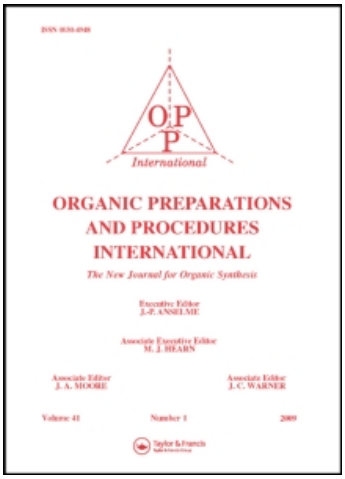

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Ferruccio Bertolini[a]; Mauro Pineschi[a]
[a] Dipartimento di Scienze Farmaceutiche, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Pisa, Italy

To cite this Article Bertolini, Ferruccio and Pineschi, Mauro(2009) 'Recent Progress in the Synthesis of 2,3-Dihydrobenzofurans', Organic Preparations and Procedures International, 41: 5, 385 — 418
To link to this Article: DOI: 10.1080/00304940903240836
URL: http://dx.doi.org/10.1080/00304940903240836

Organic Preparations and Procedures International, 41:385–418, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940903240836

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Ferruccio Bertolini and Mauro Pineschi

Dipartimento di Scienze Farmaceutiche, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

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Dipartimento di Scienze Farmaceutiche, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

Introduction

The 2,3-dihydrobenzofuran ring-system constitutes the core skeleton of an increasing number of biologically active compounds. As the name implies, 2,3-benzofuran, otherwise called benzo[b]furans, contains a ring system derived by the fusion of a benzene nucleus with a furan ring in the manner of formula **1** (*Figure* 1). The older name "coumarone" is nearly obsolete. The corresponding formal hydrogenation of the furan ring gives the 2,3-dihydrobenzofuran (**2**) nucleus (older name coumarane).

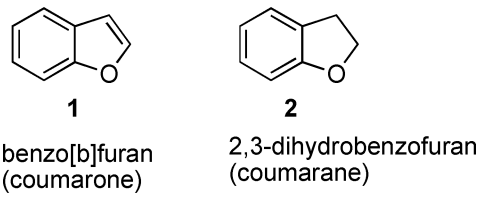
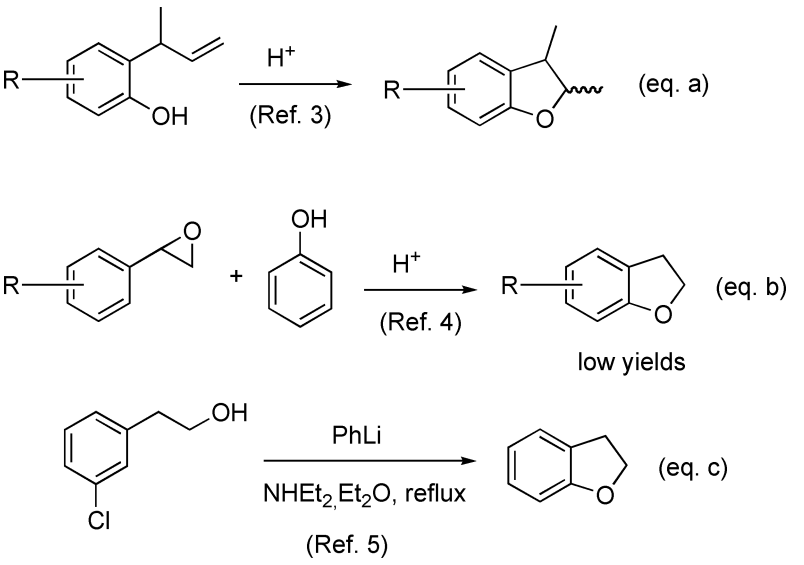


Figure 1

The dihydrobenzofuran moiety has been known for a long time, and a first report on its synthesis dates back to 1892.[1] Successively, various methods have been applied for the preparation of 2,3-dihydrobenzofurans. Clearly, many of the methods for the preparation of substituted 2,3-dihydrobenzofurans developed in the early days of the last century do not appear to be satisfactory from the standpoint of yield, selectivity and generality.[2] However, it should be noted that many of the basic principles of this older chemistry often can be found in the most recent synthetic procedures. For example, the cyclization reaction of *ortho*-allylphenols promoted by pyridinium chloride, pionereed by Claisen (*eq. a*, *Scheme 1*),[3] nowadays can be found with transition metal catalysts (see Section VIII-2). The interaction of substituted styrene oxides with phenoxide ion pionereed by Guss *et al.*,[4] in which only marginal amounts of dihydrobenzofurans were obtained (*eq. b*, *Scheme 1*), has been very

Received May 8, 2009; in final form August 4, 2009.

Address correspondence to Mauro Pineschi, Dipartimento di Scienze Farmaceutiche, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy. E-mail: pineschi@farm.unipi.it



Scheme 1

recently transformed into a valuable stereoselective synthetic procedure by our research group (see Section II).[5] The intramolecular nucleophilic cyclization of β-(*m*-chlorophenyl) ethanol obtained by refluxing diethylamine in ether with phenyllithium (*eq. c*, *Scheme 1*),[6] can now be obtained with the aid of transition metal catalysts under much milder reaction conditions (see Section VIII–1).

It should be noted that the hydrogenation of benzofuran derivatives to the corresponding 2,3-dihydrobenzofurans, which might be a reasonably straightforward method to synthesize these compounds, is difficult to achieve with respect to other heteroaromatic nuclei.[7] In fact, the catalytic hydrogenation of benzofuran, under all conditions, is accompanied by partial cleavage of the furan ring and the formation of 2-ethylcyclohexanol and β-cyclohexylethyl alcohol.[8] Also in the very active field of catalytic asymmetric hydrogenation of heteroaromatic compounds, there are very few examples regarding the use of benzofuran derivatives. For example, the asymmetric hydrogenation of benzofuran 2-carboxylic acid proceeded with very poor conversions and low *ee's*.[9]

The aim of this review is to summarize the most recent efficient and rational approaches to the synthesis of 2,3-dihydrobenzofurans up to 2008, with a particular emphasis on regio- and stereoselective processes. The synthesis of cycloalkano[b]benzofuran derivatives, in particular tetrahydrodibenzofurans (such as Pummerer's ketone), which are relevant for the synthesis of morphinic analogs will not be covered.

I. Natural Occurrence of 2,3-Dihydrobenzofurans

The benzofuran nucleus is common in natural products and appears in many forms including several examples of 2,3-dihydrobenzofurans. A well-known example of an aromatic hemiterpene containing the dihydrobenzofuran skeleton is anisoxide **3**, isolated from star anise oil (*Illicium verum*) in 1937.[10] This compound is peculiar in being optically inactive although containing a chiral center (*Figure* 2). More recently, benzodihydrofuran

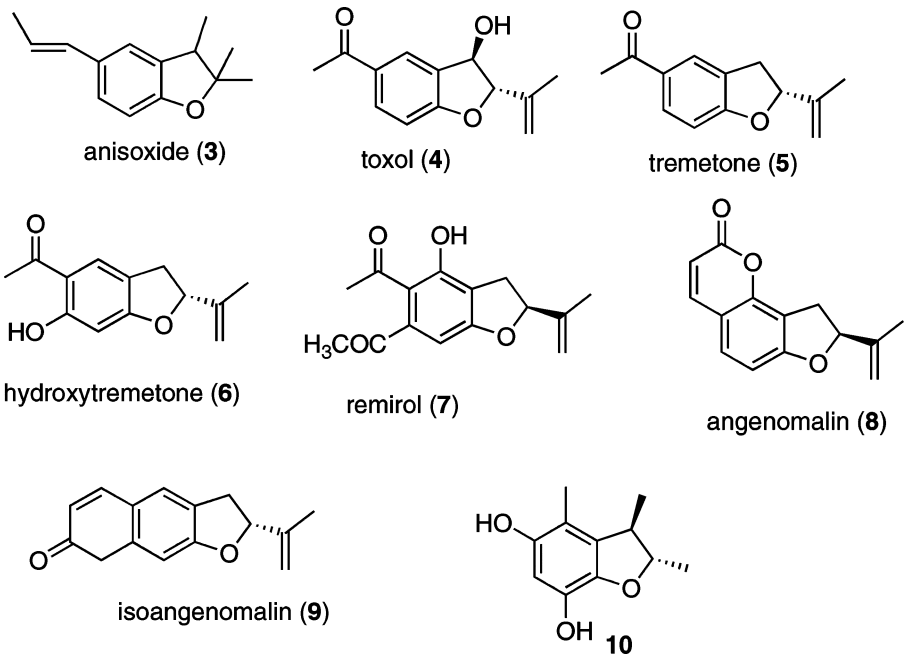


Figure 2

derivatives (**3–9**), all possessing interesting biological activities, have been found in several species of higher plants and in particular in Asteraceae.[11,12]

The absolute configuration of many of these naturally occurring chiral 2-isopropenyl-2,3-dihydrobenzofurans was recently demonstrated by chemical methods. The authors concluded that both *R* and *S* structures exist in natural plants and that this implies that different enzymatic cyclizations are possible in different kinds of plants.[13] Quite recently, a new dihydrobenzofuran derivative having antioxidant properties, 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran (**10**), was isolated from a culture broth of *Penicillum citrinum F5*.[14]

The dihydrobenzofuran ring can be found as a key structural element in the neo-lignans, which are a diverse family of biologically active plant metabolites.[15] These compounds exhibit a broad range of biological activities including, for some classes, antitumor and antiproliferative activities. For example, (2*R*, 3*S*)-3′,4-di-O-methylcedrusin **11**, identified as one of the minor constituents of the red latex called "dragon blood" ("sangre de drago") in traditional medicine, was found to act as an inhibitor of cell proliferation, stimulating the synthesis of analogs based on this scaffold.[16]

Obtusafuran (**12**), a simple dihydrobenzofuran isolated from several Dalbergia species, was shown recently to have potent induction of the anticarcinogenic marker enzyme, quinone reductase (*Figure* 3).[17] Also, neolignan kadsurenone (**13**) has attracted the most attention due to its biological activity as a platelet-activating (PAF) antagonist.[18]

From the plant kingdom, in particular from dipterocarpaceous plants, it is also possible to isolate oligostilbenes having dihydrobenzofuran moieties. These high molecular weight compounds are resveratrol (3,5,4′-trihydroxystilbene) oligomers and possess multifunctional bioactivities.[19]

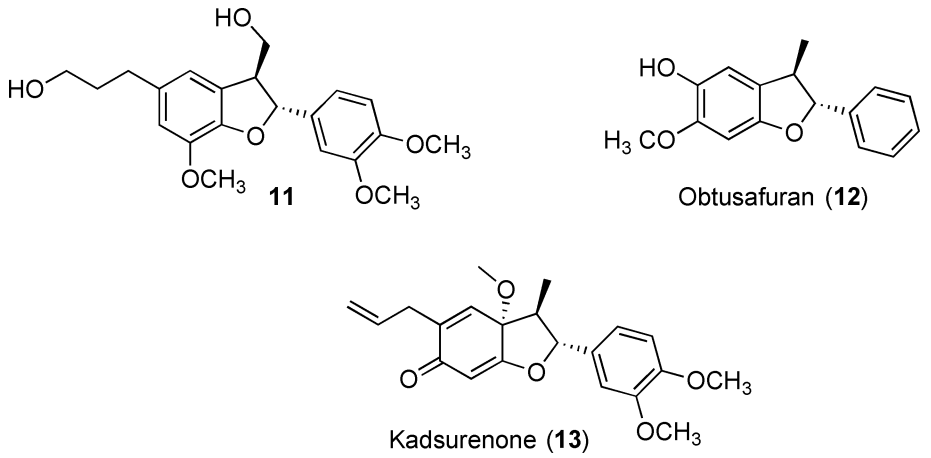
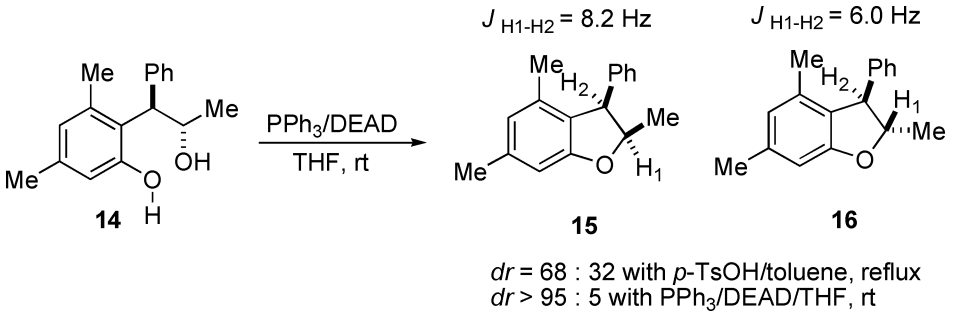


Figure 3

II. Synthesis by Dehydrative Methods

A simple synthesis of dihydrobenzofurans can be achieved by intramolecular dehydration of a molecule containing both a phenol and an alcohol functionality. The use of a Mitsunobu type dehydration (PPh_3, DEAD) to perform this trasformation was first reported by Aristoff and co-workers in 1984,[20] and since that time several reports in the literature have described this kind of dehydrative cyclization. The complete inversion of configuration, together with the high yields generally obtained, are the major advantages of the Mitsunobu type cyclization, especially when substituted chiral hydroxy phenols are employed. For example, we reported recently that hydroxyphenols, *e. g.* **14**, in turn obtained by stereoselective *ortho*-alkylation of aryl borates with aryl epoxides, were suitable precursors to prepare 3-aryl-2,3-dihydrobenzofurans such as **15** and **16** by a simple cyclodehydration (*Scheme 2*).[5] Treatment of hydroxyphenol **14** with catalytic amounts of *p*-TsOH in refluxing toluene gave an inseparable 68/32 mixture of diastereoisomeric *cis*- (**15**) and *trans*-2-methyl-3-phenyl-5,7-dimethyl-2,3-dihydrobenzofurans (**16**), while when the cyclodehydration was effected by means of an intramolecular Mitsunobu type protocol (PPh_3, DEAD, THF, rt), compound **15** was isolated with 80% yield and a high diastereocontrol (*Scheme 2*).

