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Dihydronaphthofurans: synthetic strategies and applications

Abolfazl Olyaei *[a] and Mahdieh Sadeghpour[b]

Dihydronaphthofurans (DHNs) are an important class of arene ring-fused furans which are widely found in many natural and non-natural products and drug candidates with relevant biological and pharmacological activities. Furthermore, vinylidene-naphthofurans exhibit photochromic properties when exposed to UV or sun light at room temperature. For these reasons, a vast array of synthetic procedures for the preparation of dihydronaphthofurans including annulation of naphthols with various reagents, cycloaddition reactions ([3 + 2], [4 + 1] and Diels–Alder), intramolecular transannulation, Friedel–Crafts, Wittig, Claisen rearrangement, neophyl rearrangement and other reactions under various conditions have been developed over the past decades. This review aims to describe the different strategies developed so far for the synthesis of dihydronaphthofurans and their applications. After a brief introduction to the types of dihydronaphthofurans and their biological activities, the different synthetic approaches such as chemical, photochemical, and electrochemical, methods are described and organized on the basis of the catalysts and the other reagents employed in the syntheses. The subsequent section focuses on biological and pharmacological applications and photochromic properties of the target compounds.

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1. Introduction

Furans are five-membered aromatic heterocycles containing one oxygen atom that are commonly found in many important compounds such as natural products, pharmaceuticals and polymers. Moreover, furans can be utilized as synthetic intermediates to access other useful compounds. The synthesis of this fundamental structural building block has received significant attention and a wide variety of approaches are available to the synthetic practitioner.[1] Arene ring-fused furan derivatives such as dihydronaphthofurans (DHNs) have attracted widespread interest in view of their presence in many important natural and non-natural products. Natural products

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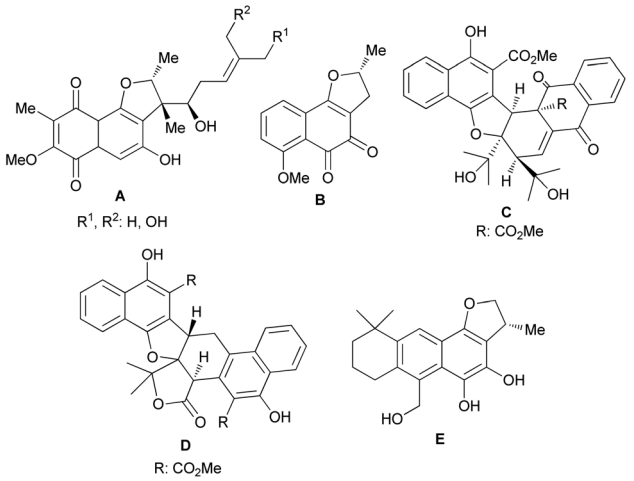

Fig. 1 Naturally occurring molecules bearing the dihydronaphthofurans.

with DHN moieties have been shown to have a wide range of biological and pharmacological properties.[2–4] For example, furaquinocins (**A**), consisting of highly oxygenated *p*-quinone rings, are antihypertensive, cytotoxic against HeLa S3 and B16 melanoma cells, and also inhibit platelet aggregation and coagulation.[2] In contrast, (−)-nocardione (**B**) with an *o*-quinone moiety is a Cdc25B tyrosine phosphatase inhibitor with moderate antifungal and cytotoxic activity.[3] Also, rubioncolin A (**C**) and rubioncolin B (**D**) were isolated from *Rubia oncotricha* in racemic forms.[4] They are also found in *Rubia cordifolia*, which is used in traditional Korean medicine to treat coughs, bladder and kidney stones, joint inflammation, uterine hemorrhage, and uteritis.[5] Interestingly, the electron rich catechol derivative aegyptinone (**E**) shows antibacterial and antifungal activity[6] (Fig. 1).

Furthermore, some of the synthesized dihydronaphthofuran derivatives exhibit a variety of interesting biological and pharmacological properties including 5-lipoxygenase inhibitor,[7] $C_{17,20}$ lyase inhibitors,[8] antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$,[9] anti-tyrosinase, antioxidant, and antibacterial,[10] inhibitors of NF-$_k$B activity,[11] α-glucosidase inhibitors,[12] inhibitor of α-chymotrypsin[13] and anti cancer activities (liver tumor growth inhibitors).[14] Moreover, vinylidene-naphthofurans are a new class of polycyclic compounds that exhibit photochromic properties when exposed to the UV or sunlight at room temperature and adsorbed in silica gel or dissolved in acidified alcoholic solutions (Fig. 2).[15–20]

This wide range of biological activities and properties has stimulated interest in the synthesis of dihydronaphthofuran derivatives. During the past decades, several synthetic approaches to 2,3-dihydronaphtho[2,1-*b*]furan, 2,3-dihydronaphtho[1,2-*b*]furan, 2,3-dihydronaphtho[2,3-*b*]furan, 1,3-dihydronaphtho[2,3-*c*]furan, 1,3-dihydronaphtho[1,2-*c*]furan and vinylidene-1,2-dihydronaphtho[2,1-*b*]furan derivatives (**F–K**) (Fig. 3) have been reported. The general methods used for the synthesis of these compounds include chemical,

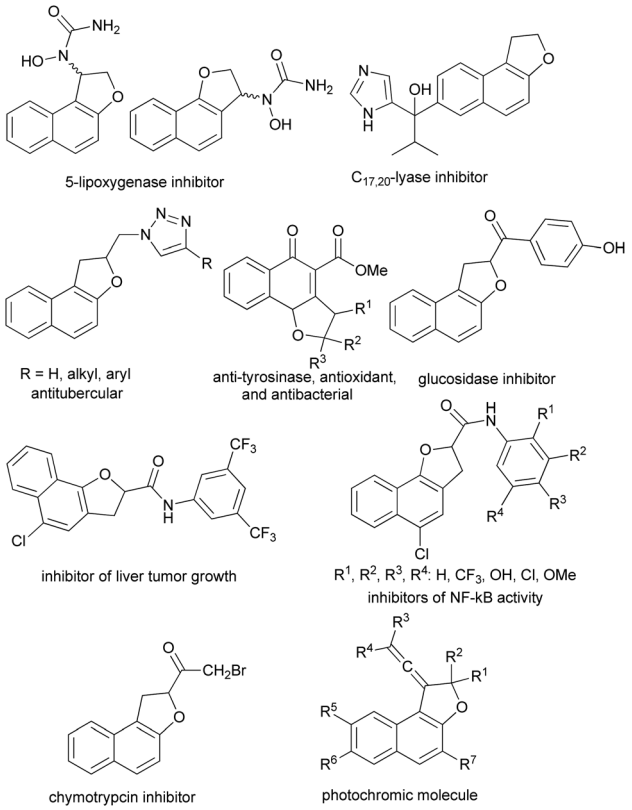

Fig. 2 Examples of biological, pharmacological and photochromic products containing dihydronaphthofuran moiety.

photochemical and electrochemical methods have been described and organized on the basis of the catalysts and the other reagents. To the best of our knowledge, there is no review on synthesis of dihydronaphthofuran derivatives. Hence, the main purpose of this review is to show all types of reactions for the synthesis of these heterocyclic compounds, such as annulation of naphthols with various reagents, cycloaddition reactions ([3 + 2], [4 + 1] and Diels–Alder), intramolecular transannulation, Friedel–Crafts, Wittig, Claisen rearrangement,

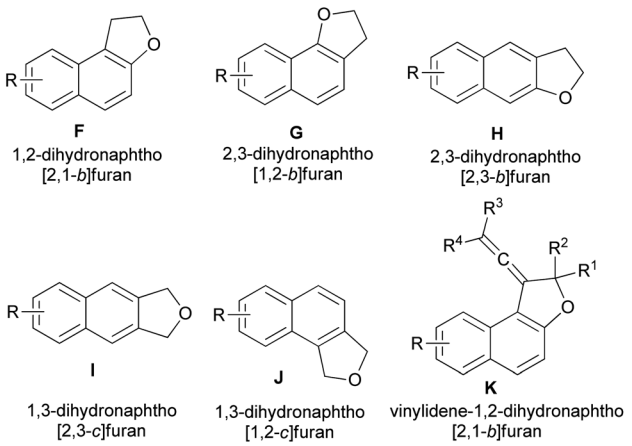

Fig. 3 Structures of dihydronaphthofurans F–K.

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neophyl rearrangement and the other reactions in various conditions and their biological, pharmacological and photochromic properties.

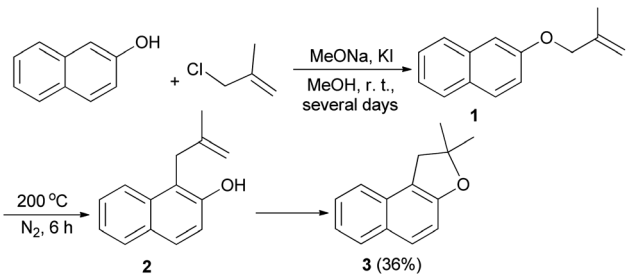
2. Synthesis of dihydronaphthofurans

2.1. Base-catalyzed synthesis

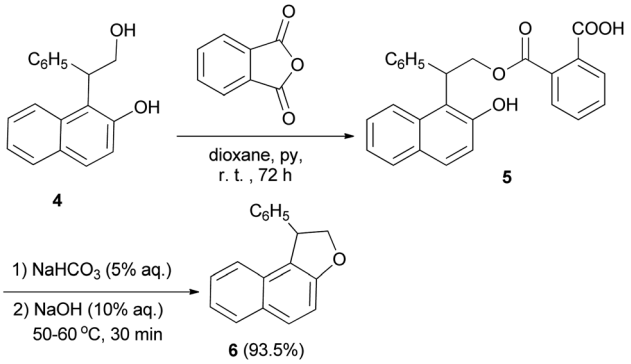
The first synthesis of 1,2-dihydronaphtho[2,1-*b*]furan has been reported by Mckusick in 1948. Sodium methoxide and potassium iodide promoted condensation of 2-naphthol with β-methyl allyl chloride in methanol at room temperature for several days afforded β-methylallyl-2-naphthyl ether (**1**). Claisen rearrangement of **1** led to the formation of intermediate **2**. The latter underwent cyclization to provide 1,2-dihydro-2,2-dimethylnaphtho[2,1-*b*]furan (**3**) in 36% yield (Scheme 1).[21]

Guss and Jules reported that the reaction of 2-(2-hydroxy-1-naphthyl)-2-phenylethanol (**4**) with phthalic anhydride in the presence of pyridine in dioxane at room temperature for 72 h, led to the formation of acid phthalate **5**. By heating in 5% sodium bicarbonate and 10% sodium hydroxide at 50–60 °C for 30 min the acid phthalate **5** was converted into the cyclized product, 1-pheny1-1,2-dihydronaphtho[2,1-*b*]furan (**6**) (Scheme 2).[22]

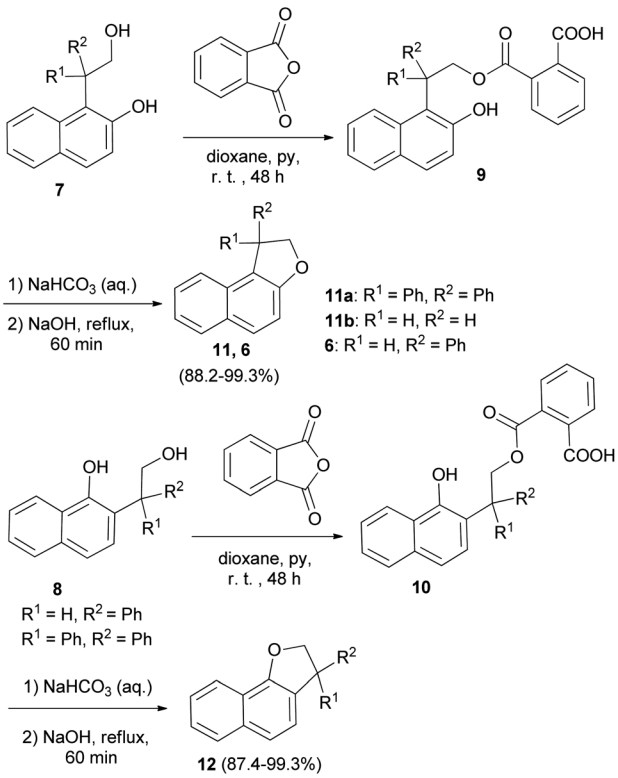
In a similar fashion, phenol–alcohols **7** and **8** were converted into the acid phthalates **9** and **10** by allowing a solution of the phenol alcohols, phthalic anhydride, pyridine and dioxane to stand at room temperature for 48 hours. Then, addition of weaker solution of sodium hydroxide to the bicarbonate solution of the esters **9** and **10** and the slurry were heated at reflux temperature for 1 hour afforded 1,2-dihydronaphtho[2,1-*b*]furans **11a–b**, **6** and 2,3-dihydronaphtho[1,2-*b*]furans **12** in 88.2–99.3% and 87.4–99.3% yields, respectively (Scheme 3).[23]



Scheme 1 Preparation of 1,2-dihydro-2,2-dimethylnaphtho[2,1-*b*]furan (**3**).



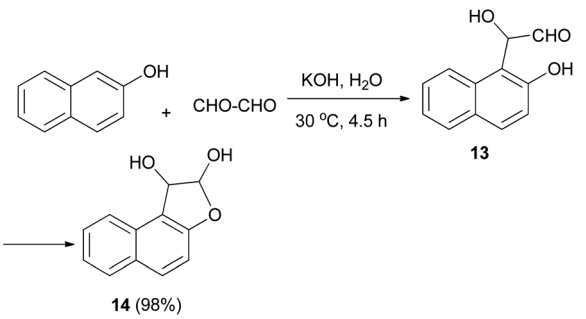
Scheme 2 Base-catalyzed synthesis of 1-pheny1-1,2-dihydronaphtho[2,1-*b*]furan (**6**).



Scheme 3 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **11a–b**, **6** and of 2,3-dihydronaphtho[1,2-*b*]furans **12**.

In 1994, Kito *et al.* explored the reaction of 2-naphthol with glyoxal in the presence of KOH in aqueous media at 30 °C for 4.5 h, which furnished 1,2-dihydronaphtho[2,1-*b*]furan-1,2-diol (**14**) in 98% yield. Hemiacetal **14** was obtained *via* cyclization of intermediate **13** (Scheme 4).[24]

In a similar manner, dihydronaphthofuran **14** could be obtained *via* treatment of 2-naphthol with aqueous glyoxal (40%) in aqueous solution of KOH at 18–21 °C for 4.5 h in 90.2% yield. Moreover, 1,2-diacetoxy-l,2-dihydronaphtho[2,1-*b*]furan (**15**) was efficiently achieved from **14** in acetic anhydride and pyridine under reflux for 24 h (Scheme 5).[25]



Scheme 4 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furan-1,2-diol (**14**).

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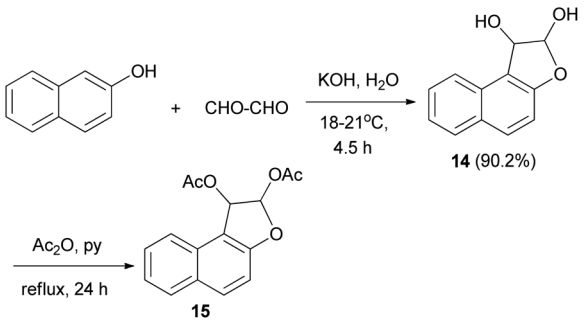
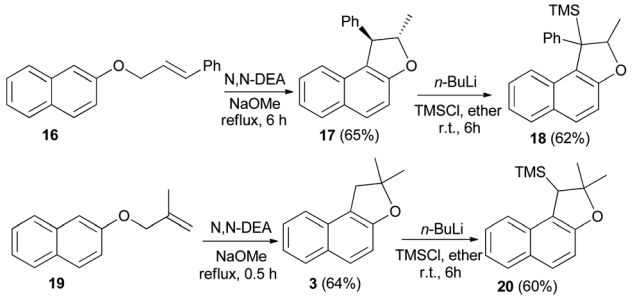


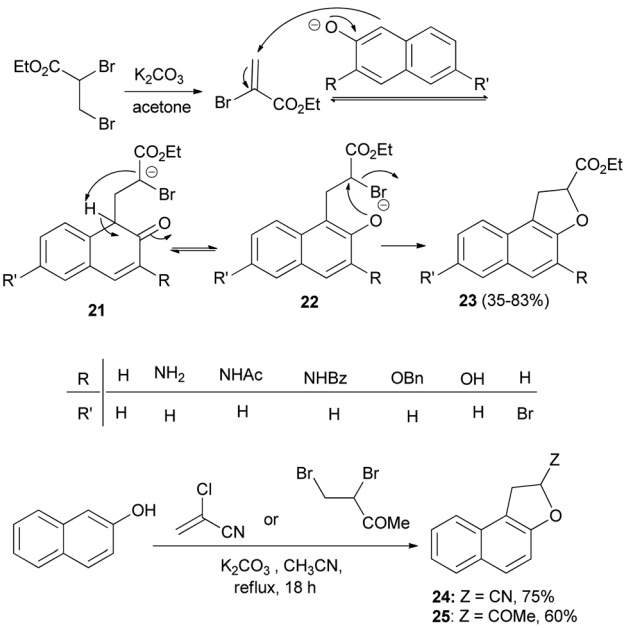
Scheme 5 Synthesis of 1,2-diacetoxy-l,2-dihydronaphtho[2,1-*b*]furan (**15**).



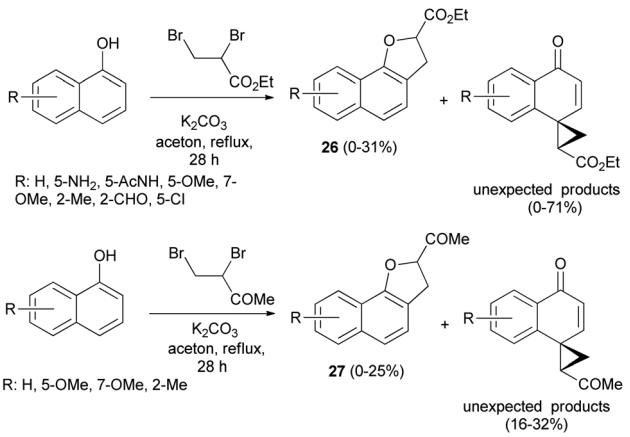
Scheme 6 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furan derivatives **3**, **17**, **18** and **20**.

Saidi *et al.*[26] reported that the reaction of 2-naphthol with alkenyl halide in acetone in the presence of K_2CO_3 and KI gave the corresponding naphthyl ethers **16** and **19.** Naphthyl ethers in *N*,*N*′-diethyl aniline (*N*,*N*′-DEA) and sodium methoxide under reflux for 0.5–8 h afforded dihydronaphthofurans **17** and **3** in 65 and 64% yields, respectively. In order to prepare trimethylsilyl-substituted dihydronaphthofurans **18** and **20**, dihydronaphthofurans **17** and **3** were treated with *n*-BuLi and then with chlorotrimethylsilane (TMS-Cl) in diethyl ether at room temperature for 6 h (Scheme 6).

A one-step synthesis of ethyl 1,2-dihydronaphtho[2,1-*b*]furan-2-carboxylates **23** from substituted naphthols and ethyl 2,3-dibromopropanoate in the presence of K_2CO_3 in refluxing acetone for 18 h has been reported by Merour *et al.*[27] First, ethyl 2,3-dibromopropanoate is easily transformed *in situ* into ethyl-2-bromoacrylate with potassium carbonate in refluxing acetone. Then, a Michael-type addition of the naphthalenolate to the 2-bromoacrylate generates the C–C bond forming intermediate **21**. Aromatization and formation of the 2-naphthalenolate anion gives the intermediate **22.** This is followed by an intramolecular nucleophilic substitution on the carbon bearing the bromo atom in **22** affording the gave the corresponding product **23** in 35–83% yields. Following the same methodology, the reaction of 2-naphthol with 2-chloroacrylonitrile and 3,4-dibromobutan-2-one in refluxing acetonitrile for 18 h afforded **24** and **25** in 75 and 60% yields, respectively (Scheme 7).



Scheme 7 One-step synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **23**–**25**.



Scheme 8 Synthesis of 2,3-dihydronaphtho[1,2-*b*]furans **26** and **27**.

Treatment of 1-naphthol derivatives with ethyl 2,3-dibromopropanoate in the presence of K_2CO_3 in refluxing acetone for 28 h led to the formation of the expected ethyl 2,3-dihydronaphtho[1,2-*b*]furan-2-carboxylates **26** in 0–31% yields and unexpected ethyl 4′-oxospiro[cyclopropane-1,1′(4′*H*)-naphthalene]-2-carboxylates in 0–71% yields besides starting materials. Also, the reaction of 1-naphthols with 3,4-dibromobutan-2-one by applying the same methodology gave 2,3-dihydronaphtho[1,2-*b*]furan-2-yl ketones **27** in 0–25% yields and unexpected products in 16–32% yields (Scheme 8).[28] Formation of **26** and **27** took place according to similar reported mechanism in Scheme 7.[27]

An efficient procedure for the conjugate addition of methyl acetoacetate to 2-(methoxycarbonyl)-1,4-naphthoquinone using K_2CO_3 has been developed. The reaction was carried out in

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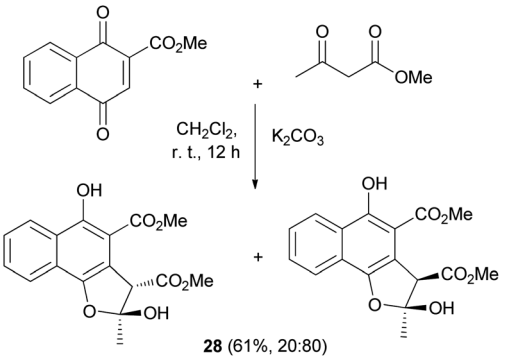
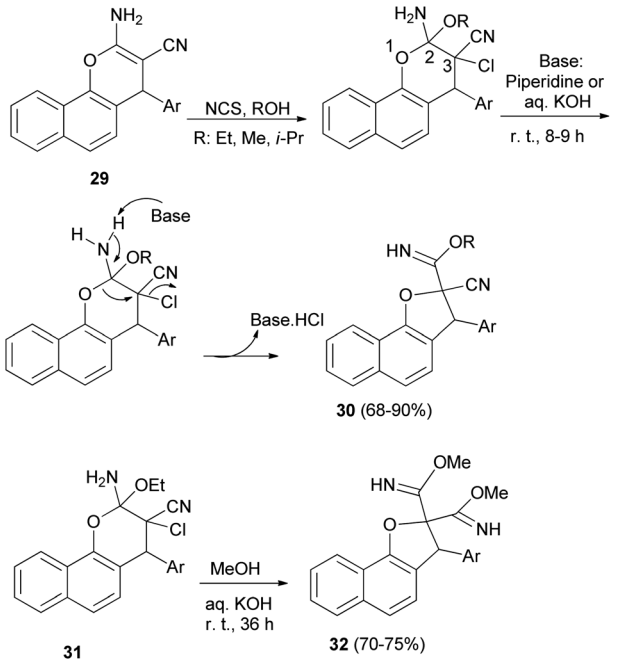


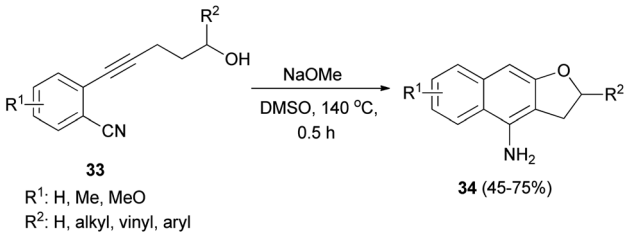
Scheme 9 Synthesis of *cis* and *trans* 2,3-dihydronaphtho[1,2-*b*]furan derivatives **28**.

