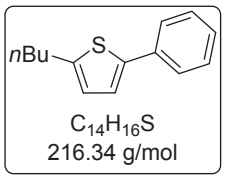


Compound **56b** was synthesized following the procedure described for the preparation of 3,5-dimethylbenzofuran (**56a**) using sodium hydride (60% m/m; 250 mg, 6.30 mmol, 1.50 eq.), trimethyloxosulfonium iodide (1.40 g, 6.30 mmol, 1.50 eq.) and 4-bromo-2-hydroxy-5-methylacetophenone (1.00 g, 4.20 mmol, 1.00 eq.). The crude product was purified by flash chromatography (silica gel, 11×2 cm, cyclohexane) to obtain the desired product as colorless crystals (428 mg, 1.90 mmol, 44%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.66 (s, 1H, *H*C$_{ar}$), 7.36 (s, 1H, *H*C$_{ar}$), 7.35 (dd, $^{3,4}J_{HH}$ = 2.5, 1.2 Hz, 1H, OC*H*), 2.49 (s, 3H, CH_3), 2.21 (d, $^4J_{HH}$ = 1.3 Hz, 3H, OCHCCH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 154.1 (O*C*), 142.1 (O*C*H), 131.5 (*C*$_{ar}$), 128.7 (*C*$_{ar}$), 120.4 (H*C*$_{ar}$), 115.4 (OCH*C*CH$_3$), 115.1 (H*C*$_{ar}$), 110.9 (H*C*$_{ar}$), 21.2 (*C*H$_3$), 8.0 (*C*H$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 7.9 min), *m*/*z* (%) 226 (85), 225 (M^+, 36), 224 (89), 223 (29), 146 (11), 145 (100), 116 (15), 115 (50), 91 (11), 72 (19); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3116w, 2975w, 2925w, 2855w, 2356w, 1576w, 1448s, 1377m, 1310m, 1281m, 1198w, 1161w, 1079s, 1036m, 1000m, 939m, 854s, 814s, 783s, 768s, 694s; **EA:** calculated for $C_{10}H_9BrO$: C = 53.36, H = 4.03; measured: C = 53.64, H = 4.13; R_f = 0.33 (silica gel, *n*pentane); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 90 °C, 32 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 250 °C, 10 min): t_R = 55.3 min, (hydrogenated product t_R = 55.9 min); **HPLC** (analyzed as 3,5-dimethyl-2,3-dihydrobenzofuran (**116**)).

7.5 Synthesis and Characterization of Substituted Thiophenes

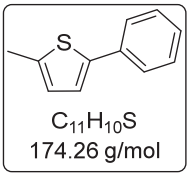
2-Butyl-5-phenylthiophene (134)



In a 25 mL Young tube 2-phenylthiophene (336 mg, 1.99 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (5 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 1.50 mL, 2.40 mmol, 1.20 eq.) was added dropwise *via* syringe. The green mixture was stirred for one hour and 1-bromobutane (0.27 mL, 2.41 mmol, 1.21 eq.) was added. The reaction mixture was stirred for 19 h at room temperature, quenched with water (5 mL) and transferred to a separation funnel. After separation of the phases, the aqueous phase was extracted with MTBE (3×5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained yellow oil was purified by flash chromatography (silica gel, 23×4 cm, *n*hexane:CH_2Cl_2, 95:5) to give the title compound **134** as colorless oil (431 mg, 1.99 mmol, 99%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.58–7.55 (m, 2H, *H*C$_{ar}$), 7.35 (m$_c$, 2H, *H*C$_{ar}$), 7.24 (m$_c$, 1H, *H*C$_{ar}$), 7.12 (d, $^3J_{HH}$ = 3.6 Hz, 1H, SC(C_6H_5)C*H*), 6.75 (d, $^3J_{HH}$ = 3.6 Hz, 1H, SC(C_4H_9)C*H*), 2.83 (t, $^3J_{HH}$ = 7.6 Hz, 2H, CH_2), 1.70 (m$_c$, 2H, CH_2), 1.43 (m$_c$, 2H, CH_2), 0.96 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 145.8 (S*C*(C_6H_5)), 141.8 (S*C*(C_4H_9)), 134.9 (*C*$_{ar}$), 128.9 (2 HC$_{ar}$), 127.1 (HC$_{ar}$), 125.6 (2 HC$_{ar}$), 125.1 (SC(C_4H_9)CH), 122.8 (SC(C_6H_5)CH), 33.9 (*C*H$_2$), 30.1 (*C*H$_2$), 22.4 (*C*H$_2$), 14.0 (*C*H$_3$); **MS** (EI), *m*/*z* (%) 216 (M^+, 33), 174 (13), 173 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3067w, 3025w, 2954w, 2927w, 2854w, 1599w, 1501m, 1466w, 1377w, 1073w, 1027w, 952w, 907m, 800w, 753s, 689m, 637w; R_f = 0.30 (silica gel, *n*hexane:CH_2Cl_2, 95:5). The NMR spectra were consistent with the literature data.[32]

2-Methyl-5-phenythiophene (135)

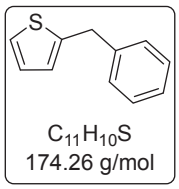


Following a modified procedure of FAGNOU *et al.*,[58] in a 25 mL Schlenk flask $Pd(OAc)_2$ (23.0 mg, 0.100 mmol, 2.20 mol%), PCy_3 (60.2 mg, 0.204 mmol, 4.48 mol%), potassium carbonate (1.04 g, 7.45 mmol, 1.64 eq.), and pivalic acid (165 mg, 1.60 mmol, 35.0 mol%) were dissolved under slightly positive argon flow in *N*,*N*-dimethylacetamid (12 mL). Also 2-methylthiophene (0.45 mL, 4.56 mmol, 1.00 eq.) and bromobenzene (0.53 mL, 4.98 mmol, 1.00 eq.) were added and the yellow reaction mixture was heated to 100 °C for 16 h. The mixture was allowed to cool to room temperature, diluted with EtOAc

(20 mL) and transferred to a separation funnel. After the organic phase was washed with water (3×30 mL), the aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained brown oil was purified by flash chromatography (silica gel, 23×4 cm, *n*pentane) to give the title compound **135** as colorless crystals (686 mg, 3.94 mmol, 86%).

m.p. 44–46 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.57–7.55 (m, 2H, *H*C$_{ar}$), 7.36 (m$_c$, 2H, *H*C$_{ar}$), 7.24 (m$_c$, 1H, *H*C$_{ar}$), 7.11 (d, $^3J_{HH}$ = 3.5 Hz, 1H, SC(C$_6$H$_5$)C*H*), 6.73 (dq, $^{3,4}J_{HH}$ = 3.5, 0.7 Hz, 1H, SC(CH$_3$)C*H*), 2.52 (s, 3H, C*H*$_3$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.1 (S*C*(C$_6$H$_5$)), 139.7 (S*C*(CH$_3$)), 134.9 (*C*$_{ar}$), 128.9 (2 HC$_{ar}$), 127.1 (HC$_{ar}$), 126.3 (SC(CH$_3$)*C*H), 125.6 (2 HC$_{ar}$), 123.0 (SC(C$_6$H$_5$)*C*H), 15.6 (*C*H$_3$); **MS** (EI), *m*/*z* (%) 175 (16), 174 (M$^+$, 100), 173 (93), 141 (16), 129 (10), 115 (11), 97 (10); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3058w, 2912w, 2855w, 1598w, 1498m, 1469w, 1443w, 1261w, 1211w, 1166w, 1154w, 1072w, 1027w, 945w, 901w, 872w, 799s, 747s, 737s, 683s, 670s; R_f = 0.23 (silica gel, *n*pentane). The NMR spectra were consistent with the literature data.[23a]

2-Benzylthiophene (139)

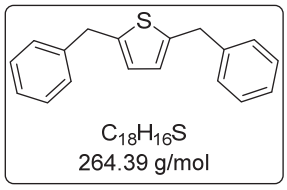


Following a modified procedure of HENRY *et al.*,[53] in a 25 mL Young tube benzylchloride (0.17 mL, 1.47 mmol, 1.00 eq.), sodium carbonate (335 mg, 3.16 mmol, 2.15 eq.), 2-thiophene boronic acid (238 mg, 1.81 mmol, 1.23 eq.) and $Pd(PPh_3)_4$ (37.0 mg, 0.03 mmol, 2.16 mol%) was dissolved under slightly positive argon flow in DME (6 mL) and water (3 mL). The mixture was heated to 100 °C for four hours, cooled to room temperature and diluted with water (10 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained yellow oil was purified by flash chromatography (silica gel, 22×2 cm, cyclohexane:EtOAc, 20:1) to give the title compound **139** as colorless oil (300 mg, 1.72 mmol, 99%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.33–7.30 (m, 2H, *H*C$_{ar}$), 7.28–7.23 (m, 3H, *H*C$_{ar}$), 7.15 (dd, $^{3,4}J_{HH}$ = 5.1, 1.2 Hz, 1H, SC*H*), 6.93 (dd, $^3J_{HH}$ = 5.2, 3.4 Hz, 1H, SCHC*H*), 6.81 (dq, $^{3,4}J_{HH}$ = 3.4, 1.1 Hz, 1H, SC(CH$_2$C$_6$H$_5$)C*H*), 4.16 (s, 2H, C*H*$_2$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.2 (*C*$_{thiophene}$), 140.5 (*C*$_{ar}$), 128.7 (2 HC$_{ar}$), 128.7 (2 HC$_{ar}$), 127.0 (HC$_{ar}$), 126.6 (*C*H$_{thiophene}$), 125.3 (*C*H$_{thiophene}$), 124.1 (*C*H$_{thiophene}$), 36.2 (*C*H$_2$);

MS (EI), *m*/*z* (%) 175 (16), 174 (M^+, 100), 173 (81), 141 (14), 129 (20), 128 (11), 115 (11), 97 (56); R_f = 0.54 (silica gel, cyclohexane:EtOAc, 20:1). The NMR spectra were consistent with the literature data.[53]

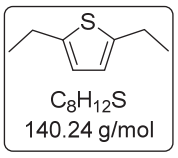
2,5-Dibenzylthiophene (140)



In a 25 mL Young tube 2-benzylthiophene (300 mg, 1.72 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (5 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 1.50 mL, 2.40 mmol, 1.25 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, benzylbromide (0.30 mL, 2.48 mmol, 1.29 eq.) was added and the cooling bath was removed. The reaction mixture was stirred over the weekend at room temperature, quenched with water (10 mL) and transferred to a separation funnel. The aqueous phase was extracted with MTBE (3×20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained yellow oil was purified by flash chromatography (silica gel, 20×2 cm, cyclohexane:EtOAc, 20:1) to give the title compound as colorless oil (396 mg, 1.50 mmol, 87%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.32–7.27 (m, 5H, HC_{ar}), 7.25–7.19 (m, 5H, HC_{ar}), 6.60 (s, 2H, S($CH_2C_6H_5$)C*H*), 4.07 (s, 4H, 2 CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.8 (2 $C_{thiophene}$), 140.5 (2 C_{ar}), 128.7 (4 HC_{ar}), 128.6 (4 HC_{ar}), 126.6 (2 HC_{ar}), 124.9 (2 $CH_{thiophene}$), 36.5 (2 CH_2); **MS** (EI), *m*/*z* (%) 265 (13), 264 (M^+, 61), 173 (100), 129 (16), 91 (11); R_f = 0.52 (silica gel, cyclohexane:EtOAc, 20:1).

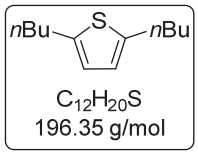
2,5-Diethylthiophene (148)



In a 25 mL Young tube 2-ethylthiophene (1.00 mL, 8.74 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (10 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 6.60 mL, 10.6 mmol, 1.21 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, 1-bromoethane (0.80 mL, 10.5 mmol, 1.20 eq.) was added and the cooling bath was removed. The reaction mixture was stirred for 24 hours at room temperature, quenched with water (15 mL) and transferred to a separation funnel. The aqueous phase was extracted with MTBE (3×25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained oil was 99% pure (^{1}H-NMR: 1% of ethylthiophene) (1.08 g, 7.54 mmol, 86%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.58 (s, 2H, SCC*H*), 2.79 (q, $^3J_{HH}$ = 7.5 Hz, 4H, 2 CH_2), 1.29 (t, $^3J_{HH}$ = 7.5 Hz, 6H, 2 CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.9 (2 S*C*(CH_2CH_3)), 122.8 (2 SCHCH), 23.6 (2 *C*H_2), 16.1 (2 *C*H_3); **MS** (EI), *m*/*z* (%) 140 (M^+, 58), 126 (12), 125 (100), 111 (13), 91 (17); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2965m, 2930w, 2893w, 2872w, 2852w, 1456w, 801m, 520s; $\boldsymbol{R_f}$ = 0.49 (silica gel, cyclohexane:EtOAc, 20:1).

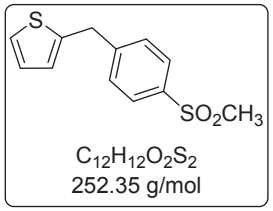
2,5-Dibutylthiophene (149)



In a 25 mL Young tube 2-butylthiophene (1.00 mL, 6.66 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (10 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 5.00 mL, 8.00 mmol, 1.20 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, 1-bromobutane (0.90 mL, 8.03 mmol, 1.21 eq.) was added and the cooling bath was removed. The reaction mixture was stirred for 20 hours at room temperature, quenched with water (15 mL) and transferred to a separation funnel. The aqueous phase was extracted with MTBE (3×15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained red oil was purified by flash chromatography (silica gel, 20×2 cm, cyclohexane:EtOAc, 20:1) to give the title compound **149** as colorless oil (1.21 g, 6.19 mmol, 93%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.56 (s, 2H, SCC*H*), 2.75 (t, $^3J_{HH}$ = 7.6 Hz, 4H, CH_2), 1.63 (m_c, 4H, CH_2), 1.39 (m_c, 4H, CH_2), 0.93 (m_c, 6H, CH_3); **MS** (EI), *m*/*z* (%) 196 (M^+, 19), 154 (15), 153 (100), 111 (16), 97 (17); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2956m, 2928m, 2871w, 2856w, 1465w, 1456w, 1436w, 1378w, 798w, 567s, 544s; $\boldsymbol{R_f}$ = 0.49 (silica gel, cyclohexane:EtOAc, 20:1).