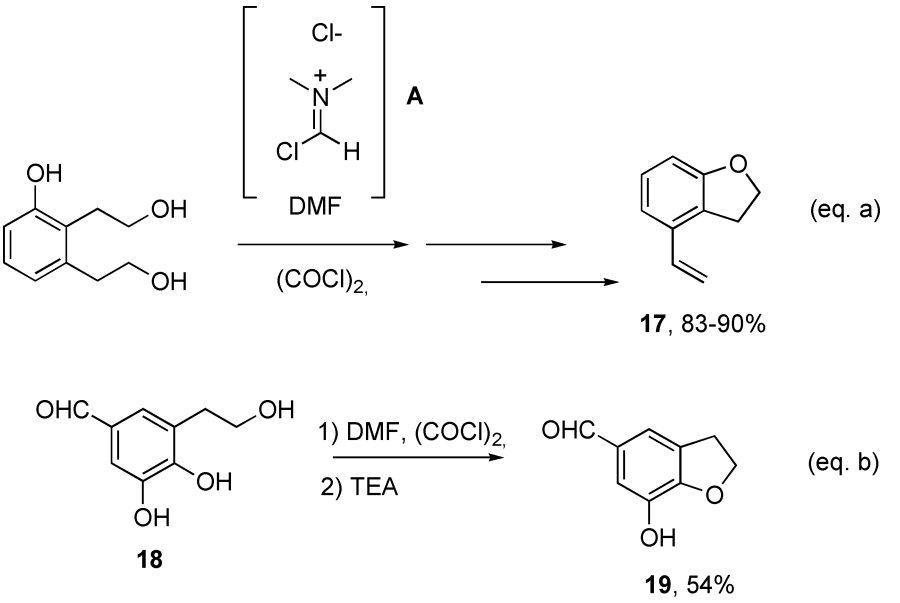


Scheme 2

It should be noted that diastereoisomeric 2,3-substituted 2,3-dihydrobenzofurans can be distinguished easily by ^{1}H NMR examination of the coupling constants of the corresponding benzylic proton ($J_{H1\text{-}H2} = 8.0$–9.5 Hz in *cis*-systems, $J_{H1\text{-}H2} = 4.0$–6.5 Hz in *trans*-systems). The ready availability of aryl epoxides also in enantioenriched forms, together with the high regio- and stereoselectivity associated with their ring-opening reaction, gives a reliable method for the preparation of these important heterocyclic targets. In particular cases, the Mitsunobu cyclization is possible only if *syn*-diastereoisomeric hydroxy phenols are used, because the *anti*-diastereoisomers give a completely different reaction pathway leading to 2,5-dihydrobenzooxepines.[21]

However, it should be noted that there are also some disadvantages associated with the Mitsunobu reaction. Diethyl azodicarboxylate (DEAD) is unstable and potentially explosive, and the by-products triphenylphosphine oxide and diethyl hydrazinedicarboxylate are of considerable mass, making the process non-ideal from the point of view of atom economy and not suitable for scale-up. For the solution of these problems, Procopiou and co-workers have reported the use of the Vilsmeier reagent **A** (from DMF, oxalyl chloride) followed by triethylamine (TEA) for the cyclization of hydroxyphenols to afford dihydrobenzofurans *via* formation of an imidate ester followed by displacement with phenoxide.[22] This chemistry is especially attractive for large-scale operations because of its atom efficiency and environmentally acceptable by-products such as DMF and triethylamine hydrochloride.

Quite recently, a practical pilot-scale synthesis of 4-vinyl-2,3-dihydrobenzofuran (**17**), a versatile early intermediate for the preparation of several melatonin agonists identified by Bristol-Myers Squibb, was accomplished using this chemistry (*eq. a*, *Scheme 3*).[23]

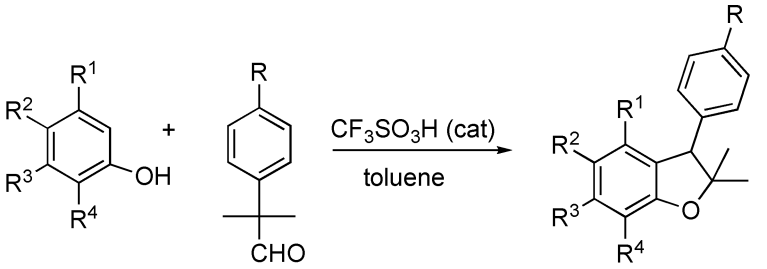


Scheme 3

Moreover, the Mitsunobu type cyclodehydration for the synthesis of 2,3-dihydrobenzofurans poses some limitation when highly substituted hydroxyphenols are utilized. For example, triol aldehyde **18** failed to deliver the corresponding 2,3-dihydrobenzofuran

19 under Mitsunobu conditions; however, a clean cyclization (54% yield for two steps) was obtained by the use of the Vilsmeier reagent (*eq. b*, *Scheme 3*).[24]

A different dehydrative approach was used by Yamashita *et al*. for the synthesis of 3-aryl-2,3-dialkyl-2,3-dihydrobenzofurans starting from phenols and 2-aryl-2,3-dialkylacetaldehyde in the presence of an acid catalyst (*Scheme 4*). However, electron-donating substituents were required on the phenol in order to have good yield of cyclized products. The full reaction mechanism for this novel ring formation was nicely elucidated by the authors.[25]

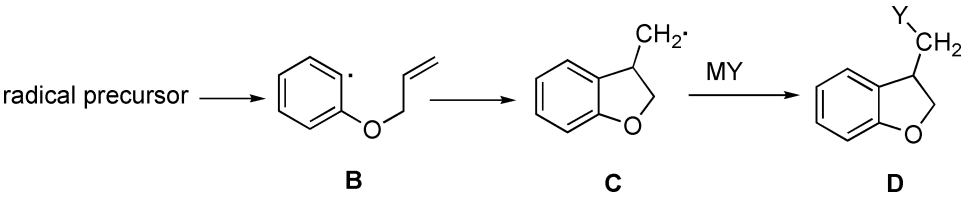


$R = CH_3, OCH_3, Cl, H; R^1 = CH_3, H; R^2 = CH_3, H, Cl; R^3 = CH_3, H; R^4 = CH_3, H$

Scheme 4

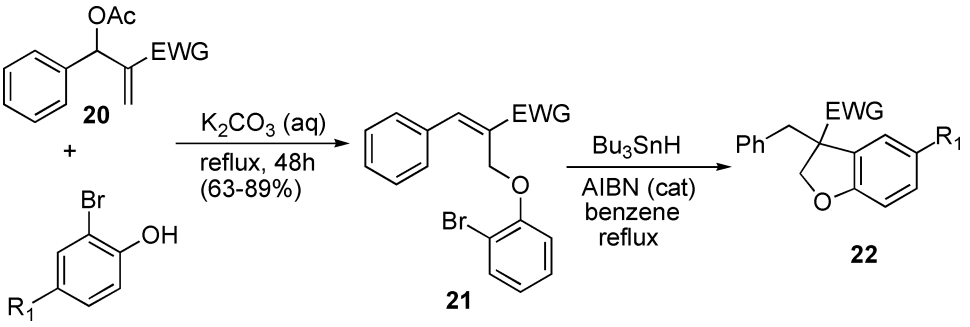
III. Radical Cyclizations and Electrocyclizations

In general, aryl radicals with *ortho* substituents containing a double bond at the 5,6-position relative to the radical center undergo rapid, regioselective cyclization (**B** → **C**) in the *exo-trig* fashion (*Scheme 5*).[26] Procedures which are able to generate both the radical and introduce a new functional group (Y) at the cyclized radical center are of special interest because they afford functionalized products suitable for further elaborations. There are several reports about the formation of dihydrobenzofurans by radical cyclization which differ from the radical precursor and the way to generate the radical **B**.



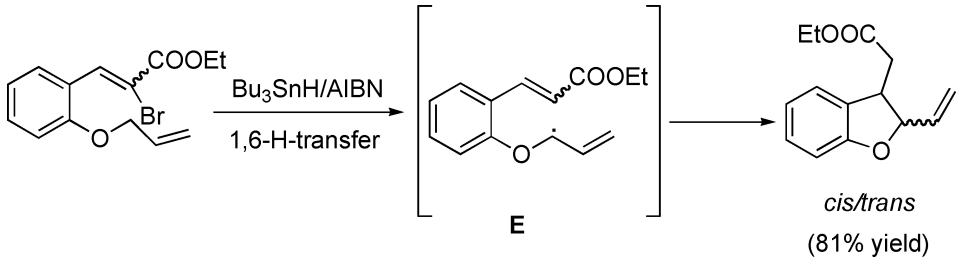
Scheme 5

The aryl radical can be generated by the reaction of aryl halides with AIBN-organotin reagents (in particular Bu_3SnH). For example, quite recently, 3,3-disubstituted 2,3-dihydrobenzofuran derivatives **22** were obtained by radical cyclization of precursors of type **21**, easily prepared by the reaction of Baylis-Hilman adduct **20** and substituted bromophenols (*Scheme 6*).[27]



Scheme 6

Furthermore, a reaction cascade involving in this case a vinyl radical formation was reported recently to give a facile access to 2,3-disubstituted-2,3-dihydrobenzofurans, albeit as diastereoisomeric mixtures. A plausible mechanism for this unsual transformation calls for a 1,6-hydrogen atom transfer to afford the more stable allyl intermediate **E**, which in turn underogoes *5-exo-trig* cyclization to give rise to the product after the final reduction by Bu_3SnH (*Scheme 7*).[28]



Scheme 7

However, it should be emphasized that there are several drawbacks using Bu_3SnH because this compound is relatively expensive, unstable and toxic. Furthermore, the tin by-products from its reactions are not always easy to separate from the reaction products and represent an ever increasing disposal problem. A partial solution to these problems can be found in the development of new methodologies that allow the *in situ* formation of tin hydride from Bu_3SnCl and the reducing agent polymethylhydrosiloxane (PMHS) in the presence of an aqueous solution of KF.[29]

In addition, the electrochemical reduction of haloarenes bearing a 2-allyloxy group in the presence of phenanthrene is know to afford the corresponding 5-*exo* cyclized products with high yields.[30] The radical cyclization of suitable unsaturated aromatic halides can be induced also with the 10-methyl-9,10-dihydroacridine/$NaBH_4$ photocatalytic system in DMF, albeit with poor isolated yields of 2,3-dihydrobenzofurans.[31]