CH_2Cl_2 at room temperature for 12 h yielded 61% of a mixture of *cis* and *trans* (20 : 80) 2,3-dihydronaphtho[1,2-*b*]furan derivatives **28** (Scheme 9).[29]

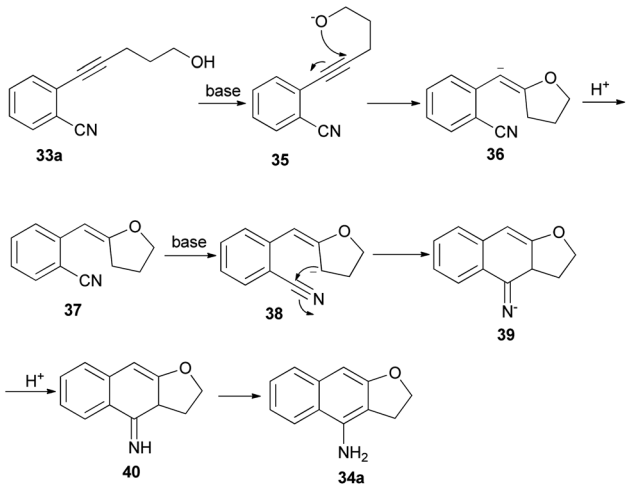
Alla *et al.*[30] noted that one-pot reaction of 2-amino-4*H*-pyran derivatives **29** with *N*-chlorosuccinimide and a base (piperidine or aqueous KOH) in alcohol medium at room temperature for 8–9 h gave dihydronaphthofurans **30** in 68–90% yields. Plausible mechanism for the formation of **30** has been arrived at Scheme 10. Initially aminopyran undergoes oxidative difunctionalization with NCS in the presence of an alcohol solvent. Subsequent addition of base to the aminopyran leads to proton abstraction from the amino group. This leads to a cascade pyran ring opening by the cleavage of the (C_2–O_1) bond, and ring closure of the (O_1–C_3) bond to dihydrofuran *via* elimination of HCl. The sequential elementary processes lead to formation of the ring contracted dihydrofuran carbimidate ester **30**. In



Scheme 10 Synthesis of dihydronaphthofurans **30** and **32** from 4*H*-pyran derivatives.



Scheme 11 Synthesis of dihydronaphthofurans **34**.



Scheme 12 Proposed mechanism for the formation of **34a**.

a similar manner, highly functionalized pyran derivatives **31** were treated with methanolic KOH (1 N) at room temperature for 36 h to obtain the products **32** in good yields (70–75%) (Scheme 10).

Base-mediated cyclization reactions of 2-(5-hydroxy-1-pentynyl)benzonitriles **33** to 4-amino-2,3-dihydronaphtho[2,3-*b*]furans **34** have been reported by Wu *et al.*[31] Treatment of **33** with NaOMe in DMSO at 140 °C for 0.5 h gave the desired products **34** in 45–75% yields (Scheme 11). The proposed mechanism for the cyclization of **33a** to **34a** is shown in Scheme 12. The first step is the deprotonation of **33a** with base to form alkoxide **35** that would undergo intramolecular 5-*exo*-dig cyclization to form the vinyl anion **36**. The vinyl anion **36** could undergo direct proton transformation to give **37**. Deprotonation of **37** with base to form anion **38**. Then, the electrocyclic ring closure reaction to give **39**. Finally protonation of **39** to give imine **40** and following the imine–enamine tautomerization, to convert the imine **40** to the final product **34a**.[31] Also, cyclization reaction of **41** with NaH in DMSO at 140 °C for 15 min afforded product **42** in 58% yield (Scheme 13).[31]

Several reports on the synthesis of hemiacetals of dihydronaphthofurans have been described by Dibble *et al.* 1,3-Dihydro-1-hydroxynapbtho[2,3-*c*]furan (**43**) and 1,3-dihydro-*l*-hydroxynaphtho[1,2-*c*]furan (**44**) could be successfully prepared in 77% and 85% yields, respectively. In this reaction, treatment of bromonaphthalene methanol (**45**) in dry diethyl ether with *n*-butyl lithium in hexane at −78 to 0 °C for 30 min afforded 3-

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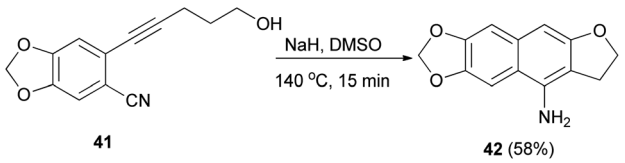
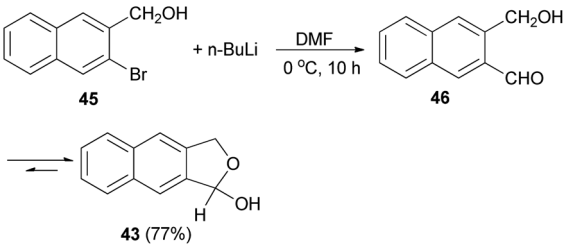
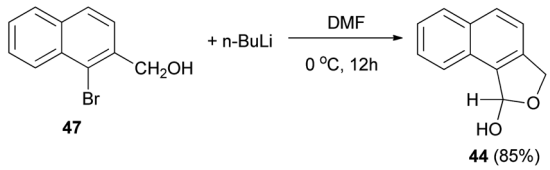


Scheme 13 Preparation of 2,3-dihydronaphtho[2,3-*b*]furan **42**.



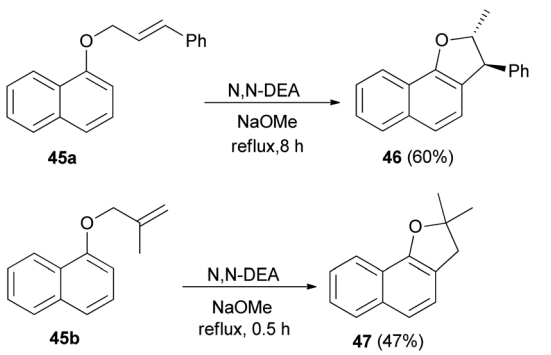
Scheme 14 Preparation of dihydronaphthofuran **43**.



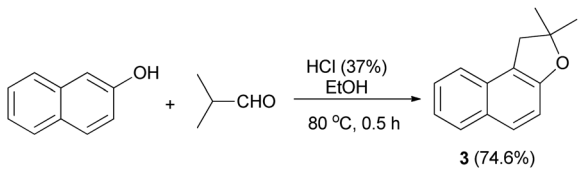
Scheme 15 Preparation of dihydronaphthofuran **44**.

(hydroxymethyl)-2-naphthaldehyde **46,** which on treatment with dry DMF at 0 °C for 10 h led to dihydronaphthofuran **43** (Scheme 14). In a similar manner, dihydronaphthofuran **44** was prepared from bromonaphthalene methanol **47** in 85% yield as shown in Scheme 15.[32]

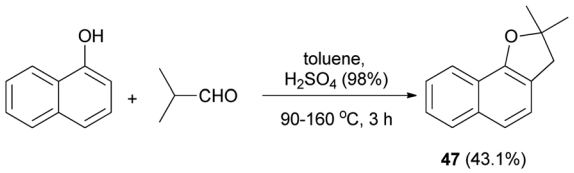
Treatment of 1-naphthol with alkenyl halide in acetone in the presence of K_2CO_3 and KI gave the corresponding allyl naphthyl ethers **45a–b.** Heating of **45** in *N*,*N*′-diethyl aniline (*N*,*N*′-DEA) and sodium methoxide under reflux for 0.5–8 h afforded 2,3-dihydronaphtho[1,2-*b*]furan derivatives **46** and **47** *via* Claisen rearrangement in 60 and 47% yields, respectively (Scheme 16).[26]



Scheme 16 Synthesis of 2,3-dihydronaphtho[1,2-*b*]furan derivatives **46** and **47**.



Scheme 17 Acid-catalyzed synthesis of dihydronaphthofuran **3**.



Scheme 18 Acid-catalyzed synthesis of 2,3-dihydro-2,2-dimethylnaphthol[1,2-*b*] furan (**47**).

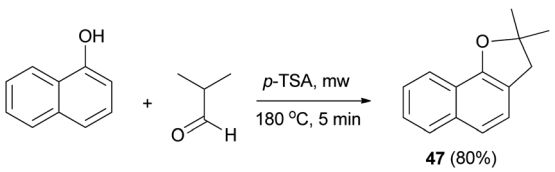
2.2. Acid-catalyzed synthesis

In 1971, Martini reported that preparation of dihydronaphthofuran **3** was accomplished by the treatment of 2-naphthol with isobutylaldehyde using HCl in EtOH at 80 °C for 0.5 h in 74.6% yield (Scheme 17).[3]

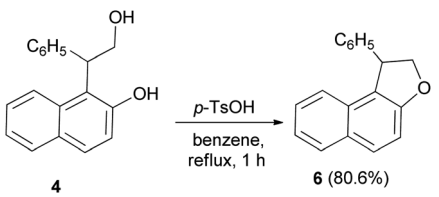
In a similar fashion, synthesis of 2,3-dihydro-2,2-dimethylnaphthol[1,2-*b*] furan (**47**) in 43.1% yield has been accomplished by the treatment of 1-naphthol with isobutylaldehyde using H_2SO_4 in toluene at 90–160 °C for 3 h (Scheme 18).[33]

Similarly, dihydronaphthofuran **47** was obtained *via* the reaction of isobutyraldehyde with 1-naphthol in the presence of catalytic amount of *p*-TSA under closed vessel solvent-free microwave irradiation conditions at 180 °C for 5 min in 80% yield (Scheme 19).[34]

Treatment of **4** with *p*-toluenesulfonic acid monohydrate in benzene under reflux condition for one hour with simultaneous removal of 50 cm^3 of benzene containing the water formed, gave dihydronaphthofuran **6** in 80.6% yield (Scheme 20).[22]



Scheme 19 *p*-TSA-catalyzed synthesis of dihydronaphthofuran **47**.



Scheme 20 Acid-catalyzed synthesis of 1-pheny1-1,2-dihydronaphtho[2,1-*b*]furan (**6**).

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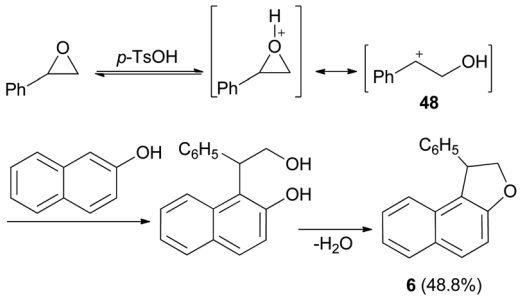
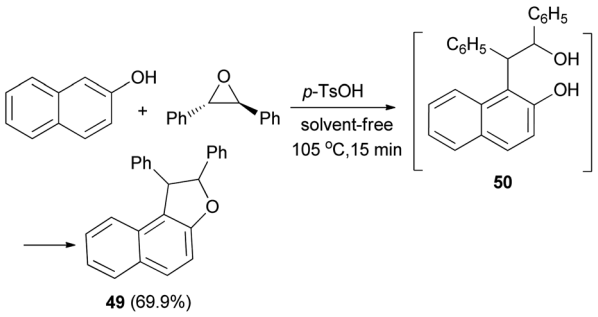


Scheme 21 Synthesis of dihydronaphthofuran **6**.

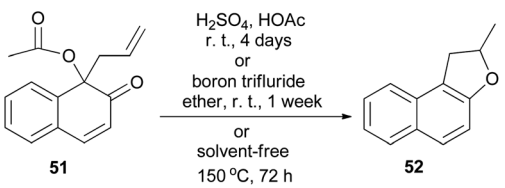


Scheme 22 Acid-catalyzed synthesis of 1,2-diphenyl-1,2-dihydronaphtho[2,1-*b*]furan (**49**).

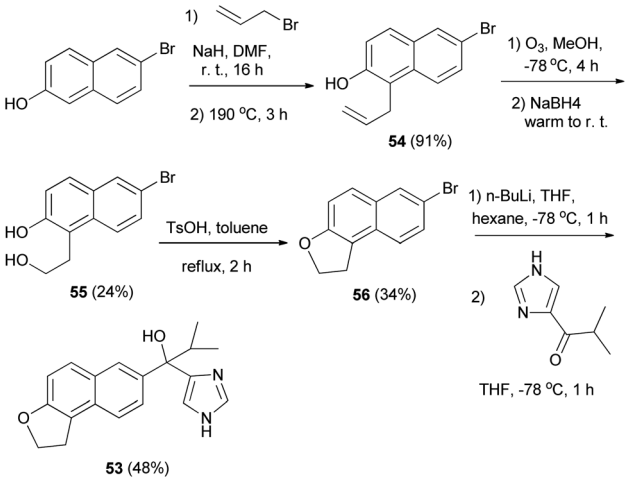
It was also shown that dihydronaphthofuran **6** was obtained by the reaction of styrene oxide with 2-naphthol in refluxing benzene for 1 h in 48.8% yield (Scheme 21). This reaction proceed *via* the acid catalyzed unimolecular ring opening of styrene oxide, followed by nucleophilic attack of naphthol to the resulting adduct **48** and cyclization, then elimination of water afforded the final product **6.**[35]

In 1953, Guss *et al.*[36] have obtained 1,2-diphenyl-1,2-dihydronaphtho[2,1-*b*]furan (**49**) in 69.9% yield from the reaction of 2-naphthol and *trans*-stilbene oxide by using *p*-toluenesulfonic acid monohydrate as catalyst in 105 °C for 15 min under solvent-free condition. Presumably a phenol–alcohol **50** was first formed and then cyclized under these reaction conditions to the desired product **49** (Scheme 22).

Miller and Lin noted that rearrangement of 1-acetoxy-1-allyl-2-naphthalenone (**51**) in 10% sulfuric acid in acetic acid at room temperature for 4 days, or in boron trifluoride etherate at room temperature for one week, gave 2-methyl-1,2-dihydronaphtho [2,1-*b*]furan (**52**) as the only product. Similarly, attempted



Scheme 23 Rearrangement of 1-acetoxy-1-allyl-2-naphthalenone (**51**) to dihydronaphthofuran **52**.



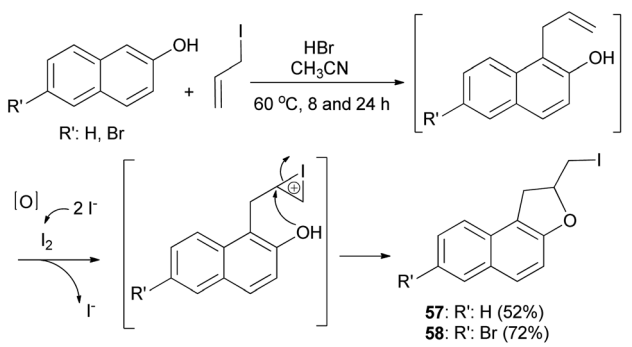
Scheme 24 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furan derivatives **53** and **56**.

thermal rearrangement at 150 °C for 3 days in the absence of solvent afforded **52** (Scheme 23).[37]

Matsunaga *et al.*[8] developed a strategy for the synthesis of 1,2-dihydronaphtho[2,1-*b*]furan **53.** The reaction was carried out *via* the key intermediate **54** as shown in Scheme 24. Allylation of 6-bromo-2-hydroxynaphthalene followed by a Claisen rearrangement at 190 °C gave the 1-allyl-2-naphthol **54.** Ozonolysis of **54** followed by treatment with $NaBH_4$ afforded the diol **55** and intramolecular dehydration under acidic conditions provided **56.** Lithiation of 1,2-dihydronaphthofuran **56** and then addition to the imidazolyl isopropyl ketone furnished 1,2-dihydronaphtho[2,1-*b*]furan **53** in 48% yield.

Hydrobromic acid-catalyzed Friedel–Crafts type reactions of 2-naphthols with allyl iodide in CH_3CN at 60 °C for 8 and 24 h led to the formation of dihydronaphthofuran **57** and 7-bromo-2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**58**) in 52% and 72% yields, respectively. Formation of products by reaction of 2-naphthols with allyl iodide is assumed to proceed *via* allylation of naphthols followed by iodocyclization to produce the corresponding products (Scheme 25).[38]

A simple and highly efficient one-pot protocol for the synthesis of novel polysubstituted 1,2-dihydronaphtho[2,1-*b*]



Scheme 25 HBr-catalyzed preparation of 1,2-dihydronaphtho[2,1-*b*]furans **57** and **58**.

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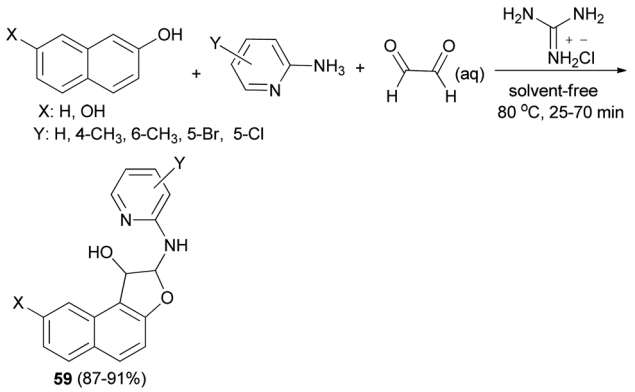
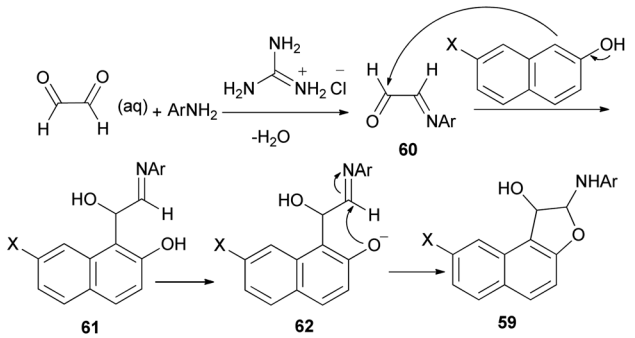
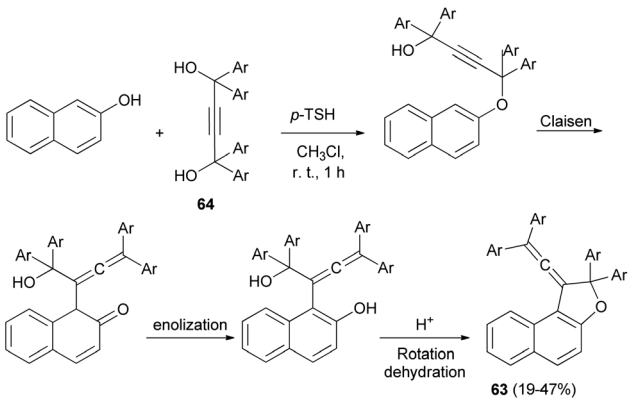


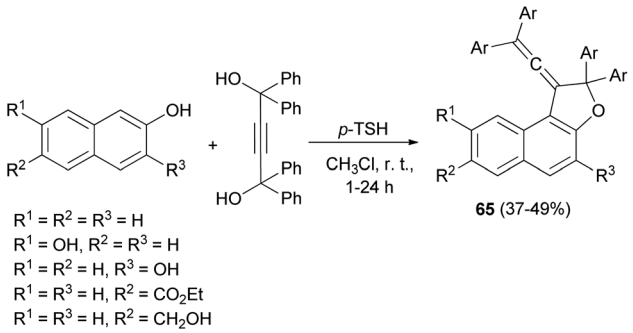
Scheme 26 Guanidinium chloride catalyzed synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **59**.



Scheme 27 Plausible mechanism for the formation of **59**.



Scheme 28 Synthesis of 1-vinylidene-naphthofurans **63**.



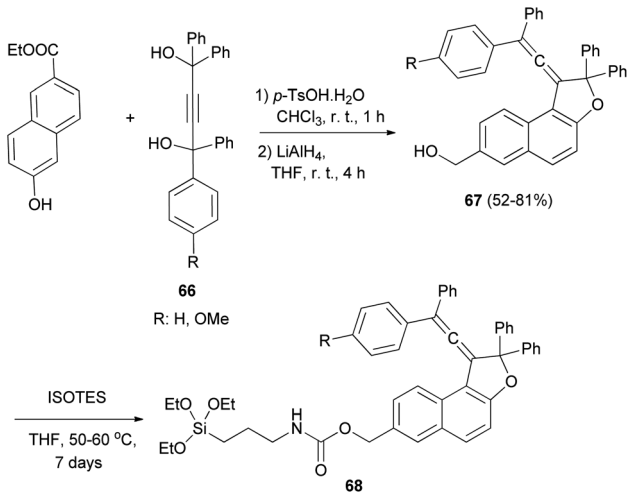
Scheme 29 *p*-TSA-catalyzed synthesis of vinylidene-naphthofurans **65**.

furans **59** in 87–91% yields has been developed by three-component coupling reaction of 2-aminopyridines, naphthols and aqueous glyoxal in the presence of guanidinium chloride as a polyfunctional organocatalyst under solvent-free conditions at 80 °C for 25–70 min (Scheme 26). A plausible mechanism for this conversion is shown in Scheme 27. The formation of products can be rationalized by the initial formation of intermediate **60** *via* condensation of amine with glyoxal. Subsequent addition of 2-naphthol to **60** affords intermediate **61** followed by intramolecular nucleophilic addition of naphthoxy ion **62** generated *in situ* by guanidinium chloride to activated imine group led to the formation of the desired products **59**.[39]

A set of new 1-vinylidene-1,2-dihydronaphtho[2,1-*b*]furans **63** in 19–47% yields was unexpectedly obtained in the reaction of 2-naphthol with readily available 1,1,4,4-tetraarylbut-2-yne-1,4-diols **64** in the presence of 4-toluenesulfonic acid monohydrate in $CHCl_3$ at room temperature for 1 h. This reaction may be assumed to proceed *via* Claisen rearrangement, enolization and rotation dehydration as shown in Scheme 28.[15]

In a similar fashion, vinylidene-naphthofurans **65** are a new class of photochromic molecules, easily synthesized by reaction of 1,1,4,4-tetraphenylbut-2-yne-1,4-diol with naphthols in the presence of 4-toluenesulfonic acid monohydrate in $CHCl_3$ at room temperature for 1–24 h in 37–49% yields (Scheme 29).[16]

Coelho *et al.* observed that the treatment of ethyl 6-hydroxy-2-naphthoate with diols **66** under acid catalysis in $CHCl_3$ at room temperature for 1 day, followed by reduction with $LiAlH_4$ in THF at room temperature for 4 h afforded the vinylidene-naphthofurans **67** in good yields (52–81%). The later compounds **67** were silanized with 3-(triethoxysilyl) propyl isocyanate (ISOTES) in THF at 50–60 °C for 7 days afforded the respective silanized products **68** as the photoactive molecules (Scheme 30).[19]



Scheme 30 Synthesis of vinylidene-naphthofurans **67** and **68**.