2-(4-(Methylsulfonyl)benzyl)thiophene (142)

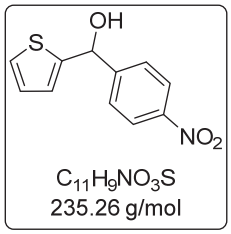


Compound **142** was synthesized following the procedure described for the synthesis of 2-benzylthiophene (**139**) using 2-methylsulfonyl benzylbromide (625 mg, 1.51 mmol, 1.00 eq.), sodium carbonate (339 mg, 3.20 mmol, 2.12 eq.), 2-thiophene boronic acid (240 mg, 1.82 mmol, 1.21 eq.) and $Pd(PPh_3)_4$ (37.4 mg, 0.03 mmol, 2.13 mol%). The obtained brown oil was purified by flash chromatography (silica gel,

15×2 cm, cyclohexane:EtOAc, 3:1) to give the title compound as orange oil (259 mg, 1.03 mmol, 63%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.90–7.85 (m, 2H, HC_{ar}), 7.46–7.42 (m, 2H, HC_{ar}), 7.19 (dd, $^{3,4}J_{HH}$ = 5.2, 1.2 Hz, 1H, SC*H*), 6.96 (dd, $^{3}J_{HH}$ = 5.2, 3.4 Hz, 1H, SCHC*H*), 6.83 (dq, $^{3,4}J_{HH}$ = 3.3, 1.0 Hz, 1H, SCHCHC*H*), 4.25 (s, 2H, CH_2), 3.04 (s, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 146.9 (C_{ar}), 141.9 ($C_{thiophene}$), 138.9 (C_{ar}), 129.6 (2 HC_{ar}), 127.9 (2 HC_{ar}), 127.2 ($CH_{thiophene}$), 126.0 ($CH_{thiophene}$), 124.8 ($CH_{thiophene}$), 44.7 (CH_3), 36.0 (CH_2); **MS** (EI), *m*/*z* (%) 254 (10), 253 (17), 252 (M^+, 100), 251 (19), 173 (77), 172 (30), 171 (32), 129 (26) 128 (17), 97 (67), 45 (27); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3747w, 2357w, 1408w, 1303m, 1149m, 1090w, 959w, 592w, 563m, 524s; R_f = 0.18 (silica gel, cyclohexane:EtOAc, 3:1).

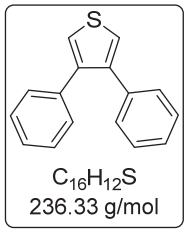
(4-Nitrophenyl)(thiophene-2-yl)methanol (144)



Following a modified procedure of GUPTA *et al.*,[86] in a 100 mL three-necked round bottom flask equipped with a thermometer, TMEDA (0.91 mL, 5.97 mmol, 1.20 eq.) was dissolved in dry Et_2O (10 mL) and cooled to 0 °C. At this temperature subsequent *n*BuLi (1.6 M in hexanes, 3.80 mL, 6.08 mmol, 1.37 eq.) and thiophene (0.40 mL, 4.95 mmol, 1.00 eq.) were added and stirred for another one hour. In a separate two-necked round bottom flask 4-nitrobenzaldehyde (918 mg, 6.01 mmol, 1.21 eq.) was dissolved in dry THF (10 mL) and cooled with water/ice bath. The aldehyde was then added to the lithiated thiophene in solution over a period of 16 min, which upon addition turned brown. The cooling bath was removed and the mixture was stirred at room temperature for one hour. After quenching with aqueous saturated NH_4Cl solution (20 mL) and diluting with MTBE (20 mL), the mixture was transferred to a separation funnel. The phases were separated and the organic phase was washed with water (2×30 mL) and brine (30 mL), the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained brown oil was purified by flash chromatography (silica gel, 24×4 cm, *n*pentane:EtOAc, 3:1) to give the title compound **144** as yellow-brown solid (898 mg, 3.82 mmol, 77%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 8.26–8.13 (m, 2H, HC_{ar}), 7.68–7.58 (m, 2H, HC_{ar}), 7.31 (dd, $^3J_{HH}$ = 4.8, 1.5 Hz, 1H, SC*H*), 6.98–6.92 (m, 2H, $H_{thiophene}$), 6.17 (d, $^3J_{HH}$ = 3.3 Hz, 1H, C*H*(OH)), 2.63 (s, 1H, O*H*); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3743m, 2926w, 2367w, 2323w, 1515m, 1346m, 646w, 554m, 537s; R_f = 0.18 (silica gel, *n*pentane:EtOAc, 20:5). The NMR spectra were consistent with the literature data.[87]

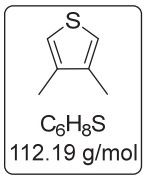
3,4-Diphenylthiophene (131a)



Following a modified procedure of YANO *et al.*,[60] in a 100 mL three-necked round bottom flask $Pd(PPh_3)_4$ (293 mg, 0.25 mmol, 5.05 mol%) was dissolved in degased DME (12 mL) and added dropwise 3,4-dibromothiophene (0.56 mL, 4.96 mmol, 1.00 eq.). Degased aqueous 2 M solution of sodium carbonate (2.11 g, 19.9 mmol, 4.00 eq.) was added and the mixture stirred for 5 min. Phenylboronic acid (1.57 g, 12.5 mmol, 2.51 eq.) in degased EtOH (15 mL) was added and heated to 90 °C. After 21 hours the mixture was cooled to room temperature, filtered over celite and washed with CH_2Cl_2 (3×40 mL). The reaction mixture was transferred to a separation funnel and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained mixture of brown oil solid was purified by flash chromatography (silica gel, 24×4 cm, cyclohexane) to give a white solid (1.16 mg, 4.92 mmol, 99%).

m.p. 111–112 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.32 (s, 2H, SC*H*), 7.29–7.18 (m, 10H, HC_{ar}); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 141.9 (2 SCH*C*(C_6H_5)), 136.7 (2 C_{ar}), 129.2 (4 HC_{ar}), 128.8 (4 HC_{ar}), 127.0 (2 HC_{ar}), 124.2 (2 SCH); **MS** (EI), *m*/*z* (%) 237 (20), 236 (M^+, 100), 235 (76), 234 (30), 221 (22), 202 (19), 189 (11), 117 (14), 104 (12); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3100w, 3093w, 1437m, 1180w, 1164w, 1073w, 934w, 920w, 866m, 849w, 804s, 777m, 756s, 735m, 725m, 694s, 679m, 654m, 616m, 609m, 550s, 535m, 519m; R_f = 0.23 (silica gel, cyclohexane). The NMR spectra were consistent with the literature data.[54]

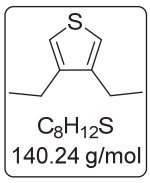
3,4-Dimethylthiophene (131c)



Following a modified procedure of WÜRTHNER *et al.*,[59] in a 100 mL three-necked round bottom flask 3,4-dibromothiophene (**130**) (0.56 mL, 4.96 mmol, 1.00 eq.) and Ni(dppp)Cl_2 (142 mg, 0.26 mmol, 5.23 mol%) were dissolved in dry THF (20 mL) and cooled to 0 °C. At this temperature methyl magnesium bromide (3.0 M in Et_2O, 4.00 mL, 12.0 mmol, 2.42 eq.) was added and the mixture was refluxed for 16 hours. The brown reaction mixture was quenched with aqueous saturated NH_4Cl solution (20 mL) and transferred to a separation funnel. The phases were separated and the aqueous phase was extracted with MTBE (3×20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained mixture was used without further purification (501 mg, 4.46 mmol, 90%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.88 (s, 2H, SC*H*), 2.17 (s, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 137.5 (2 SCHCCH_3), 120.8 (2 SCH), 14.7 (2 CH_3); **MS** (EI), *m*/*z* (%) 112 (M^+, 78), 111 (100), 97 (44), 77 (14), 45 (19), 43 (14); **IR** ($\tilde{\nu}$ [cm^{-1}]) 1685w, 1653w, 1481w, 1436m, 1157m, 1119m, 1100m, 1070m, 1055w, 1027w, 998w, 717s, 691s, 547s, 537s; $\boldsymbol{R_f}$ = 0.66 (silica gel, cyclohexane:EtOAc 1:1). The NMR spectra were consistent with the literature data.[54]

3,4-Diethylthiophene (131d)

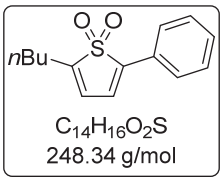


Compound **131d** was synthesized following the procedure described for the synthesis of 3,4-dimethylthiophene (**131c**) using 3,4-dibromothiophene (**130**) (0.56 mL, 4.96 mmol, 1.00 eq.), Ni(dppp)Cl_2 (140 mg, 0.26 mmol, 5.14 mol%) and ethylmagnesium bromide (0.9 M in THF, 14.0 mL, 12.6 mmol, 2.54 eq.). The obtained brown oil was used without further purification (627 mg, 4.47 mmol, 90%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.91 (s, 2H, SC*H*), 2.54 (q, $^3J_{HH}$ = 7.5 Hz, 4H, CH_2), 1.25 (t, $^3J_{HH}$ = 7.5 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 143.5 (2 SCHC(CH_2CH_3)), 119.6 (2 SCH), 22.0 (2 CH_2), 13.8 (2 CH_3); **MS** (EI), *m*/*z* (%) 140 (M^+, 45), 125 (100), 111 (13), 97 (16), 91 (12), 45 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3100w, 3054w, 2963w, 2933w, 2874w, 1672w, 1436m, 1174m, 1170m, 1156m, 1120m, 1099m, 862w, 782w, 720s, 693s, 536s; $\boldsymbol{R_f}$ = 0.63 (silica gel, cyclohexane:EtOAc, 3:1).

7.6 Synthesis and Characterization of Substituted Thiophene 1,1-Dioxides

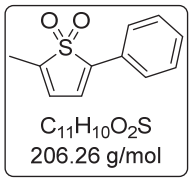
2-Butyl-5-phenylthiophene 1,1-dioxide (136)



In a 25 mL Schlenk tube 2-butyl-5-phenylthiophene (**134**) (918 mg, 4.24 mmol, 1.00 eq.) was dissolved in AcOH (4 mL) and 30% hydrogen peroxide (2.60 mL, 25.5 mmol, 6.00 eq.) was added dropwise *via* syringe. The cloudy mixture was heated for two hours and became yellow after one hour. The reaction mixture was cooled to room temperature and aqueous saturated $NaHCO_3$ was added slowly until a pH of 8–9 was reached. It was extracted with CH_2Cl_2 (3×20 mL), the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained yellow solid was purified by flash chromatography (silica gel, 24×3 cm, cyclohexane:EtOAc, 75:25) to give a pale solid, which was dissolved in a minimum of CH_2Cl_2 and *n*pentane was added. The precipitated solid was washed with *n*pentane and dried (326 mg, 1.31 mmol, 31%).

m.p. 96–97 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.73–7.70 (m, 2H, *H*C$_{ar}$), 7.46–7.40 (m, 3H, *H*C$_{ar}$), 6.85 (d, $^3J_{HH}$ = 4.8 Hz, 1H, $SO_2C(C_6H_5)CH$), 6.45 (dt, $^{3,4}J_{HH}$ = 4.8, 2.1 Hz, 1H, $SO_2C(C_4H_9)CH$), 2.57 (m$_c$, 2H, C*H*$_2$), 1.70 (m$_c$, 2H, C*H*$_2$), 1.46 (m$_c$, 2H, C*H*$_2$), 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3H, C*H*$_3$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 145.1 ($SO_2C(C_6H_5)$), 141.3 ($SO_2C(C_4H_9)$), 130.1 (*C*$_{ar}$), 129.3 (2 HC$_{ar}$), 127.5 (HC$_{ar}$), 126.4 (2 HC$_{ar}$), 121.9 ($SO_2C(C_4H_9)CH$), 120.6 ($SO_2C(C_6H_5)CH$), 28.8 (*C*H$_2$), 24.2 (*C*H$_2$), 22.4 (*C*H$_2$), 13.9 (*C*H$_3$); **MS** (EI), *m*/*z* (%) 248 (M^+, 38), 158 (13), 157 (100), 155 (47), 141 (32), 128 (11), 115 (34), 105 (14), 102 (33), 91 (22); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3071w, 3061w, 2963w, 2932m, 2900w, 2890w, 2863w, 2855w, 2356w, 1496m, 1457w, 1447m, 1418m, 1286s, 1270s, 1142s, 1117s, 1079w, 970w, 852w, 770w, 729w, 680w, 666w, 637w, 615w, 592s; **EA:** calculated for $C_{14}H_{16}O_2S$: C = 67.71, H = 6.49; measured: C = 67.68, H = 6.55; R_f = 0.38 (silica gel, cyclohexane:EtOAc, 75:25).

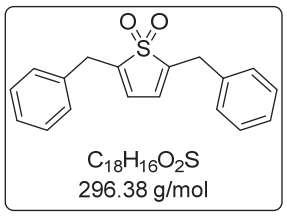
2-Methyl-5-phenylthiophene 1,1-dioxide (137)



In a 100 mL three-necked round bottom flask 2-methyl-5-phenylthiophene (**135**) (202 mg, 1.15 mmol, 1.00 eq.) was dissolved in CH_2Cl_2/acetone (2/10 mL) and the freshly prepared dimethyldioxirane[85] (~0.07 M in acetone, 20.0 mL, 4.60 mmol, 4.00 eq.) was added. The pale yellow mixture was stirred for 18 hours, evaporated under reduced pressure and the obtained yellow solid was purified by flash chromatography (silica gel, 20×2 cm, cyclohexane:EtOAc, 75:25) to give a pale solid, which was dissolved in a minimum of CH_2Cl_2 and *n*pentane was added. The precipitated solid was washed with *n*pentane and dried (112 mg, 0.54 mmol, 47%).

m.p. 128–129 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.66–7.63 (m, 2H, *H*C$_{ar}$), 7.39–7.33 (m, 3H, *H*C$_{ar}$), 6.77 (d, $^3J_{HH}$ = 4.7 Hz, 1H, $SO_2C(C_6H_5)CH$), 6.40 (dq, $^{3,4}J_{HH}$ = 3.8, 1.8 Hz, 1H, $SO_2C(CH_3)CH$), 2.13 (d, $^4J_{HH}$ = 1.8 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.4 ($SO_2C(C_6H_5)$), 140.5 ($SO_2C(CH_3)$), 130.2 (*C*$_{ar}$), 129.3 (2 HC$_{ar}$), 127.4 (HC$_{ar}$), 126.3 (2 HC$_{ar}$), 122.9 ($SC(CH_3)CH$), 120.6 ($SO_2C(C_6H_5)CH$), 9.6 (CH_3); **MS** (EI), *m*/*z* (%) 206 (M^+, 58), 159 (12), 158 (100), 157 (35), 141 (11), 129 (10), 115 (32), 102 (94), 76 (13); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3067w, 2360w, 1280m, 1133m, 1115m, 761m, 694s, 572s, 504s; **EA:** calculated for $C_{11}H_{10}O_2S$: C = 64.05, H = 4.89; measured: C = 64.03, H = 4.96; R_f = 0.17 (silica gel, cyclohexane:EtOAc, 75:25).