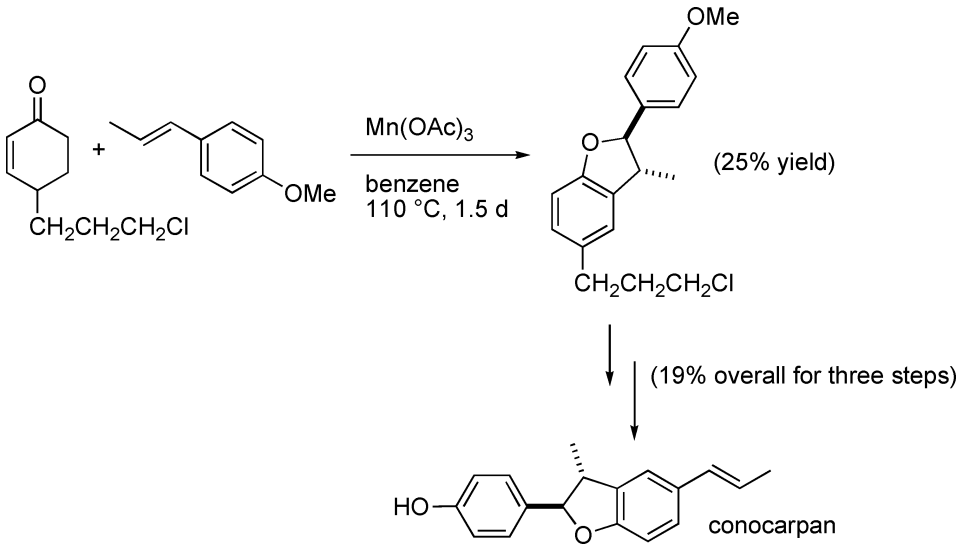
The radical intermediate **C** (see *Scheme 5*) formed after the intial cyclization can undergo a reduction by a hydrogen donor to obtain the corresponding reduced product or reaction with a different reagent in a tandem process. For example, 3-substituted 2,3-dihydrobenzofurans have been obtained in very good yields by radical nucleophilic

substitution ($S_{RN}1$ reaction) with Me_3Sn^-, Ph_2P^- and $^-CHNO_2$ anions after the intial "photostimulation" in liquid ammonia of the radical precursor *ortho* substituted with a suitable double bond.[32]

The formation of functionalized dihydrobenzofurans by radical cyclization can also be effected starting from suitable diazonium tetrafluoroborates in the presence of stoichiometric amounts of copper salts.[33]

A tandem cyclization-carboxylation under electrochemical conditions in mild conditions (room temperature, atmospheric CO_2 pressure) was also reported to give dihydrobenzofuran carboxylic acid derivatives.[34]

A different approach based on radical intermediates can be found in the oxidative cycloaddition of a 2-cyclohexenone (or α-tetralone) with alkenes promoted by $Mn(OAc)_3$. Although the yields are modest, this one-pot reaction provides simple access to substituted 2,3-dihydrobenzofurans. In particular, the oxidative cycloaddition of 2-cyclohexenone with β-methylstyrenes provides a new route to benzofuranoid lignans with an application to the synthesis of conocarpan in three steps with an overall yield of 19% (*Scheme 8*)



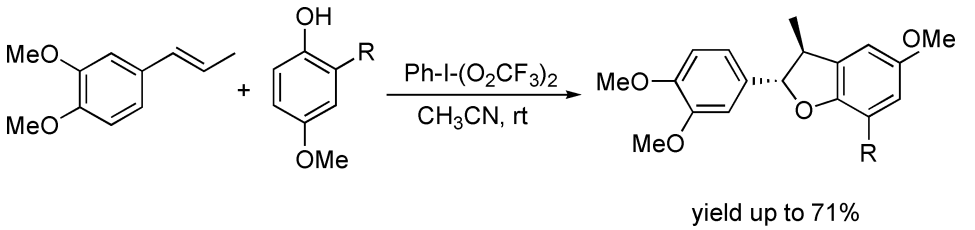
Scheme 8

Unfortunately, the more suitable precursor 4-allyl-2-cyclohexenone for conocarpan synthesis gave a complex mixture of products since addition can occur inter- or intramolecularly to the allyl group.[35]

IV. Biomimetic Couplings and Cycloadditions

Over the years, the use of biomimetic-inspired reactions has been used extensively for the synthesis of many families of natural products. These biomimetic reactions represent also one of the most common approaches for the preparation of a great number of biological active compounds in which the 2,3-dihydrobenzofuran ring system represents the core skeleton.[36]

In this respect, Buchi reported in 1978 the preparation of benzofuran neo-lignans, a group of secondary plant metabolities characterized by the presence of two arylpropanoid units,[15] by the reaction of a *para*-quinone ketal and *(E)*-isosafrole in the presence of trinitrobenzenesulfonic acid.[37] More recently, Swenton and co-workers reported that benzofuran neo-lignans could also be obtained in good yields and high stereoselectivities by oxidation of *para*-methoxy-substituted phenols with iodobenzene *bis*-trifluoroacetate in the presence of electron-rich styrene derivatives (*Scheme 9*).[38]

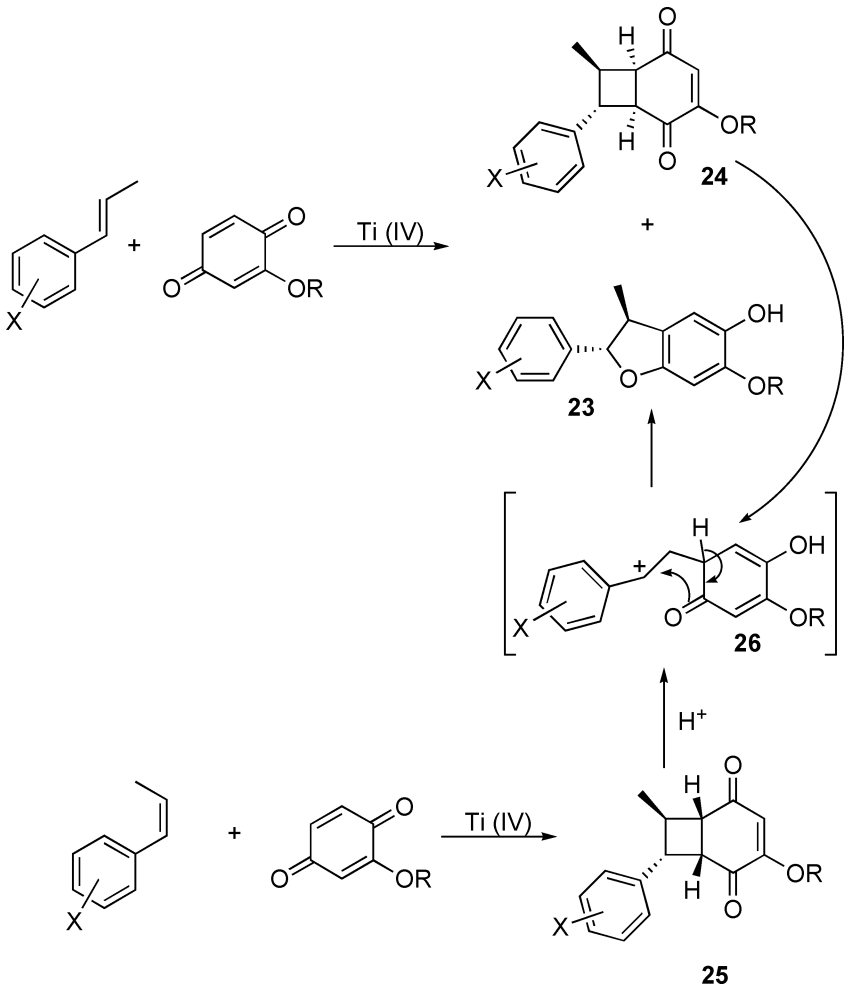


Scheme 9

It is worth mentioning that this kind of approach, which foresees the coupling of a quinone and a phenylpropenyl moiety, was extensively adopted in the following years for the preparation of a number of 2,3-dihydrobenzofurans. In particular, Engler and co-workers reported that *trans* or *cis* β-methylstyrenes reacted with 2-alkoxy-1,4-benzoquinones in the presence of titanium(IV) catalysts to give mixtures of *trans*-dihydrobenzofurans of type **23** and cyclobutanes of type **24** or **25**, the corresponding [2+2] cycloadducts (*Scheme 10*).[39] Although *trans*-2,3-dihydrobenzofurans could easily be obtained in good yields also upon treatment of cyclobutanes of type **24** and **25** with protic acid (presumably *via* intermediate **26**), the authors reported that the amount of 2,3-dihydrobenzofuran derivative directly obtained in the reaction mixture was strongly affected by the type of β-methylstyrene used. Thus, while *trans*-methyl styrenes bearing electron-donating groups in the *ortho* or *para* positions gave 2,3-dihydrobenzofurans of type **23** with fair to good yields, the use of *cis*-methylstyrenes afforded the formation of less clean reaction mixtures where cyclobutanes of type **25** represented the main products. Moreover, the nature of the Ti(IV) catalyst also had a dramatic effect on the type of product obtained: $TiCl_4$ gave mainly the dihydrobenzofuran adducts, whereas $TiCl_4/Ti(OiPr)_4$ mixtures produced more 2+2 cycloadducts.

The same research group reported that this type of condensation could also be achieved by the Lewis acid promoted reaction between alkoxy *p*-quinone monoimides, the aza-analogues of quinones, and phenylpropenyl moieties.[40] In particular, the addition of β-methylstyrenes bearing strong electron-donating groups to solutions of 2-alkoxy-4-(*N*-phenylsulfonyl)benzoquinone monoamines and $BF_3 \cdot Et_2O$ in dichloromethane at low temperature afforded *trans*-2,3-dihydrobenzofurans in good yields and high stereoselectivities (*Scheme 11*). However, it should be noted that the formation of 2,3-dihydrobenzofurans was not exclusive and, in some cases, small amounts of dihydroindoles were found.

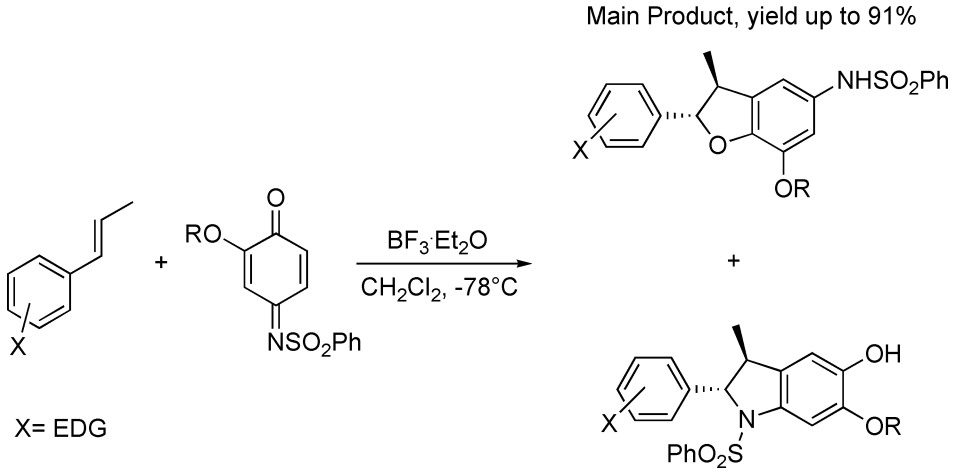
The nature and the amount of the Lewis acid promoter is able to provide convenient access to either substituted 2-aryl-2,3-dihydrobenzofurans or 2-aryl-2,3-dihydroindoles.



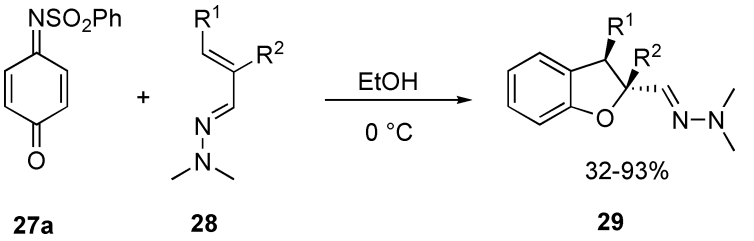
Scheme 10

In particular, while the use of a slight excess (1.0 to 1.3 equiv) of a monodentate Lewis acid, such as BF_3Et_2O, gave 2,3-dihydrobenzofurans as the main products (*Scheme 11*), the reaction of the same starting materials in the presence of a large excess of a bidentate Lewis acid, such as Ti(IV) complexes, resulted in the nearly exclusive formation of the corresponding 2,3-dihydroindoles.

It should be noted that the use of quinones imides for the preparation of 2,3-dihydrobenzofurans was exploited by several research groups in the following years. In particular, Barret and co-workers reported the [3+2] cycloaddition of *para*-benzoquinones monoimides and a variety of azadienes in the absence of a Lewis acid.[41] Thus, the slow addition of an alcoholic solution of *para*-quinone benzenesulfonimide **27a** to a solution of an azadiene of type **28** allowed the isolation of the corresponding 2,3-dihydrobenzofurans **29** with high regio- and stereoselectivity and in moderate to excellent yields (*Scheme 12*).