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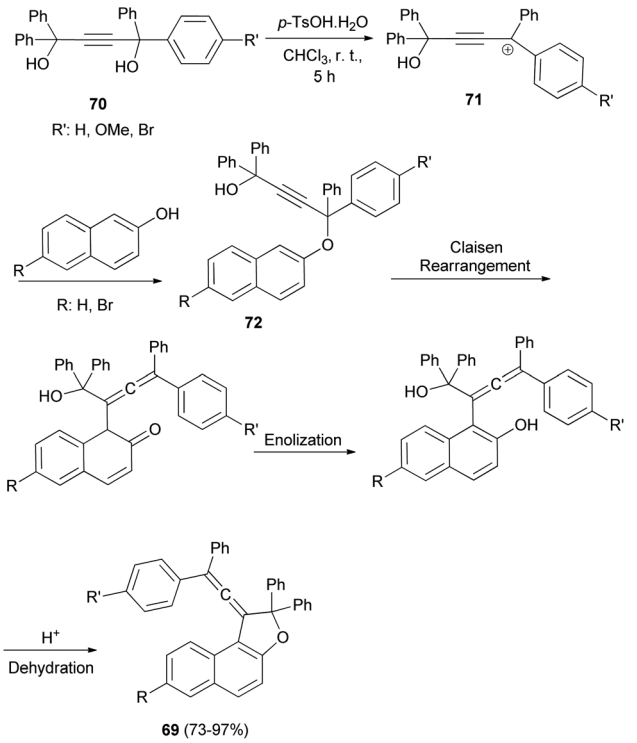
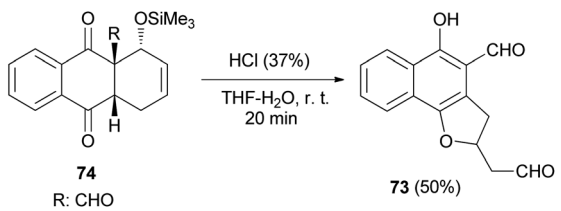


Scheme 31 Synthesis of photochromic vinylidene-naphthofurans **69**.

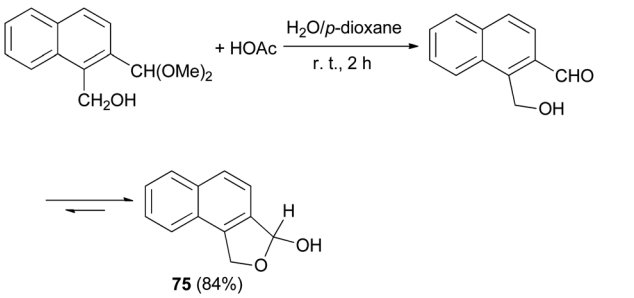
In a similar manner, a series of novel photochromic vinylidene-naphthofurans **69** was synthesized by reaction of 2-naphthols with tetraarylbut-2-yne-1,4-diol (**70**) in the presence of *p*-TSA in $CHCl_3$ at room temperature for 5 h in 73–97% yields. This one-pot reaction occurs *via* a domino reaction (Scheme 31): under acid-catalysis the diol **70** is converted into a propargylic carbocation **71**, which upon reaction with 2-naphthol provides a propargylic aryl ether **72**. Then, this intermediate performs a [3,3]-sigmatropic Claisen rearrangement followed by enolization and acid-catalyzed intramolecular dehydration affording the final vinylidene-naphthofuran **69**.[20]

4-Formyl-5-hydroxy-2-(2′-oxoethyl)2,3-dihydronaphtho[1,2-*b*]furan (**73**) was readily achieved in 50% yield by acid induced fragmentation of the Diels–Alder adduct **74** in 90% aqueous THF at room temperature for 20 min (Scheme 32).[40]

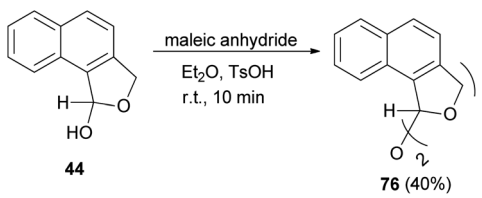
Smith *et al.*[32] synthesized 1,3-dihydro-3-hydroxynaphtho[1,2-*c*]furan (**75**) in 84% yield from the reaction of 1-(hydroxymethy1)-2-(dimethoxymethy1)naphthalene with HOAc in water and *p*-dioxane at room temperature for 2 h (Scheme 33).



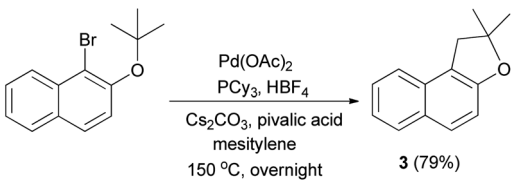
Scheme 32 Synthesis of 2,3-dihydronaphtho[1,2-*b*]furan **73**.



Scheme 33 Preparation of dihydronaphthofuran **75**.



Scheme 34 Preparation of bis-dihydronaphthofuran **76**.



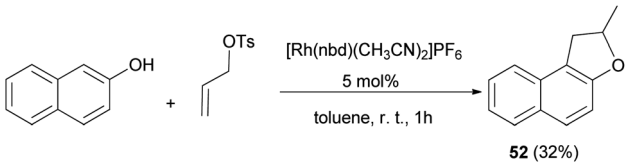
Scheme 35 $Pd(OAc)_2$ catalyzed synthesis of dihydronaphthofuran **3**.

Also, bis(1,3-dihydro-*l*-naphthol[1,2-*c*]furanyl)ether (**76**) was obtained in 40% yield by the reaction of **44** with maleic anhydride in diethyl ether as a solvent using a catalytic amount of TsOH at room temperature for 10 min (Scheme 34).[32]

2.3. Transition-metal catalyzed synthesis

In 2007, Lafrance *et al.*[41] have obtained dihydronaphthofuran **3** in 79% yield *via* the reaction of 1-bromo-2-(*tert*-butoxy)naphthalene in the presence of $Pd(OAc)_2$ (5 mol%), PCy_3, HBF_4 (6 mol%) in conjunction with Cs_2CO_3 as base and 2,2-dimethylpropionic acid (pivalic acid, 30 mol%) as additive in mesitylene at 150 °C for overnight (Scheme 35).

A simple procedure for the preparation of 2-methyl-1,2-dihydronaphtho[2,1-*b*]furan (**52**) in 32% yield by allylation of 2-naphthol with allyl tosylate in the presence of



Scheme 36 $[Rh(nbd)(CH_3CN)_2]PF_6$ catalyzed synthesis of 1,2-dihydronaphthofuran **52**.

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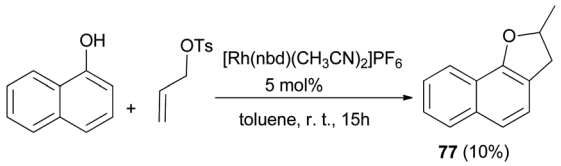


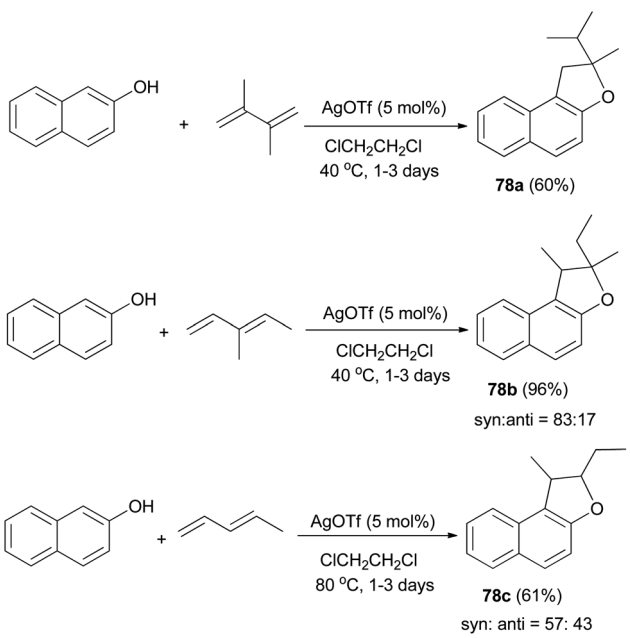
Scheme 37 Transition-metal catalyzed synthesis of 2-methyl-2,3-dihydronaphtho[1,2-*b*]furan (**77**).

$[Rh(nbd)(CH_3CN)_2]PF_6$ as catalyst in toluene at room temperature for 1 h was described by Tsukada *et al.* (Scheme 36).[42]

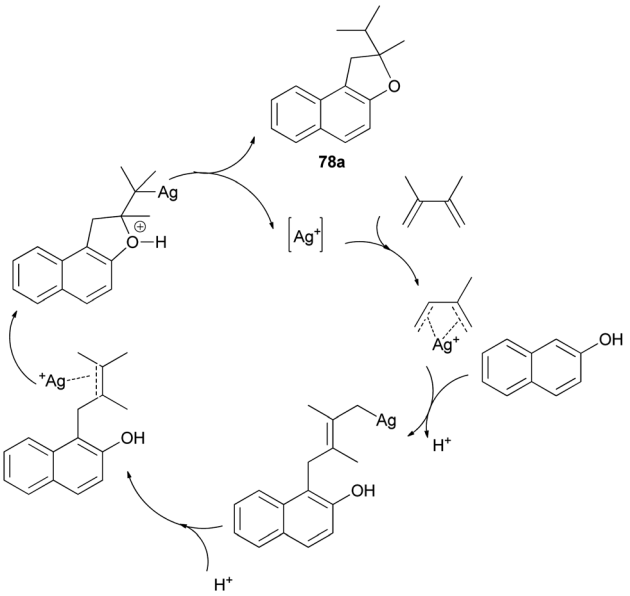
Similarly, 2-methyl-2,3-dihydronaphtho[1,2-*b*]furan (**77**) in 10% yield was obtained *via* the above reaction condition (Scheme 37).[42]

Mild, efficient, and economical Ag(I)-catalyzed sequential C–C/C–O bond formations between 2-naphthol and dienes in dichloroethane at 40 and 80 °C for 1–3 days were developed to afford a variety of 1,2-dihydronaphtho[2,1-*b*]furans **78a–c** in 60–96% yields (Scheme 38). A plausible mechanism for formation of products **78a** is shown in Scheme 39. Activation of the diene by coordination to Ag(I) is followed by intermolecular nucleophilic attack by the arene. The reactions of 2-naphthol with 1-substituted-1,3-diene substrates occur by either 1,2- or 1,4-addition. The resulting Ag–C bond is protonated to give 2-allylphenol intermediate then recoordination of C–C π-bond by Ag(I) activates the olefin toward intramolecular nucleophilic attack by the phenolic oxygen. Subsequent proton transfer produces the final product and regenerates the Ag(I) catalyst.[43]

In a similar fashion, reusable scandium/ionic liquid catalyst system for sequential C–C and C–O bond formations between 2-naphthol and dienes with atom economy has been reported for the synthesis of **78a–c** in toluene at 60 and 100 °C for 18–24 h in 60–95% yields (Scheme 40).[44]



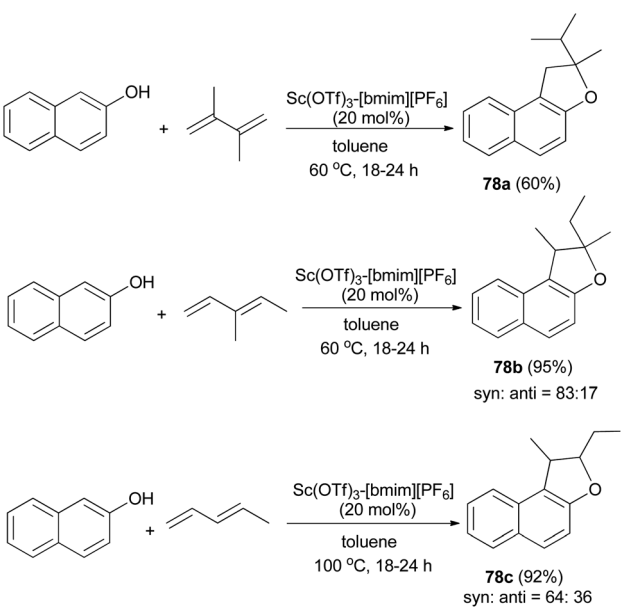
Scheme 38 AgOTf-catalyzed synthesis of dihydronaphthofurans **78**.



Scheme 39 Plausible mechanistic pathway for the formation of **78a**.

It was also shown that air-and moisture-stable $Cu(OTf)_2$-bipy catalyze the addition of 2-naphthol to 1,3-diene in dichloroethane at 50 °C for 18 h in a tandem hydroalkoxylation-rearrangement-hydroalkylation sequence, furnishing *O*-heterocycles such as 2-isopropyl-2-methyl-1,2-dihydronaphtho[2,1-*b*]furan (**78a**) in 60% yield (Scheme 41).[45]

Palladium chloride-catalyzed intramolecular activation of electroneutral arylcyclopropane **79** in the presence of benzoquinone as oxidant in dioxane at 80 °C for 12 h resulted 2-ethyl-2-methyl-1,2-dihydronaphtho[2,1-*b*]furan (**80**) in 64% yield *via* cyclopropane isomerization followed by a Wacker oxidation (Scheme 42).[46]



Scheme 40 $Sc(OTf)_3$-[bmim][PF_6]-catalyzed synthesis of dihydronaphthofurans **78**.

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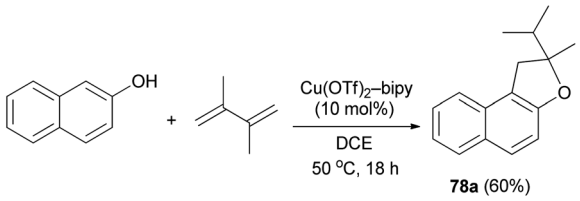
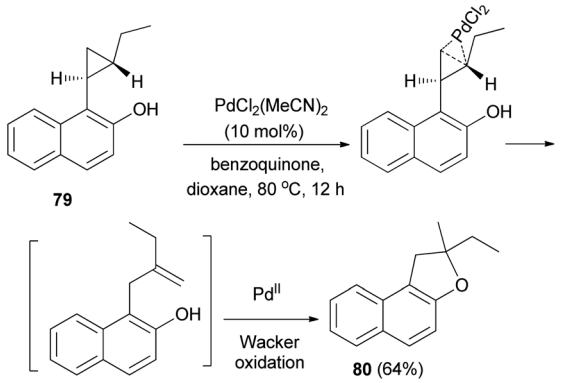


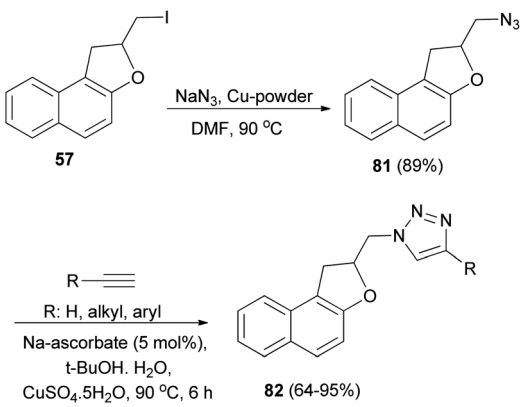
Scheme 41 $Cu(OTf)_2$-bipy catalyzed synthesis of dihydronaphthofuran **78a**.



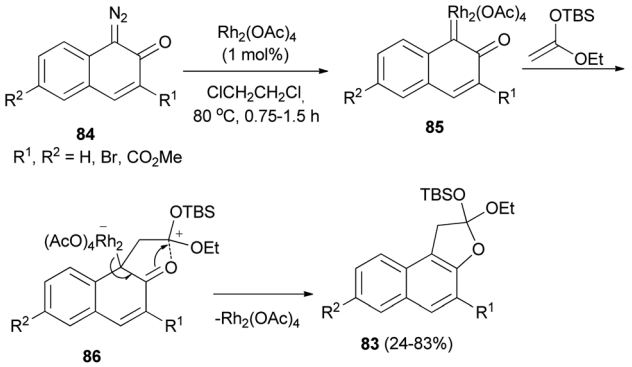
Scheme 42 $PdCl_2$-catalyzed synthesis of dihydronaphthofuran **80**.

Tripathi *et al.*[9] investigated reaction of dihydronaphthofuran **57** with NaN_3 in the presence of Cu-powder in DMF at 80 °C gave 2-(azidomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**81**) in 89% yield. [3 + 2] Cycloaddition of **81** with different alkynes in the presence of sodium ascorbate and $CuSO_4 \cdot 5H_2O$ (1 mol%) in 2 : 1 mixture of *tert*-butyl alcohol and water at 90 °C for 6 h afforded dihydronaphthofurans **82** in 64–95% yields (Scheme 43).

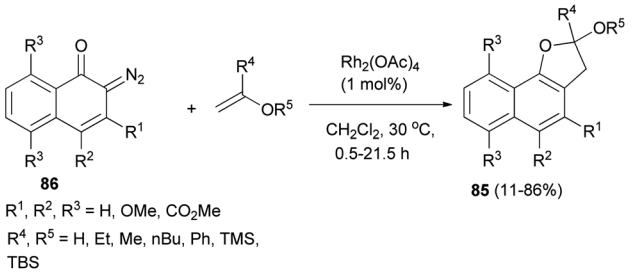
Kitamura *et al.*[47] developed $Rh_2(OAc)_4$-catalyzed synthesis of dihydronaphthofurans **83** in 24–83% yields by the cycloaddition reaction of diazonaphthoquinones **84** with enol ethers in dichloroethane at 80 °C for 0.75–1.5 h. A possible reaction mechanism is illustrated in (Scheme 44). Initially, $Rh_2(OAc)_4$ reacts with **84** to form Rh^{II} carbene complex **85**. Nucleophilic attack by the enol ether on carbene complex **85** proceeds to form



Scheme 43 Preparation of dihydronaphthofurans **81** and **82**.



Scheme 44 Rhodium-catalyzed synthesis of dihydronaphthofurans **83**.



Scheme 45 Rhodium-catalyzed synthesis of 2,3-dihydronaphtho[1,2-*b*]furan derivatives **85**.

86. Then, aromatization drives the cyclization to form naphthofuran **83** with release of $Rh_2(OAc)_4$.

In a similar fashion, synthesis of 2,3-dihydronaphtho[1,2-*b*]furan derivatives **85** in 11–86% yields has been achieved by the cycloaddition reaction of diazonaphthoquinones **86** with enol ethers in CH_2Cl_2 at 30 °C for 0.5–21.5 h (Scheme 45).[47]

Reaction of vinylidene-naphthofuran derivatives **87a–c** with boronic acid in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in refluxing toluene for 4–5 h afforded photochromic vinylidene-naphthofurans **88a–c** in 79–85% yields. The reaction of **88c** with BBr_3 in dry CH_2Cl_2 at room temperature for 5 h afforded photochromic vinylidene-naphthofuran **89** in 76% yield (Scheme 46).[20]

$PtCl_2$-catalyzed cyclization of *o*-diethynylbenzene derivatives **90** bearing a hydroxyethyl group in toluene under an argon atmosphere at 80 °C for 1–40 h afforded dihydronaphthofuran derivatives **93a–c** in 11–76% yields. Formation of **93** can be rationalized by initial intramolecular cyclization of the hydroxy group to an activated ethynyl group in **91** to form intermediate **92**, followed by attack of the second ethynyl group to give **93** (Scheme 47).[48]

Lee and Xia described a novel approach for the synthesis of diverse dihydronaphtho[1,2-*b*]furans **94** in 11–96% yields from 1,4-naphthoquinones **95** and olefins **96** in the presence of ceric ammonium nitrate in CH_3CN at room temperature for 20–30 min *via* formal [3 + 2] cycloaddition reaction (Scheme 48). This methodology was also used successfully to synthesize the biologically important natural product furomollugin in only 2

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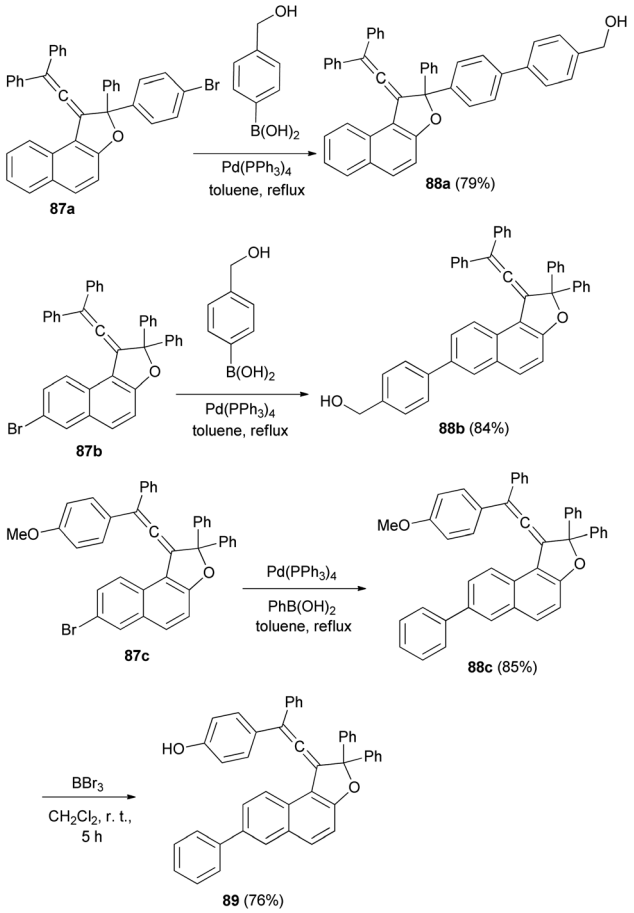
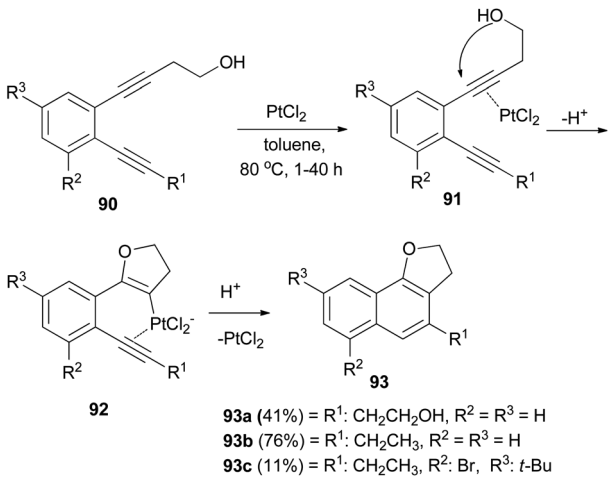
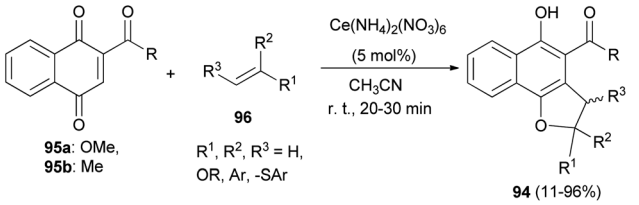


Scheme 46 Synthesis of photochromic vinylidene-naphthofurans **88** and **89**.