2,5-Dibenzylthiophene 1,1-dioxide (141)

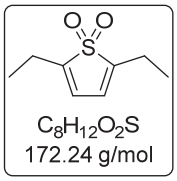


Compound **141** was synthesized following the procedure described for the synthesis of 2-butyl-5-phenylthiophene 1,1-dioxide (**136**) using 2,5-dibenzylthiophene (**140**) (838 mg, 3.17 mmol, 1.00 eq.), AcOH (7 mL) and 30% hydrogen peroxide (2.00 mL, 19.6 mmol, 6.18 eq.). The obtained yellow oil was purified by flash chromatography (silica gel, 22×4 cm, cyclohexane:EtOAc, 75:25) to give a pale solid, which was dissolved in a minimum of CH_2Cl_2 and *n*pentane was added. The precipitated solid was washed with *n*pentane and dried (255 mg, 0.86 mmol, 27%).

m.p. 88–90 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.36–7.23 (m, 10H, *H*C$_{ar}$), 5.92 (s, 2H, SO_2CCH), 3.76 (s, 4H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.3 (2 $SO_2C(CH_2C_6H_5)$), 135.1 (2 *C*$_{ar}$), 129.4 (4 HC$_{ar}$), 129.0 (4 HC$_{ar}$), 127.4 (2 HC$_{ar}$), 123.3 (2 SO_2CCH), 30.3 (2 CH_2); **MS** (EI), *m*/*z* (%) 233 (18), 232 (M^+–SO_2, 92),

217 (12), 215 (11), 154 (12), 153 (12), 141 (56), 128 (22), 117 (10), 115 (25), 91 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3083w, 3061w, 3028w, 2360w, 1734w, 1601w, 1493m, 1454m, 1280s, 1126s, 1026m, 852w, 695s, 543s; **EA:** calculated for $C_{18}H_{16}O_2S$: C = 72.95, H = 5.44; measured: C = 72.53, H = 5.51; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{18}H_{17}O_2S^+$: 297.0941, found: 297.0944 $[M+H]^+$; calc. *m*/*z* for $C_{18}H_{20}NO_2S^+$: 314.1207, found: 314.1209 $[M+NH_4]^+$; calc. *m*/*z* for $C_{18}H_{16}NaO_2S^+$: 319.0766, found: 319.0763 $[M+Na]^+$; calc. *m*/*z* for $C_{18}H_{16}KO_2S^+$: 335.0502, found: 335.0503 $[M+K]^+$; calc. *m*/*z* for $C_{36}H_{32}NaO_4S_2^+$: 615.1638, found: 615.1634 $[2M+Na]^+$; calc. *m*/*z* for $C_{36}H_{32}KO_4S_2^+$: 631.1370, found: 631.1374 $[2M+K]^+$; R_f = 0.42 (silica gel, cyclohexane:EtOAc, 75:25).

2,5-Diethylthiophene 1,1-dioxide (150)

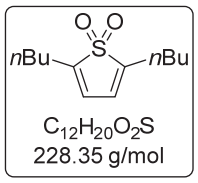


In a 50 mL Schlenk tube 2,5-ethylthiophene (**148**) (567 mg, 4.04 mmol, 1.00 eq.), urea hydrogen peroxide (3.16 g, 32.6 mmol, 8.07 eq.) was dissolved in dry THF (10 mL) and trifluoroacetic acid anhydride (3.40 mL, 24.0 mmol, 5.93 eq.) was added dropwise *via* syringe over a period of 25 min. After one hour stirring aqueous saturated $NaHCO_3$ was added slowly until a pH of 8–9 was reached. It was extracted with CH_2Cl_2 (3×40 mL), the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude solid was purified by flash chromatography (silica gel, 27×3 cm, cyclohexane:EtOAc, 3:1) to give a colorless solid (440 mg, 2.50 mmol, 62%).

m.p. 52–56 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.27 (t, $^3J_{HH}$ = 1.3 Hz, 2H, SO_2CCH), 2.51 (q, $^3J_{HH}$ = 7.4 Hz, 4H, CH_2), 1.26 (t, $^3J_{HH}$ = 7.4 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 145.5 (2 $SO_2C(C_2H_5)$), 121.2 (2 SO_2C), 17.7 (2 CH_2), 11.1 (2 CH_3); **MS** (EI), *m*/*z* (%) 172 (M^+, 29), 124 (24), 109 (100), 93 (47), 91 (31), 79 (27), 77 (38), 65 (11), 43 (10), 41 (13); **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_8H_{13}O_2S^+$: 173.0630, found: 173.0631 $[M+H]^+$; calc. *m*/*z* for $C_8H_{12}NaO_2S^+$: 195.0448, found: 195.0450 $[M+Na]^+$; calc. *m*/*z* for $C_{16}H_{25}O_4S_2^+$: 345.1184, found: 345.1189 $[2M+H]^+$; calc. *m*/*z* for $C_{16}H_{24}NaO_4S_2^+$: 367.1005, found: 367.1008 $[2M+Na]^+$; **IR** ($\tilde{\nu}$ [cm^{-1}]) 3083w, 2978, 2881w, 2356w, 1441m, 1280s, 1257s, 1128s, 1080m, 849s, 713m, 634m, 548s; R_f = 0.27 (silica gel, cyclohexane:EtOAc, 75:25); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_R = 51.3 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-

1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): $t_{R(trans)}$ = 42.8 min.

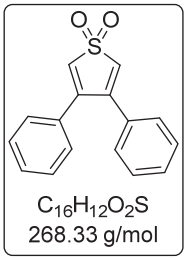
2,5-Dibutylthiophene 1,1-dioxide (151)



Compound **151** was synthesized following the procedure described for the synthesis of 2-butyl-5-phenylthiophene 1,1-dioxide (**136**) using 2,5-dibutylthiophene (**149**) (1.28 g, 5.50 mmol, 1.00 eq.), AcOH (10 mL) and 30% hydrogen peroxide (3.40 mL, 33.3 mmol, 6.05 eq.). The obtained yellow oil was purified by flash chromatography (silica gel, 22×4 cm, cyclohexane:EtOAc, 75:25) to give a colorless oil (255 mg, 2.09 mmol, 38%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.26 (t, $^4J_{HH}$ = 1.1 Hz 2H, SO_2CCH), 2.47 (t, $^3J_{HH}$ = 7.6 Hz, 4H, CH_2), 1.70–1.54 (m_c, 4H, CH_2), 1.46–1.31 (m_c, 4H, CH_2), 0.94 (t, $^3J_{HH}$ = 7.4 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.1 (2 $SO_2C(C_4H_9)$), 121.8 (2 SO_2CCH), 28.8 (2 CH_2), 24.1 (2 CH_2), 22.4 (2 CH_2), 13.8 (2 CH_3); **MS** (EI), *m*/*z* (%) 228 (M^+, 19), 186 (12), 138 (14), 137 (100), 121 (11), 107 (17), 95 (21), 93 (27), 91 (22), 85 (11), 81 (19), 80 (13), 79 (46), 77 (23), 67 (13), 55 (18), 43 (25), 41 (29); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2958w, 2931w, 2873w, 2863w, 1715w, 1465w, 1456w, 1289m, 1144m, 1110w, 534s; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{12}H_{21}O_2S^+$: 229.1255, found: 229.1257 $[M+H]^+$; calc. *m*/*z* for $C_{12}H_{24}NO_2S^+$: 246.1520, found: 246.1522 $[M+NH_4]^+$; calc. *m*/*z* for $C_{12}H_{20}NaO_2S^+$: 251.1078, found: 251.1076 $[M+Na]^+$; calc. *m*/*z* for $C_{12}H_{20}KO_2S^+$: 267.0822, found: 267.0816 $[M+K]^+$; calc. *m*/*z* for $C_{24}H_{40}NaO_4S_2^+$: 479.2259, found: 479.2260 $[2M+Na]^+$; R_f = 0.37 (silica gel, cyclohexane:EtOAc, 75:25).

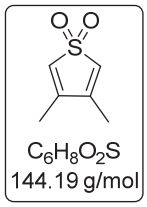
3,4-Diphenylthiophene 1,1-dioxide (152)



Compound **152** was synthesized following the procedure described for the synthesis of 2,5-diethylthiophene 1,1-dioxide (**150**) using 3,4-diphenylthiophene (**131a**) (445 mg, 1.88 mmol, 1.00 eq.), urea hydrogen peroxide (1.48 g, 15.4 mmol, 8.20 eq.) and trifluoroacetic acid anhydride (1.60 mL, 11.3 mmol, 5.99 eq.). The crude solid was purified by flash chromatography (silica gel, 23×2 cm, cyclohexane:EtOAc, 4:1) to give a white solid (244 mg, 0.91 mmol, 48%).

m.p. 172–173 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.38 (m_c, 2H, HC_{ar}), 7.29 (m_c, 4H, HC_{ar}), 7.07–7.04 (m, 4H, HC_{ar}), 6.63 (s, 2H, SO_2CH); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 145.2 (2 SO_2CHC), 131.5 (2 C_{ar}), 130.2 (2 SO_2CH *C*), 128.6 (4 HC_{ar}), 128.6 (4 HC_{ar}), 127.6 (2 HC_{ar}); **MS** (EI), *m*/*z* (%) 268 (M^+, 45), 240 (11), 239 (62), 221 (16), 220 (59), 202 (15), 192 (21), 191 (60), 189 (20), 165 (14), 161 (15), 105 (100), 102 (62), 77 (33), 76 (26), 63 (10), 51 (12); **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{16}H_{12}NaO_2S^+$: 291.0450, found: 291.0452 $[M+Na]^+$; calc. *m*/*z* for $C_{32}H_{24}NaO_4S^+$: 559.1008, found: 559.1010 $[2M+Na]^+$; **IR** ($\tilde{\nu}$ [cm^{-1}]) 3064w, 2370w, 1748m, 1489w, 1444w, 1302w, 1215w, 1117m, 908w, 904w, 755m, 734m, 727m, 694m, 691m, 689m, 682m, 645w, 555s, 543s; R_f = 0.38 (silica gel, cyclohexane:EtOAc, 4:1).

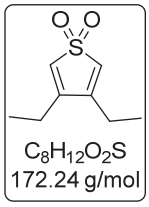
3,4-Dimethylthiophene 1,1-dioxide (153)



Compound **153** was synthesized following the procedure described for the synthesis of 2,5-diethylthiophene 1,1-dioxide (**150**) using 3,4-dimethylthiophene (**131c**) (677 mg, 6.03 mmol, 1.00 eq.), urea hydrogen peroxide (4.79 g, 49.4 mmol, 8.19 eq.) and trifluoroacetic acid anhydride (5.20 mL, 36.6 mmol, 6.07 eq.). The crude solid was purified by flash chromatography (silica gel, 27×4 cm, cyclohexane:EtOAc, 1:1) to give a pale yellow solid (361 mg, 2.50 mmol, 42%).

m.p. 104–105 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.28 (d, $^4J_{HH}$ = 1.2 Hz, 2H, SO_2CH), 2.04 (d, $^4J_{HH}$ = 1.2 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.9 (2 SO_2CHC), 126.2 (2 SO_2CH), 14.5 (2 CH_3); **MS** (EI), *m*/*z* (%) 144 (M^+, 60), 115 (54), 97 (13), 96 (100), 95 (46), 81 (16), 79 (10), 77 (19), 68 (34), 67 (84), 65 (19), 53 (33), 51 (16), 45 (26), 43 (61), 41 (37), 40 (19); **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_6H_9O_2S^+$: 145.0318, found: 145.0318 $[M+H]^+$; calc. *m*/*z* for $C_6H_8NaO_2S^+$: 167.0137, found: 167.0137 $[M+Na]^+$; **IR** ($\tilde{\nu}$ [cm^{-1}]) 3100w, 3076m, 1636w, 1565w, 1452w, 1437m, 1388m, 1374m, 1308m, 1276s, 1187m, 1175s, 1154m, 1092s, 1089s, 1031m, 1015w, 998m, 867s, 786s, 677m, 581s, 577s, 570s, 567s; R_f = 0.29 (silica gel, cyclohexane:EtOAc, 1:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_R = 68.6 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 67.4 min.

3,4-Diethylthiophene 1,1-dioxide (154)



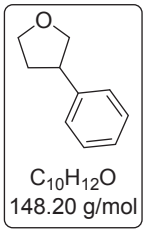
Compound **154** was synthesized following the procedure described for the synthesis of 2,5-diethylthiophene 1,1-dioxide (**150**) using 3,4-diethylthiophene (**131d**) (721 mg, 5.14 mmol, 1.00 eq.), urea hydrogen peroxide (4.01 g, 41.4 mmol, 8.04 eq.) and trifluoroacetic acid anhydride (4.40 mL, 31.0 mmol, 6.03 eq.). The crude solid was purified by flash chromatography (silica gel, 25×4 cm, cyclohexane:EtOAc, 4:1 then 2:1) to give a colorless solid (513 mg, 2.98 mmol, 58%).

m.p. 120–121 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.25 (t, $^4J_{HH}$ = 1.6 Hz, 2H, SO_2CH), 2.35 (dq, $^{3,4}J_{HH}$ = 7.2, 1.6 Hz, 4H, CH_2), 1.19 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 149.0 (2 $SO_2CHC(C_2H_5)$), 124.7 (2 SO_2CH), 21.4 (2 CH_2), 11.3 (2 CH_3); **MS** (EI), *m*/*z* (%) 172 (M^+, 23), 143 (41), 124 (35), 109 (100), 91 (11), 81 (22), 79 (16), 77 (19), 67 (11), 65 (11), 57 (25), 53 (14), 51 (10), 41 (16); **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_8H_{13}O_2S^+$: 173.0630, found: 173.0631 $[M+H]^+$; calc. *m*/*z* for $C_8H_{12}NaO_2S^+$: 195.0449, found: 195.0450 $[M+Na]^+$; **IR** ($\tilde{\nu}$ [cm^{-1}]) 3096w, 3078m, 2974m, 2940w, 1569w, 1448m, 1423m, 1386m, 1382m, 1300w, 1277s, 1264m, 1248s, 1172m, 1157m, 1120w, 1092s, 1055m, 1043w, 996w, 970m, 859m, 819s, 807m, 760m, 580s, 575s, 555s, 531m, 517m, 512m, 508m; R_f = 0.19 (silica gel, cyclohexane:EtOAc, 75:25); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_R = 72.2 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 75.3 min.

7.7 Characterization of Substituted Tetrahydrofurans and Dihydrobenzofurans

Hydrogenation products 4-methyl-2-phenyl-tetrahydrofuran (**113**)[46, 88], 2-phenyl-tetrahydrofuran (**105**)[89] and 2-(4-(trifluoromethyl)phenyl)tetrahydrofuran (**107**)[90] are known compounds. Hydrogenation product, 6-bromo-3,5-dimethyl-2,3-dihydro-benzofuran (**117**), was analyzed after lithiation with subsequent aqueous workup as the unhalogenated product, 3,5-dimethyl-2,3-dihydrobenzofuran (**116**).