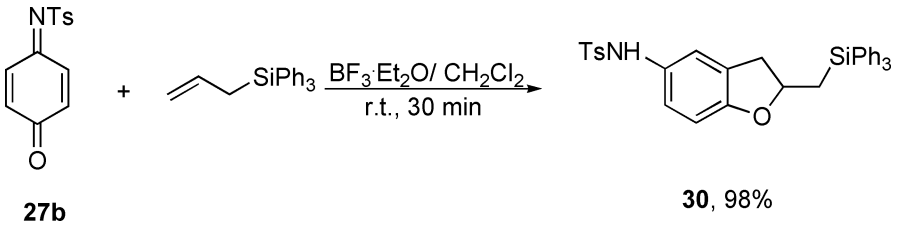


Scheme 11



Scheme 12

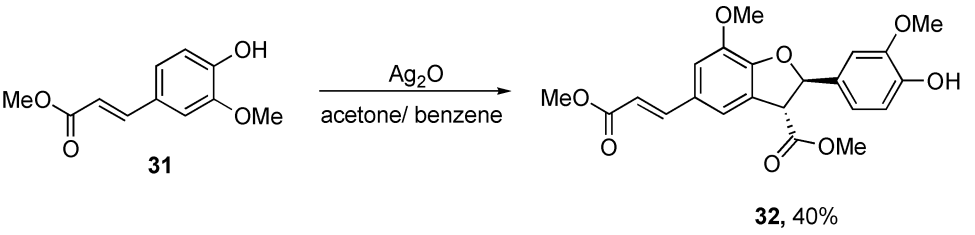
Additionally, Nair and co-workers reported that allylsilanes can be employed successfully in the reaction with *p*-quinone monoimides for the formation of 2,3-dihydrobenzofurans.[42] The reaction of *para*-quinone tosylimide **27b** with allyltriphenylsilane in the presence of $BF_3{\cdot}Et_2O$ at room temperature gave the corresponding dihydrobenzofuran **30** with a very high yield (*Scheme 13*).



Scheme 13

In this case, the authors assumed that the formation of the heterocycle was a consequence of the initial addition of allylsilane in a conjugate fashion to the imine moiety, followed by the quenching of the silyl cation by the keto oxygen.

A different approach for the preparation of dihydrobenzofuran neo-lignans was reported by Lemiére and co-workers.[43] In particular, the oxidative biomimetic dimerization

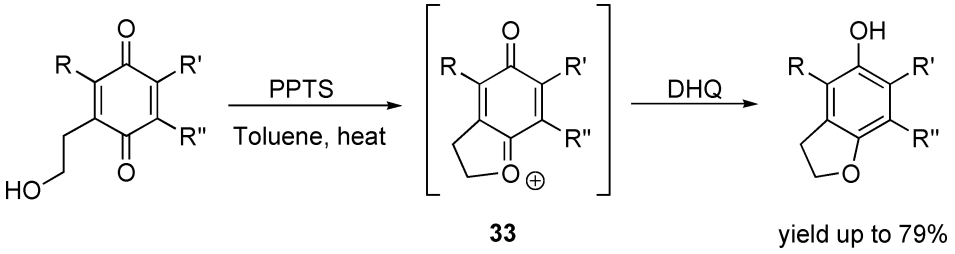


Scheme 14

of ferulic acid methyl ester **31** with Ag_2O allowed the isolation of the corresponding *trans*-2,3-dihydrobenzofuran **32** with a high stereoselectivity and a moderate yield (*Scheme 14*).

It is worth mentioning that a variety of *trans*-2,3-dihydrobenzofurans derived from ferulic and caffeic acids have been described more recently as crucial intermediates for the preparation of a class of benzofuran neo-lignans having antiangiogenic activity.[44]

Beside these examples of *intermolecular* processes, Benbow reported the construction of the 2,3-dihydrobenzofuran skeleton by *intramolecular* acid-catalyzed cyclization of 2-(2′-hydroxyethyl)quinones with pyridinium *p*-toluenesulfonate (PPTS) as catalyst in the presence of dihydro-1,4-benzoquinone (DHQ).[45] In particular, DHQ plays a crucial role in this reaction given that it is able to reduce *in situ* the oxonium ion intermediate **33**, formed by an *intramolecular* cyclization of the hydroxy group promoted by the acid catalyst (*Scheme 15*).

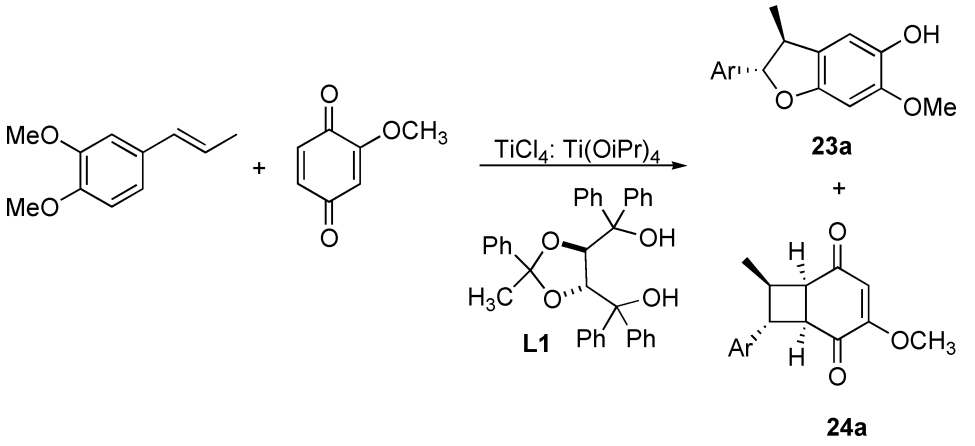


Scheme 15

V. Biomimetic Asymmetric Synthesis

As mentioned earlier, 2,3-dihydrobenzofuran molecular motifs are common in natural products. For this reason, a great interest has been devoted to the development of asymmetric reactions able to provide rapid access to optically active 2,3-dihydrobenzofurans. With regard to "biomimetic" reactions, it should be noted that much effort has been expended on asymmetric variants of well established reactions, using chiral auxiliaries, reagents and catalysts. Based on the results described in the previous section (see *Scheme 10*), Engler and co-workers reported that the use of the chiral diol **L1** in the Ti(IV)-catalyzed coupling of (*E*)-1,2-dimethoxy-4-(prop-1-enyl)benzene and 2-methoxy-1,4-benzoquinone afforded mixtures of optically active *trans*-dihydrobenzofuran **23a** and cyclobutane **24a** (*Scheme 16*).[46]

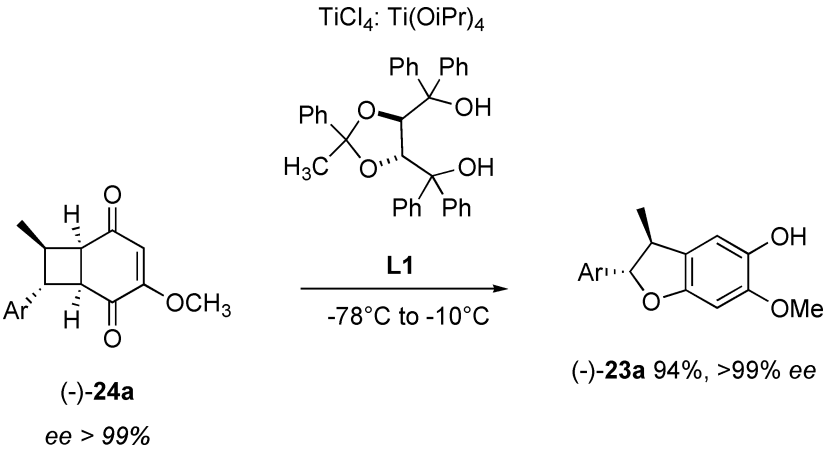
The authors surveyed empirically several reaction conditions in order to obtain selectively one of the two possible cycloaddition products. In particular, they found that 2.5



Scheme 16

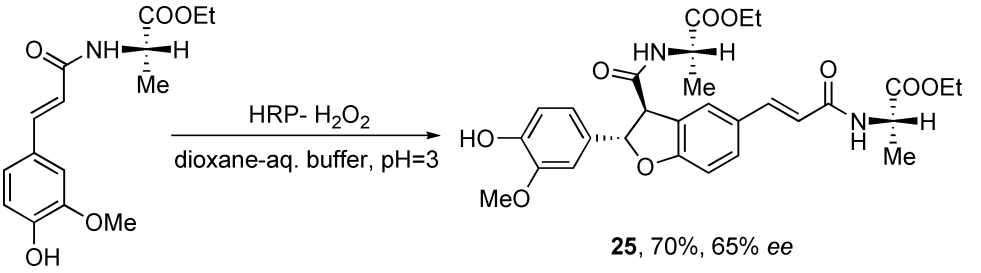
equiv. of each Ti(IV) catalyst and chiral diol **L1** with respect to the quinone at –78°C led to the formation of compound **24a** as the main product in high yield and enantiomeric purity while the 2,3-dihydrobenzofuran **23a** was obtained in a poor yield and a low enantioselectivity. However, the slow warming of the reaction mixture produced the dihydrobenzofuran **23a** with a very high yield and a good enantiomeric excess. These results can be explained by the rearrangement of the cyclobutane to the 2,3-dihydrobenzofuran, a process which does not occur at –78°C but plays a crucial role at a higher reaction temperature.

This working hypothesis was demonstrated by subjecting the enantiomerically pure cyclobutane (-)-**24a**, obtained by recrystallization of enantiomerically enriched material, at –78°C to Ti-diol **L1** complex followed by warming the reaction to –30°C. Under these conditions, 2,3-dihydrobenzofuran (-)-**23a** was obtained in very high yield and without the loss of optical purity (*Scheme 17*).



Scheme 17

Another approach to the preparation of optically active 2,3-dihydrobenzofurans was described by Orlandi and co-workers.[47] In particular, the authors reported the horseradish (HRP)-peroxidase-catalyzed oxidative phenol coupling of a ferulic acid amide having the ethyl *S*-analinate group as chiral auxiliary. Using hydrogen peroxide as oxidant the corresponding 2,3-dihydrobenzofuran **25** was obtained with 70% yield and 65% *ee* (*Scheme 18*).



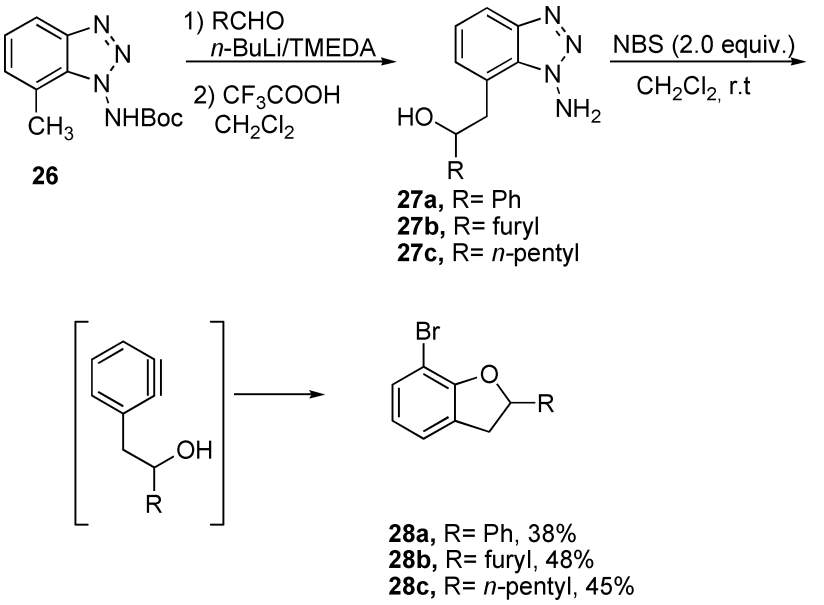
Scheme 18

VI. Synthesis *via* Benzyne

Substituted arynes are utilized as versatile synthetic intermediates and has been used in well-known organic transformations such as Diels-Alder reactions. Nevertheless, the use of arynes in organic synthesis has been limited historically by the strongly basic conditions used for the benzyne generation, which usually involved the elimination of hydrogen halides from halobenzenes. To overcome this drawback, several different milder approaches for the benzyne generation have been developed, such as the fluoride-induced desilylation of *ortho*-silylhalobenzenes, or the use of a variety of heteroaromatic benzyne precursors such as benzothiadiazole-*S,S*-dioxide and 1-aminobenzotriazole.[48] In particular, Rees and Campbell highlighted that 1-aminobenzotriazole rapidly disintegrates in the presence of oxidants such as N-bromosuccinimide (NBS) or $Pb(OAc)_4$ to afford the corresponding benzyne under mild conditions and in stark contrast with base-induced eliminations.[49]

Based on this work, Knight and co-workers more recently reported the use of a class of 7-substitued-1-aminobenzotriazoles for the synthesis of 2,3-dihydrobenzofurans. In particular, the exposure of compounds **27a–c**, derived from the Boc-triazole **26** after a first treatment with an aldehyde in presence of *n*-BuLi and tetramethylethylendiamine (TMEDA) followed by deprotection of the Boc protecting group by trifluoroacetic acid in dichloromethane, to 2.0 equivalents of NBS in dichloromethane at room temperature leads to the formation of the corresponding benzyne intermediates, which rapidly undergo intramolecular trapping by the hydroxyl function to give the corresponding 2-alkyl-7-bromo-2,3-dihydrobenzofurans **28a–c** (*Scheme 19*).[50]