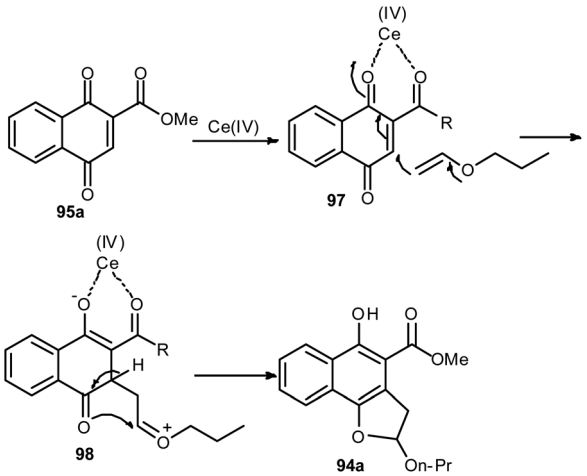


Scheme 47 $PtCl_2$-catalyzed cyclization of *o*-diethynylbenzenes to dihydronaphthofurans **93**.

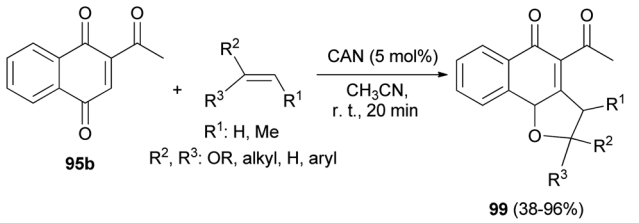
steps. The formation of **94** can be explained by the mechanism proposed in Scheme 49. The methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (**95a**) first forms complex **97** in the presence of CAN. The vinyl group of ethyl vinyl ether then



Scheme 48 Ceric ammonium nitrate-catalyzed synthesis of dihydronaphtho[1,2-*b*]furans **94**.



Scheme 49 Plausible mechanistic pathway for formation of **94**.



Scheme 50 Ammonium cerium(IV) ammonium nitrate-catalyzed synthesis of 2,3-dihydronaphtho[1,2-*b*]furans **99**.

attacks **97** to give another intermediate **98.** Isomerization of **98** followed by intramolecular cyclization then gives the final product **94a.**[49]

Similarly, 2,3-dihydronaphtho[1,2-*b*]furans **99** were synthesized in 38–96% yields by the reaction of 2-acetylnaphthalene-1,4-dione (**95b**) with olefins in the presence of cerium(IV) ammonium nitrate (CAN, 5.0 mol%) as catalyst in CH_3CN at room temperature for 20 min (Scheme 50).[10]

Also, Lee *et al.*[50] have described the reaction of 1,4-dihydroxynaphthalene-2-carboxylate **95a** and the corresponding olefins in MeCN in the presence of cerium(IV) ammonium nitrate (5.0 mol%) at room temperature for 20 min *via* [3 + 2] cycloaddition reaction afforded dihydronaphthofuran derivatives **100** in 30–96% yields (Scheme 51).

Recently Katukojvala *et al.* found that 2,3-dihydronaphtho [1,2-*b*]furans **101** could be prepared in 62–93% yields from

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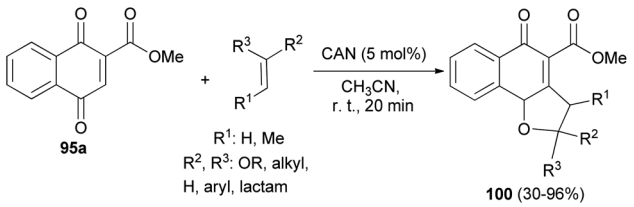
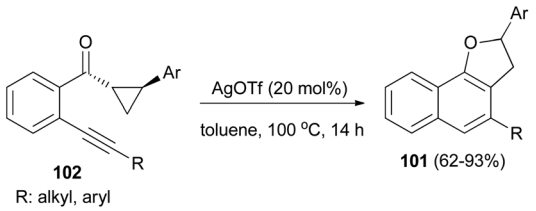
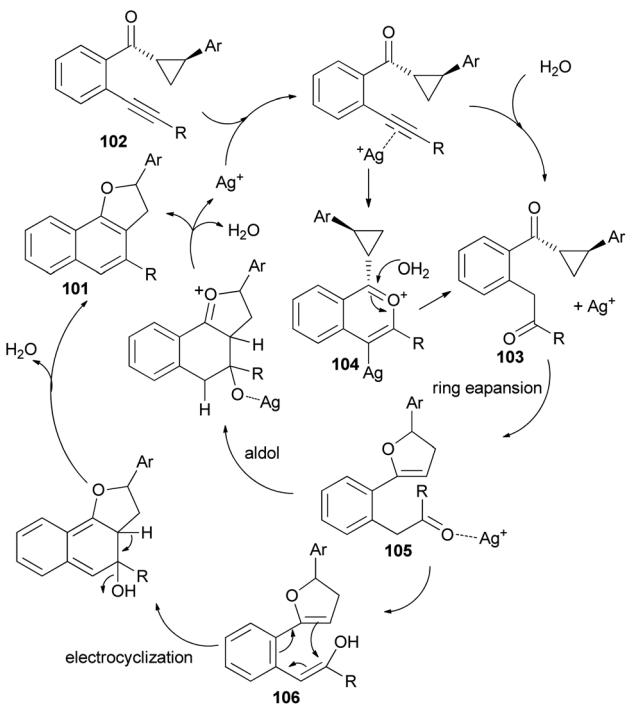


Scheme 51 CAN-catalyzed synthesis of 2,3-dihydronaphtho[1,2-*b*]furan derivatives **100**.

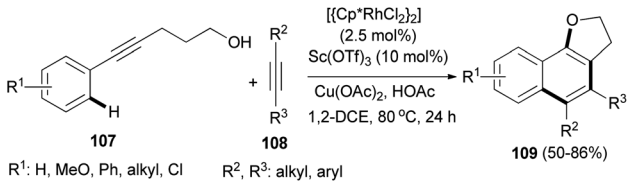


Scheme 52 AgOTf-catalyzed synthesis of 2,3-dihydronaphtho[1,2-*b*]furans **101**.

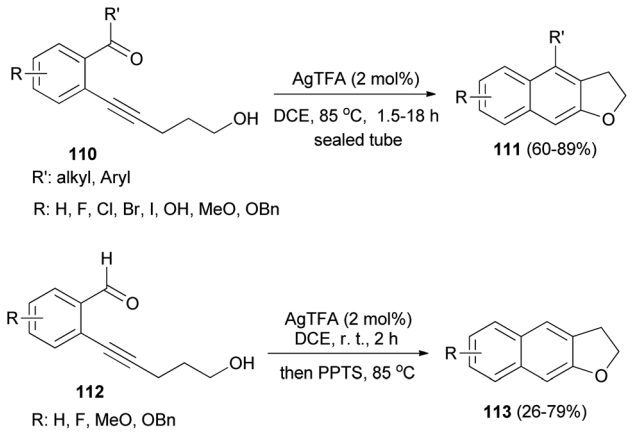
intramolecular transannulation of ((2-alkynyl)aryl)cyclopropyl ketones **102** in the presence of AgOTf (20 mol%) as catalyst in toluene at 100 °C for 14 h (Scheme 52). As shown in Scheme 53, a plausible mechanism for the transannulation reaction was proposed. The first step involves Ag(I)-catalyzed, neighbouring carbonyl group directed regioselective hydration of the alkyne moiety of **102** *via* the benzo[*c*]-pyrylium cation **104** to give the intermediate diketone **103**. In the next step, Ag(I)-catalyzed regioselective ring expansion of the donor–acceptor cyclopropyl ring of **103** leads to the transient 2,3-dihydrofuran **105**.



Scheme 53 Proposed mechanism of the formation of **101**.



Scheme 54 $Sc(OTf)_3$ and rhodium catalyzed synthesis of 2,3-dihydronaphtho[1,2-*b*]furans **109**.



Scheme 55 AgTFA-catalyzed synthesis of 2,3-dihydronaphtho[2,3-*b*]furans **111** and **113**.

Subsequent intramolecular benzannulation of 105 *via* either aldol condensation or 6π-electrocyclization of trienol **106** leads to the 2,3-dihydronaphtho[1,2-*b*]furan **101**.[51]

The cascade reaction of alkynols **107** with alkynes **108** under combined $Sc(OTf)_3$ and rhodium catalyst, $Cu(OAc)_2$ and HOAc in dichloroethane under nitrogen atmosphere at 80 °C for 24 h led to the formation of 2,3-dihydronaphtho[1,2-*b*]furans **109** in 50–86% yields (Scheme 54).[52]

ortho-Carbonylarylacetylenols **110** have been employed for the synthesis of 2,3-dihydronaphtho[2,3-*b*]furans **111** in 60–89% yields *via* AgTFA (2 mol%) catalyzed annulation reaction in DCE at 85 °C for 1.5–18 h. In a similar fashion, annulation of *ortho*-formylarylacetylenol **112** in the presence of AgTFA and PPTS gave 2,3-dihydronaphtho[2,3-*b*]furans **113** in 26–79% yields (Scheme 55).[53]

The reaction mechanism of this transformation was then proposed as shown in pathway A of Scheme 56. First, alkyne was activated by Ag-catalyst with the assistance of *ortho*-carbonyl neighboring group to form oxo-carbenium ion intermediate **114**. After downstream process, this intermediate was then converted to intermediate **115** which further collapsed to give 1,5-diketone **116**. Under the presence of mild Ag-Lewis acid, this intermediate was activated and underwent the cyclization to obtain dihydrofuran intermediate **117**. Next, the second cyclization proceeded followed by tautomerization and dehydration providing 2,3-dihydronaphtho[2,3-*b*]furan product **111a**. Moreover, the mechanism in pathway B is also possible and cannot be ruled out. In pathway B, intermediate **115** underwent the cyclization to give spiro acetal **118** which could be converted to

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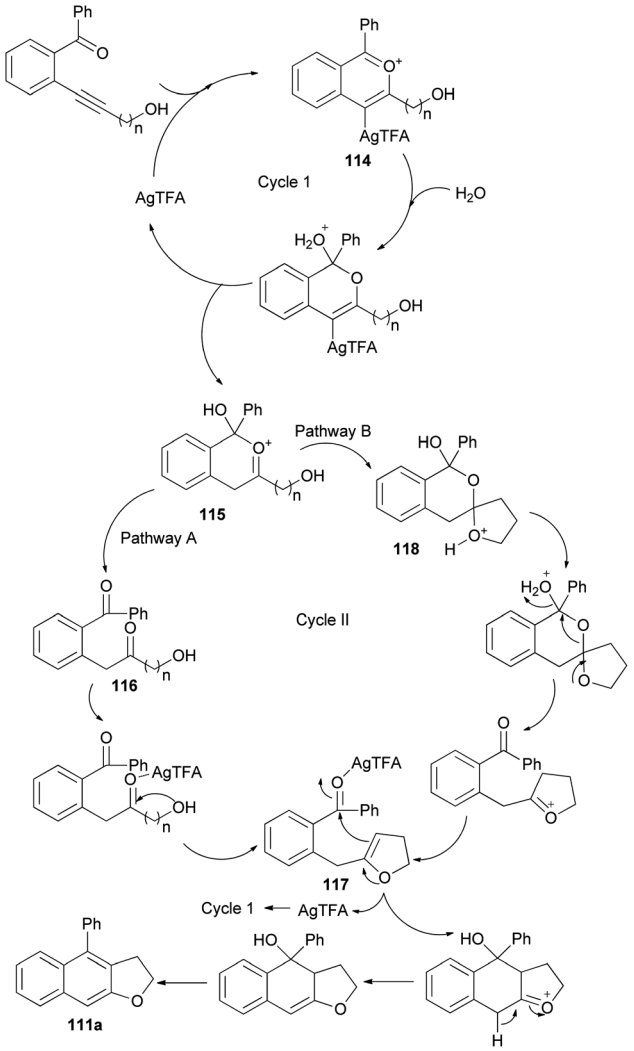


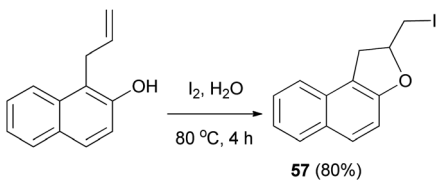
Scheme 56 Proposed reaction mechanism for the synthesis of **111a**.

dihydrofuran intermediate **117**. This intermediate could also be transformed to the desired product *via* the reaction mechanism in pathway A.[53]

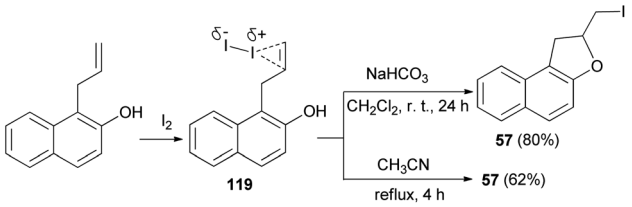
2.4. Iodine-assisted synthesis

Tripathi *et al.*[54] demonstrated that synthesis of 2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**57**) in 80% yield by reaction of 1-allyl-2-naphthol with iodine in water at 80 °C for 4 h (Scheme 57).

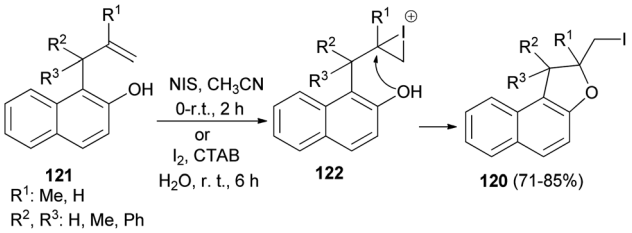
Similarly, an efficient method was developed for the synthesis of dihydronaphthofuran **57** in 80% yield by the



Scheme 57 Synthesis of 2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**57**).



Scheme 58 Synthesis of dihydronaphthofuran **57** in the presence of I_2.

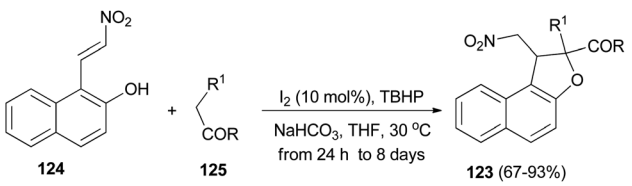


Scheme 59 Synthesis of dihydronaphthofurans **120**.

treatment of allyl naphthol with molecular iodine in the presence of $NaHCO_3$ in CH_2Cl_2 at room temperature for 24 h. The key step involve iodocyclization. In a similar manner, *ortho*-allylnaphthol on reaction with molecular iodine in CH_3CN under reflux condition for 4 h gave dihydronaphthofuran **57** in 62% yield (Scheme 58). This reaction is assisted by the hydroxyl group, involves formation of iodonium ion **119** and proceeds through non radical mechanism pathway.[55]

A number of 2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan derivatives **120** in 71–85% yields have been synthesized from the corresponding allylhydroxy naphthalene precursors **121** involving *N*-iodosuccinimide in acetonitrile at 0–5 °C and then at room temperature for 2 h or by employing molecular iodine in aqueous micelle using CTAB as surfactant at 0–5 °C and then at room temperature for 6 h. At first the allylhydroxy precursor **121** may generate the iodonium intermediate **122**, which undergoes 5-*exo*-trig cyclization to from the cyclized product **120** (Scheme 59).[56]

Recently Deng *et al.*[57] found that dihydronaphthofurans **123** in 67–93% yields could be prepared from readily available 1-(2-nitrovinyl)naphthalen-2-ol **124** and malonate esters **125** in the presence of I_2 (10 mol%), $NaHCO_3$ and TBHP as oxidant in THF at 30 °C for 24 h to 8 days (Scheme 60). A tentative mechanism is proposed in Scheme 61. As depicted in Scheme 61, I_2 could be transformed into hypoiodite $[IO]^-$ under basic conditions initially, then, which is further oxidized by TBHP to form the



R1: CO_2Me, CO_2Et, CO_2i-Pr, CO_2t-Bu, CO_2Bn,
R: OMe, OEt, O*i*-Pr, O*t*-Bu, OBn,

Scheme 60 Iodine-catalyzed synthesis of dihydronaphthofurans **123**.

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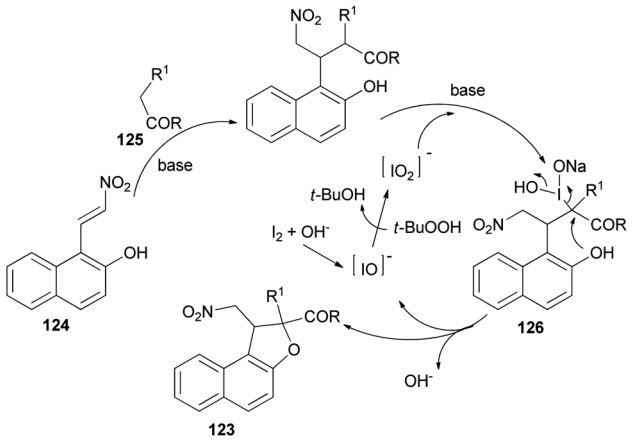
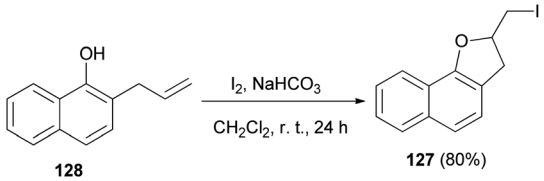


Scheme 61 Tentative mechanism for the formation of **123**.

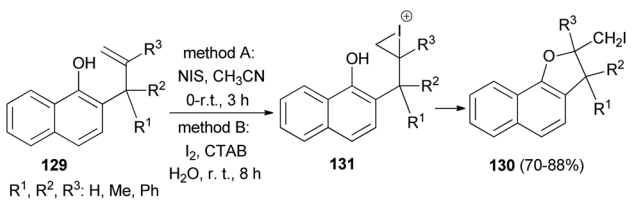


Scheme 62 Synthesis of 2-(iodomethyl)-2,3-dihydronaphtho[1,2-*b*]furan (**127**) in the presence of I_2.

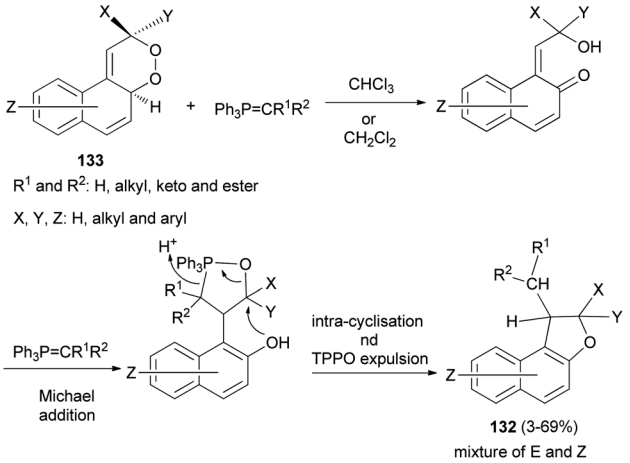
iodite $[IO_2]^-$. The Michael adduct formed by the reaction of malonate ester **125** and nitroalkene **124** could possibly react with the *in situ* formed reactive species $[IO_2]^-$ to give the intermediate **126**, which could be captured by intramolecular phenolic hydroxyl to construct dihydronaphthofuran **123** and releasing hypoiodite species $[IO]^-$ for the next catalytic cycle.

An efficient method was developed for the synthesis of 2-(iodomethyl)-2,3-dihydronaphtho[1,2-*b*]furan (**127**) in 80% yield by the reaction of 2-allyl-1-naphthol **128** with molecular iodine in the presence of $NaHCO_3$ in CH_2Cl_2 at room temperature for 24 h (Scheme 62).[58]

Regioselective iodocyclization of a series of allylhydroxy naphthalene precursors **129** involving *N*-iodosuccinimide (method A) and environment friendly green approach associated with surfactant (CTAB)-promoted molecular-iodine-mediated (method B) 5-*exo*-trig cyclization strategies has been explored. Method A: the reaction mixture in CH_3CN was magnetically stirred for 150 minutes at 0–5 °C and then at room temperature for further 30 minutes afforded dihydronaphthofurans **130** in 70–76% yields. Method B: the reaction mixture



Scheme 63 Regioselective 5-*exo*-trig heterocyclization of 2-allyl-1-naphthols 129 to dihydronaphthofurans **130**.

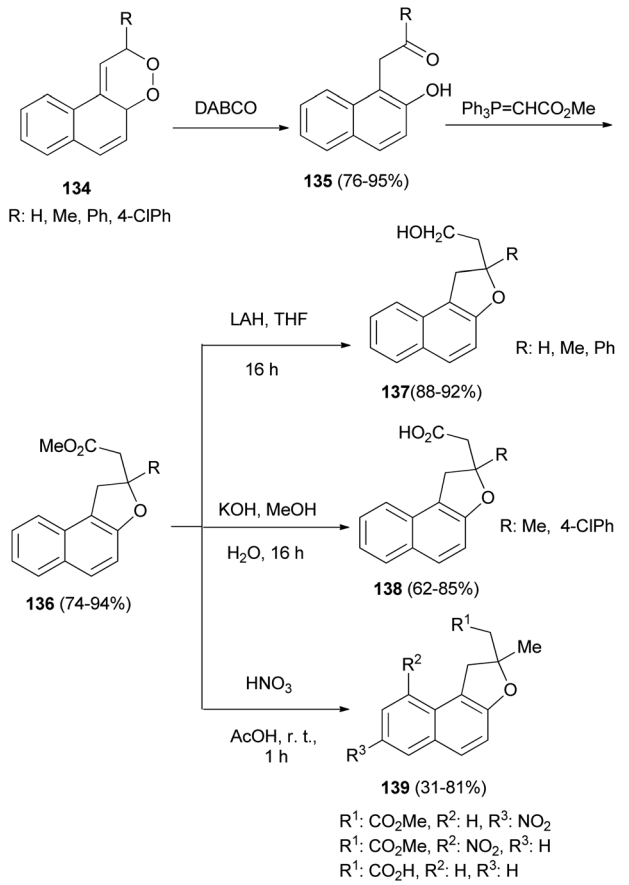


Scheme 64 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **132**.

in water was stirred at room temperature for an additional period of 8 h gave dihydronaphthofurans **130** in 80–88% yields. The transformation is believed to proceed *via* the iodonium intermediate **131** (Scheme 63).[59]

2.5. Syntheses *via* phosphorus, nitrogen and sulfur ylides

Taylor *et al.*[60] described practical synthesis of functionalized 1,2-dihydronaphtho[2,1-*b*]furans **132** from substituted 2,4*a*-



Scheme 65 Synthesis of dihydronaphthofuran derivatives **136–139**.