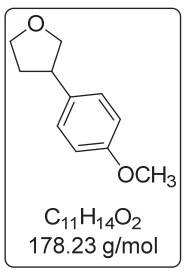
3-Phenyltetrahydrofuran (100)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.27–7.14 (m, 5H, HC_{ar}), 4.08 (dd, $^3J_{HH}$ = 7.7, 7.6 Hz, 1H, CH_2), 4.01 (dt, $^3J_{HH}$ = 8.3, 8.3, 4.5 Hz, 1H, CH_2), 3.86 (dd, $^3J_{HH}$ = 8.1, 8.0 Hz, 1H, CH_2), 3.67 (dd, $^3J_{HH}$ = 8.2, 7.8 Hz, 1H, CH_2), 3.34 (quint, $^3J_{HH}$ = 7.9, 7.9, 7.9, 7.9 Hz, 1H, C*H*), 2.30 (m_c, 1H, CH_2), 1.95 (qd, $^3J_{HH}$ = 12.3, 8.1, 8.1, 8.1 Hz, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.8 (C_{ar}), 128.7 (2 HC_{ar}), 127.4 (2 HC_{ar}), 126.6 (HC_{ar}), 74.8 (CH_2), 68.7 (CH_2), 45.2 (CH), 34.8 (CH_2); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 6.8 min), *m*/*z* (%) 148 (M^+, 42), 118 (56), 117 (100), 115 (21), 91 (33), 77 (10), 51 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3062w, 3028w, 2968w, 2929w, 2854w, 1603w, 1493m, 1454w, 1356w, 1208w, 1183w, 1067m, 1053m, 1030w, 968w, 904w, 819w, 757s, 699s, 667w, 624w; **EA:** calculated for $C_{10}H_{12}O$: C = 81.04, H = 8.16; measured: C = 80.78, H = 8.29; R_f = 0.47 (silica gel, cyclohexane:EtOAc, 2:1); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 60 kPa H_2, 95 °C, 60 min, 5.0 K/min, 160 °C, 5 min): $t_{R(major)}$ = 24.9 min, $t_{R(minor)}$ = 25.7 min; **[α]$_D^{20}$** −17.3 (*c* 1.16, CH_2Cl_2, 98% *ee*). The NMR spectra were consistent with the literature data.[91]

3-(4-Methoxyphenyl)tetrahydrofuran (101)

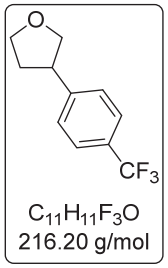


Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.17 (m_c, 2H, HC_{ar}), 6.86 (m_c, 2H, HC_{ar}), 4.12 (t, $^3J_{HH}$ = 7.9 Hz, 1H, CH_2), 4.06 (dt, $^3J_{HH}$ = 8.4, 8.3, 4.5 Hz, 1H, CH_2), 3.91 (dd, $^{2,3}J_{HH}$ = 15.5, 8.1 Hz, 1H, CH_2), 3.80 (s, 3H, CH_3), 3.68 (t, $^3J_{HH}$ = 8.1 Hz, 1H, CH_2), 3.31–3.40 (m, 1H, C*H*), 2.34 (dtd, $^{2,3}J_{HH}$ = 12.2, 7.6, 7.6, 4.5 Hz, 1H, CH_2), 1.97 (qd, $^{2,3}J_{HH}$ = 12.3, 8.2, 8.2, 8.2 Hz, 1H, CH_2);

^{3}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 158.4 (C_{ar}), 134.7 (C_{ar}), 128.3 (2 HC_{ar}), 114.1 (2 HC_{ar}), 74.9 (CH_2), 68.6 (CH_2), 55.4 (CH_3), 44.4 (CH), 34.9 (CH_2); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 10.3 min), *m*/*z* (%) 178 (M^+, 64), 149 (14), 148 (100), 133 (35), 121 (50), 105 (36), 91 (25), 77 (56), 65 (25), 51 (26); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2932w, 2908w, 2854w, 2835w, 1611w, 1583w, 1513s, 1463m, 1454w, 1442w, 1354w, 1305w, 1243s, 1178s, 1117w, 1053s, 1033s, 969w, 901w, 828s, 811m, 773w, 602m; **EA:** calculated for $C_{11}H_{14}O_2$: C = 74.13, H = 7.92; measured: C = 74.15; H = 8.21; R_f = 0.17 (silica gel, cyclohexane:EtOAc, 10:1); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 60 kPa H_2, 50 °C, 50 min, 5.0 K/min, 160 °C, 10 min): t_R = 74.4 min; **HPLC** (IC, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 225 nm): $t_{R(major)}$ = 32.8 min, $t_{R(minor)}$ = 34.2 min; **[α]$_D^{20}$** +16.2 (*c* 1.17, CH_2Cl_2, 95% *ee*) from hydrogenation with (*R*)-enantiomer of catalyst.

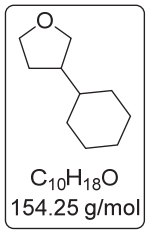
3-(4-(Trifluoromethyl)phenyl)tetrahydrofuran (102)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.57 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H, HC_{ar}), 7.37 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H, HC_{ar}), 4.14 (dd, $^{3}J_{HH}$ = 8.4, 7.6 Hz, 1H, CH_2), 4.09 (dt, $^{3}J_{HH}$ = 8.4, 8.3, 4.7 Hz, 1H, CH_2), 3.93 (dd, $^{2,3}J_{HH}$ = 16.0, 7.7 Hz, 1H, CH_2), 3.76 (dd, $^{3}J_{HH}$ = 8.5, 6.9 Hz, 1H, CH_2), 3.46 (quint, $^{3}J_{HH}$ = 7.5, 7.5, 7.4, 7.4 Hz, 1H, CH), 2.41 (dtd, $^{2,3}J_{HH}$ = 12.5, 8.0, 7.8, 4.7 Hz, 1H, CH_2), 2.00 (m_c, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 147.3 (C_{ar}), 129.0 (q, $^{2}J_{CF}$ = 32.4 Hz, C_{ar}), 127.7 (2 HC_{ar}), 125.7 (q, $^{3}J_{CF}$ = 3.8 Hz, 2 C_{ar}), 124.1 (q, $^{1}J_{CF}$ = 261.1 Hz, CF_3), 74.6 (OCH_2), 68.6 (OCH_2CH_2), 45.0 (OCH_2CH), 34.8 (OCH_2CH_2); **^{19}F{^{1}H}-NMR** (376.5 MHz, $CDCl_3$, 300 K): δ (ppm) −62.7 (CF_3); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 7.1 min), *m*/*z* (%) 216 (M^+, 16), 197 (10), 186 (69), 159 (15), 118 (11), 117 (100), 115 (27); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2973w, 2936w, 2866w, 2861w, 1700w, 1619m, 1452w, 1422w, 1322s, 1161s, 1112s, 1088m, 1067s, 1016s, 970w, 907w, 836s, 764w; **EA:** calculated for $C_{11}H_{11}F_3O$: C = 61.11, H = 5.13; measured: C = 61.19, H = 5.37; R_f = 0.37 (silica gel, cyclohexane:EtOAc, 2:1); **GC** (γ-Cyclodextrin-trifluoroacetyl, Chiraldex, 30 m × 0.25 mm, 60 kPa H_2, 95 °C, 32 min, 5.0 K/min, 160 °C, 5 min): $t_{R(major)}$ = 32.3 min, $t_{R(minor)}$ = 33.1 min; **[α]$_D^{20}$** −9.2 (*c* 1.18, CH_2Cl_2, >97% *ee*).

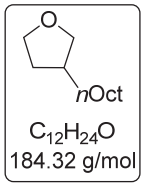
3-Cyclohexyltetrahydrofuran (103)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.92 (t, $^3J_{HH}$ = 7.8 Hz, 1H, CH_2), 3.85 (dt, $^3J_{HH}$ = 8.4, 3.3 Hz, 1H, CH_2), 3.72 (dt, $^3J_{HH}$ = 8.5, 6.6 Hz, 1H, CH_2), 3.36 (t, $^3J_{HH}$ = 8.4 Hz, 1H, CH_2), 1.95 (m, 2H, CH_2), 1.67 (m, 5H, CH_2), 1.51 (m, 1H, CH), 1.19 (m, 4H, CH_2), 0.97 (m, 2H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 72.2 (*C*H_2), 68.5 (*C*H_2), 46.0 (*C*H), 41.7 (*C*H), 32.5 (*C*H_2), 32.2 (*C*H_2), 30.8 (*C*H_2), 26.6 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 6.8 min), m/*z* (%) 154 (M^+, 10), 136 (18), 121 (13), 108 (15), 107 (16), 95 (14), 94 (20), 93 (14), 83 (32), 82 (92), 81 (62), 80 (16), 79 (31), 77 (13), 69 (11), 68 (27), 67 (100), 65 (10), 55 (80), 54 (24), 53 (31); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2919s, 2849s, 2668w, 2361w, 2337w, 1781w, 1700w, 1448s, 1348w, 1260w, 1187w, 1118w, 1086s, 1070m, 1050m, 1038m, 966w, 907m, 890m; **EA:** caclulated for $C_{10}H_{18}O$: C = 77.87, H = 11.76; measured: C = 77.92, H = 11.65; R_f = 0.11 (silica gel, *n*pentane:EtOAc, 50:1); **GC** (6-Methyl-2,3-pentyl-γ-cyclodextrin (60% in polysiloxane PS086), 30 m × 0.25 mm × 0.125 µm, 60 kPa H_2, 60 °C, 30 min, 1.0 K/min, 100 °C, 5 min, 10.0 K/min, 180 °C, 5 min): $t_{R(minor)}$ = 51.8 min, $t_{R(major)}$ = 52.6 min; **[α]$_D^{20}$** −6.6 (*c* 1.28, CH_2Cl_2, >98% *ee*). The NMR spectra were consistent with the literature data.[91]

3-Octyltetrahydrofuran (104)

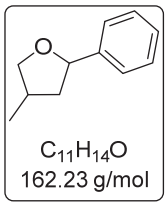


Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.89 (t, $^3J_{HH}$ = 7.7 Hz, 1H, CH_2), 3.83 (dt, $^3J_{HH}$ = 8.2, 4.1 Hz, 1H, CH_2), 3.73 (dd, $^{2,3}J_{HH}$ = 15.4, 7.9 Hz, 1H, CH_2), 3.31 (t, $^3J_{HH}$ = 7.8 Hz, 1H, CH_2), 2.15 (dt, $^{2,3}J_{HH}$ = 14.7, 7.4 Hz, 1H, CH_2), 2.02 (dtd, $^{2,3}J_{HH}$ = 12.1, 7.5, 4.6 Hz, 1H, CH_2), 1.48 (dq, $^{2,3}J_{HH}$ = 12.0, 7.9 Hz, 1H, CH), 1.41–1.21 (m, 14H, CH_2), 0.88 (t, $^3J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 73.7 (*C*H_2), 68.1 (*C*H_2), 39.6 (*C*H), 33.5 (*C*H_2), 32.7 (*C*H_2), 32.0 (*C*H_2), 29.9 (*C*H_2), 29.7 (*C*H_2), 29.4 (*C*H_2), 28.8 (*C*H_2), 22.8 (*C*H_2), 14.3 (*C*H_3); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 13.0 min), *m*/*z* (%) 138 (20), 137 (59), 112 (12), 110 (15), 109 (24), 97 (18), 96 (31), 95 (77), 84 (21), 83 (47), 82 (42), 81 (37), 71 (23), 70 (47), 69 (56), 68 (36), 67 (37), 57 (34), 56 (47), 55 (86), 54 (20), 53 (12), 43 (63), 42 (32), 41 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2957m, 2922s, 2853s, 1466w, 1099w, 1059w, 909m, 660m;

EA: calculated for $C_{12}H_{24}O$: C = 78.20, H = 13.12; measured: C = 78.02, H = 12.91; R_f = 0.48 (silica gel, cyclohexane:EtOAc, 4:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 95 °C, 50 min, 0.1 °C/min, 96 °C, 0 min, 10 °C/min, 180 °C, 10 min): $t_{R(minor)}$ = 55.3 min, $t_{R(major)}$ = 57.3 min; **[α]$_D^{20}$** −2.0 (*c* 0.21, CH_2Cl_2, 95% *ee*).

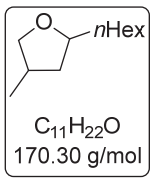
2-Phenyl-4-methyltetrahydrofuran (113)



Synthesized following the general working procedure for hydrogenations with iridium catalysts. The mixture of *cis*:*trans* (92:8) isomers could not be separated on semipreparative HPLC (OD, *n*hexane:*i*PrOH, 95:5, 6 mL/min).

GC (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min): diastereomers: t_R = 13.8 min; **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 40 kPa H_2, 90 °C, 10 min, 0.1 °C/min, 92 °C, 10 °C/min, 180 °C, 10 min): t_{R1} = 34.4 min, t_{R2} = 34.6 min, t_{R3} = 35.2 min, t_{R4} = 35.4 min.

2-Hexyl-4-methyltetrahydrofuran (114)

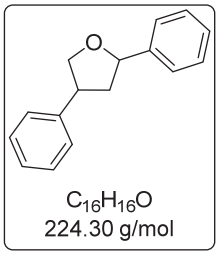


Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* (90:10) isomers could not be separated.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.99–3.98 (m, 2H, CH_2 *trans*), 3.88–3.80 (m, 2H, CH_2 *cis*), 3.34 (t, $^3J_{HH}$ = 7.9 Hz, 1H, C*H cis*), 3.24 (m$_c$, 1H, C*H trans*), 3.37–2.24 (m, 1H, CH_2 *cis*), 2.15–2.09 (m, 1H, CH_2 *cis*), 1.67–1.54 (m, 1H, C*H cis*), 1.49–1.21 (m, 10H, 5 CH_2 *cis*), 1.03 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3 *cis*), 0.87 (t, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3 *cis*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 80.5 (C_q *cis*), 79.0 (C_q *trans*), 75.0 (*C*H *trans*), 74.5 (*C*H *cis*), 41.1 (*C*H_2 *cis*), 39.8 (*C*H_2 *trans*), 36.3 (*C*H_2 *cis*), 34.5 (*C*H_2 *cis*), 33.3 (*C*H_2 *trans*), 32.0 (*C*H_2 *cis*), 29.6 (*C*H_2 *cis*), 26.5 (*C*H_2 *cis*), 26.4 (*C*H_2 *trans*), 22.8 (*C*H_2 *cis*), 18.1 (*C*H_3 *cis*), 18.3 (*C*H_3 *trans*), 14.2 (*C*H_3 *cis*); **GC-MS** (EI, 70 eV, Me_2Si, 60 °C, 2 min, 10 °C/min, 270 °C, 10 min, t_R = 10.2 min), *m*/*z* (%) 86 (10), 85 (100), 67 (17), 57 (27), 55 (14), 43 (21), 41 (36); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2956m, 2925s, 2871m, 2855m, 1457w, 1378w, 1106w, 1041w, 1015w, 646w; **EA:** calculated for $C_{12}H_{24}O$: C = 77.58, H = 13.02; measured: C = 77.49, H = 12.86; R_f = 0.15 (silica gel, cyclohexane:EtOAc, 20:1); **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 90 °C, 32 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 250 °C, 10 min): $t_{R(cis)}$ = 33.4 min, $t_{R(trans)}$ = 33.8 min; **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA,

25 m × 0.25 mm × 0.25 µm, 40 kPa H_2, 90 °C, 10 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 180 °C, 10 min): $t_{R(major)}$ = 24.0 min, $t_{R(minor)}$ = 24.7 min. The NMR spectra were consistent with the literature data.[92]

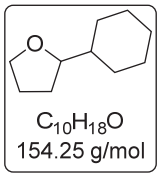
2,4-Diphenyltetrahydrofuran (112)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* isomers was separated by flash chromatography (silica gel, cyclohexane:EtOAc, 20:1).