It is worth mentioning that adducts of type **27** derived from ketones failed to react under these reaction conditions. Apparently, the bromine present in the reaction mixture competed successfully with the low nucleophilic tertiary alcohols, thus favoring the formation of the corresponding dibromo derivatives. To overcome this problem, the authors examined a variety of alternative oxidants finding in *N*-iodosuccinimide (NIS) the best compromise.[51] In particular, intramolecular trapping of benzynes was achieved using several 7-substituted 1-aminobenzotriazoles bearing secondary and tertiary alcohols in the



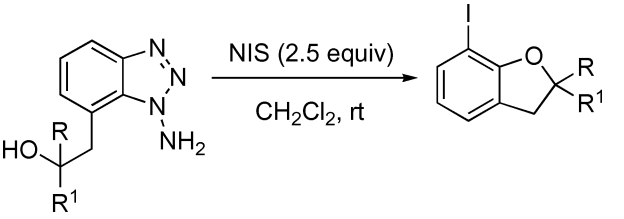
26

27a, R= Ph
27b, R= furyl
27c, R= *n*-pentyl

28a, R= Ph, 38%
28b, R= furyl, 48%
28c, R= *n*-pentyl, 45%

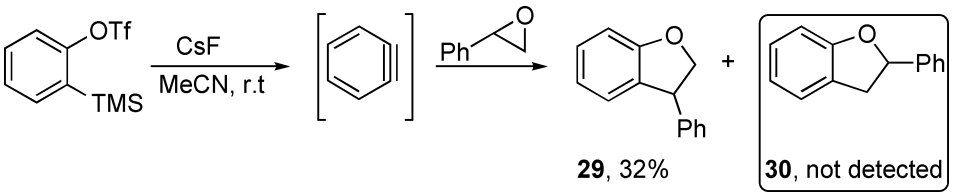
Scheme 19

presence of 2.5 equivalents of NIS in dichloromethane to give the corresponding 7-iodo-2,3-dihydrobenzofurans in good to excellent yields (*Scheme 20*). It should be noted that the presence of an iodine atom in the product offers possibilities for further elaborations of the 2,3-dihydrobenzofuran skeleton.[52]



Scheme 20

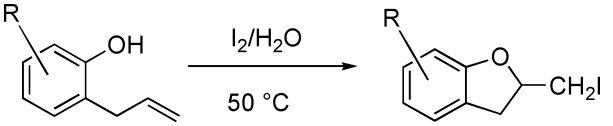
Another example of the preparation of 2,3-dihydrobenzofurans *via* benzyne has been described recently by Peña and co-workers.[53] In this work, the formation of the benzyne was achieved under mild conditions by treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate with CsF in MeCN at room temperature. The following insertion of the benzyne intermediate into the C-O bond of styrene oxide gave the dihydrobenzofuran **29** in 32% yield. Although the low yield indicated the formation of a mixture of products, it is worth mentioning that the regioisomeric dihydrobenzofuran **30** was not detected in the reaction mixture (*Scheme 21*).



Scheme 21

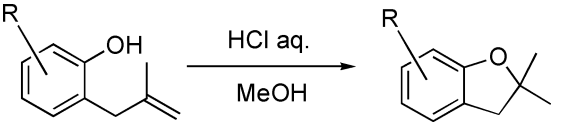
VII. Intramolecular Substitutions of *ortho*-Allylphenols without Metal Catalysts

As substituted *ortho*-allylphenols can be accessed easily by means of the [3,3]-Claisen rearrangement of the corresponding *O*-allylphenols, the former compounds can be used in a very simple manner to prepare 2,3-dihydrobenzofurans. For example, Fousteris *et al.* developed an elegant method for the synthesis of 2-(iodomethyl)dihydrobenzofurans *via* water promoted iodocyclization of 2-allylphenols (*Scheme 22*). The cyclization occurred through an *exo* process, as generally observed in these cases.[54] This simple procedure is easy to perform and allows the transformation of various substituted 2-allylphenols in the absence of any additive and organic solvents.



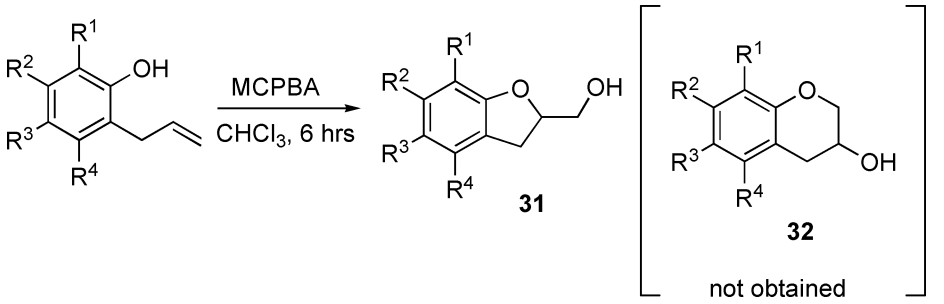
Scheme 22

In addition, simple acidic conditions are able to activate the double bond of *ortho*-allylphenols for the intramolecular substitution. Simple exposure of C-methallylated compounds to acidic reaction conditions (35% aq. HCl-MeOH) gave the 2,2-dimethylbenzofurans with exclusive attack of the phenol at the intermediate tertiary carbocation (S*cheme 23*). This simple method constituted the key step for the synthesis of 5-aminocoumarans developed for the treatment of traumatic and ischemic central nervous system injuries.[55]



Scheme 23

The double bond of an allylphenol can also be rendered electrophilic by epoxidation. Subsequent epoxide opening by the phenolic oxygen gives 2-hydroxymethyl-2,3-dihydrobenzofurans **31** through an *exo* opening rather than isomeric 3-hydroxychromans **32** deriving from an *endo* opening of the oxirane (*Scheme 24*).[56]



Scheme 24

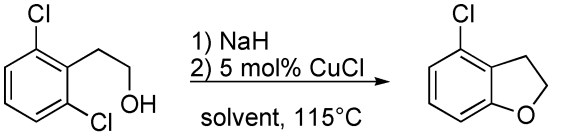
By the exploitation of Jacobsen kinetic resolution of terminal epoxides, enantiomerically enriched 2,3-dihydrobenzofurans can be obtained also, as recently demonstrated by Bhoga.[57]

In addition, substituted *ortho*-allylphenols can be very conveniently used by means of transition metal-catalyzed hydroalkoxylation processes (see Section VIII–2).

VIII. Transition Metal-Catalyzed Processes

1. Transition Metal-catalyzed Nucleophilic Substitutions

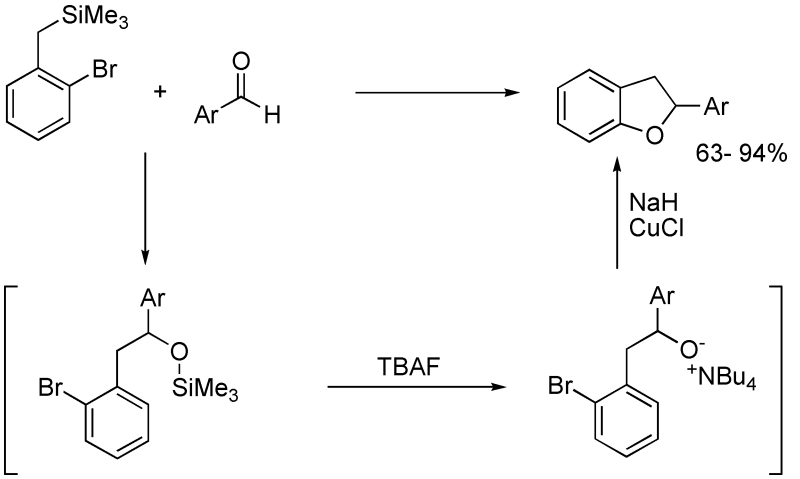
The intramolecular C-O formation between aryl halides and alcohols represents another possible approach for the construction of the 2,3-dihydrobenzofuran skeleton. In this respect, historically one of the most representative examples of this class of transformation is provided by the Ullman reaction. Although it represents a well-known and widely used method for the preparation of aryl ethers,[58] the intramolecular version of this reaction has been scarcely investigated, mainly because of the large excess of alkoxide required to have a reasonable yield of the reaction product. Nevertheless, Zhu and co-workers reported the cyclization of 2-(2,6-dichlorophenyl)ethanol in the presence of 0.05 equiv. of CuCl and a slightly excess of NaH to give the corresponding 2,3-dihydrobenzofuran with a high yield.[59] Even if the reaction could be carried out with a wide range of solvents, the author reported that the use of pyridine or toluene (with 5 mol% of ethyl acetate) at 115°C gave the highest conversion (*Scheme 25*).



Solvent	Conversion (%)	Yield (%)
Pyridine	94.9	77.4
Toluene/EtOAc	99.7	89.5

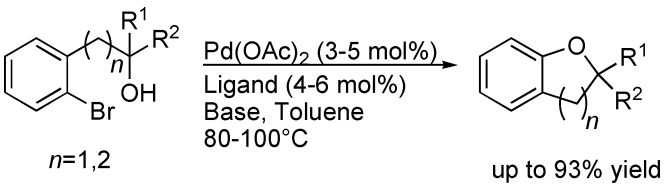
Scheme 25

A significant advance towards the synthesis of 2,3-dihydrobenzofurans *via* intramolecular Ullman-type cyclization has been described more recently by Wang and co-workers.[60] The benzylation reaction between (2-bromobenzyl)trimethylsilane and an aldehyde afforded a silyl ether which could be converted to the corresponding tetrabutylammonium alkoxide by the addition of a stoichiometric amount of TBAF. The final addition of NaH and CuCl to the reaction mixture favored the cyclization giving the corresponding 2-aryl-2,3-dihydrobenzofurans in good to excellent yields (*Scheme 26*). This approach was adopted to avoid the formation of hydrated products, which greatly reduced the overall yield of the desired dihydrobenzofuran after the cyclization of the corresponding alcohol with NaH and a copper salt.



Scheme 26

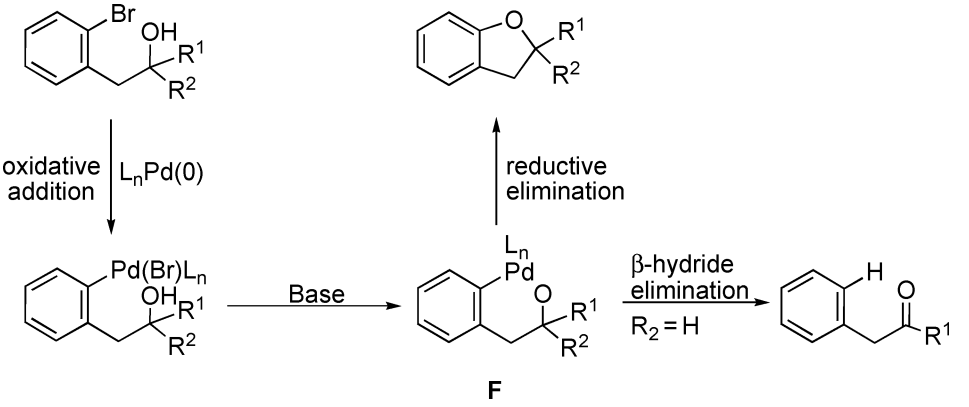
The intramolecular Pd-catalyzed C-O bond formation is another potentially attractive means to assemble oxygen heterocycles. Although the use of palladium has found wide application, the Pd-catalyzed couplings of Ar-X with alcohols for a long time remained a difficult goal in organic synthesis. More than a decade ago, Buchwald described the intramolecular Pd-catalyzed substitution of an aryl bromide with an alcohol.[61] The reaction was carried out using $Pd(OAc)_2$ as catalyst in the presence of a bidentate phosphorus-based ligand (Tol-BINAP or DPPF) and a base (mainly K_2CO_3 or NaO*t*Bu) in toluene at 80–100°C to give the corresponding heterocycles in fair to very good yields (*Scheme 27*).



Scheme 27

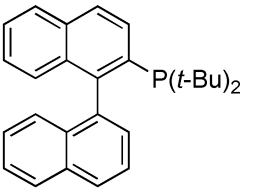
It should be noted that this approach is efficient when tertiary alcohol substrates are used. Application of this method for the cyclization of primary or secondary alcohols proved

to be unsuccessful because of the formation of substantial amounts of the corresponding debrominated ketones or aldehydes. Reasonably, the formation of carbonyl compounds can be explained by considering the competition between the reductive elimination and β-hydride elimination of the palladacycle **F** deriving from the oxidative addition of $Pd(O)L_n$ to the aryl halide (*Scheme 28*).