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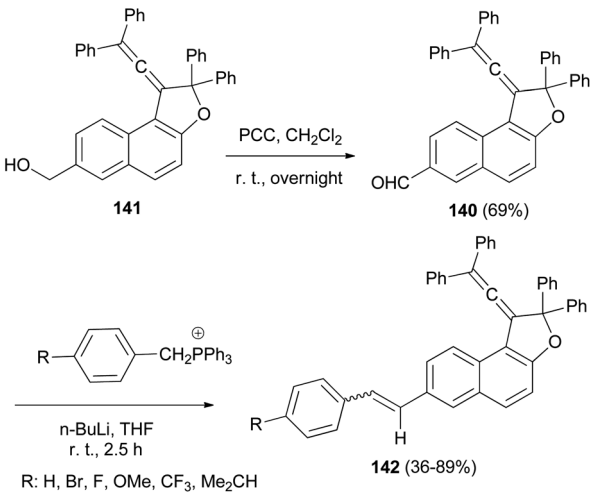
dihydronaphtho[2,1-*c*][l,2]dioxines **133** and stabilised phosphorus ylides. Interaction of **133** in anhydrous chloroform or dichloromethane under a nitrogen gas atmosphere with ylide at a temperature of 60 °C or ambient temperature for 3–7 days resulted in the formation of *E* and *Z* isomers of **132** in 3–69% yields (Scheme 64).

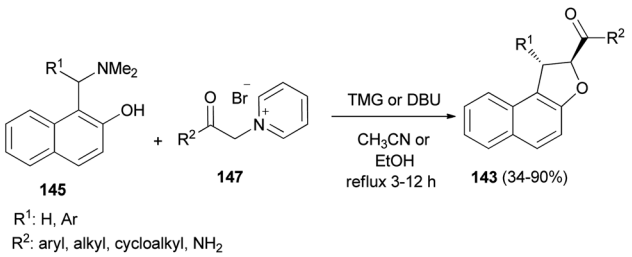
Rose bengal bis(triethylammonium) salt sensitized photooxidation of 1-vinylnapthalenes gave the 1,2-dioxines **134.** 1,2-Dioxines **134** underwent rearrangement when allowed to react with DABCO to afford the 1-(β-keto)-2-naphthols **135** in excellent yield. Reaction of the naphthols **135** with methyl (triphenylphosphoranylidene) acetate afforded the requisite dihydronaphthofurans **136** in 74–94% yields *via* a Wittig/oxy-Michael sequence. Saponification of the esters **136** afforded the acids **137** in 62–85% yields and $LiAlH_4$ reduction of **136** gave the alcohols **138** in 88–92% yields. Reaction of dihydronaphthofurans **136** with nitric acid in glacial acetic acid at room temperature for 1 h afforded 1,2-dihydronaphtho[2,1-*b*]furan derivatives **139** in 31–81% yields (Scheme 65).[61]

1-(2,2-Diphenylvinylidene)-2,2-diphenyl-1,2-dihydronaphtho[2,1-*b*]furan-7-carbaldehyde (**140**) in 69% yield could be prepared by the reaction of dihydronaphthofuran **141** in the presence of pyridinium chlorochromate in CH_2Cl_2 at room temperature for overnight. 1,2-Dihydronaphtho[2,1-*b*]furans **142** were prepared in 36–89% yields by the Wittig reaction of **140** with triarylphosphonium salt in the presence of *n*-BuLi in THF at room temperature for 2.5 h (Scheme 66).[17]

Diastereoselective synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **143** in 34–90% yields has been developed by the reactions of *o*-quinone methides **144** from 2-naphthol Mannich base **145** with pyridinium methylides **146** in the presence of 1,1,3,3-tetramethylguanidine (TMG) or DBU in refluxing CH_3CN or EtOH under an argon atmosphere for 3–12 h (Scheme 67).[62] A mechanistic rationale portraying the probable sequence of events is given in Scheme 68. The first step is the formation of the two reaction intermediates. *o*-QM **144** is formed by the thermal decomposition of the Mannich base and deprotonation



Scheme 66 Synthesis of photochromic 1-vinylidenenaphthofurans **142**.

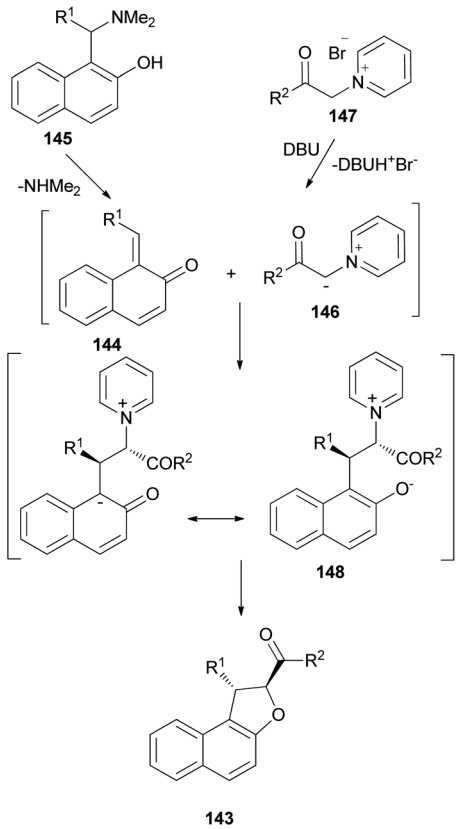


Scheme 67 Diastereoselective synthesis of *trans*-1,2-dihydronaphtho[2,1-*b*]furans **143**.

of the pyridinium salt **147** gives ylide **146.** The second step is a Michael-type addition of a pyridinium ylide **146** to the electron-deficient *o*-QM to afford the zwitterion intermediate **148** which react further to give products **143.**

In a similar manner, 2-aryl-1,2-dihydronaphtho[2,1-*b*]furans **149** in 29–45% yields were synthesized by the reaction of 2-naphthol Mannich base and pyridinium salts **150** in refluxing DMF for 5 h under an argon atmosphere (Scheme 69).[62]

Spasov *et al.*[12] have shown the reaction of 1-((dimethylamino)methyl)naphthalen-2-ol (**151**) and 1-(2-(3-hydroxyadamantan-1-yl)-2-oxoethyl)pyridin-1-ium bromide (**152**) in refluxing a mixture of acetonitrile-DMF (3 : 1) for 10 h afforded 1,2-dihydronaphtho[2,1-*b*]furan **153** in 69% yield. In a similar manner, the reaction of **151** with 1-(2-(4-hydroxyphenyl)-2-oxoethyl)pyridin-1-ium bromide (**154**) in DMF at 90 °C for



Scheme 68 Proposed mechanism for the formation of **143**.

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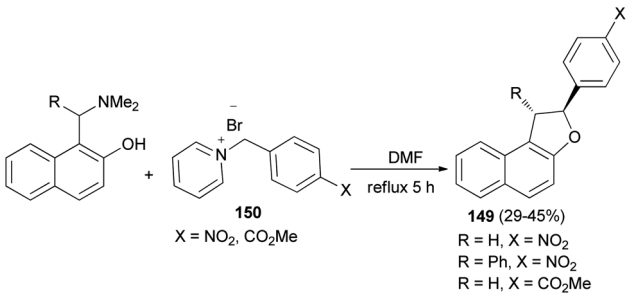
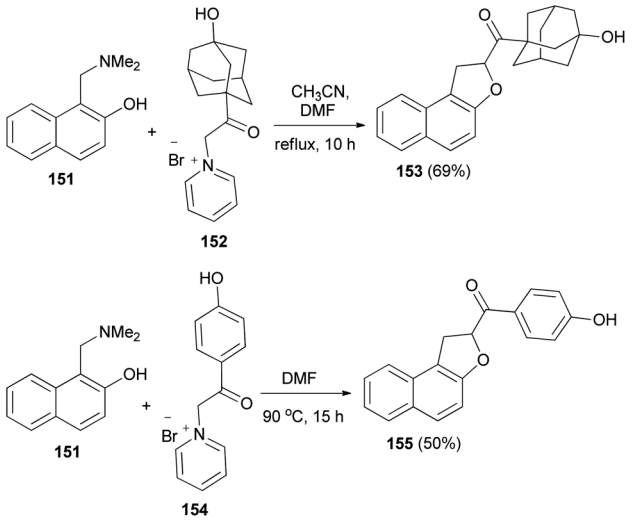


Scheme 69 Preparation of 2-aryl-1,2-dihydronaphtho[2,1-*b*]furans **149**.

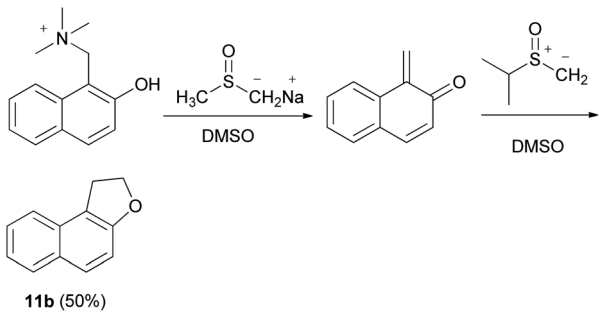


Scheme 70 Synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **153** and **155**.

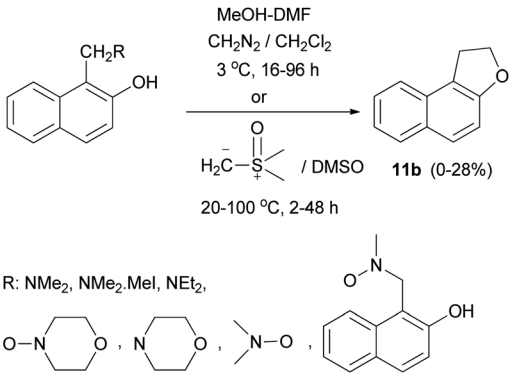
15 h gave 1,2-dihydronaphtho[2,1-*b*]furan **155** in 50% yield (Scheme 70).

1,2-Dihydronaphtho[2,l-*b*]furan (**11b**) could also be obtained in 50% yield from the Mannich base methiodide of 2-naphthol *via* the corresponding quinone methide in the presence of dimethyl sulfoxonium methylide in dimethyl sulfoxide (DMSO) and base (B = Na^+-CH_2SOCH_3) (Scheme 71).[63]

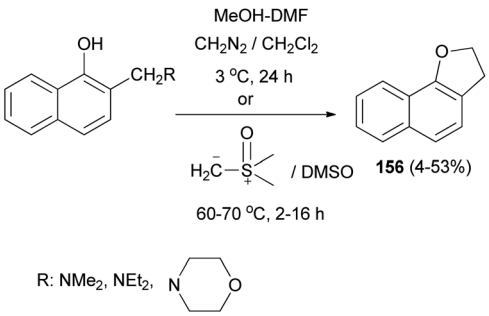
In a similar manner, dihydronaphthofuran **11b** was obtained by the reaction of Mannich bases, Mannich base methiodides,



Scheme 71 Mannich base synthesis of dihydronaphthofuran **11b**.



Scheme 72 Synthesis of dihydronaphthofuran **11b** from phenolic Mannich bases.

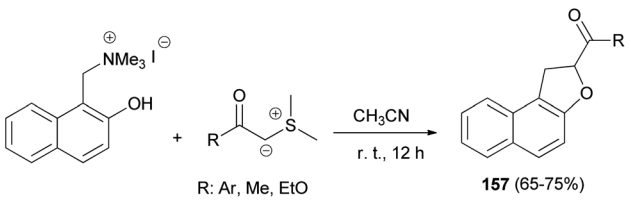


Scheme 73 Synthesis of 2,3-dihydronaphtho[1,2-*b*] furan (**156**).

and Mannich base *N*-oxides derived from naphthols with diazomethane in CH_2Cl_2 at 3 °C for 16–96 h or with dimethylsulphoxonium methylide in DMSO at 20–100 °C for 2–48 h in 0–28% yields (Scheme 72).[64]

Also, 2,3-dihydronaphtho[1,2-*b*]furan (**156**) was obtained in 4–53% yields *via* the reaction of Mannich bases, Mannich base methiodides, and Mannich base *N*-oxides derived from 1-naphthols with diazomethane in CH_2Cl_2 at 3 °C for 24 h or with dimethylsulphoxonium methylide in DMSO at 60–70 °C for 2–16 h (Scheme 73).[64]

A simple and general route to the synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **157**, substituted in position 2 by an acyl or aroyl group, starting from phenolic Mannich base methiodides and the carbonyl-stablished sulphonium ylide in CH_3CN has been developed. The reaction proceeds readily at room temperature for 12 h and usually affords desired products **157** in 65–75% yields (Scheme 74). The formation of the



Scheme 74 Synthesis of 2-acyl- or 2-aroyl-substituted 1,2-dihydronaphtho[2,1-*b*]furans **157**.

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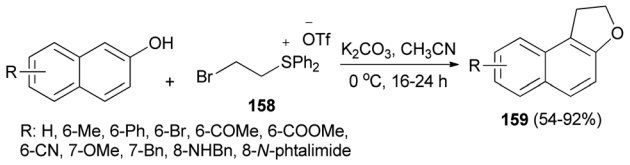


Scheme 75 Preparation of dihydronaphthofurans **159**.

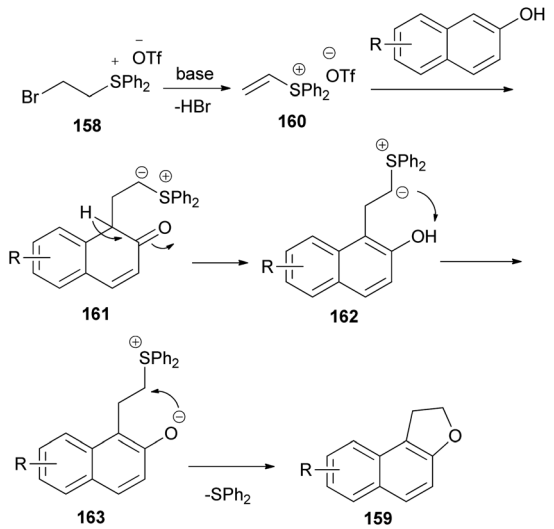
products can be rationalised by assuming the known behaviour of stabilised sulphonium ylides towards system bearing an electrophilic centre and a nucleophilic heteroatom.[65]

The work of Yan *et al.*[66] demonstrated that annulation reaction of β-naphthols with (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate salt (**158**) in the presence of K_2CO_3 in CH_3CN at 0 °C under an argon atmosphere for 16–24 h led to the formation of dihydronaphthofurans **159** in moderate to good yields (54–92%) (Scheme 75). A tentative reaction mechanism is outlined in Scheme 76. The reaction begins with the generation of a vinylsulfonium salt **160** *via* the elimination of hydrogen bromide from **158.** The vinylsulfonium salt **160** reacts with β-naphthols to give sulfonium ylides **161,** which then tautomerize to intermediates **162.** After a proton transfer, the zwitterions **163** are formed. The subsequent intramolecular SN_2 reaction led to the formation of products **159** and eliminates diphenyl sulfide.

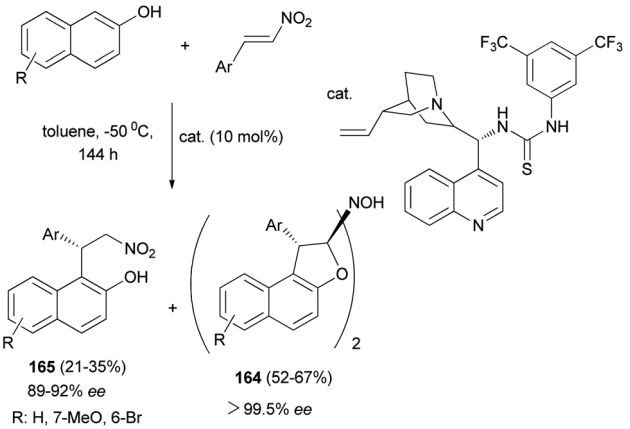
2.6. Enantioselective synthesis

Chen *et al.*[67] described synthesis of enantiopure 1,2-dihydronaphtho[2,1-*b*]furanyl-2-hydroxylamine derivatives **164** in 52–67% yields with 99.5% ee and products **165** by the asymmetric Michael-type Friedel–Crafts alkylation of 2-naphthols with nitroolefins in toluene in the presence of bifunctional thiourea-tertiary amine organocatalyst at −50 °C for 144 h (Scheme 77).

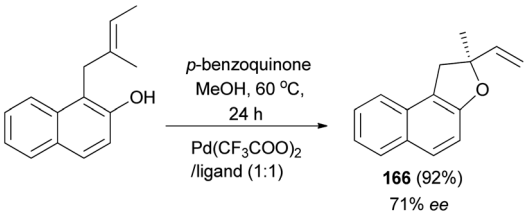
The work of Zhang *et al.* demonstrated that 2-methyl-2-vinyl-1,2-dihydronaphtho[2,1-*b*]furan (**166**) was synthesized in 92% yield with enantioselectivity 71% ee by intramolecular Wacker-



Scheme 76 Proposed reaction mechanism for the formation of **159**.



Scheme 77 Organocatalyzed synthesis of dimeric tricyclic 1,2-dihydronaphtho[2,1-*b*]furanyl-2-hydroxylamine derivatives **164**.

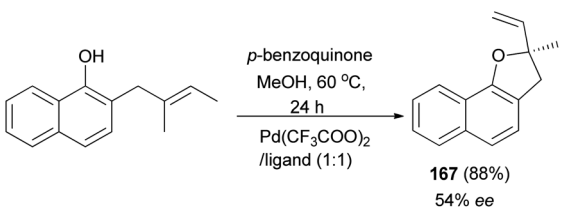


Scheme 78 Pd-catalyzed synthesis of dihydronaphtofuran **166**.

type cyclizations of *o*-substituted allyl naphthol in the presence of $Pd(CF_3COO)_2$/tetraoxazoline as ligand (Pd/ligand 1 : 1) and *p*-benzoquinone in methanol at 60 °C for 24 h (Scheme 78).[68]

In a similar fashion, 2-methyl-2-vinyl-2,3-dihydronaphtho[1,2-*b*]furan (**167**) was synthesized in 88% yield and enantioselectivity 54% ee (Scheme 79).[68]

Asymmetric organocatalytic synthesis of optically active dihydronaphthofurans **168a–c** has been reported. Treatment of *trans*-2-nonenal **169** with H_2O_2 in CH_2Cl_2 at room temperature for 24 h afforded 2,3-epoxy aldehyde **170.** Then, the reaction of 2,3-epoxy aldehyde **170** with $BnNH_2$ at room temperature in the presence of $MgSO_4$ gave epoxy imine **171** as 1,2-di-electrophilic species. Friedel–Crafts alkylation of 2-naphthols with epoxy imine at room temperature afforded intermediate **172.** Subsequent 5-*exo*-tet epoxide opening of **172** through the hydroxyarenic oxygen atom in the presence of DBU at room temperature led to the formation of dihydronaphthofurans **168** in 57–83%



Scheme 79 Enantioselective synthesis of 2-methyl-2-vinyl-2,3-dihydronaphtho[1,2-*b*]furan (**167**).

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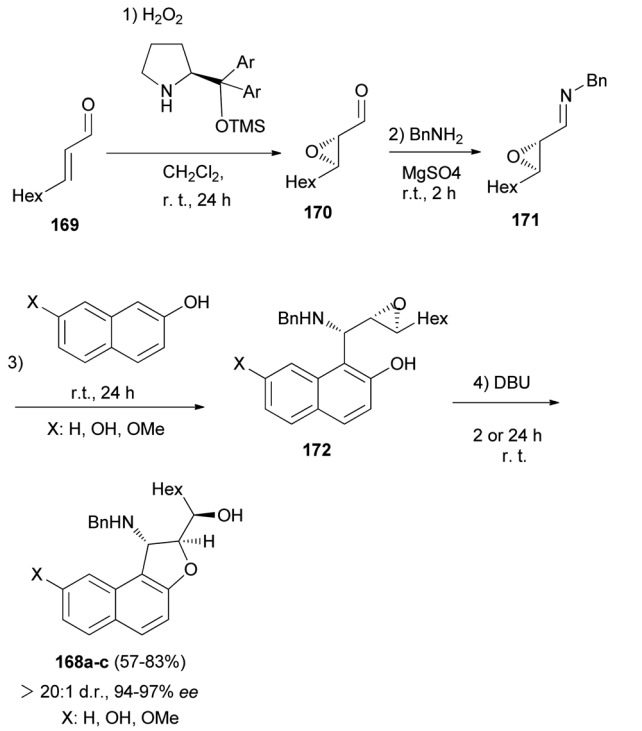
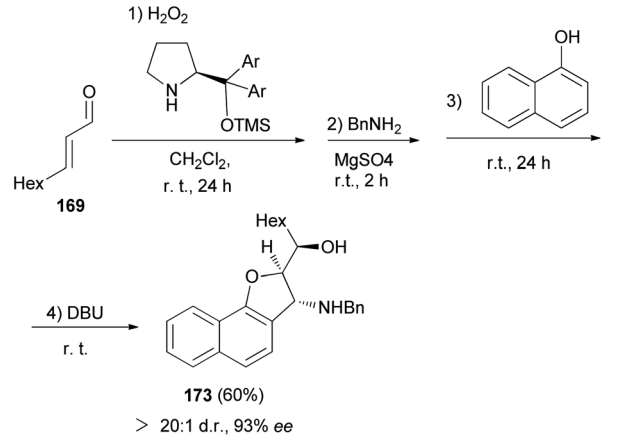


Scheme 80 Enantioselective synthesis of dihydronaphthofurans 168a–c.