***trans*-2,4-Diphenyltetrahydrofuran (*trans*-2a) – calyxolane A** **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.40–7.23 (m, 10H, *H*C$_{ar}$), 5.24 (dd, $^3J_{HH}$ = 7.8, 5.8 Hz, 1H, C*H*), 4.48 (dd, $^3J_{HH}$ = 8.5, 7.4 Hz, 1H, CH_2), 3.96 (t, $^3J_{HH}$ = 8.2 Hz, 1H, CH_2), 3.55 (quint, $^3J_{HH}$ = 7.8, 7.8, 7.8, 7.8 Hz, 1H, C*H*), 2.49 (dt, $^{2,3}J_{HH}$ = 12.6, 7.7 Hz, 1H, CH_2), 2.34 (ddd, $^{2,3}J_{HH}$ = 12.6, 8.3, 5.8 Hz, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 143.7 (*C*$_{ar}$), 142.2 (*C*$_{ar}$), 128.8 (2 *C*$_{ar}$), 128.5 (2 *C*$_{ar}$), 127.5 (2 *C*$_{ar}$), 127.3 (*C*$_{ar}$), 126.8 (*C*$_{ar}$), 125.6 (2 *C*$_{ar}$), 80.7 (*C*H), 75.3 (*C*H_2), 44.6 (*C*H), 42.9 (*C*H_2); ***cis*-2,4-Diphenyltetrahydrofuran (*cis*-2b) – calyxolane B** sample contains 6% **calyxolane A** **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.45–7.22 (m, 10H, *H*C$_{ar}$), 5.07 (dd, $^3J_{HH}$ = 10.1, 5.7 Hz, 1H, C*H*), 4.36 (t, $^3J_{HH}$ = 8.2 Hz, 1H, CH_2), 4.03 (t, $^3J_{HH}$ = 8.5 Hz, 1H, CH_2), 3.64 (dq, $^3J_{HH}$ = 10.6, 8.2, 8.1 Hz, 1H, C*H*), 2.76 (ddd, $^{2,3}J_{HH}$ = 12.8, 7.2, 5.8 Hz, 1H, CH_2), 2.02 (m, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 142.8 (*C*$_{ar}$), 141.8 (*C*$_{ar}$), 128.7 (2 *C*$_{ar}$), 128.6 (2 *C*$_{ar}$), 127.5 (*C*$_{ar}$), 127.4 (2 *C*$_{ar}$), 126.8 (*C*$_{ar}$), 125.8 (2 *C*$_{ar}$), 82.0 (*C*H), 75.2 (*C*H_2), 46.2 (*C*H), 43.9 (*C*H_2); **GC-MS** (EI, 70 eV, Me_2Si, 100 °C, 2 min, 10 °C/min, 270 °C, 10 min, $t_{R(cis)}$ = 15.0 min, $t_{R(trans)}$ = 15.1 min), *m*/*z* (%) 224 (M^+, 39), 195 (13), 194 (81), 193 (93), 179 (61), 178 (35), 165 (21), 146 (25), 133 (27), 120 (21), 118 (23), 117 (100); $\boldsymbol{R_f}$ = 0.16 (*cis*), 0.24 (*trans*) (silica gel, cyclohexane:EtOAc, 20:1); **GC** (6-Methyl 2,3-pentyl-γ-cyclodextrin (60% in polysiloxane PS086), 30 m × 0.25 mm × 0.125 µm, 60 kPa H_2, 95 °C, 30 min, 5.0 K/min, 180 °C, 30 min): $t_{R(cis)}$ = 55.8 min, $t_{R(trans)}$ = 56.2 min. The NMR spectra were consistent with the literature data.[93]

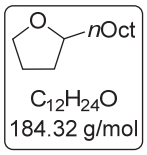
2-Cyclohexyltetrahydrofuran (108)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.84–3.79 (m, 1H, OCH_2), 3.74–3.68 (m, 1H, OCH_2), 3.51–3.46 (m, 1H, CH), 1.94–0.92 (m, 15H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 84.1 (OCH), 67.8 (OCH_2), 43.2 (CH), 30.1 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 6.8 min), *m*/*z* (%) 71 (100), 70 (26), 43 (16); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2923m, 2850m, 1707m, 1696m, 1669w, 1660w, 1448m, 1437w, 1259w, 1064w, 1030w, 1016w, 807w, 545w, 533s, 502s; R_f = 0.21 (silica gel, cyclohexane:EtOAc, 20:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 60 °C, 1 °C/min, 120 °C, 10 °C/min, 180 °C, 10 min): $t_{R(major)}$ = 31.6 min, $t_{R(minor)}$ = 32.9 min; **[α]$_D^{20}$** +0.97 (*c* 0.47, CH_2Cl_2, 82% *ee*). The NMR spectra were consistent with the literature data.[94]

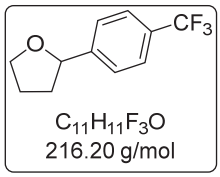
2-Octyltetrahydrofuran (109)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.85 (dd, $^{2,3}J_{HH}$ = 14.5, 7.3 Hz, 1H, OCH_2), 3.77 (m_c, 1H, OCHC$_8$H$_{17}$), 3.70 (dd, $^{3}J_{HH}$ = 14.3, 7.9 Hz, 1H, OCH_2), 2.00–1.80 (m, 3H, OCH$_2$CH_2CH_2), 1.61–1.52 (m, 1H, OCH$_2$CH$_2$CH_2), 1.47–1.38 (m, 3H, CH_2), 1.27 (m_c, 11H, CH_2), 0.88 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 79.6 (OCH_2), 67.8 (OCH), 35.9 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 60 °C, 3 min, 3 °C/min, 140 °C, 40 min, 250 °C, 5 min, t_R = 24.5 min), *m*/*z* (%) 71 (100), 43 (13); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2954m, 2921s, 2853s, 1461w, 1378w, 1061m, 921w, 816w, 723w, 668m; **EA:** calculated for $C_{12}H_{24}O$: C = 78.20, H = 13.12; measured: C = 78.25, H = 12.96; R_f = 0.16 (silica gel, cyclohexane:EtOAc, 20:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 95 °C, 45 min, 10 °C/min, 180 °C, 10 min): $t_{R(major)}$ = 36.4 min, $t_{R(minor)}$ = 37.6 min. **[α]$_D^{20}$** +0.4 (*c* 0.75, $CHCl_3$, 46% *ee*). The NMR spectra were consistent with the literature data.[89]

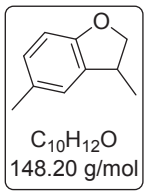
2-(4-Trifluoromethyl)phenyltetrahydrofuran (107)



Synthesized following the general working procedure for hydrogenations with iridium catalysts. When palladium on charcoal was used, the tetrahydrofuran ring was opened to give the corresponding alcohol.

GC (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min): t_R = 13.0 min; **HPLC** (IC, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 220 nm): t_{R1} = 10.0 min, t_{R2} = 11.4 min; **[α]$_D^{20}$** +0.7 (*c* 0.50, CH_2Cl_2, 69% *ee*). The NMR spectra were consistent with the literature data.[89]

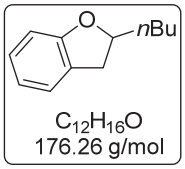
3,5-Dimethyl-2,3-dihydrobenzofuran (116)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.96 (s, 1H, *H*C$_{ar}$), 6.92 (d, $^3J_{HH}$ = 8.1 Hz, 1H, *H*C$_{ar}$), 6.68 (d, $^3J_{HH}$ = 8.1 Hz, 1H, *H*C$_{ar}$), 4.66 (t, $^3J_{HH}$ = 8.8 Hz, 1H, OC*H*$_2$), 4.06–4.02 (m, 1H, OC*H*$_2$), 3.50 (m$_c$, 1H, OCH$_2$C*H*), 2.29 (s, 3H, aryl-C*H*$_3$), 1.31 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C*H*$_3$); **^{13}C{^{1}H}NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 157.7 (*C*$_{ar}$), 132.4 (*C*$_{ar}$), 129.8 (*C*$_{ar}$), 128.4 (H*C*$_{ar}$), 124.5 (H*C*$_{ar}$), 109.1 (H*C*$_{ar}$), 78.7 (*C*H$_2$), 36.7 (*C*H), 20.9 (*C*H$_3$), 19.4 (*C*H$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 6.9 min), *m*/*z* (%) 148 (M^+, 62), 133 (100), 105 (68), 77 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2961w, 2923w, 2915w, 2009w, 2866w, 1490s, 1469m, 1456m, 1452m, 1436w, 1375w, 1242m, 1215m, 1205m, 1192m, 1138w, 1121w, 1109m, 1036w, 967s, 939w, 879w, 807s, 790m, 644w, 626w, 610w, 582w, 518m, 507s, 502w; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxan, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 90 °C, 32 min, 0.1 °C/min, 92 °C, 0 min, 10 °C/min, 250 °C, 10 min): t_R = 55.8 min; R_f = 0.20 (silica gel, *n*heptane:EtOAc, 20:1); **HPLC** (OJ, *n*heptane:*i*PrOH 100:0, 0.5 mL/min, 25 °C, 200 nm): $t_{R(major)}$ = 16.4 min, $t_{R(minor)}$ = 20.9 min; **[α]$_D^{20}$** +3.0 (*c* 0.10, CH_2Cl_2, 92% *ee*).

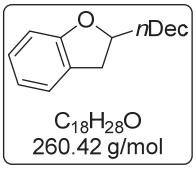
2-Butyl-2,3-dihydrobenzofuran (119)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.14 (dd, $^{3,4}J_{HH}$ = 7.3, 0.7 Hz, 1H, HC_{ar}), 7.10 (m_c, 1H, HC_{ar}), 6.81 (dt, $^{3,4}J_{HH}$ = 7.4, 0.8 Hz, 1H, HC_{ar}), 6.75 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, HC_{ar}), 4.76 (m_c, 1H, OC*H*), 3.29–3.21 (m, 1H, OCHCH_2), 2.85 (dd, $^{2,3}J_{HH}$ = 15.4, 7.9 Hz, 1H, OCHCH_2), 1.88–1.80 (m, 1H, CH_2), 1.72–1.63 (m, 1H, CH_2), 1.51–1.36 (m, 4H, CH_2), 0.93 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.8 (C_{ar}), 128.0 (HC_{ar}), 127.1 (OC_{ar}), 125.0 (HC_{ar}), 120.2 (HC_{ar}), 109.4 (HC_{ar}), 83.5 (OCH), 36.0 (CH_2), 35.6 (CH_2), 27.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 60 kPa, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, t_R = 33.4 min), *m*/*z* (%) 174 (M^+, 55), 134 (10), 133 (76), 120 (43), 119 (29), 108 (13), 107 (100), 105 (18), 91 (35), 77 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2956m, 2929m, 2871w, 2859w, 1706w, 1610w, 1597m, 1494w, 1480s, 1461m, 1448w, 1436w, 1230s, 1207w, 1175w, 1097w, 1057w, 1015w, 970w, 867m, 804w, 747s, 710w; R_f = 0.38 (silica gel, cyclohexane:EtOAc, 20:1); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 230 nm): $t_{R(major)}$ = 8.6 min, $t_{R(minor)}$ = 11.8 min; **[α]$_D^{20}$** +63.7 (*c* 0.33, CH_2Cl_2, 95% *ee*). The NMR spectra were consistent with the literature data.[33]

2-Decyl-2,3-dihydrobenzofuran (120)

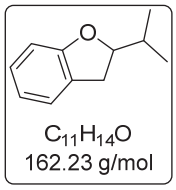


Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.14 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H, HC_{ar}), 7.09 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H, HC_{ar}), 6.81 (dt, $^{3,4}J_{HH}$ = 7.5, 0.7 Hz, 1H, HC_{ar}), 6.76 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H, HC_{ar}), 4.76 (m_c, 1H, OC*H*), 3.26 (dd, $^{2,3}J_{HH}$ = 15.4, 8.9 Hz, 1H, OCHCH_2), 2.85 (dd, $^{2,3}J_{HH}$ = 15.4, 7.9 Hz, 1H, OCHCH_2), 1.88–1.79 (m, 1H, CH_2), 1.71–1.62 (m, 1H, CH_2), 1.53–1.20 (m, 16H, CH_2), 0.89 (t, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 159.8 (C_{ar}), 128.0 (HC_{ar}), 127.1 (C_{ar}), 125.0 (HC_{ar}), 120.2 (HC_{ar}), 109.4 (HC_{ar}), 83.6 (OCH), 36.3 (CH_2), 35.6 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 25.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 10.3 min), *m*/*z* (%) 260 (M^+, 50), 133 (47), 120 (72), 119 (25), 108 (16), 107 (100), 91 (19), 77 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2922m, 2829m, 1723w, 1707w, 1695w, 1599w, 1480m, 1462w, 1448w, 1232m, 1170w, 870w, 862w, 809w, 747m, 721w, 710w, 680w;

R_f = 0.50 (silica gel, *n*pentane:EtOAc, 20:1); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 25 °C, 230 nm): $t_{R(major)}$ = 8.1 min, $t_{R(minor)}$ = 8.9 min; **[α]$_D^{20}$** +24.7 (*c* 0.55, CH_2Cl_2, 99% *ee*). The NMR spectra were consistent with the literature data.[33]

2-Isopropyl-2,3-dihydrobenzofuran (121)

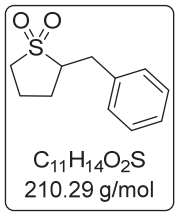


Synthesized following the general working procedure for hydrogenations with palladium on charcoal.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): *δ* (ppm) 7.21–7.07 (m, 2H, *H*C$_{ar}$), 6.83 (ddd, $^{3,4}J_{HH}$ = 7.5, 7.5, 0.8 Hz, 1H, *H*C$_{ar}$), 6.76 (d, $^3J_{HH}$ = 8.0 Hz, 1H, *H*C$_{ar}$), 4.58–4.47 (m, 1H, OC*H*), 3.24–3.14 (m, 1H, OCHCH_2), 2.95 (dd, $^{2,3}J_{HH}$ = 15.6, 8.6 Hz, 1H, OCHCH_2), 1.97 (dq, $^3J_{HH}$ = 13.5, 6.7 Hz, 1H, OCHC(CH$_3$)$_2$*H*) 1.04 (d, $^3J_{HH}$ = 6.7 Hz, 1H, CH_3), 0.97 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): *δ* (ppm) 160.1 (*C*$_{ar}$), 128.0 (HC$_{ar}$), 127.3 (*C*$_{ar}$), 125.0 (HC$_{ar}$), 120.1 (HC$_{ar}$), 109.2 (HC$_{ar}$), 88.5 (OCH), 33.4 (*C*H(CH$_3$)$_2$), 33.0 (*C*H$_2$), 18.4 (*C*H$_3$), 17.9 (*C*H$_3$); **GC-MS** (EI, 70 eV, 5% polyphenylmethylsiloxane, 100 kPa, 50 °C, 2 min, 30 °C/min, 250 °C, 5 min, t_R = 6.6 min), *m*/*z* (%) 162 (M^+, 59), 147 (50), 133 (18), 119 (40), 118 (11), 107 (100), 91 (46); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2958w, 2931w, 2872w, 1610w, 1597w, 1505w, 1480s, 1461s, 1436w, 1388w, 1367w, 1361w, 1323w, 1319w, 1230s, 1196w, 1179w, 1166w, 1097w, 1016w, 984m, 1001w, 887w, 860m, 804w, 745s, 714w, 705w, 658w; R_f = 0.47 (silica gel, *n*pentane:EtOAc, 20:1); **HPLC** (OD-H, *n*heptane:*i*PrOH 99:1, 0.5 mL/min, 24 °C, 230 nm): $t_{R(major)}$ = 8.3 min, $t_{R(minor)}$ = 9.4 min; **[α]$_D^{20}$** +11.8 (*c* 0.39, CH_2Cl_2, 97% *ee*). The NMR spectra were consistent with the literature data.[33]

7.8 Characterization of Substituted Dihydro- and Tetrahydrothiophene 1,1-Dioxides

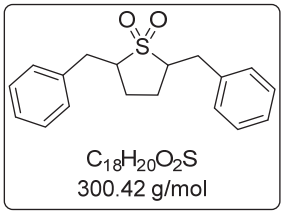
2-Benzyltetrahydrothiophene 1,1-dioxide (165a)



In a 25 mL Young tube tetrahydrothiophene 1,1-dioxide (0.20 mL, 2.08 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (5 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 1.50 mL, 2.40 mmol, 1.16 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, benzylbromide (0.55 mL, 4.54 mmol, 2.18 eq.) was added and the cooling bath was removed. The reaction mixture was stirred for 15 h at room temperature, quenched with water (10 mL) and transferred to a separation funnel. The aqueous phase was extracted with MTBE (2×20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained oil was purified by flash chromatography (silica gel, 20×2 cm, cyclohexane:EtOAc, 20:1 then 3:1) to give the product **165a** as a colorless oil (301 mg, 1.43 mmol, 69%).