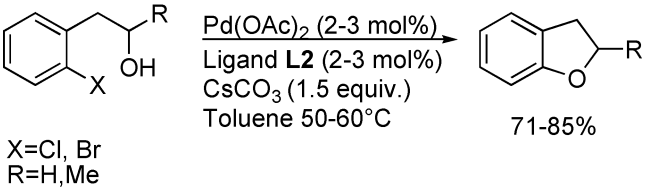


Scheme 28

To overcome this problem, the authors investigated several different ligands. During this study, they found that bulky, electron-rich *o*-biphenyl- and binapthylphosphines, efficiently used in many other Pd-catalyzed cross-coupling reactions, could be successfully employed in this transformation. In particular, the use of ligand **L2** allowed the cyclization of both primary and secondary alcohol substrates to the corresponding 2,3-dihydrobenzofurans in good yields.[62] It is worth mentioning that the secondary alcohols required higher temperatures and higher amounts of catalyst to go to completion with respect to the primary alcohols (*Scheme 29*).



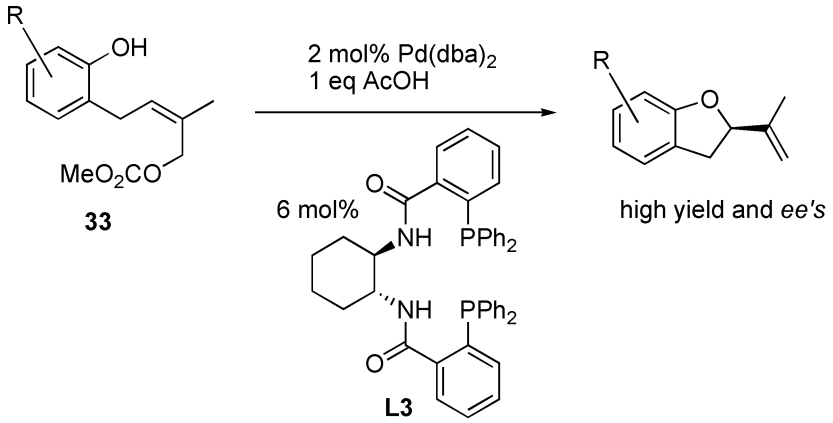
L2



Scheme 29

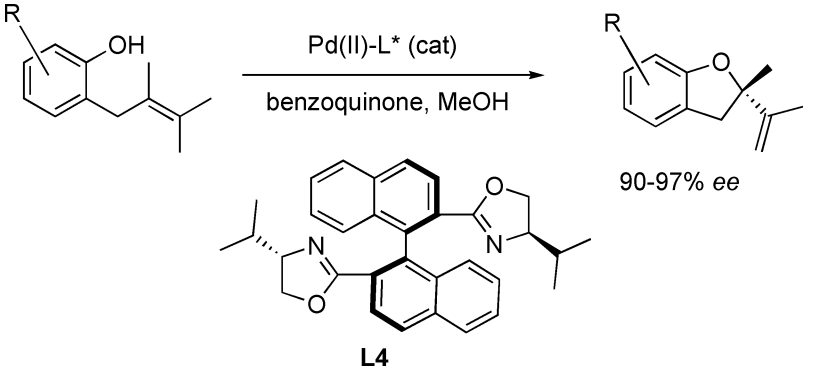
2. Transition Metal-catalyzed Intramolecular Hydroalkoxylations

Pd-catalyzed reactions involving π-allylpalladium intermediates represent a very common and well-known class of chemical transformations and have found great utility in several synthetic processes. In this respect, the possibility of using this approach for the preparation of oxygen heterocycles such as 2,3-dihydrobenzofurans has also been investigated. For example, differently substituted allylic carbonates of type **33** have been used in a palladium-catalyzed reaction to give the enantiomerically enriched 2-isopropenyl-2,3-dihydrobenzofuran nucleus, which is an important chiral building block for the synthesis of the toxins tremetone, hydroxytremetone, and fomannoxin (see *Figure* 2). By the use of Trost ligand **L3**, it was possible to create the stereogenic center at the 2-position of the dihydrobenzofuran with high enantioselectivities (up to 94% *ee*) (*Scheme 30*).[63]



Scheme 30

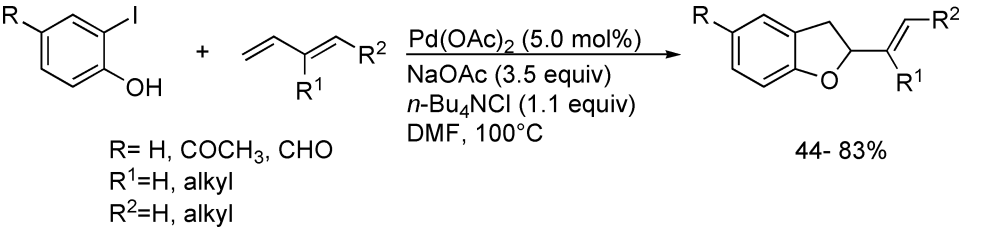
Asymmetric transformations able to give the 2-isopropenyl-2,3-dihydrobenzofuran nucleus starting from prochiral *ortho*-allylphenols have been developed as well. A striking example of this process can be found in the Wacker-type asymmetric cyclization of substituted *ortho*-allylphenols catalyzed by Pd(II)-complexed with *bis*(oxazolines) containing the axial chirality of 1,1′-binaphthyl (boxax) **L4** (*Scheme 31).* It was found that an excess



Scheme 31

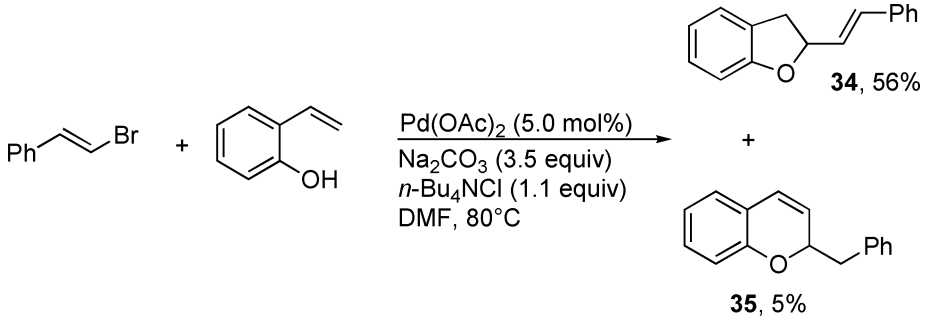
of benzoquinone and the use of MeOH as the reaction solvent are required to obtain high yields of cyclized products.[64]

Following the seminal contribution of Dieck and co-workers on the Pd-catalyzed annulation of iodoaniline and 1,3-dienes,[65] Larock reported the heteroannulation of 1,3-dienes with substituted *o*-iodophenols in the presence of $Pd(OAc)_2$ as catalyst (*Scheme 32*).[66] This reaction, which was carried out in the presence of a base (mainly NaOAc) and *n*-Bu_4NCl in DMF at 100°C, afforded the corresponding 2,3-dihydrobenzofurans in moderate to very good yields, although mixtures of isomers were detected when the reaction was performed using branched dienes.



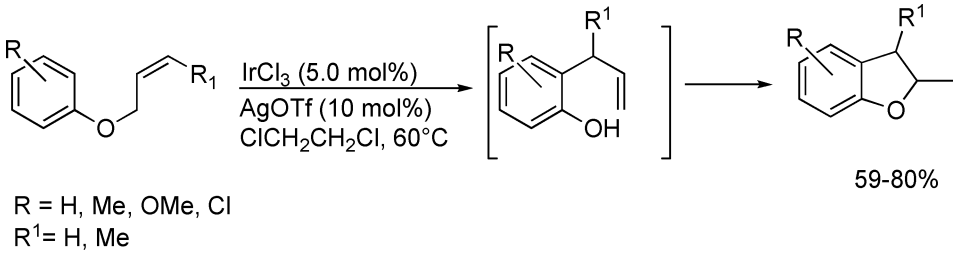
Scheme 32

Larock and co-workers reported that a complementary method for the preparation of 2,3-dihydrobenzofurans could be provided by the Pd-catalyzed cross-coupling of vinyl halides with alkenylphenols.[67] In particular, the reaction conditions described above for the reaction of *o*-iodophenols with 1,3-dienes were successfully applied in the reaction between *β*-bromostyrene and *o*-vinylphenol to give the 2,3-dihydrobenzofuran **34** in an acceptable yield though a small amount (ca. 5%) of 2-benzyl-2H-1-benzopyran **35** was also observed (*Scheme 33*). It should be noted that several different conditions were examined during this study but no consistent advantages with regard to the yield and the selectivity of the process were observed when other solvents or bases were used or when the reaction was carried out using *β*-iodostyrene.



Scheme 33

As described so far, palladium salts are used preferentially as catalysts in intramolecular hydroalkoxylation reactions; however, Liu recently reported that $IrCl_3$ could also be efficiently adopted in this kind of transformation.[68] Several allyl aryl ethers underwent a tandem Claisen rearrangement and intramolecular hydroaryloxylation in the presence of



Scheme 34

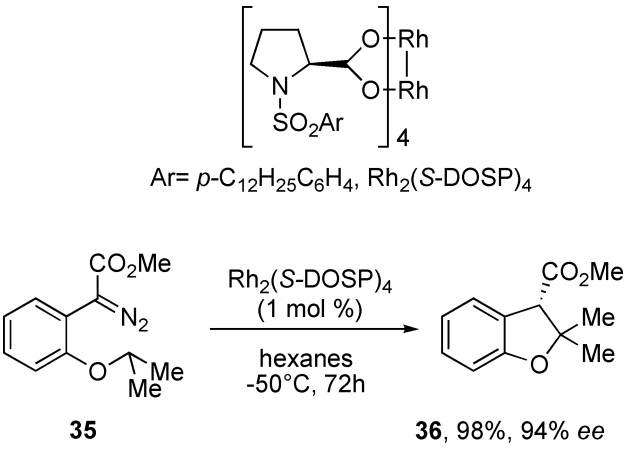
5.0 mol% of $IrCl_3$ and 10 mol% of AgOTf to give the corresponding 2,3-dihydrobenzofurans in moderate to good yields (*Scheme 34*).

It is worth mentioning that neither $IrCl_3$ or AgOTf was able to promote individually the formation of dihydrobenzofurans from the starting material. It is reasonable to conclude that the silver salt increased the electrophilicity of the metal centre by abstraction of a chloride, favoring the *in situ* generation of a more reactive iridium catalyst able to promote the tandem reaction.

3. Transition Metal-catalyzed Insertion-Cyclizations

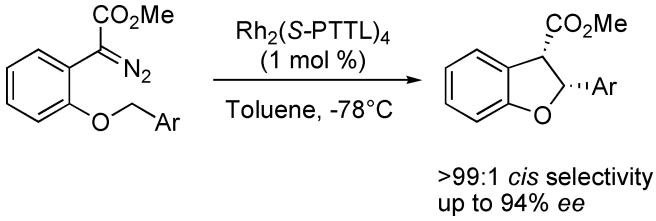
Transition metal-catalyzed carbenoid insertion into a saturated C-H bond represents an interesting methodology for the formation of new carbon-carbon bonds. In particular, this kind of transformation (mainly carried out using Rh or Ru catalysts) can be an effective and valuable approach for the enantioselective synthesis of a variety of heterocycles, including 2,3-dihydrobenzofurans.

Considering the effectiveness of rhodium catalysts in the *intermolecular* C-H insertion of aryldiazoacetates, Davies and co-workers investigated conditions for the development of the corresponding *intramolecular* version. In this respect, they found that the use of Rh_2(*S*-DOSP)$_4$ in hexanes at –50°C allowed the cyclization of aryldiazoacetate **36** to give the corresponding 2,3-dihydrobenzofuran **37** with a high yield and enantioselectivity (*Scheme 35*).[69]



Scheme 35

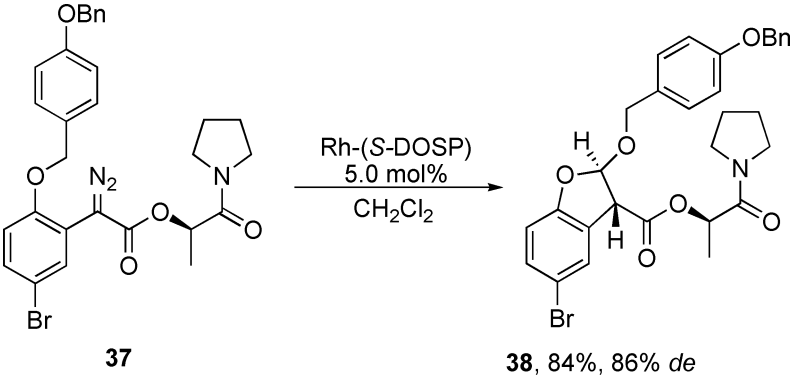
The extent of the asymmetric induction is strictly dependent on the site of C-H insertion. While a high enantioselectivity is obtained for the insertion into a methine C-H bond, the intramolecular cyclization into methyl and methylene C-H bonds occurred with a lower enantioselectivity and, in the second case, the formation of mixtures of *cis* and *trans* 2,3-dihydrobenzofurans was observed. However, it is worth mentioning that the substitution pattern at the C-H insertion site is related to the nature of the chiral dirhodium catalyst used. For example, the use of dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], $Rh_2(PTTL)_4$, allowed the cyclization to 2,3-dihydrobenzofurans to occur with a high stereoselectivity, in particular when the reaction occurred from insertion into a methylene C-H bond (*Scheme 36*).[70]



Scheme 36

It should be noted that the presence of a substituent other than an aryl group at the insertion site produced a decrease or a reversal of diastereoselectivity. This result suggests that the phenyl ring played a crucial role for the high stereoselectivity of the reaction.