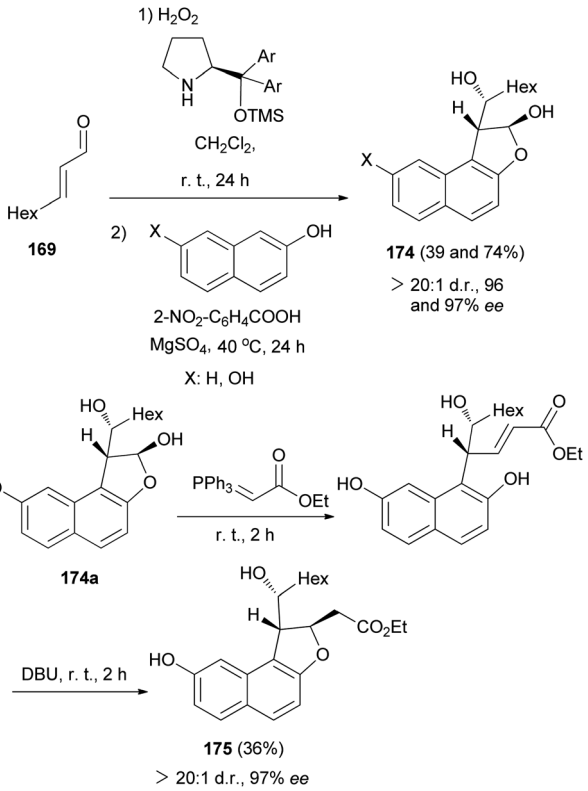


Scheme 81 Enantioselective synthesis of 2,3-dihydronaphtho[1,2-*b*] furan 173.

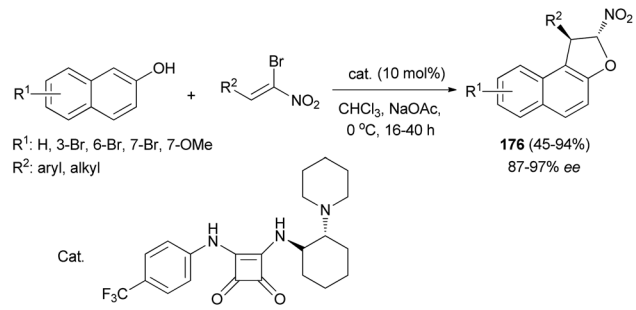
yields and excellent enantioselectivities (94–97% ee) (Scheme 80).[69]

Moreover, 2,3-dihydronaphtho[1,2-*b*]furan **173** in 60% yield and excellent enantioselectivitie (93% ee) was obtained *via* the same reaction conditions that it has been reported for the synthesis of **168** (Scheme 81).[69]

In a similar fashion, reaction of 2,3-epoxy aldehyde **170** with naphthols in the absence of $BnNH_2$ and DBU gave dihydronaphthofurans **174** in 39 and 74% yields and excellent enantioselectivities (96 and 97% ee). Also, dihydronaphthofuran **174a** (X: OH) *via* the Wittig reaction, using the stabilized phosphorus ylide, and subsequent base-induced oxa-



Scheme 82 Enantioselective synthesis of 1,2-dihydronaphtho[2,1-*b*] furans 174 and 175.



Scheme 83 Squaramide catalyzed synthesis of *trans*-dihydroarylfurans 176.

Michael addition proved successful, thus affording access to the dihydrobenzofuran **175** in 36% yield and 97% ee (Scheme 82).[69]

Asymmetric synthesis of *trans*-dihydroarylfurans **176** in 45–94% yields and excellent ee's (up to 97%) *via* a Friedel–Crafts/substitution domino reaction of (*Z*)-bromonitroalkenes and 2-naphthols in the presence of squaramide as catalyst and co-base (sodium acetate) in $CHCl_3$ at 0 °C for 16–40 h has been reported (Scheme 83).[70]

Also, a chiral multiple catalysis with two chiral units has been proved effective in the domino Friedel–Crafts alkylation of 2-naphthols with α-bromonitroalkenes. This efficient domino reaction affords chiral 1,2-dihydronaphtho[2,1-*b*] furans **176** in good to high yields (up to 93% yield) and high enantioselectivities (91% enantiomeric excess) (Scheme 84).[71]

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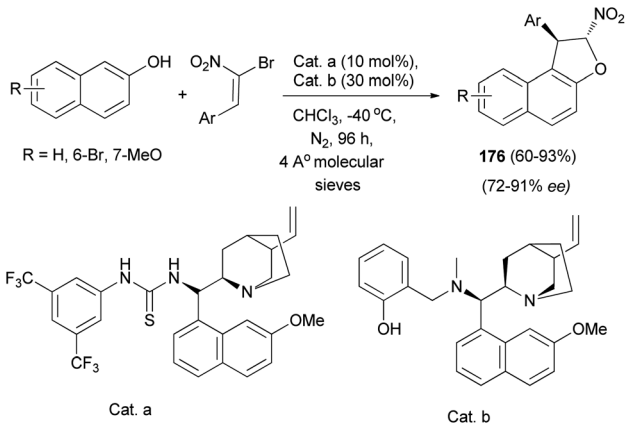
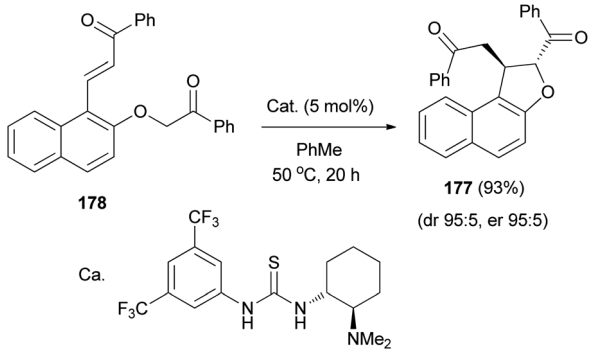


Scheme 84 Chiral multiple catalysis synthesis of 1,2-dihydronaphtho[2,1-*b*] furans **176**.

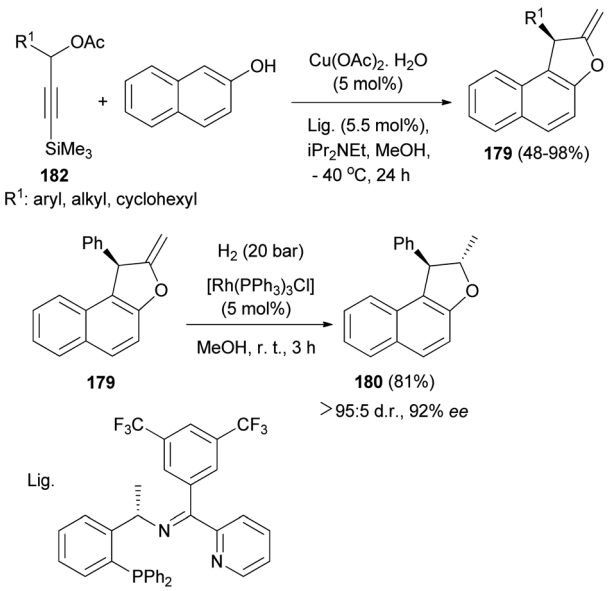


Scheme 85 Tertiary amine-thiourea catalyzed synthesis of dihydronaphthofuran **177**.

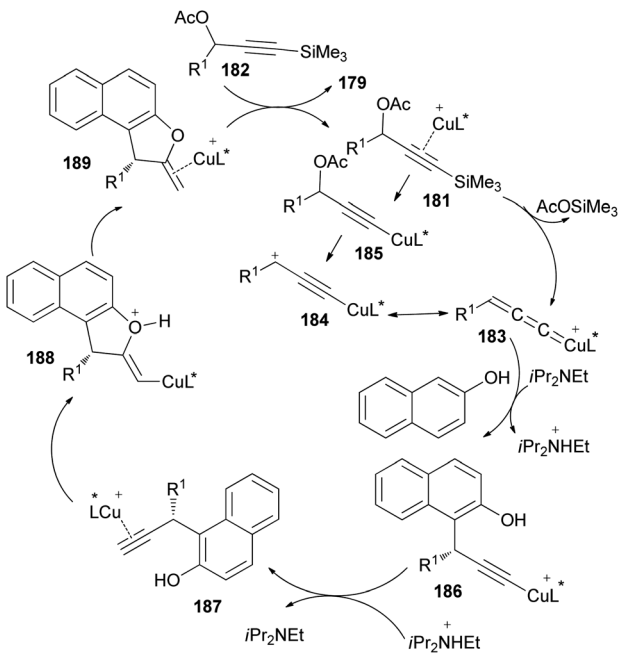
The diastereo- and enantioselective synthesis of 2,3-disubstituted *trans*-2,3-dihydronaphthofuran **177** (95 : 5 dr, 95 : 5 er) *via* intramolecular Michael addition has been developed using keto-enone substrate **178** and a bifunctional tertiary amine-thiourea catalyst (5 mol%) in toluene at 50 °C for 20 h in 93% yield (Scheme 85).[72]

A copper-catalyzed asymmetric [3 + 2] cycloaddition of 3-trimethylsilylpropargylic esters with 2-naphthols has been realized and proceeds by a desilylation-activated process. Under the catalysis of Cu-$(OAc)_2 \cdot H_2O$ in combination with a structurally optimized ketimine P,N,N-ligand and iPr_2NEt in MeOH at −40 °C for 24 h a wide range of optically active 1,2-dihydronaphtho[2,1-*b*]furans **179** were obtained in good yields (48–98%) and with high enantioselectivities (up to 93% ee). Hydrogenation of (*R*)-2-methylene-1-phenyl-1,2-dihydronaphtho[2,1-*b*]furan **179** in the presence of $[Rh(PPh_3)_3Cl]$ (5 mol%) in MeOH at room temperature for 3 h afforded (1*R*, 2*S*)-2-methyl-1-phenyl-1,2-dihydronaphtho[2,1-*b*]furan **180** in 81% yield and excellent diastereoselectivity without the obvious erosion in enantioselectivity (Scheme 86).[73]

A reaction pathway for the preparation of **179** is proposed as shown in Scheme 87. In the first step, a copper complex forms the π-complex **181** with **182.** A copper-promoted Si–C(sp) bond cleavage of **181**, followed by the elimination of an acetoxyl moiety, affords the copper allenylidene complex **183** or its



Scheme 86 Cu-$(OAc)_2 \cdot H_2O$-catalyzed enantioselective synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **179** and **180**.



Scheme 87 Proposed mechanism for the synthesis of **179**.

resonance structure **184.** The intramolecular Cu–Si exchange by the elimination of $AcOSiMe_3$ proceeds more readily than the intermolecular base-assisted reaction with terminal propargylic esters for the formation of copper acetylide complex **185**, which should be answered for the observed activation. The nucleophilic attack of the C_α atom of β-naphthol at the C_γ atom of the allenylidene complex **183** gives the copper acetylide complex **186**, which is then converted into the copper π–alkyne complex **187.** Intramolecular nucleophilic attack of the hydroxy group on the C_β atom of **187** generates an alkenyl complex **188,** which is

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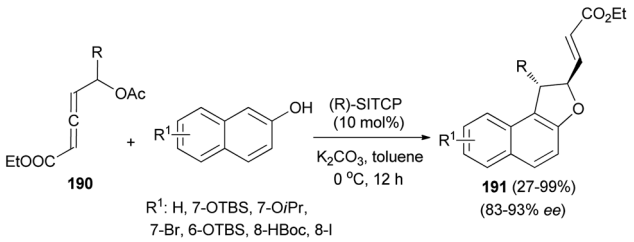
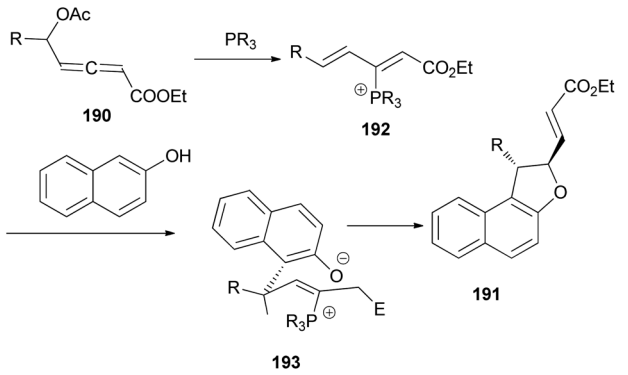


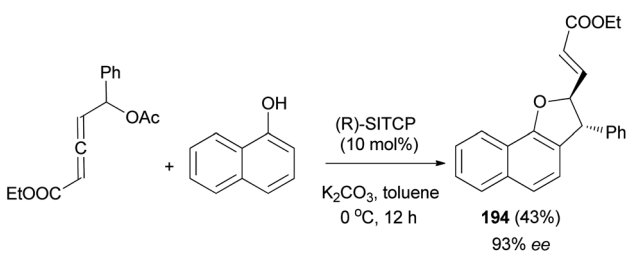
Scheme 88 Phosphine-catalyzed asymmetry synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **191**.



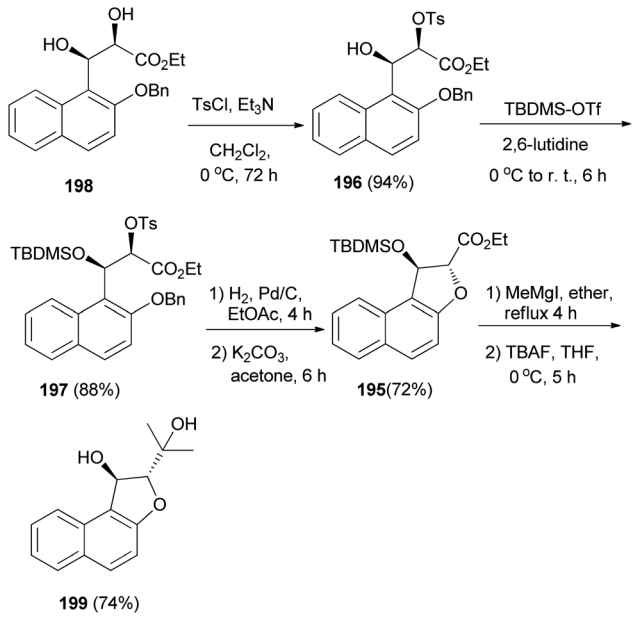
Scheme 89 A plausible mechanism for the preparation of **191**.

transformed into the copper π–alkene complex **189**. The starting **181** is then regenerated from **189** by liberating **179** through ligand exchange with another **182**.[73]

Wang and Tong demonstrated that phosphine-catalyzed asymmetric [3 + 2] annulations of δ-acetoxy allenoates **190** with 2-naphthols in the presence of K_2CO_3 in toluene at 0 °C for 12 h afforded 1,2-dihydronaphtho[2,1-*b*]furans **191** in moderate to excellent yields (27–99%) and with high enantioselectivity (83–93%) (Scheme 88). In the presence of phosphine catalyst, allenoate **190** can be readily converted into 3-phosphonium-2,4-dienoate **192** *via* 1,4-addition of phosphine and subsequent 1,2-elimination of acetate group. For **192**, the αC-position has more steric hindrance than the δC-position. Therefore, to minimize the steric repulsion, 2-naphthol would preferentially attack intermediate **192** at its δC-position *via* a Friedel–Crafts type process to afford intermediate **193**, which underwent oxa-Michael addition *via* a half-chair conformation, thus finally leading to product **191** (Scheme 89).[74]



Scheme 90 Enantioselective synthesis of 2,3-dihydronaphtho[1,2-*b*]furan derivative **194**.



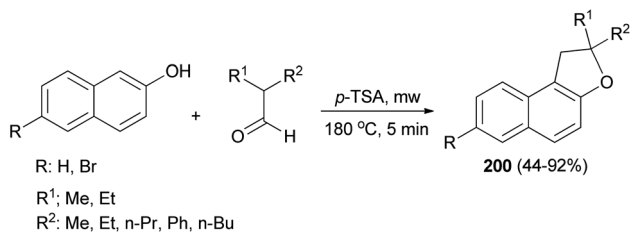
Scheme 91 Enantioselective synthesis of dihydronaphthofurans **195** and **199**.

Similarly, phosphine-catalyzed asymmetric [3 + 2] annulation of δ-acetoxy allenoate with 1-naphthol afforded 2,3-dihydronaphtho[1,2-*b*]furan derivative **194** in 43% yield with high enantioselectivity (93% ee) (Scheme 90).[74]

The enantioselective synthesis of naphtho-annulated oxa-heterocycle dihydronaphthofuran **195** in 72% yield was accomplished by using β-hydroxy-α-tosyloxy esters **196** and **197** as chiral building blocks, which are easily accessible through the regioselective α-tosylation of Sharpless asymmetric dihydroxylation-derived *syn*-2,3-dihydroxy ester **198.** Treatment of dihydronaphthofuran **195** with methylmagnesium iodide in refluxing ether for 4 h followed addition of tetra-*n*-butylammonium fluoride (TBAF) at 0 °C and stirring for 5 h afforded (2*S*,3*S*)-2-(1-hydroxy-1-methyl-ethyl)-1,2-dihydronaphtho[2,1-*b*]furan-1-ol (**199**) in 74% yield (Scheme 91).[75]

2.7. Microwave-assisted synthesis

The reaction of 2,2-dialkylacetaldehydes with electron-rich 2-naphthols in the presence of *p*-TSA under closed-vessel solvent-free microwave irradiation condition at 180 °C for 5 min resulted in the formation of corresponding 1,2-dihydronaphtho



Scheme 92 Microwave assisted synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **200**.

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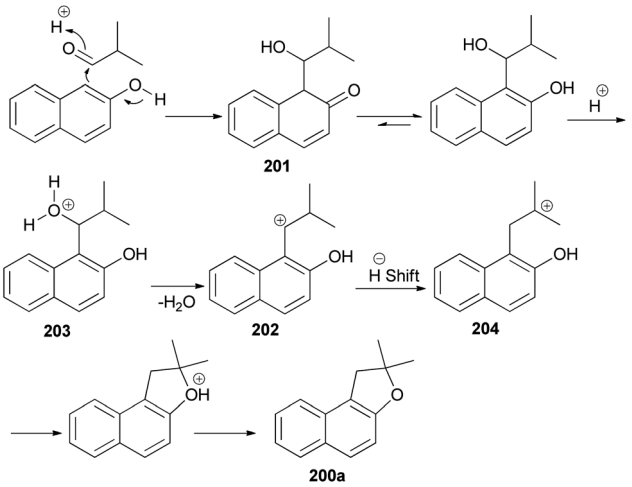
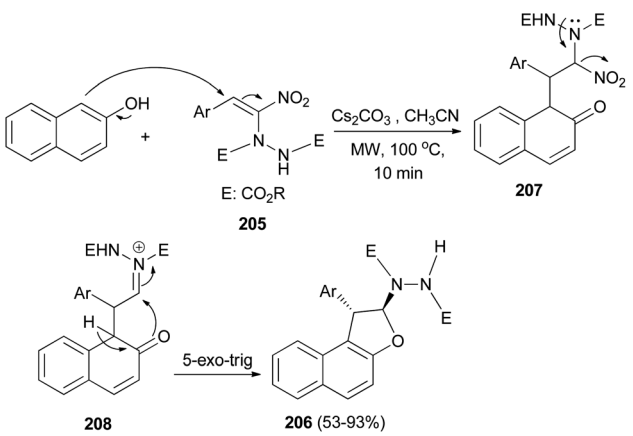


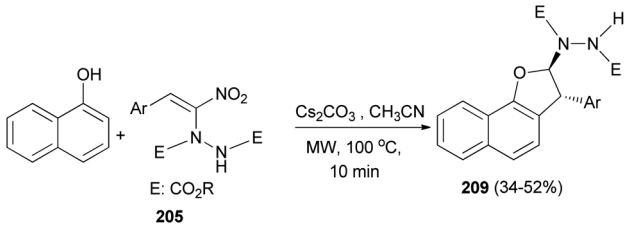
Scheme 93 Proposed mechanism of formation of **200a**.

[2,1-*b*]furans **200** in 44–92% yields (Scheme 92). The reaction was carried out *via* oxidative annulation process. In several cases, small amounts of 14-alkyl-14-*H*-dibenzo[*a*,*j*]xanthenes were also formed.[34,76] The proposed mechanism using isobutyraldehyde and 2-naphthol as starting materials is shown in Scheme 93. Nucleophilic C attack of 2-naphthol led to formation of a secondary alcohol intermediate **201** which formed a secondary benzylic carbocation **202** through corresponding oxonium ion **203** under catalytic amount of *p*-TSA. 1,2-Hydride shift leading a tertiary carbocation **204** followed by nucleophilic attack by the naphthol oxygen led to formation of **200a**.[76]

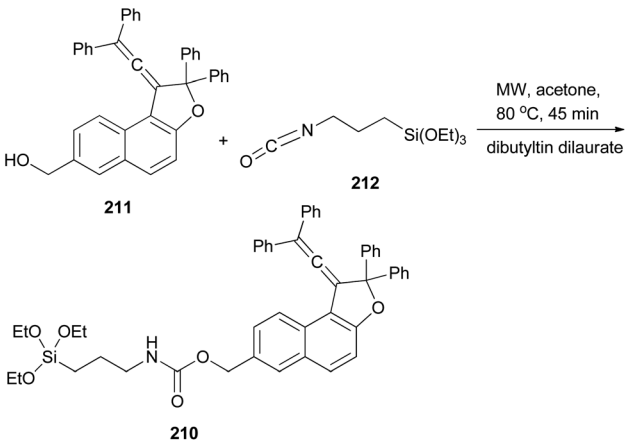
Namboothiri *et al.*[77] exploited [3 + 2] annulation of β-naphthol with hydrazinonitroalkene **205** in the presence of Cs_2CO_3 in CH_3CN under microwave radiation at 100 °C for 10 min afforded *trans*-1,2-dihydronaphtho[2,1-*b*]furans **206** in 53–93% yields. The proposed mechanism, taking β-naphthol as the representative arenol, envisages Cs_2CO_3 mediated addition of naphthol to MBH adduct **205** in a Michael fashion leading to the formation of intermediate **207** which forms an acyliminium type intermediate **208** with the loss of nitro group. Enolization



Scheme 94 [3 + 2] annulation of 2-naphthol with hydrazinonitroalkene **205** to dihydronaphthofurans **206**.



Scheme 95 Microwave-assisted synthesis of *trans*-2,3-dihydronaphtho[1,2-*b*]furans **209**.



Scheme 96 Synthesis of photochromic 1-vinylidene-naphtho[2,1-*b*]furan **210**.

of **208** and intramolecular 5-*exo*-trig cyclization gives rise to product **206** (Scheme 94).

Also, *trans*-2,3-dihydronaphtho[1,2-*b*]furans **209** was obtained in 34–52% yields *via* the reaction of 1-naphthol with hydrazinonitroalkene **205** (Scheme 95).[77]

Freire *et al.*[18] have shown that synthesis of novel photochromic 1-(2,2-diphenylvinylidene-2,2-diphenyl-1,2-dihydronaphtho[2,1-*b*]furan-7-yl)methyl (3-(triethoxysilyl)propyl) carbamate (**210**) was accomplished by the treatment of **211** with IsoTES **212** by a microwave-assisted reaction in the presence of dibutyltin dilaurate as catalyst in acetone at 80 °C during 45 min (Scheme 96).