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.34–7.21 (m, 5H, HC_{ar}), 3.34 (dd, $^{2,3}J_{HH}$ = 14.0, 4.9 Hz, 1H, $SO_2CH(CH_2C_6H_5)$), 3.18 (m_c, 2H, CH_2), 3.05 (m_c, 1H, CH_2), 2.73 (dd, $^{2,3}J_{HH}$ = 14.0, 10.0 Hz, 1H, CH_2), 2.23–2.14 (m, 2H, CH_2), 2.09–1.95 (m, 1H, CH_2), 1.89–1.76 (m, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 137.3 (C_{ar}), 129.0 (2 HC_{ar}), 128.9 (2 HC_{ar}), 127.1 (HC_{ar}), 62.4 ($SO_2CH(CH_2C_6H_5)$), 51.5 (CH_2), 33.7 (CH_2), 29.1 (CH_2), 20.1 (CH_2); **MS** (EI), *m*/*z* (%) 210 (M^+ 16), 146 (39), 145 (19), 144 (20), 143 (25), 129 (37), 118 (25), 117 (100), 115 (28), 104 (24), 92 (11), 91 (97), 67 (15), 65 (14); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2976w, 2881w, 2878w, 2364w, 2247w, 1715m, 1311w, 1289m, 1144m, 539s; R_f = 0.10 (silica gel, cyclohexane:EtOAc, 75:25).

2,5-Dibenzyltetrahydrothiophene 1,1-dioxide (163)

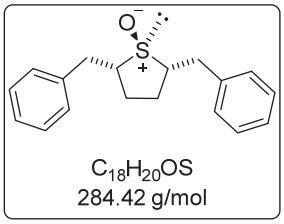


In a 25 mL Young tube 2-benzyltetrahydrothiophene 1,1-dioxide (300 mg, 1.43 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (5 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 1.10 mL, 1.76 mmol, 1.23 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, benzylbromide (0.21 mL, 1.71 mmol, 1.20 eq.) was added and the cooling bath was removed. The reaction mixture was stirred for 21 hours at room temperature, quenched with water (10 mL) and transferred to a separation funnel. The aqueous

phase was extracted with MTBE (3×20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The obtained oil was purified by flash chromatography (silica gel, 21×2 cm, cyclohexane:EtOAc, 4:1). The product **163** was obtained as a mixture of both isomers (60:40, *cis*:*trans*). The colorless oil (176 mg, 0.06 mmol, 41%) solidifies upon standing. Reduction of 2,5-dibenzylthiophene 1,1-dioxide (**141**) with palladium on charcoal gave the fully reduced compound **163** in a ratio of 82:18 (*cis*:*trans*).

m.p. 68–69 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.33–7.30 (m, 5H, HC_{ar} both diastereomers), 7.28–7.21 (m, 7H, HC_{ar} both diastereomers), 3.40–3.36 (m, 2H, $CH_2(C_6H_5)$ both diastereomers), 3.35–3.30 (m, 2H, SO_2CH *cis*), 3.26–3.20 (m, 2H, SO_2CH *trans*), 2.74 (dd, $^{2,3}J_{HH}$ = 14.0, 10.7 Hz, 2H, $CH_2(C_6H_5)$ both diastereomers), 2.13–2.06 (m, 2H, SO_2CHCH_2 *trans*), 2.06–1.99 (m, 2H, SO_2CHCH_2 *cis*), 1.89–1.83 (m, 2H, SO_2CHCH_2 *cis*), 1.68–1.61 (m, 2H, SO_2CHCH_2 *trans*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 137.3 (2 C_{ar} *cis*), 137.2 (2 C_{ar} *trans*), 129.1 (4 HC_{ar} *cis*), 129.0 (4 HC_{ar} *trans*), 128.9 (4 HC_{ar} *cis*), 128.9 (4 HC_{ar} *trans*), 127.1 (2 HC_{ar} *cis*), 127.1 (2 HC_{ar} *trans*), 63.2 (2 $SO_2CH(CH_2C_6H_5)$ *trans*), 62.0 (2 $SO_2CH(CH_2C_6H_5)$ *cis*), 34.6 (2 CH_2 *trans*), 33.8 (2 CH_2 *cis*), 27.4 (2 CH_2 *trans*), 25.6 (2 CH_2 *cis*); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3027w, 2858w, 2362w, 1490w, 1458w, 1292m, 1250m, 1120m, 758m, 694s, 615m, 555s, 498s; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{18}H_{21}O_2S^+$: 301.1259, found: 301.1257 $[M+H]^+$; calc. *m*/*z* for $C_{18}H_{24}NO_2S^+$: 318.1523, found: 318.1522 $[M+NH_4]^+$; calc. *m*/*z* for $C_{18}H_{20}NaO_2S^+$: 323.1079, found: 323.1076 $[M+Na]^+$; calc. *m*/*z* for $C_{18}H_{20}KO_2S^+$: 339.0815, found: 339.0816 $[M+K]^+$; calc. *m*/*z* for $C_{36}H_{40}NaO_4S_2^+$: 623.2262, found: 623.2260 $[2M+Na]^+$; R_f = 0.29 (silica gel, cyclohexane:EtOAc, 4:1).

2-(*cis*)-Dibenzyltetrahydrothiophene 1-oxide (166)

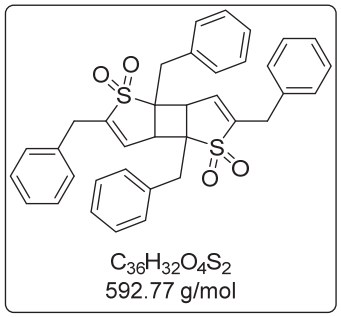


In a 25 mL Young tube tetrahydrothiophene 1-oxide (0.18 mL, 1.97 mmol, 1.00 eq.) was dissolved under slightly positive argon flow in dry THF (5 mL) and cooled to −78 °C. At this temperature *n*BuLi (1.6 M in hexanes, 1.50 mL, 2.40 mmol, 1.22 eq.) was added dropwise *via* syringe. The mixture was stirred for one hour, benzylbromide (0.29 mL, 2.39 mmol, 1.22 eq.) was added and the cooling bath was removed. The reaction mixture was stirred at room temperature for 22 hours, quenched with water (15 mL) and transferred to a separation funnel. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the

solvent was removed under reduced pressure. Only 20 mg from the obtained oil (414 mg) were submitted to semipreparative HPLC (Reprospher 100 Si 5 µm, 250 × 20 mm, *n*hexane:*i*PrOH 90:10) and the pure product ***cis*-166** was obtained as a white solid (3 mg).

m.p. 87–88 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.34–7.19 (m, 10H, HC_{ar}), 3.31–3.24 (m, 2H, C*H*), 3.17 (dd, $^{2,3}J_{HH}$ = 14.1, 5.7 Hz, 2H, CH_2), 2.74 (dd, $^{2,3}J_{HH}$ = 13.9, 9.3 Hz, 2H, CH_2), 2.35–2.26 (m, 2H, CH_2), 1.81–1.72 (m, 2H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 138.0 (2 C_{ar}), 129.1 (4 HC_{ar}), 128.9 (4 HC_{ar}), 127.1 (2 HC_{ar}), 70.9 (2 HC), 36.2 (2 CH_2), 29.2 (2 CH_2); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3075w, 2922m, 2370w, 1496m, 1455m, 1445m, 1143m, 1030m, 1015s, 1002m, 988m, 973m, 947m, 921m, 758m, 747m, 710s, 704s, 695s, 689m, 621m, 533m; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{18}H_{21}OS^+$: 285.1308, found: 285.1307 $[M+H]^+$; calc. *m*/*z* for $C_{18}H_{20}NaOS^+$: 307.1127, found: 307.1129 $[M+Na]^+$; calc. *m*/*z* for $C_{18}H_{20}KOS^+$: 323.0866, found: 323.0864 $[M+K]^+$; calc. *m*/*z* for $C_{36}H_{41}O_2S_2^+$: 569.2542, found: 569.2542 $[2M+H]^+$; calc. *m*/*z* for $C_{36}H_{40}NaO_2S_2^+$: 591.2362, found: 591.2365 $[2M+Na]^+$; R_f = 0.13 (silica gel, cyclohexane:EtOAc, 1:3).

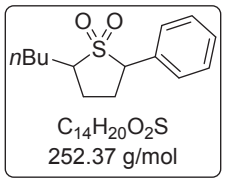
2,3b,5,6b-Tetrabenzyl-3a,3b,6a,6b-tetrahydrocyclobuta[1,2-b:3,4-b']dithiophene-1,1,4,4-tetraoxide (167)



The dimer **167** was formed from 2,5-dibenzylthiophene 1,1-dioxide (**141**) after letting the monomer standing on air and light for about three months.

m.p. 239–240 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.25–7.16 (m, 12H, HC_{ar}), 7.15–7.14 (m, 4H, HC_{ar}), 7.04–7.00 (m, 4H, HC_{ar}), 5.51 (dt, $^{3,4}J_{HH}$ = 4.8, 1.7 Hz, 2H, SO_2CCH), 4.11–4.09 (m, 2H, SO_2CCHCH), 3.68 (dd, $^3J_{HH}$ = 8.7, 3.4 Hz, 4H, CH_2), 3.37 (d, $^2J_{HH}$ = 16.8 Hz, 2H, CH_2), 3.25 (d, $^2J_{HH}$ = 16.8 Hz, 2H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 149.0 (4 C_{ar}), 135.2 (2 SO_2C), 129.3 (2 SO_2CCH), 129.1 (4 HC_{ar}), 129.0 (4 HC_{ar}), 128.9 (4 HC_{ar}), 128.8 (4 HC_{ar}), 127.4 (2 HC_{ar}), 127.0 (2 HC_{ar}), 63.1 (2 SO_2C), 47.3 (2 SO_2CCH), 35.9 (2 CH_2), 30.6 (2 CH_2); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2925w, 2360w, 1419m, 1292s, 1202w, 1124m, 1079m, 1058w, 1028w, 941w, 907w, 873m, 852m, 805w, 774w, 731m, 709m, 694m, 691m, 639m, 620w, 596m, 569m; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{36}H_{32}NaO_4S_2^+$: 615.1634, found: 615.1639 $[M+Na]^+$; calc. *m*/*z* for $C_{72}H_{64}NaO_8S_4^+$: 1207.3376, found: 1207.3382 $[2M+Na]^+$; R_f = 0.38 (silica gel, cyclohexane:EtOAc, 3:1).

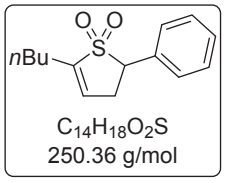
2-Butyl-5-phenyltetrahydrothiophene 1,1-dioxide (156)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* (84:16) isomers could not be separated.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.41–7.37 (m, 5H, HC_{ar}), 4.22 (m_c, 1H, SO_2CH), 3.17 (m_c, 1H, SO_2CH), 2.47–2.32 (m, 2H, CH_2), 2.08–1.93 (m, 2H, CH_2), 1.66–1.57 (m, 2H, CH_2), 1.54–1.34 (m, 4H, CH_2), 0.93 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 130.8 (C_{ar}), 129.3 (2 HC_{ar}), 129.0 (HC_{ar}), 128.9 (2 HC_{ar}), 66.0 (SO_2CH), 59.8 (SO_2CH), 29.5 (CH_2), 28.0 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 14.0 (CH_3); **MS** (EI), *m*/*z* (%) 104 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2956m, 2946m, 2934m, 2871w, 2860w, 2367w, 2358w, 1497w, 1454w, 1305m, 1244w, 1129m, 698w, 646w, 603w, 594w, 534s; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{14}H_{21}O_2S^+$: 253.1255, found: 253.1257 $[M+H]^+$; calc. *m*/*z* for $C_{14}H_{24}NO_2S^+$: 270.1520, found: 270.1522 $[M+NH_4]^+$; calc. *m*/*z* for $C_{14}H_{20}NaO_2S^+$: 275.1077, found: 275.1076 $[M+Na]^+$; calc. *m*/*z* for $C_{14}H_{20}KO_2S^+$: 291.0813, found: 291.0816 $[M+K]^+$; calc. *m*/*z* for $C_{28}H_{40}NaO_4S_2^+$: 527.2258, found: 527.2260 $[2M+Na]^+$; R_f = 0.30 (silica gel, cyclohexane:EtOAc, 3:1); **HPLC** (AD-H, *n*heptane:*i*PrOH 90:10, 0.5 mL/min, 25 °C, 220 nm): $t_{R(trans)}$ = 27.5 min, $t_{R2(cis)}$ = 34.1 min, $t_{R3(trans)}$ = 38.6 min, $t_{R4(cis)}$ = 47.1 min.

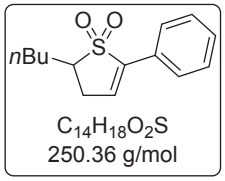
2-Butyl-5-phenyl-4,5-dihydrothiophene 1,1-dioxide (155)



Synthesized following the general working procedure for hydrogenations with iridium catalysts. The mixture of **155**, **156** and **157** (51:18:31, GC-MS) was separated by semi-preparative HPLC (AD, *n*Hex:*i*PrOH, 95:5, 8.0 mL/min, 25 °C). Compound **155** was obtained in its pure form, while dihydrothiophene **157** was obtained as a mixture with tetrahydrothiophene **156** (1.0:0.5, ^{1}H-NMR).

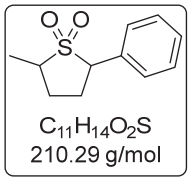
^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.44–7.37 (m, 5H, HC_{ar}), 6.39 (ddt, $^{3,4}J_{HH}$ = 4.1, 2.8, 1.6 Hz, 1H, CH), 4.42 (dd, $^3J_{HH}$ = 8.3, 7.1 Hz, 1H, CH), 3.16 (dddt, $^{2,3,4}J_{HH}$ = 18, 8.1, 4.0, 1.9 Hz, 1H, CH_2), 2.98 (ddq, $^{2,3}J_{HH}$ = 18, 7.3, 2.5 Hz, 1H, CH_2), 2.47 (m_c, 2H, CH_2), 1.66 (m_c, 2H, CH_2), 1.47–1.39 (m, 2H, CH_2), 0.95 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 144.6 (SO_2C_{ar}), 131.2 (C_{ar}), 130.1 (SO_2CCH), 129.3 (2 HC_{ar}), 129.3 (HC_{ar}), 129.1 (2 HC_{ar}), 64.8 (SO_2CH), 32.4 (CH_2), 29.6 (CH_2), 24.3 (CH_2), 22.4 (CH_2), 13.9 (CH_3); **MS** (EI), *m*/*z* (%) 129 (39), 128 (11), 105 (11), 104 (100).