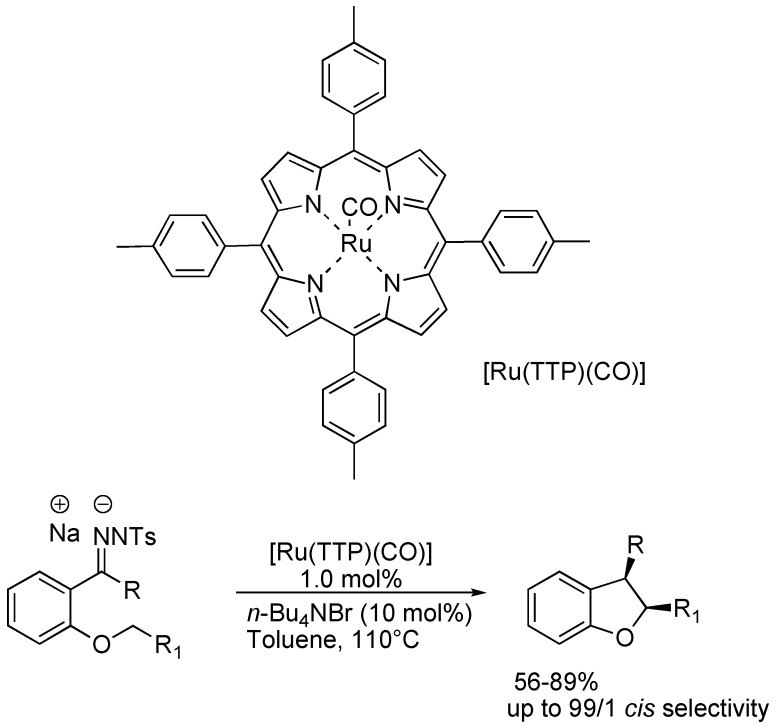
A further confirmation about the influence of the substituent adjacent to the target C-H bond on the diastereoselectivity of the reaction was reported by Fukuyama and co-workers.[71] It was found that the cyclization of compound **37** in the presence of the Davies catalyst gave the corresponding *trans*-2,3-dihydrobenzofuran **38** with a high yield and stereoselectivity (*Scheme 37*).



Scheme 37

In this case, the increased bulk of the ester moiety is responsible for the high *trans*-selectivity. Moreover, the asymmetric induction was exclusively dependent on the chiral auxiliary and not on the catalyst: the reaction carried out in the presence of the Rh-(*R*-DOSP) gave the compound **38** with the same configuration.[72]

Che and co-workers reported the ruthenium(II) porphyrin catalyzed cyclization of aryl tosylhydrazones to form *cis*-2,3-dihydrobenzofurans *via* carbenoid C-H insertion.[73,74] Treatment of the sodium salts of tosylhydrazones with [Ru(TTP)(CO)] (1.0 mol%) in the presence of a phase transfer catalyst such as *n*-Bu_4NBr (10 mol%) in toluene at 110°C afforded the corresponding *cis*-2,3-dihydrobenzofurans in good yields and high diastereoselectivity (*Scheme 38*).

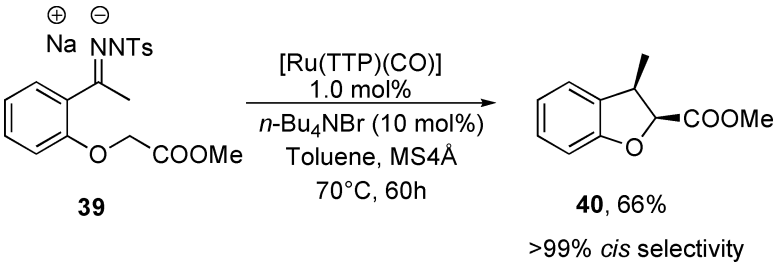


Scheme 38

It should be noted that the use of other solvents such as dichloromethane or THF resulted in a sluggish reaction and only low yields of products were recovered in those cases. Moreover, the high stability of Ru-porphyrin complexes gave the possibility to warm the reaction mixture without the decomposion of the catalyst. For this reason, substrates containing electron-withdrawing ester substituents (such as **39**), not reactive for the Rh(II)-catalyzed C-H insertion reaction, underwent facile C-H insertion under this reaction conditions to give the corresponding 2,3-dihydrobenzofuran **40** in 66% yield with complete *cis*-selectivity (*Scheme 39*).

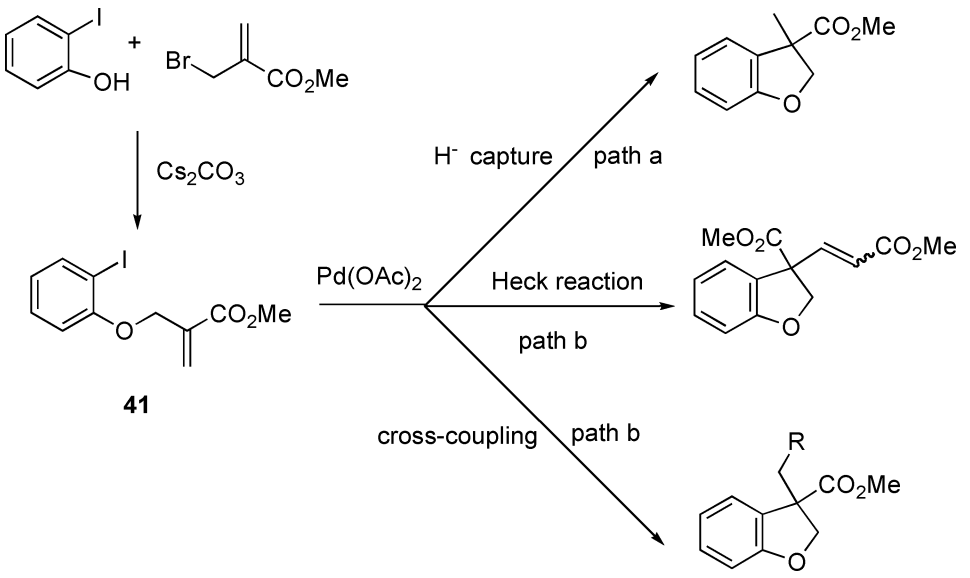
4. Palladium-catalyzed Intramolecular Heck-type Cyclizations

Among the variety of new synthetic approaches to develop new chemical processes to 2,3-dihydrobenzofurans, palladium-catalyzed reactions are part of the most attractive methodologies, since they proceed under mild conditions and are tolerant to a wide variety of functional groups. For example, various palladium-catalyzed cascade reactions of methyl



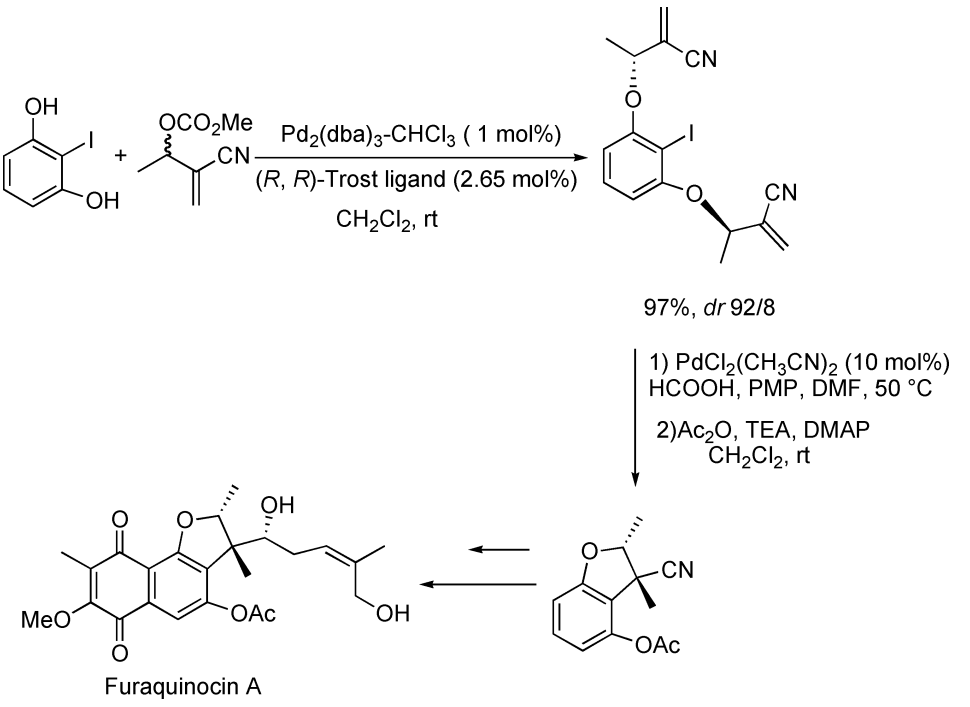
Scheme 39

bromomethacrylates with 2-iodophenol can afford structurally diverse 3,3-disubstituted-2.3-dihydrobenzofurans.[75] After the intial allylic substitution to give **41**, the carbopalladate intermediate, which is formed after a 5-*exo-trig* cyclization, can be captured with a hydride (*path a*), subjected to an intermolecular Heck reaction using methyl acrylate (*path b*), or subjected to a subsequent cross-coupling with an organometallic reagent, such as an organoboronic acid (*path c*) (*Scheme 40*). For *paths a* and *b* the reaction can be performed also in a one-pot procedure with acceptable yields of the final products.



Scheme 40

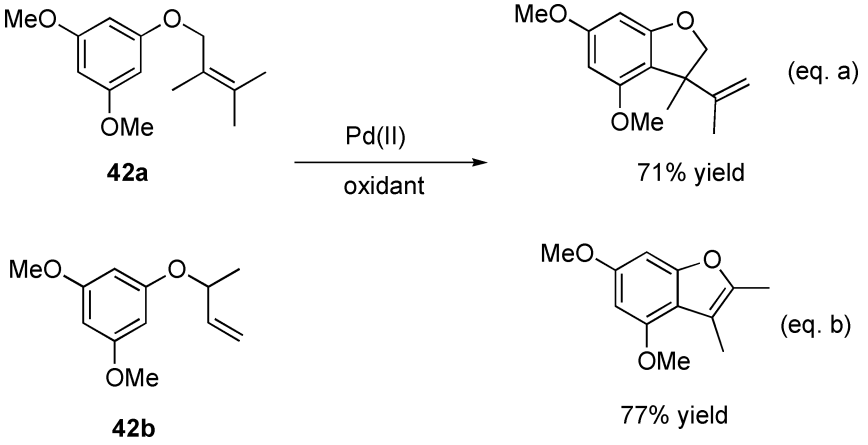
In the reductive Heck-type cyclization carried out under normal reaction conditions ($PdCl_2(CH_3CN)_2$, HCOOH, triethylamine, DMF, 50°C) significant competing pathways can be found in 6-*endo* cyclization and reionization of the substrate. Switching to the sterically hindered base pentamethylpiperidine (PMP) great improvements in yields and reproducibility can be obtained. This approach has been used in the construction of the dihydrobenzofuran framework in the total synthesis of Furaquinocin A, B, and E, a class of antibiotics isolated from *Streptomices sp*. KO-3998.[76] The enantioselectivity of the process is provided by a palladium-catalyzed dynamic asymmetric transformation on carbonates



Scheme 41

derived from Baylis-Hillman adduct. The subsequent reductive Heck cyclization allowed the stereoselective preparation of the dihydrobenzofuran framework (*Scheme 41*).