2.8. Photochemical methods

Rossi *et al.*[78] published synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **213a–c** in very good yields by $S_{RN}1$ photostimulated reactions in liquid ammonia from adequate 2-(allyloxy)-1-halonaphthalene and Me_3Sn^-, Ph_2P^-, and $^-CH_2NO_2$ anions. The mixture of 2-(allyloxy)-1-chloronaphthalene in EtOH, liquid ammonia and Me_3SnCl in dried diethyl ether and Na was irradiated for 120 min using two medium-pressure mercury lamps emitting maximally at 366 nm gave 1,2-dihydronaphtho[2,1-*b*]furan **213a** in 84% yield. The reaction of 2-(allyloxy)-1-bromonaphthalene was performed by a procedure similar to that described for the other two nucleophiles, Ph_3P and Na in *t*-BuOH and CH_3NO_2, *t*-BuOK in acetone afforded 1,2-dihydronaphtho[2,1-*b*]furans **213b–c** in 98% and 85% yields,

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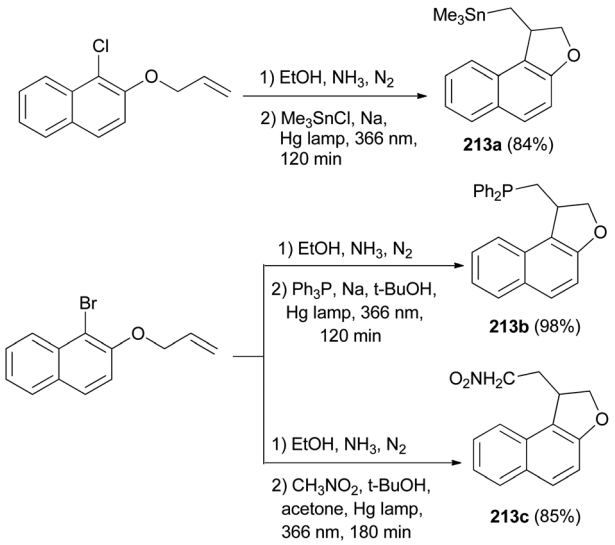
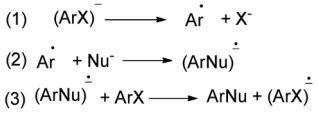


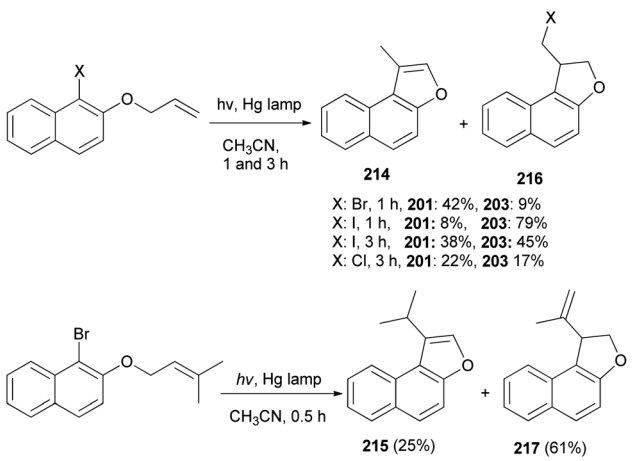
Scheme 97 Photostimulated synthesis of 1,2-dihydronaphtho[2,1-*b*] furans **213**.



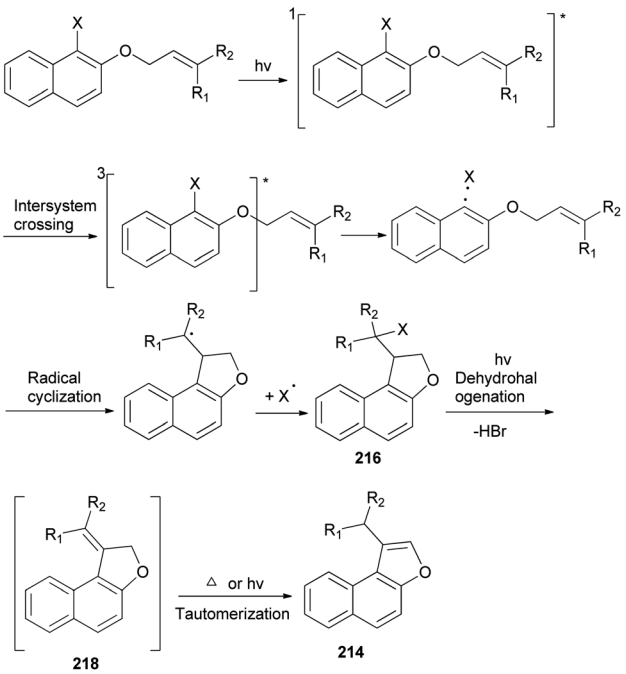
Scheme 98 Propagation steps of an $S_{RN}1$ mechanism.

respectively (Scheme 97). The propagation steps of an $S_{RN}1$ mechanism are presented in Scheme 98.

A mixture of naphtho[*b*]furans **214–215** and dihydronaphthofuran **216–217** were obtained from allyl halonaphthyl ethers employing photo induced radical cyclization with 100 W high-pressure mercury lamp in CH_3CN under Ar atmosphere for 0.5–3 h (Scheme 99). In addition, observations made in this effort suggest that a plausible mechanism for these photoreactions (Scheme 100) begins with homolytic C–halogen bond



Scheme 99 Photochemical synthesis of naphtho[*b*]furans **214–215** and dihydronaphthofurans **216–217**.



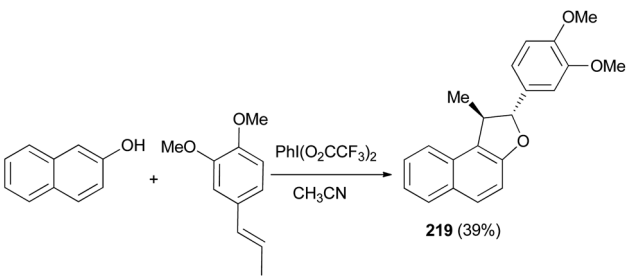
Scheme 100 Plausible mechanism for the preparation of **214–217**.

cleavage in the triplet states of the substrates to generate radical pairs, which undergo 5-*exo* type cyclization and halogen atom capture to produce the initially formed 2-halomethyl substituted naphthodihydrofurans **216** similar to atom-transfer radical cyclizations. Subsequently, photoinduced dehydrohalogenation of **216** takes place to generate alkylidene dihydrofuran intermediates **218** that undergo tautomerization to generate the naphthofuran product **214**. In the case of $R_1 = CH_3$, $R_2 = CH_3$, the photochemical dehydrohalogenation leads to the respective formation of **218** and the regioisomeric product **217**, which is photochemically tautomerized to **215**.[79]

2.9. Electrochemical methods

Treatment of 2-naphthol with 1,2-dimethoxy-4-propenylbenzene in the electrochemical oxidation using iodobenzene bis-trifluoroacetate ($PhI(O_2CCF_3)_2$) as oxidant in CH_3CN, gave a very low yield of l,2-dihydronaphtho[2,1-*b*] furan **219** (Scheme 101).[80]

Anodic oxidation of 4-methoxynaphthol and electron-rich styrenes gave 2,3-dihydronaphtho[1,2-*b*]furan derivatives **220**



Scheme 101 Electrochemical synthesis of dihydronaphthofuran **219**.

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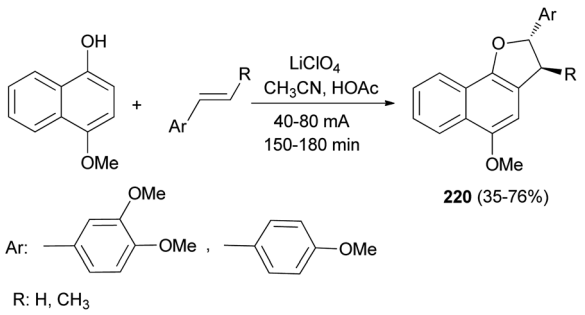
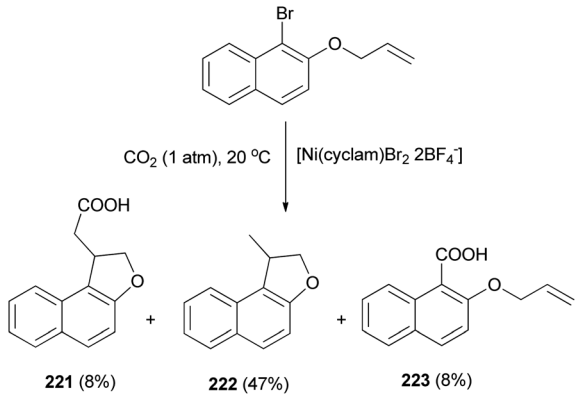


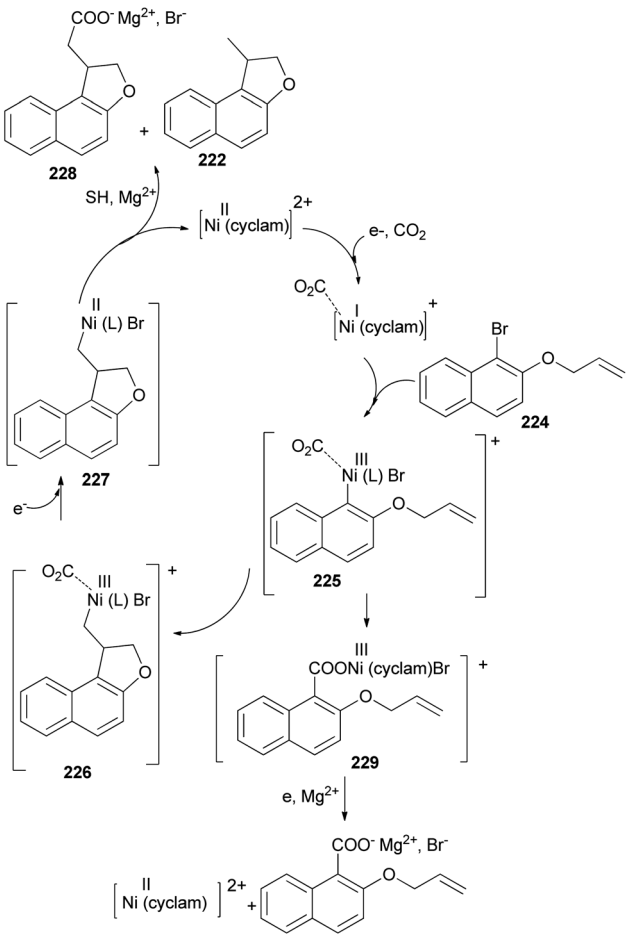
Scheme 102 Electrochemical synthesis of 2,3-dihydronaphtho [1,2-*b*] furan derivatives **220**.

in 35–76% yields. Reactions were conducted with a current density of 40–80 mA for 150–180 min in 8 : 1 CH_3CN/HOAc using a platinum anode and cathode and perchlorate as supporting electrolyte (Scheme 102).[80]

The electrochemical reduction of 2-(allyloxy)-1-bromonaphthalene under CO_2 pressure (1 atm) allows the synthesis of dihydronaphthofurans **221** and **222** in 8 and 47% yields, respectively. This novel intramolecular cyclization–carboxylation reaction is carried out in single-compartment cells (Mg/C as the electrodes) at 20 °C and is catalyzed by [Ni(cyclam)Br_2 $2BF_4^-$]. In this method, three types of products **221–223** were obtained as indicated in Scheme 103.[81] A catalytic cycle is proposed in Scheme 104. The electrochemical reduction of $Ni(cyclam)^{2+}$ affords Ni^I species. Oxidative addition of the Ni^I species (coordinated to CO_2) to the C-(aryl)-halogen bond of **224**. After oxidative addition, the formation of Ni^{III} intermediate species **225** is proposed. This Ni^{III} intermediate induces a radical character to the aryl moiety, resulting in a rapid intramolecular cyclization on the double bond in the side chain, leading to **226**. Further one-electron reduction of Ni^{III} intermediate species **226** should form an alkylnickel(II) species **227**, able to undergo CO_2 uptake, forming a nickel(II) carboxylate. Competitive protonation of **227** by the electrolytic medium (solvent) affords cyclized, noncarboxylated **222**. In the one-compartment cell procedure with a magnesium anode, the presence of the magnesium ions issued from the anodic



Scheme 103 Electrochemical synthesis of dihydronaphthofurans **221** and **222**.



Scheme 104 Proposed mechanism for the synthesis of **221–223**.

oxidation process, enables the formation of a magnesium carboxylate **228** liberating the nickel species for further recycling. Magnesium carboxylate **228** is stable under the reaction conditions, it accumulates during electrolysis and it is simply hydrolyzed to **221** at the end of the reaction. In a competitive reaction, intermediate **225** can also be directly reduced and carboxylated to afford the corresponding carboxylic acid derivatives **223** *via* intermediate **229**.[81]

2.10. Synthesis by radical methods

The work of Hayashi and Lawson[82] demonstrated that various dihydronaphthofurans **230–232** were prepared by reaction of naphthofuran carboxylic acids **233–235** with sodium amalgam in alkali solution of NaOH at room temperature for 7 and 18 h led to the formation of dihydronaphthofuran carboxylic acids **236–238**. Then, dihydronaphthofuran carboxylic acids were treated with an excess of ethereal diazomethane at 0 °C to give **230–232** in 95, 76 and 15.2% yields, respectively (Scheme 105).

Cyclization of 1-bromo-2-(prop-2-enyloxy)naphthalene was employed by Beckwith *et al.* to the synthesis of 1-methyl-1,2-dihydronaphtho[2,1-*b*]furan (**222**) in 64% yield. The reaction was carried out in the presence of Bu_3SnH and AIBN as initiator in dry benzene under reflux condition for 16 h (Scheme 106).

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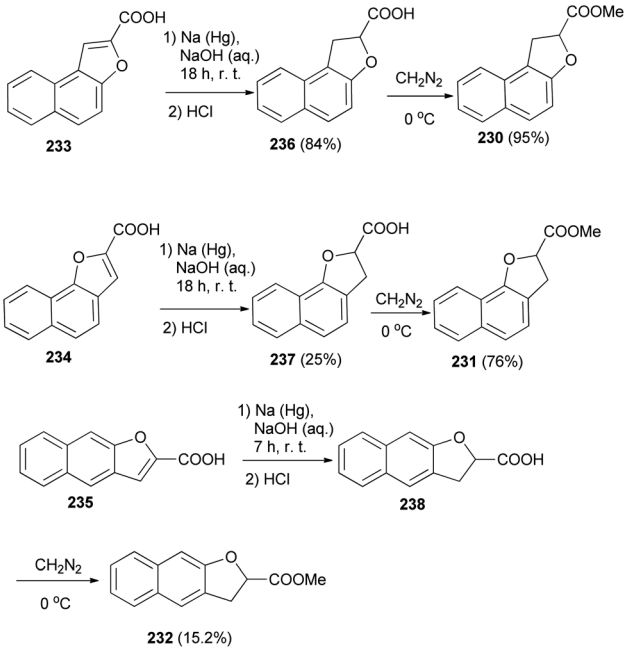
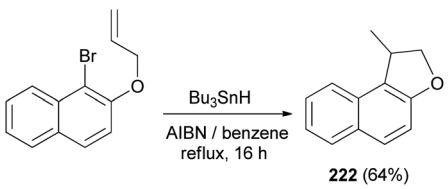


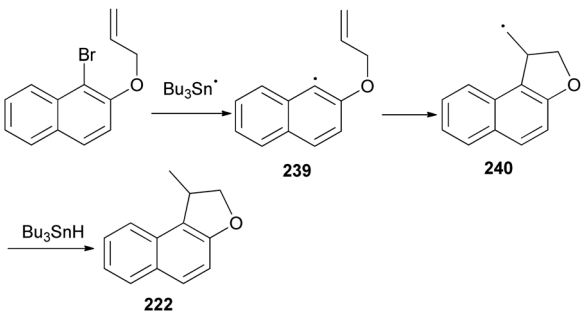
Scheme 105 Synthesis of dihydronaphthofuran **230–232** and **236–238**.



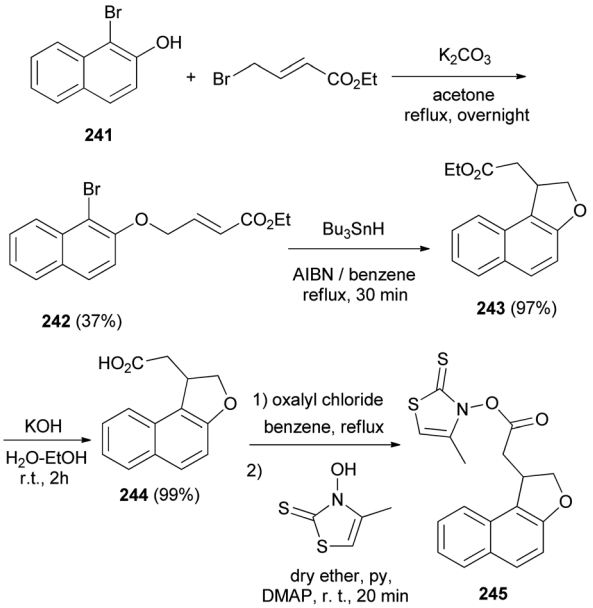
Scheme 106 Synthesis of dihydronaphthofuran **222**.

Presumably the mechanism involves generation of the radical **239** from 1-bromo-2-(prop-2-enyloxy)naphthalene followed by cyclization of radical **239** to **240** and transfer of a hydrogen atom from Bu_3SnH to the primary radical **240** afforded the final product **222** according to the pathway given in Scheme 107.[83]

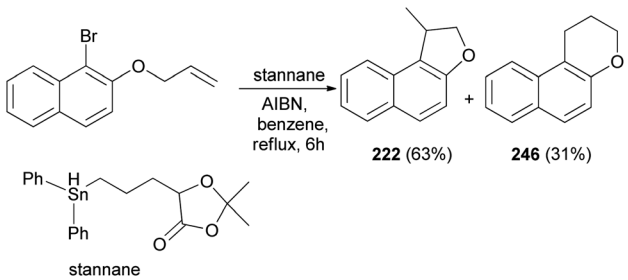
Similarly, it was noted that reaction of ethyl 1-bromo-2-hydroxynaphthalene (**241**) with ethyl-4-bromocrotonate and K_2CO_3 in dry acetone under reflux for overnight to afford ethyl 4-(l-bromo-2-naphthyl)but-2-enoate (**242**) in 37% yield. The reaction of compound **242** with Bu_3SnH and AIBN in refluxing dry benzene for 30 min gave ethyl 1,2-dihydronaphtho[2,l-*b*]furan-*l*-



Scheme 107 Plausible mechanism for the formation of **222**.



Scheme 108 Preparation of dihydronaphthofurans **243–245**.



Scheme 109 Synthesis of dihydronaphthofuran **222**.

acetate (**243**) in 97% yield. Treatment of **243** with KOH in water–ethanol (1 : 1 v/v) at room temperature for 2 h resulted l,2-dihydronaphtho[2,1-*b*]furan-*l*-acetic acid (**244**) in 99% yield. The conversion of **244** into thiohydroxamate **245** can be efficiently performed in refluxing benzene using oxalyl chloride and then in dry ether using 3-hydroxy-4-methylthiazole-2(3*H*)-thione, pyridine and DMAP at room temperature for 20 min (Scheme 108).[83]

Clive and Wang[84] demonstrated that 1-methyl-1,2-dihydronaphtho[2,1-*b*]furan (**222**) in 63% yield and 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**246**) in 31% yield were synthesized by radical cyclization of 2-(allyloxy)-1-bromonaphthalene in the presence of stannane and AIBN in refluxing benzene for 6 h (Scheme 109).

Triarylaminium salt was disclosed as an efficient initiator for the novel Friedel–Crafts alkylation/annulation cascade reaction between chalcone epoxides **247** and 2-naphthols in $CHCl_3$ at room temperature for 0.5 h to construct diastereomer polysubstituted 1,2-dihydronaphtho[2,1-*b*]furans **248** in 61–83% yields (Scheme 110). In this process, chalcone epoxides **247** acted as valuable halogen-free pre-electrophiles.[85]

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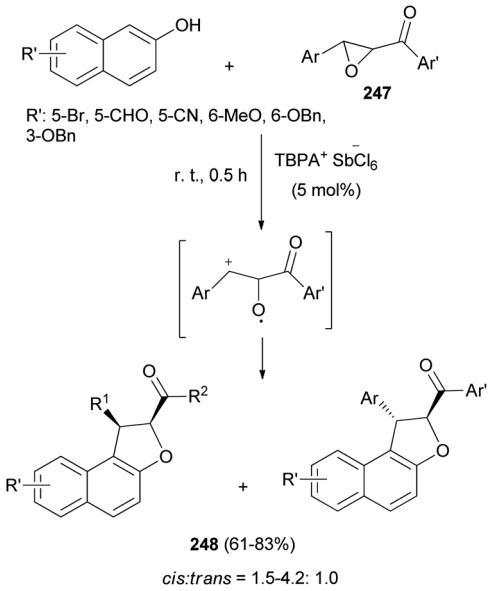
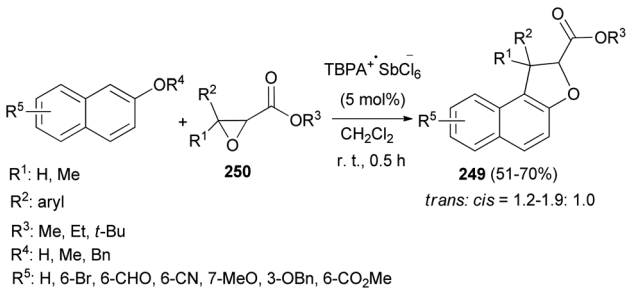
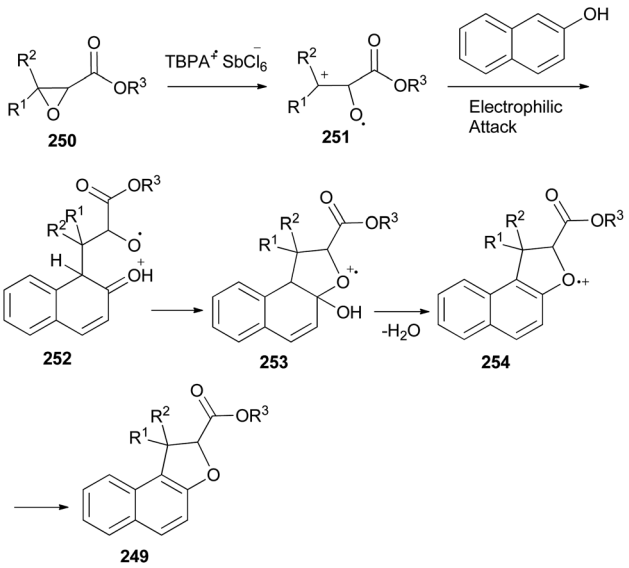


Scheme 110 $TBPA^{+}\cdot SbCl_6^{-}$-catalyzed synthesis of 1,2-dihydronaphtho[2,1-*b*]furans **248**.