2-Butyl-5-phenyl-2,3-dihydrothiophene 1,1-dioxide (157)



^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.43–7.37 (m, 5H, HC_{ar}), 6.71 (dd, $^3J_{HH}$ = 4.3, 2.8 Hz, 1H, C*H*), 3.35 (m_c, 1H, C*H*), 3.16 (ddd, $^{2,3}J_{HH}$ = 18, 8.1, 4.3 Hz, 1H, CH_2), 2.98 (ddd, $^{2,3}J_{HH}$ = 18, 6.8, 2.8 Hz, 1H, CH_2), 2.46–2.32 (m, 2H, CH_2), 2.17–1.93 (m, 2H, CH_2), 1.74–1.64 (m, 2H, CH_2), 0.95 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3); **MS** (EI), *m*/*z* (%) 250 (29), 143 (45), 130 (25), 129 (36), 128 (24), 115 (24), 105 (30), 103 (12), 102 (100), 91 (14).

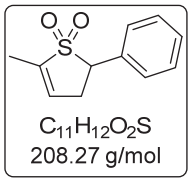
2-Methyl-5-phenyltetrahydrothiophene 1,1-dioxide (159)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* (84:16) isomers could not be separated.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.41–7.37 (m, 5H, HC_{ar}), 4.23 (m_c, 1H, SO_2CH *cis*), 4.14–4.09 (m, 1H, SO_2CH *trans*), 3.35–3.26 (m, 1H, SO_2CH *cis*), 3.24–3.14 (m, 1H, SO_2CH *trans*), 2.48–2.36 (m, 3H, CH_2 *cis*), 2.01–1.91 (m, 1H, CH_2 *cis*), 1.44 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3 *cis*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 130.9 (C_{ar}), 129.3 (2 HC_{ar}), 129.1 (HC_{ar}), 128.9 (2 HC_{ar}), 65.8 (SO_2CH), 55.0 (SO_2CH), 27.7 (CH_2), 26.2 (CH_2), 13.0 (CH_3); **MS** (EI), *m*/*z* (%) 104 (100); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3030w, 2933w, 2873w, 1601w, 1496m, 1452m, 1307s, 1278m, 1252m, 1123s, 766w, 718w, 699w, 592w, 586w; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{11}H_{15}O_2S^+$: 211.0784, found: 211.0787 $[M+H]^+$; calc. *m*/*z* for $C_{11}H_{18}NO_2S^+$: 228.1050, found: 228.1053 $[M+NH_4]^+$; calc. *m*/*z* for $C_{11}H_{14}NaO_2S^+$: 233.0608, found: 233.0607 $[M+Na]^+$; calc. *m*/*z* for $C_{11}H_{14}KO_2S^+$: 249.0341, found: 249.0346 $[M+K]^+$; calc. *m*/*z* for $C_{22}H_{28}NaO_4S_2^+$: 443.1318, found: 443.1321 $[2M+Na]^+$; R_f = 0.13 (silica gel, cyclohexane:EtOAc, 3:1); **HPLC** (OD-H, *n*heptane:*i*PrOH 95:5, 0.5 mL/min, 25 °C, 220 nm): $t_{R(cis1)}$ = 54.5 min, $t_{R(trans1)}$ = 60.2 min, $t_{R(cis2)}$ = 67.2 min, $t_{R(trans2)}$ = 75.4 min.

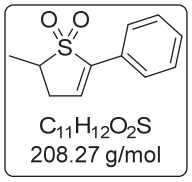
2-Methyl-5-phenyl-4,5-dihydrothiophene 1,1-dioxide (158)



Synthesized following the general working procedure for hydrogenations with iridium catalysts. The mixture of **158** and **160** (71:29, GC-MS) was separated by semi-preparative HPLC (OD, *n*Hex:*i*PrOH, 90:10, 8.0 mL/min). Both mono-reduced compounds were obtained in their pure form.

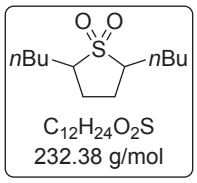
^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.45–7.37 (m, 5H, *H*C$_{ar}$), 6.41 (m$_c$, 1H, C*H*), 4.42 (dd, $^3J_{HH}$ = 8.1, 7.3 Hz, 1H, C*H*), 3.16 (dddt, $^{2,3,4}J_{HH}$ = 18, 8.0, 3.9, 2.0 Hz, 1H, CH_2), 2.97 (ddd, $^{2,3}J_{HH}$ = 18, 7.2, 2.5 Hz, 1H, CH_2), 2.12 (dt, $^3J_{HH}$ = 2.5, 1.8 Hz, 3H, CH_3); **MS** (EI), *m*/*z* (%) 208 (15), 129 (33), 128 (15), 104 (100), 103 (11), 78 (14).

2-Methyl-5-phenyl-2,3-dihydrothiophene 1,1-dioxide (160)



^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.69–7.67 (m, 2H, *H*C$_{ar}$), 7.42–7.41 (m, 3H, *H*C$_{ar}$), 6.72 (dd, $^3J_{HH}$ = 3.8, 3.2 Hz, 1H, C*H*), 3.46 (dq, $^3J_{HH}$ = 14, 7.0 Hz, 1H, C*H*), 3.11 (ddd, $^{2,3}J_{HH}$ = 18, 8.1, 4.1 Hz, 1H, CH_2), 2.50 (ddd, $^{2,3}J_{HH}$ = 18, 6.1, 3.0 Hz, 1H, CH_2), 1.52 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3); **MS** (EI), *m*/*z* (%) 208 (23), 129 (50), 128 (13), 115 (11), 105 (21), 103 (10), 102 (100).

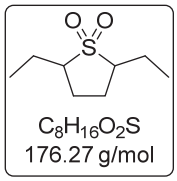
2,5-Dibutyltetrahydrothiophene 1,1-dioxide (168)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* (90:10) isomers could not be separated.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.01–2.93 (m, 2H, SO_2C*H*), 2.24–2.15 (m, 2H, CH_2), 2.00–1.89 (m, 2H, CH_2), 1.80–1.71 (m, 2H, CH_2), 1.53–1.31 (m, 10H, CH_2), 0.93 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 60.6 (2 SO_2CH), 29.5 (2 *C*H_2), 27.8 (2 *C*H_2), 26.3 (2 *C*H_2), 22.7 (2 *C*H_2), 14.0 (2 *C*H_3); **MS** (EI), *m*/*z* (%) 111 (46), 97 (68), 85 (14), 84 (14), 83 (64), 69 (100), 67 (12), 57 (25), 56 (43), 55 (72), 43 (33), 42 (21), 41 (44); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3735w, 2956w, 2933w, 2860w, 1457w, 1294w, 1111w, 604w, 564m, 542s; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_{12}H_{25}O_2S^+$: 233.1568, found: 233.1570 $[M+H]^+$; calc. *m*/*z* for $C_{12}H_{28}NO_2S^+$: 250.1834, found: 250.1835 $[M+NH_4]^+$; calc. *m*/*z* for $C_{12}H_{24}NaO_2S^+$: 255.1392, found: 255.1389 $[M+Na]^+$; calc. *m*/*z* for $C_{24}H_{48}NaO_4S_2^+$: 487.2885, found: 487.2886 $[2M+Na]^+$; R_f = 0.37 (silica gel, cyclohexane:EtOAc, 3:1).

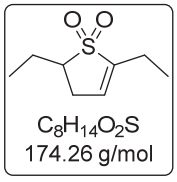
2,5-Diethyltetrahydrothiophene 1,1-dioxide (170)



Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The mixture of *cis*:*trans* (95:5) isomers could not be separated.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 2.96–2.88 (m, 2H, SO_2CH), 2.24–2.16 (m, 2H, CH_2), 2.04–1.93 (m, 2H, CH_2), 1.80–1.71 (m, 2H, CH_2), 1.61–1.49 (m, 2H, CH_2), 1.07 (t, $^3J_{HH}$ = 7.4 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 62.3 (2 SO_2CH), 26.0 (2 CH_2), 21.6 (2 CH_2), 12.0 (2 CH_3); **MS** (EI), *m*/*z* (%) 111 (19), 70 (23), 69 (100), 57 (10), 56 (36), 55 (53), 42 (16), 41 (48); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2964w, 2938w, 2915w, 2878w, 2854w, 1461w, 1456w, 1448w, 1383w, 1286m, 1273m, 1243w, 1152w, 1108m, 1076w, 1016w, 749w, 710w, 515s; **HRMS** (ESI, 4500 V, 180 °C) calc. *m*/*z* for $C_8H_{16}O_2S^+$: 177.0942, found: 177.0944 $[M+H]^+$; calc. *m*/*z* for $C_8H_{20}NO_2S^+$: 194.1207, found: 194.1209 $[M+NH_4]^+$; calc. *m*/*z* for $C_8H_{16}NaO_2S^+$: 199.0765, found: 199.0763 $[M+Na]^+$; calc. *m*/*z* for $C_{16}H_{32}NaO_4S_2^+$: 375.1630, found: 375.1634 $[2M+Na]^+$; R_f = 0.21 (silica gel, cyclohexane:EtOAc, 3:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): $t_{R(trans1)}$ = 53.0 min, $t_{R(trans2)}$ = 56.2 min, $t_{R(cis)}$ = 61.0 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): $t_{R(trans)}$ = 57.8 min; $t_{R(cis)}$ = 60.5 min.

2,5-Diethyl-2,3-dihydrothiophene 1,1-dioxide (171)



Synthesized following the general working procedure for hydrogenations with iridium catalysts.

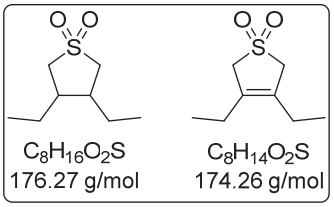
^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.19 (dq, $^{3,4}J_{HH}$ = 4.1, 2.0 Hz, 1H, SO_2CCH), 3.11 (quint, $^3J_{HH}$ = 7.5 Hz, 1H, SO_2CH), 2.94–2.84 (m, 1H, CH_2), 2.35 (m_c, 1H, CH_2), 2.11–2.00 (m, 2H, CH_2), 1.71–1.60 (m, 2H, CH_2), 1.22 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3), 1.13 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 146.4 (SO_2C), 129.4 (SO_2CCH), 60.2 (SO_2CH), 31.2 (CH_2), 22.1 (CH_2), 17.4 (CH_2), 11.9 (CH_3), 11.8 (CH_3); **MS** (EI), *m*/*z* (%) 174 (36), 157 (18), 126 (14), 107 (12), 95 (12), 81 (59), 79 (29), 77 (10), 68 (25), 67 (100), 57 (33), 56 (13), 55 (39), 53 (22), 43 (16), 41 (52); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2971m, 2938m, 2880w, 2848w, 1718w, 1653w, 1460m, 1439m, 1384w, 1345w, 1282s, 1220m, 1137s, 1118s, 1072m, 1025m, 1007m, 967m, 891m, 838m, 734m, 709m, 643m, 621m, 590m, 574m, 548m, 527m, 511m, 484m; R_f = 0.18 (silica gel, cyclohexane:EtOAc, 3:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA,

25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_{R1} = 63.5 min; t_{R2} = 65.1 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 63.2 min; **[α]$_D^{20}$** +8.7 (*c* 0.95, CH_2Cl_2, 1% *cis*, >99% *ee*). The NMR spectra were consistent with the literature data.[95]

3,4-Diethyltetrahydrothiophene 1,1-dioxide (154a), 3,4-diethyl-2,5-dihydrothiophene 1,1-dioxide (154b) and 3,4-diethyl-2,3-dihydrothiophene 1,1-dioxide (154c)

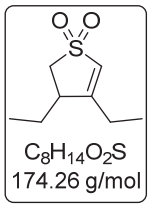
Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The product mixture of fully reduced (70%) (*dr* = 5:1, *cis*:*trans*) and rearranged product (27%) and mono reduced product (4%) could not be separated.

3,4-Diethyltetrahydrothiophene 1,1-dioxide (154a) and 3,4-diethyl-2,5-dihydrothiophene 1,1-dioxide (154b) (72:28)



^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.76 (s, 4H, SO_2CH_2 rearranged product), 3.31 (dd, $^{2,3}J_{HH}$ = 13.3, 7.2 Hz, 2H, SO_2CH_2, *cis*), 3.13 (dd, $^{2,3}J_{HH}$ = 13.2, 7.2 Hz, 2H, SO_2CH_2 *trans*), 2.97 (dd, $^{2,3}J_{HH}$ = 13.1, 6.6 Hz, 2H, SO_2CH_2 *trans*), 2.76 (dd, $^{2,3}J_{HH}$ = 13.2, 10.7 Hz, 2H, SO_2CH_2 *cis*), 2.40–2.35 (m, 2H, C*H trans*), 2.20 (q, $^3J_{HH}$ = 7.5 Hz, 4H, CH_2 rearranged product), 2.11–2.04 (m, 2H, C*H cis*), 1.86–1.76 (m, 2H, CH_2 *cis*), 1.57–1.47 (m, 4H, CH_2 *trans*), 1.36–1.27 (m, 2H, CH_2 *cis*), 1.01 (t, $^3J_{HH}$ = 7.6 Hz, 6H, CH_3 rearranged product), 0.96 (t, $^3J_{HH}$ = 7.3 Hz, 6H, CH_3 *trans*), 0.93 (t, $^3J_{HH}$ = 7.5 Hz, 6H, CH_3 *cis*); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 131.0 (2 SO_2CH_2C rearranged product), 58.9 (2 SO_2CH_2 rearranged product), 57.3 (2 SO_2CH_2 *cis*), 55.9 (2 SO_2CH_2 *trans*), 43.3 (2 SO_2CH_2CH *cis*), 42.0 (2 SO_2CH_2CH *trans*), 25.2 (2 CH_2CH_3 *cis*), 22.0 (2 CH_2CH_3 rearranged product), 21.1 (2 CH_2CH_3 *trans*), 12.6 (2 CH_3 rearranged product), 12.2 (2 CH_3 *trans*), 11.9 (2 CH_3 *cis*); R_f = 0.26 (silica gel, cyclohexane:EtOAc, 3:1).