The oxidative Heck-type reaction is a very efficient process that involves the reaction of an unfunctionalized arene directly with an olefin, thus obviating the necessity for pre-activation (halogenation) of the substrate. In this area, a major advance in oxidative



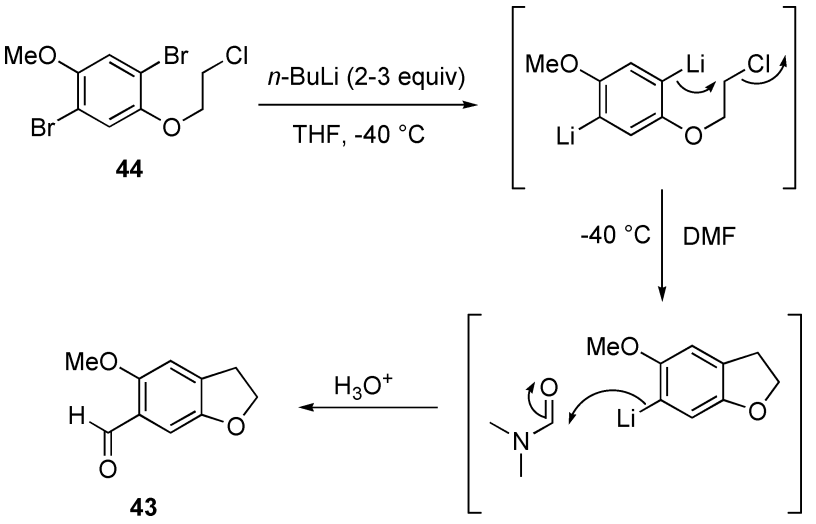
Scheme 42

annulation for the synthesis of an array of heterocycles, including 2,3-dihydrobenzofurans, using a catalytic palladium(II) system was recently developed by Stoltz. Thus, when aryl allyl ethers of type **42**, in which the allyl group consisted of tri- or tetrasubstituted olefins, were exposed to $Pd(OAc)_2$ (10 mol%), ethyl nicotinate (20 mol%), NaOAc (20 mol%) and 1.0 equiv of benzoquinone, in *t*-AmOH:AcOH (4:1) at 100°C, the corresponding 2,3-dihydrobenzofurans were obtained in good to excellent yields (*path a, Scheme 42*).[77] Dihydrobenzofurans are produced in these reactions when there are no hydrogens at the point of C-C bond formation, otherwise benzofurans are obtained (*path b, Scheme 42*). Clearly, as electrophilic Pd(II) is involved in the reaction mechanism, this method is limited to the use of very electron-rich aromatic systems.

IX. Anionic Cyclizations

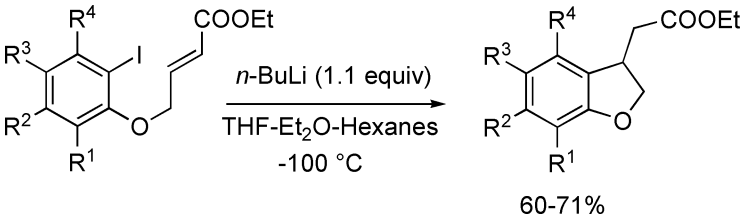
The intramolecular addition of *ortho*-substituted metallated aryloxy ethers bearing appropriate leaving groups or unsaturations through a 5-*exo-trig* cyclization process occupies a place of choice in the arsenal of synthetic strategies for the assembling of five-membered heterocyclic systems. In particular, the Parham cyclization process, which hinges upon aromatic lithiation, usually carried out by lithium-halogen exchange, has been exploited for this purpose. For example, an efficient practical preparation of aldehyde **43**, a key intermediate for the synthesis of endothelin antagonists, was based on a sequential Parham cyclization and an intermolecular reaction with DMF.[78] The authors found that treatment of a pre-cooled mixture of *n*-butyllithium with dibromide **44** at – 40°C resulted in clean conversion to the target aldehyde in 75% yield after addition of DMF (*Scheme 43*).

This type of cyclization can be effected also by the use of organomagnesium reagents generated *in situ* by iodine-magnesium exchange reactions with *i*-PrMgCl. This procedure is compatible with ester and tosylate functions already present in the molecule and yields can be improved by carrying out the ring-closure in the presence of catalytic amounts (1 mol%) of CuCN-2LiCl.[79]



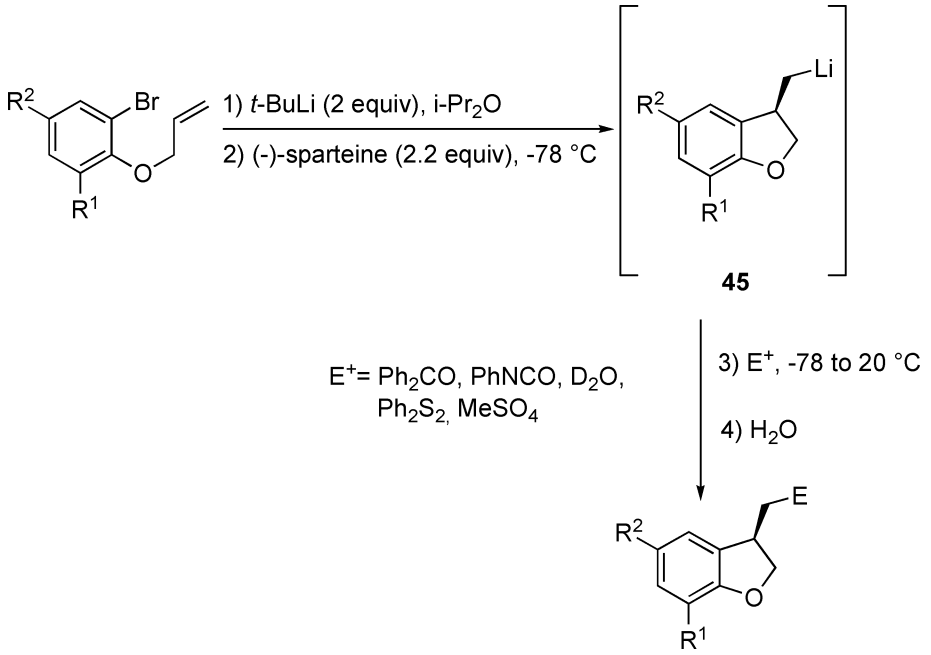
Scheme 43

An efficient general synthesis of 3-substituted 2,3-dihydrobenzofurans can also be accomplished by an intramolecular Michael-type addition of *ortho*-iodophenoxy crotonates. In this case the iodine-lithium exchange has to be performed at a very low temperature (–100°C) (*Scheme 44*).[80]



Scheme 44

More recently, an intramolecular carbolithiation of allyl-2-lithioaryl ethers was described by Barluenga and co-workers. This process is also amenable to the synthesis of enantiomerically enriched compounds (up to 87% *ee*) by using stochiometric amounts of (-)-sparteine. The organolithium intermediate **45** thus formed can be trapped with a variety of electrophiles to give 3-substituted 2,3-dihydrobenzofurans (*Scheme 45*).[81]

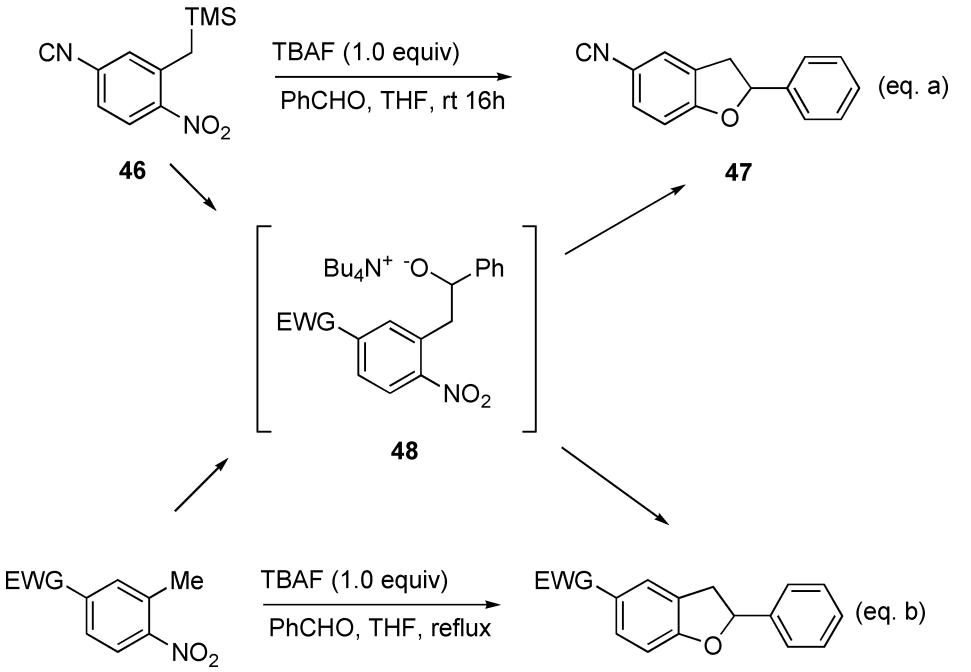


Scheme 45

X. Miscellaneous Methods

Two decades ago, Bartoli and co-workers investigated the reaction of 4-cyano-1-nitro-2[(trimethylsilyl)methyl]benzene **46** with benzaldehyde.[82] In the presence of an equimolar

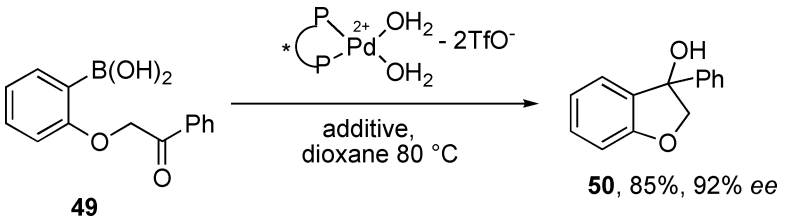
amount of TBAF, 5-cyano-2,3-dihydro-2-phenylbenzofuran (**47**) was obtained in 70% yield in a two step procedure *via* intermediate **48** (*eq. a, Scheme 46*). Inspired by this work, much more recently, it was found that when the same reaction was carried out directly with commercially available *ortho*-nitrotoluenes in the presence of 2 equivalents of *i*-Pr_2NEt (Hünig's base), high yields of the corresponding 2,3-dihydrobenzofurans were obtained. This simple variation allows an efficient one-pot preparation of highly functionalized 2-aryl-5-substituted-2,3-dihydrobenzofurans that may serve as platforms for further manipulation and applications to parallel synthesis (*eq. b, Scheme 46*).[83]



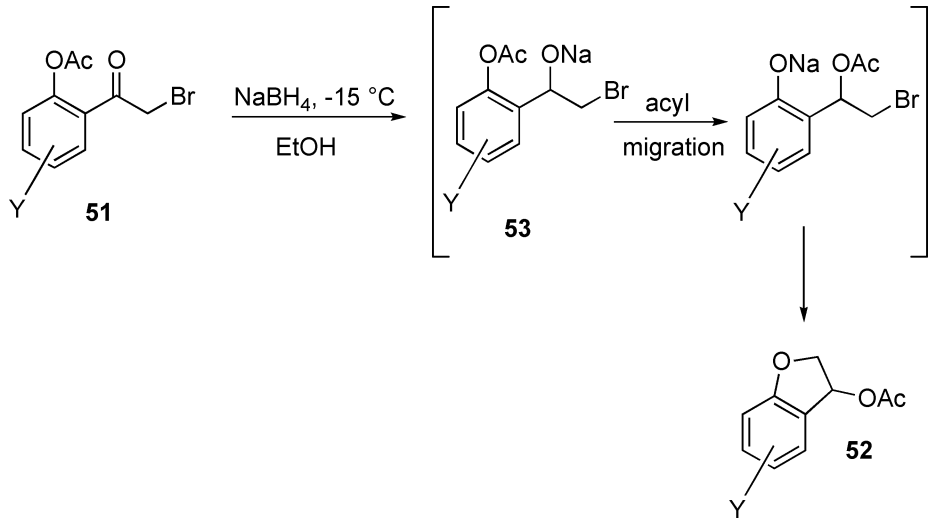
Scheme 46

In a completely different approach, the intramolecular addition of arylboronic acids to ketones (see compound **49**) to yield several heterocycles, including 2,3-dihydrobenzofurans, has been realized with catalytic amounts (5 mol%) of cationic chiral palladium-complexes and easily available (*R*)-Binap. It is remarkable that the corresponding optically active tertiary alcohols, *e. g.* **50**, have been obtained in good to excellent yields and high enantioselectivities under mild reaction conditions while an anion exchange resin was employed as an additive [Amberlite IRA-400 (OH)] (*Scheme 47*).[84]

The reduction of substituted 2-acetoxy-ω-bromoacetophenones of type **51** with $NaBH_4$ is a valuable entry to 3-acetoxydihydrobenzofurans **52** in high yields. The method is applicable to acetophenones with both electron-donating and electron-withdrawing substituents. The process involve an acyl migration from the acetate moiety on the aromatic ring to the sodium salt of the reduced ketone **53**, as shown in *Scheme 48*.[85]



Scheme 47



Scheme 48

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