3,4-Diethyl-2,3-dihydrothiophene 1,1-dioxide (154c)



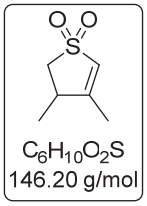
Synthesized following the general working procedure for hydrogenations with iridium catalysts.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.31 (q, $^4J_{HH}$ = 1.7 Hz, 1H, SO_2CH), 3.42 (dd, $^{2,3}J_{HH}$ = 13.4, 8.3 Hz, 1H, CH_2), 3.04 (dd, $^{2,3}J_{HH}$ = 13.5, 4.0 Hz, 1H, CH_2), 2.42–2.32 (m, 5H, CH), 2.18–2.11 (m, 2H, CH_2), 1.85–1.80 (m, 2H, CH_2), 1.16 (t, $^3J_{HH}$ = 7.3 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 138.5 (C_q), 125.4 (SO_2CH), 54.3 (CH_2), 43.3 (CH), 29.9 (2 CH_2), 11.1 (2 CH_3); **MS** (EI), *m*/*z* (%) 174 (76), 157 (44), 146 (68), 145 (14), 131 (11), 129 (30), 115 (16), 113 (12), 108 (11), 107 (19), 99 (11), 98 (36), 97 (17), 96 (14), 95 (30), 93 (30), 91 (13), 85 (28), 83 (13), 82 (19), 81 (52), 80 (17), 79 (80), 77 (28), 69 (20), 68 (14), 67 (82), 66 (11), 65 (21), 57 (20), 56 (16), 55 (72), 54 (12), 53 (58), 52 (10), 51 (17), 45 (13), 44 (11), 43 (39), 41 (100), 40 (15); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3077w, 2961m, 2927m, 2874w, 2857w, 1727m, 1629w, 1460m, 1412w, 1382w, 1288m, 1258s, 1228m, 1140m, 1122m, 1091s, 1073m, 1013m, 950w, 923w, 892w, 862m, 791s, 744m, 705m, 661w, 576m, 524m, 489m; R_f = 0.11 (silica gel, cyclohexane:EtOAc, 3:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_{R1} = 71.3 min, t_{R2} = 72.2 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 74.3 min.

3,4-Dimethyl-2,3-dihydrothiophene 1,1-dioxide (153c) and 3,4-dimethyl-2,5-dihydrothiophene 1,1-dioxide (153b)

Synthesized following the general working procedure for hydrogenations with palladium on charcoal. The product mixture of mono reduced product (59%) and rearranged product (41%) was separated by flash chromatography (silica gel, 10×1 cm, cyclohexane:EtOAc, 3:1).

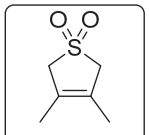
3,4-Dimethyl-2,3-dihydrothiophene 1,1-dioxide (153c)



^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 6.29 (q, $^4J_{HH}$ = 1.5 Hz, 1H, SO_2CH), 3.49 (ddd, $^{2,3}J_{HH}$ = 13.4, 8.1 Hz, 1H, CH_2), 3.07–3.00 (m, 1H, CH), 2.95 (dd, $^{2,3}J_{HH}$ = 13.4, 4.1 Hz, 1H, CH_2), 1.78 (t, $^4J_{HH}$ = 1.2 Hz, 3H, CH_3), 1.32 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 155.7 (SO_2CHC), 126.4 (SO_2CH), 57.1 (CH_2), 37.6 (CH), 18.6 (CH_3), 16.6 (CH_3); **MS** (EI), *m*/*z* (%) 146 (34), 129 (15), 117 (44), 98 (16), 83 (10), 82 (23), 81 (16), 80 (11), 79 (23), 69 (26), 67 (80), 65 (20), 55 (16), 54 (12), 53 (23), 43 (49), 42 (44), 41 (100), 40 (15);

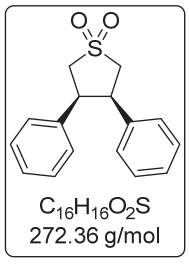
IR ($\tilde{\nu}$ [cm^{-1}]) 3074w, 2974w, 2879w, 1738w, 1631w, 1439w, 1416w, 1378w, 1281s, 1226m, 1175m, 1140s, 1108m, 1089s, 1000w, 918w, 875m, 779m, 721w, 607m, 595m, 569m, 537m, 499w, 479m, 464m; R_f = 0.10 (silica gel, cyclohexane:EtOAc, 3:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_{R1} = 68.3 min, t_{R2} = 69.2 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 64.6 min.

3,4-Dimethyl-2,5-dihydrothiophene 1,1-dioxide (153b)



m.p. 124–128 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 3.72 (d, $^4J_{HH}$ = 1.2 Hz, 4H, CH_2), 1.78 (t, $^4J_{HH}$ = 1.2 Hz, 6H, CH_3); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 125.8 (2 SO_2CH_2C), 60.9 (2 SO_2CH_2), 14.8 (2 CH_3); **MS** (EI), *m*/*z* (%) 83 (12), 82 (40), 69 (22), 67 (61), 65 (12), 64 (31), 56 (20), 55 (22), 54 (15), 53 (10), 48 (17), 43 (16), 42 (100), 41 (70), 40 (13); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2955w, 2922w, 2856w, 1739w, 1443w, 1403w, 1386w, 1289m, 1262m, 1198w, 1176m, 1134w, 1108s, 822m, 726w, 563s, 483s; R_f = 0.15 (silica gel, cyclohexane:EtOAc, 3:1); **GC** (β-Cyclodextrin, Diethyl-*t*BuSilyl-086, MEGA, 25 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 100 °C, 60 min, 10 °C/min, 180 °C, 10 min): t_R = 64.3 min; **GC** (14% Cyanopropylphenyl/86% Dimethylpolysiloxane, Restek Rtx-1701, 30 m × 0.25 mm × 0.25 µm, 60 kPa H_2, 130 °C, 60 min, 7 °C/min, 250 °C, 10 min): t_R = 81.2 min. The NMR spectra were consistent with the literature data.[96]

3,4-(*cis*)-Diphenyltetrahydrothiophene 1,1-dioxide (152a)

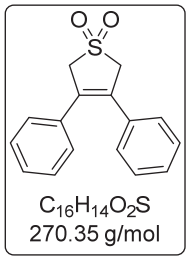


m.p. 180–181 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.21–7.13 (m, 6H, HC_{ar}), 6.83 (dd, $^{3,4}J_{HH}$ = 8.0, 1.6 Hz, 4H, HC_{ar}), 4.05 (td, $^3J_{HH}$ = 5.7, 2.9 Hz, 2H, CH), 3.67 (dd, $^{2,3}J_{HH}$ = 13.6, 7.7 Hz, 2H, SO_2CH_2), 3.53 (dd, $^{2,3}J_{HH}$ = 13.5, 7.8 Hz, 2H, SO_2CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 136.7 (2 C_{ar}), 126.5 (4 HC_{ar}), 128.3 (4 HC_{ar}), 127.7 (2 HC_{ar}), 55.9 (2 CH_2), 47.4 (2 CH); **MS** (EI), *m*/*z* (%) 104 (100), 103 (10), 78 (11); **IR** ($\tilde{\nu}$ [cm^{-1}]) 3027w, 3005w, 2365w, 1491m, 1455m, 1424w, 1416w, 1297s, 1282m, 1267m, 1255w, 1225m, 1202m, 1184w, 1132m, 1121s, 1115s, 1083m, 1075m, 1033w, 927w, 911m, 859m, 853m, 766s, 760s, 733w, 695m, 674m, 652m, 623m, 617m, 590m, 557m; R_f = 0.25 (silica gel, cyclohexane:EtOAc, 3:1).

3,4-Diphenyl-2,5-dihydrothiophene 1,1-dioxide (152b) and 3,4-diphenyl-2,3-dihydrothiophene 1,1-dioxide (152c)

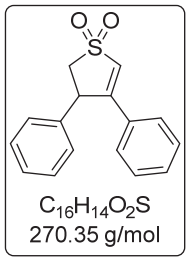
Synthesized following the general working procedure for hydrogenations with iridium catalysts (CRABTREE catalyst with BAr_F as counterion was used). The product mixture of rearranged product (89%) and mono reduced product (11%) was purified by flash chromatography (silica gel, 8×1 cm, cyclohexane:EtOAc, 5:1).

3,4-Diphenyl-2,5-dihydrothiophene 1,1-dioxide (152b)



m.p. 176–177 °C; **^{1}H-NMR** (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.28–7.21 (m, 6H, *H*C$_{ar}$), 7.11–7.08 (m, 4H, *H*C$_{ar}$), 4.31 (s, 4H, 2 $SO_2C\mathit{H}_2$); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 139.4 (2 *C*$_{ar}$), 134.8 (2 *C*$_{ar}$), 131.1 (2 HC$_{ar}$), 128.8 (4 HC$_{ar}$), 128.6 (4 HC$_{ar}$), 61.3 (2 *C*H$_2$); **MS** (EI), *m*/*z* (%) 207 (39), 206 (100), 205 (70), 204 (19), 203 (22), 202 (18), 191 (40), 190 (18), 189 (14), 178 (16), 165 (15), 129 (17), 128 (35), 127 (11), 115 (22), 103 (11), 102 (15), 101 (16), 91 (71), 89 (18), 77 (31), 76 (12), 51 (15), 44 (10); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2965w, 2923w, 1741w, 1599w, 1490w, 1443w, 1391m, 1298s, 1250m, 1204m, 1189w, 1133m, 1121s, 1067m, 1031w, 1003w, 977w, 933m, 913w, 898w, 885w, 789m, 759s, 729w, 694s, 637w, 623w, 598m, 502m, 482m, 465m; R_f = 0.20 (silica gel, cyclohexane:EtOAc, 5:1); **HPLC** (AD-H, *n*heptane:*i*PrOH 80:20, 0.5 mL/min, 25 °C, 258 nm): t_R = 17.2 min.

3,4-Diphenyl-2,3-dihydrothiophene 1,1-dioxide (152c)



^{1}H-NMR (400.1 MHz, $CDCl_3$, 300 K): δ (ppm) 7.39–7.27 (m, 10H, *H*C$_{ar}$), 7.03 (d, $^4J_{HH}$ = 1.5 Hz, 1H, $SO_2C\mathit{H}$), 4.80 (ddd, $^{3,4}J_{HH}$ = 9.2, 3.0, 1.5 Hz, 1H, C*H*), 3.93 (dd, $^{2,3}J_{HH}$ = 13.8, 9.1 Hz, 1H, CH_2), 3.39 (dd, $^{2,3}J_{HH}$ = 13.8, 3.0 Hz, 1H, CH_2); **^{13}C{^{1}H}-NMR** (100.6 MHz, $CDCl_3$, 300 K): δ (ppm) 152.3 (SO_2CHC), 139.5 (*C*$_{ar}$), 132.0 (*C*$_{ar}$), 130.7 (HC$_{ar}$), 129.5 (2 HC$_{ar}$), 129.0 (2 HC$_{ar}$), 127.7 (2 HC$_{ar}$), 127.6 (2 HC$_{ar}$), 126.7 (HC$_{ar}$), 99.0 (*C*H), 57.3 (*C*H), 43.3 (*C*H$_2$); **MS** (EI), *m*/*z* (%) 270 (34), 207 (26), 206 (14), 205 (14), 105 (13), 104 (100), 103 (13), 102 (17), 91 (27), 78 (13), 77 (12); **IR** ($\tilde{\nu}$ [cm^{-1}]) 2952w, 2923m, 2853m, 1736w, 1603w, 1494w, 1456w, 1377w, 1295m, 1260m, 1218w, 1122m, 1073m, 1029m, 932w, 804m, 754m, 700m, 606w, 519m, 495m; R_f = 0.11 (silica gel, cyclohexane:EtOAc, 5:1); **HPLC** (AD-H, *n*heptane:*i*PrOH 80:20, 0.5 mL/min, 25 °C, 258 nm): t_{R1} = 26.1 min, t_{R2} = 44.4 min.

7.9 Crystallographic Data

	152a	**166**	**167**
molecular formula	$C_{36}H_{32}O_4S_2$	$C_{18}H_{20}OS$	$C_{16}H_{16}O_2S$
molecular weight [g/mol]	272.37	284.42	592.78
calculated density [mg/m^{-3}]	1.367	1.276	1.356
description	colorless needle	colorless block	colorless block
crystal size [mm^3]	0.03×0.08×0.21	0.04×0.11×0.23	0.03×0.16×0.19
absorption coefficient [mm^{-1}]	2.123	1.866	1.986
transmission min/max	0.84/0.94	0.81/0.93	0.73/0.94
temperature [K]	123	123	123
radiation (wavelength)	Cu K_α (λ = 1.54178 Å)	Cu K_α (λ = 1.54178 Å)	Cu K_α (λ = 1.54178 Å)
crystal system	monoclinic	monoclinic	monoclinic
space group	P 2_1/c	C /c	C 2/c
a [Å]	14.1058(9)	24.7153(16)	18.6087(7)
b [Å]	5.8637(3)	11.2473(7)	9.2478(4)
c [Å]	16.6087(10)	22.1394(14)	18.2691(11)
α [°]	90	90	90
β [°]	105.510(4)	105.788(3)	112.5780(10)
γ [°]	90	90	90
V [Å^3]	1323.72(14)	5922.1(7)	2903.0(2)
Z	4	16	4
F (000)	576	2432	1248
Θ-range of data collection [°]	3.251/68.294	4.150/68.338	5.148/68.288
measured reflections	10564	23164	10339
independent reflections	2361 (merging r = 0.031)	7636 (merging r = 0.032)	2617 (merging r = 0.024
observed reflections	2102 (I>2.0σ(I))	7386 (I>2.0σ(I))	2570 (I>2.0σ(I))
refined parameters	172	722	190
R	0.0311	0.0291	0.0350
R_W	0.0400	0.0386	0.0403
goodness of fit	1.0722	1.0471	1.0855

7.10 List of Abbreviations

acac	acetylacetone
Ac	acetate
aq.	aqueous
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl, phenylmethyl
Bu	butyl
°C	Celsius
calc.	calculated
CAN	ceric ammonium nitrate
cat.	catalyst
COD	1,5-cyclooctadien
conv.	conversion
Cy	cyclohexane
d (NMR)	doublet
DIAD	diisopropyl azodicarboxylate
DMA	dimethylacetamide
DME	dimethylether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,2-bis(diphenylphosphino)propane
de	diastereomeric excess
dr	diastereomeric ratio
δ (NMR)	chemical shift in ppm
EI (MS)	electron ionization

ee	enantiomeric excess
eq.	stoichiometric equivalent
ESI (MS)	electrospray ionization
Et	ethyl
Hal	halogen
Hex	hexane
HPLC	high performance liquid chromatography
Hz	hertz
IR	Infrared spectroscopy
*i*Pr	isopropyl
J_{xy}	coupling constant between nuclei *x* and *y*
L	ligand
M	molar (Molarity)
m (IR)	medium (signal intensity)
m (NMR)	multiplet
m_c (NMR)	center-symmetrical multiplet
Me	methyl
m.p.	melting point
ms	molecular sieves
MS	mass spectrometry
MTBE	methyl-*t*butylether
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
n.d.	not detected
Np	neopentyl
*o*Tol	*ortho*-tolyl

Pd/C	palladium on charcoal
Ph	phenyl
ppm	parts per million, 10^{-6}
PPTS	pyridinium *p*toluenesulfonate
Pr	propyl
q (NMR)	quartet
rac	racemic
R_f	retention factor
RT	room temperature
s (IR)	strong (signal intensity)
s (NMR)	singlet
t (NMR)	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t_R	retention time
$\tilde{\nu}$	vawenumber in cm^{-1}
w (IR)	weak (signal intensity)
Xyl	xylyl
9-BBN	9-borabicyclo[3.3.1]nonane

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