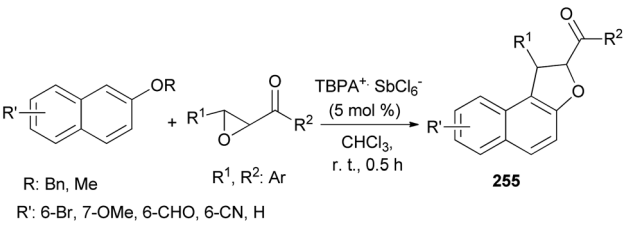


Scheme 111 $TBPA^{+}\cdot SbCl_6^{-}$-catalyzed synthesis of *trans*/*cis*-dihydronaphthofurans **249**.

An efficient chemoselective tandem Friedel–Crafts alkylation/cyclization reaction of glycidic esters with 2-naphthol derivatives in CH_2Cl_2 at ambient temperature for 0.5 h initiated by stable radical cation triarylaminium salt [tris(4-bromophenyl)aminium hexachloroantimonate, $TBPA^{+}\cdot SbCl_6^{-}$] (0.5 mol%) led to the formation of the mixture of *trans*/*cis*-dihydronaphthofurans **249** in 51–70% yields (Scheme 111). A plausible mechanism for formation of **249** is depicted in Scheme 112. The glycidic ester (**250**) was first activated by single electron oxidation to give distonic radical cation intermediate **251**. 2-Naphthol (as an example) was then attacked by the benzylic cation of intermediate **251** to form the dihydrofurylium distonic radical cation intermediate **252**. Then oxygen radical combined with the carbocation to construct radical cation intermediate **253**. And then the radical cation intermediate **254** was formed by eliminating a molecule of water from intermediate **253**. Intermediate **254** would then undergo single electron transfer from substrate **250** to produce the major product **249** and regenerate intermediate **251** at the same time. Chain propagation continued until all substrates were converted into the products.[86]



Scheme 112 Proposed mechanism for the synthesis of **249**.

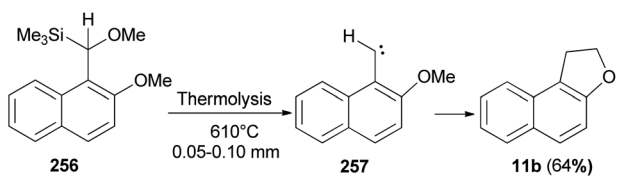


Scheme 113 $TBPA^{+}\cdot SbCl_6^{-}$-catalyzed synthesis of dihydronaphthofurans **255**.

Wang *et al.*[87] concluded that tandem reaction between chalcone epoxides and 2-naphthyl ethers in the presence of stable triarylaminium salt (5 mol%) in $CHCl_3$ at room temperature for 0.5 h afforded dihydronaphthofurans **255** (Scheme 113). And after subsequent aerobic oxidative aromatization in one pot, a series of polysubstituted naphtho[2,1-*b*]furans were delivered. It should be noted that compounds 255 have not isolated. The reaction mechanism similar to the proposed mechanism for the synthesis of **249**.

2.11. Other synthetic methods

Thermolysis of [methoxy(2-methoxy-*l*-naphthyl)methyl]trimethylsilane (**256**) at 610 °C/0.05–0.10 mm yields 1,2-dihydronaphtho[2,l-*b*]furan (**11b**) in 64% yield presumably by



Scheme 114 Thermolysis of compound **256** to 1,2-dihydro-naphtho[2,l-*b*]furan (**11b**).

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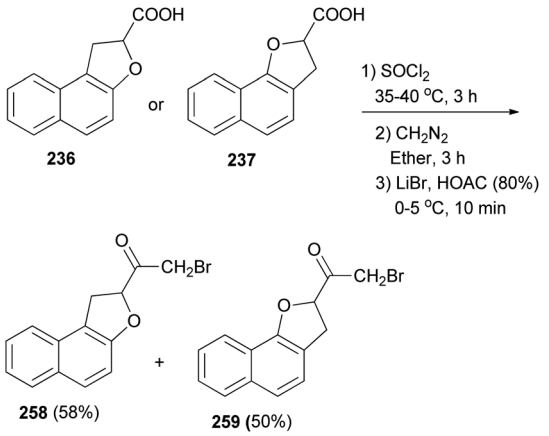


Scheme 115 Synthesis of dihydronaphthofurans **258** and **259**.

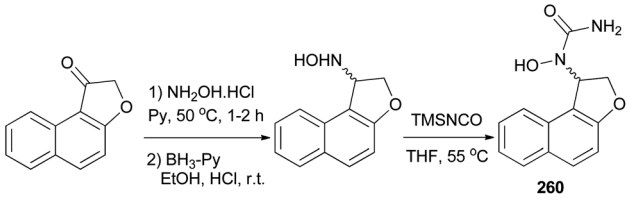
insertion of 2-methoxy-1-naphthylmethylene (**257**) into a C–H bond of its *o*-methoxy group (Scheme 114).[88]

2-Bromo-1-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)ethanone (**258**) in 58% yield and 2-bromo-1-(2,3-dihydronaphtho[1,2-*b*]furan-2-yl)ethanone (**259**) in 50% yield have been synthesized from compounds **236** and **237** with $SOCl_2$ at 35–40 °C for 3 h. Subsequently, the crude acid chlorides in diethyl ether were treated with diazomethane for 3 h and after that with LiBr in HOAC (80%) at 0–5 °C for 10 min (Scheme 115).[13]

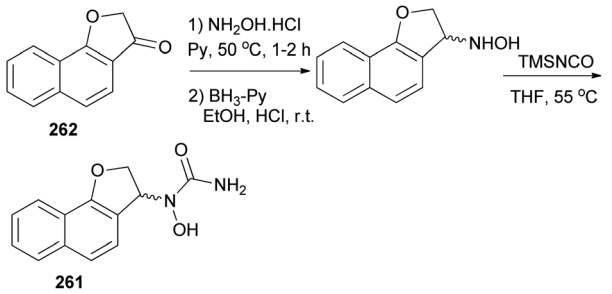
Admas *et al.*[7] demonstrated that *N*-hydroxyurea derivative of dihydronaphthofuran **260** has been prepared in 12% yield from the corresponding ketone in three steps, oximation, reduction, and hydroxyurea formation (Scheme 116).

In a similar fashion, *N*-hydroxyurea derivative of dihydronaphthofuran **261** could be prepared in 18% yield from the corresponding ketone **262** in three steps, oximation, reduction, and hydroxyurea formation (Scheme 117).

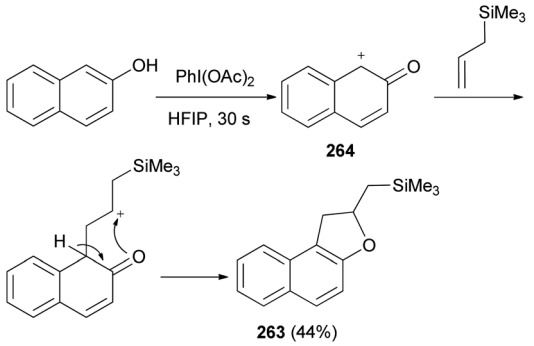
Canesi *et al.*[89] demonstrated that treatment of 2-naphthol with allylsilane in hexafluoroisopropanol (HFIP) for 30 s in the presence of iodobenzene diacetate gave ((1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methyl)trimethylsilane (**263**) in 44% yield. This reaction proceed *via* formal [2 + 3] cycloaddition is based on a common electrophilic intermediate **264** generated by an environmentally benign hypervalent iodine reagent in perfluorinated protic solvents. This intermediate can react with different sufficiently reactive allylsilane to lead in one step to different heterocyclic rings such as dihydronaphthofuran **263** (Scheme 118).



Scheme 116 Synthesis of *N*-hydroxyurea of dihydronaphthofuran **260**.



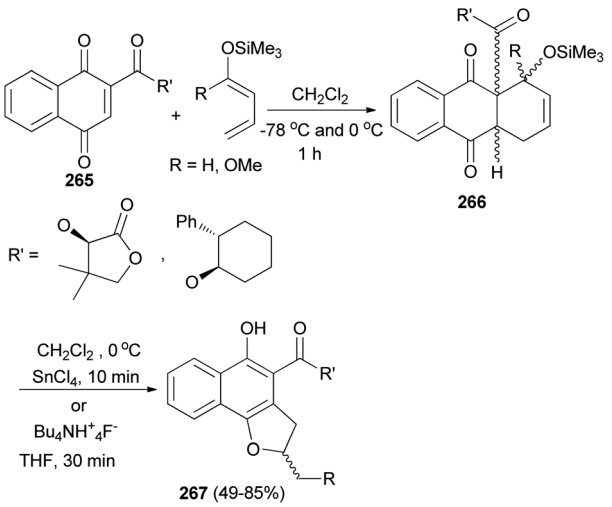
Scheme 117 Synthesis of *N*-hydroxyurea derivative of dihydronaphthofuran **261**.



Scheme 118 Iodobenzene diacetate catalyzed synthesis of 1,2-dihydronaphtho [2,1-*b*]furan **263**.

The Diels–Alder addition of naphthoquinone **265** to 1-trimethylsilyloxybuta-1,3-diene in CH_2Cl_2 at −78 °C and 0 °C for 1 h afforded Diels–Alder adducts **266.** Individual treatment of adducts **266** with tin(IV) chloride in CH_2Cl_2 at 0 °C for 10 min or with tetrabutyl ammonium fluoride in THF for 30 min afforded 2,3-dihydronaphtho[1,2-*b*]furan **267** in 49–85% yields (Scheme 119).[90]

A series of 2,3-dihydronaphtho[1,2-*b*]furan-2-carboxylic acid *N*-substituted phenyl amide analogs **268** were synthesized by



Scheme 119 Preparation of 2,3-dihydronaphtho[1,2-*b*]furans **267**.

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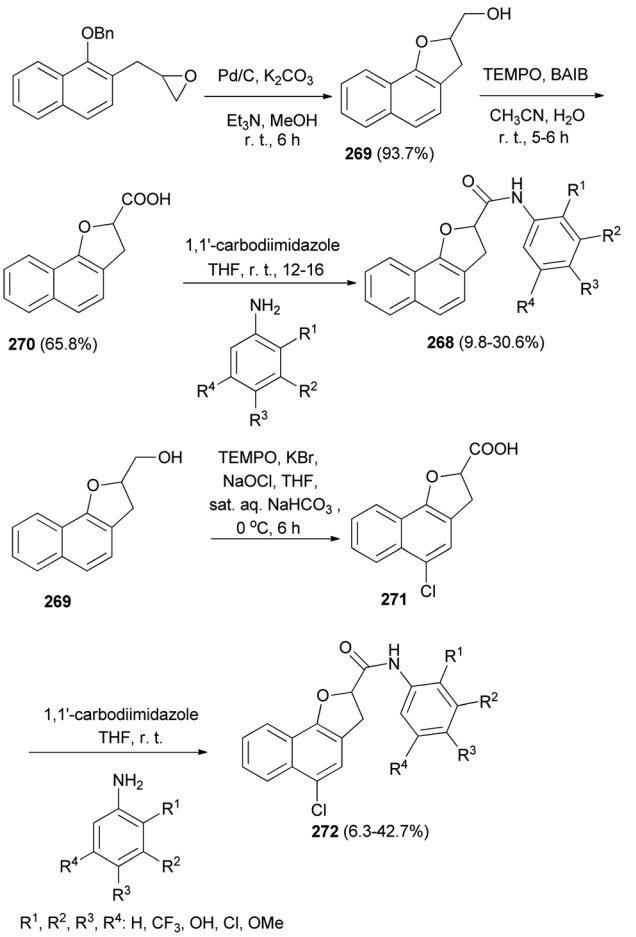
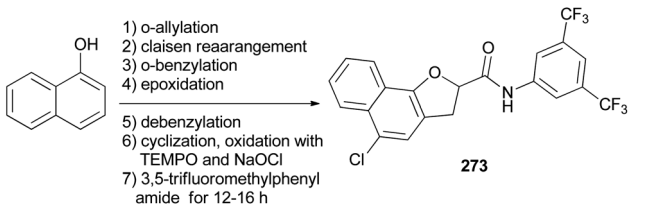
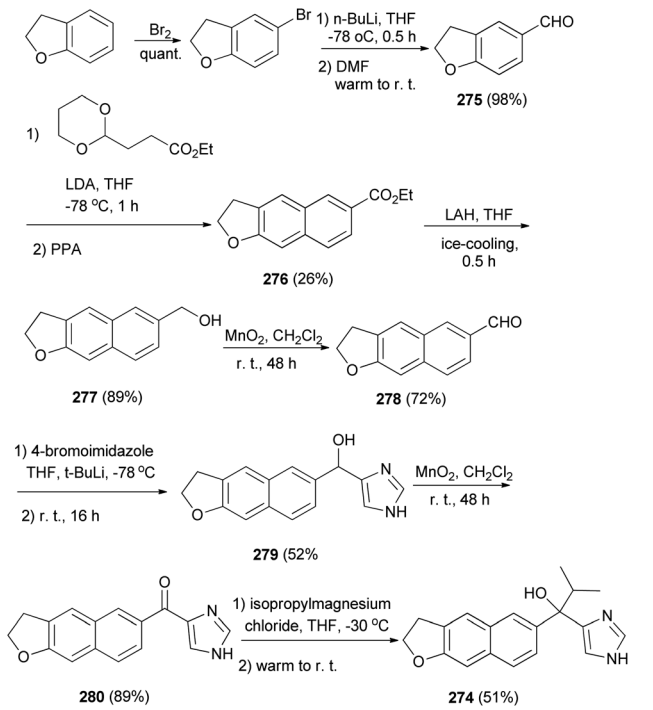


Scheme 120 Synthesis of 2,3-dihydro- and 5-chloro-2,3-dihydronaphtho-[1,2-*b*]furan-2-carboxylic acid *N*-(substituted phenyl)amide analogs **268** and **272**.



Scheme 121 Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2,3-dihydronaphtho[1,2-*b*]furan-2-carboxamide (NHDC) (**273**).



Scheme 122 Synthesis of 2,3-dihydronaphtho[2,3-*b*]furans **274** and **276–280**.

Kwak *et al.*[11] A mixture of 2-((1-(benzyloxy)naphthalen-2-yl) methyl)oxirane, 10% Pd/C, K_2CO_3, Et_3N (catalytic amount) and MeOH was stirred for 8 h at room temperature afforded (2,3-dihydronaphtho[1,2-*b*]furan-2-yl)methanol (**269**) in 93.7% yield. Treatment of **269** with TEMPO and BAIB in CH_3CN/H_2O at room temperature for 5–6 h gave 2,3-dihydronaphtho[1,2-*b*] furan-2-carboxylic acid (**270**) in 65.8% yield. Stirring a mixture of **270** and 1,1′-carbodiimidazole in anhydrous THF for 1 h followed by addition of substituted aniline to the reaction mixture at room temperature and stirring for 12–16 h afforded 2,3-dihydronaphtho[1,2-*b*]furan-2-carboxylic acid *N*-(substituted phenyl)amide analogs **268** in 9.8–30.6% yields. Also, treatment of **269** with TEMPO, KBr, NaOCl, THF and sat. aq. $NaHCO_3$ at 0 °C for 6 h gave 5-chloro-2,3-dihydronaphtho-[1,2-*b*]furan-2-carboxylic acid (**271**); then addition of 1,1′-carbodiimidazole in anhydrous THF and substituted aniline at room temperature to the reaction mixture led to the formation of 5-chloro-2,3-dihydronaphtho-[1,2-*b*]furan-2-carboxylic acid *N*-(substituted phenyl)amide derivatives **272** in 6.3–42.7% yields (Scheme 120).

Hong and coworkers reported that synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2,3-dihydronaphtho[1,2-*b*]furan-2-carboxamide (NHDC) (**273**) from 1-naphthol through a series of reactions including *o*-allylation, Claisen rearrangement, *o*-benzylation, epoxidation of allyl compound, debenzylation followed by cyclization, oxidation with TEMPO and NaOCl, and amide coupling with 3,5-trifluoromethylphenylamide for 12–16 h (Scheme 121).[14]

2,3-Dihydronaphtho[2,3-*b*]furan derivative **274** was synthesized as shown in Scheme 122. Bromination of 2,3-dihydro-1-benzofuran followed by formylation gave aldehyde **275**, which was converted to **276** by treatment with acetal ester. Reduction of **276** by LAH afforded 2,3-dihydronaphtho[2,3-*b*]furan derivative **277** and then oxidation with MnO_2 led to the formation of aldehyde **278**. Since Katritzky's imidazole introduction into **278** afforded alcohol **279**, followed by oxidation of alcohol to the ketone group with MnO_2 leading to the formation of product **280**. A Grignard reaction of **280** with i-PrMgCl provided **274** in 51% yield.[8]

Interaction of **43** with absolute ethanol in the presence of Dowex 50W-X8 resin under reflux condition for 10 h gave

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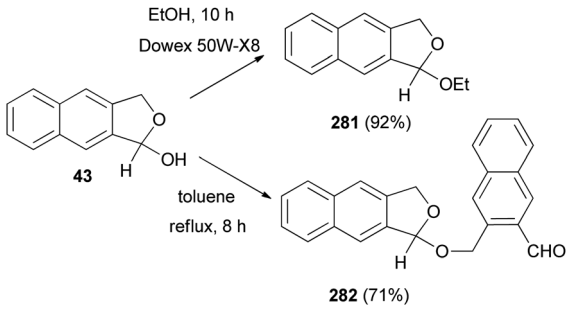


Scheme 123 Preparation of dihydronaphthofurans 281 and 282.

1-ethoxy-1,3-dihydronaphtho[2,3-*c*]furan (**281**) in 92% yield. Also, treatment of **43** in a flask equipped with a Dean–Stark trap in refluxing toluene for 8 h afforded 1-[(3-formyl-2-naphthalenyl)methoxy]-1,3-dihydronaphtho[2,3-*c*]furan (**282**) in 71% yield (Scheme 123).[32]

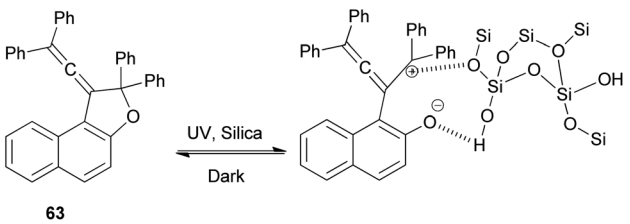
3. Dihydronaphthofuran applications

3.1. Biological activities

Dihydronaphthofuran derivatives have received considerable attention in view of the interesting biological and pharmacological properties associated with this heterocyclic scaffold. For example, *N*-hydroxyurea derivatives of dihydronaphthofurans **260** and **261**, which were weaker inhibitors of 5-lipoxygenase, had IC_{50} values in excess of 10 μM in human whole blood.[7] A series of dihydronaphthofuran derivatives such as **53** and **274** evaluated as $C_{17,20}$-lyase inhibitors. 1,2-Dihydronaphtho[2,1-*b*]furan **53** showed equipotent $C_{17,20}$-lyase inhibition activities on rate and human 26 and 25, respectively, and 11β-hydroxylase activity on rate 77. Also, 2,3-dihydronaphtho[2,3-*b*]furan **261** showed equipotent $C_{17,20}$-lyase inhibition activities on rate and human 21 and 23, respectively, and 11β-hydroxylase activity on rate 350.[8] Many functionalized dihydronaphthofurans **81** and **82** are widely employed as antitubercular activity against *Mycobacterium tuberculosis* H_{37}Rv. 2-Azidomethyldihydronaphthofurans **81** proved to be potent antitubercular with MIC 3.12 mg ml^{-1} comparable to the standard drug ethambutol. Among 1-(2,3-dihydronaphthofuran-2-yl-methyl)[1,2,3]triazoles only *n*-pentyl substituent on compound **82** exhibited mild antitubercular activity with MIC 12.5 mg ml^{-1}.[9] Furthermore, dihydronaphthofuran **258** exhibit a powerful inhibitor for α-chimotrypsine. This compound inactivate the enzyme rapidly and its action was stereo specific, confirming that the binding site of α-chimotrypsine is planar, elongated and curve.[13] Evaluating of biological properties for the synthesized 5-hydroxy-4-acetyl-2,3-dihydronaphtho[1,2-*b*]furans **99** indicated that they have anti-tyrosinase, antioxidant, and antibacterial activities.[10] The synthesized furomollugin analogs **100** were evaluated for direct scavenging activity against a variety of reactive oxygen and nitrogen species, such as 1,1-diphenyl-2-picrylhyrazyl (DPPH), nitric oxide (NO), and hydrogen peroxide (H_2O_2) assays. The results showed that they had effective antioxidant power. Moreover, the antibacterial activities of those compounds were also evaluated and the highly active compounds were selected for further determination of minimal inhibitory concentrations (MICs). It was found that they have highly active against the Gram negative bacteria *Escherichia coli* (KCTC-1924) and inhibited Gram-positive bacteria *Staphylococcus aureus* (KCTC-1916) growth.[50] A series of 2,3-dihydronaphtho [1,2-*b*]furan-2-carboxylic acid *N*-substituted phenyl amide analogs such as 2,3-dihydro-and 5-chloro-2,3-dihydronaphtho-[1,2-*b*]furan-2-carboxylic acid *N*-(substituted phenyl) amide **268** and **272** showed biological activities such as inhibitors of NF-$_k$B activity and anticancer agents. In addition, these compounds exhibited potent cytotoxicity at low concentrations against HCT-116, NCI-H23, and PC-3 cell lines.[11] *N*-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2,3-dihydronaphtho[1,2-*b*]furan-2-carboxamide (NHDC) (**273**) inhibits liver tumor growth through activation of HNF 4α.[14] Treatment with different concentrations (1–10.8 μM) of NHDC for various periods (0–72 h) inhibited liver cancer cells (HepG2, Hep3B) growth as well as colony formation followed by induction of apoptosis in a concentration dependent manner. NHDC also induced expression of the apoptosis regulating genes as well as inhibiting the action of STAT3. These inhibitory effects were associated with enhancement of expression and DNA binding activity of HNF 4α.[14] A series of 1,2-dihydronaphtho[2,1-*b*]furan derivatives such as **154** and **155** was synthesized as analogues of known natural α-glucosidase inhibitors. They have demonstrated significant potency with IC_{50} values ranging from 6.50 to 722.2 μM, as well as hypoglycemic activity exceeding the reference drug acarbose.[12]

3.2. Photochromic properties

Vinylidene-naphthofurans are a new class of photochromic molecules, with a unique structure combining an allene group linked to a dihydrofuran ring. These uncoloured molecules show acidochromism in solution and photochromic properties when adsorbed in silica gel or dissolved in acidified alcoholic solutions but not in common solvents or in the solid state. Mechanism of the photochromic behaviour for those compounds is thermally reversible. For example, vinylidenenaphthofuran **63** exhibit photochromism at room temperature when adsorbed in silica gel. UV or sunlight irradiation leads, in a few seconds, to the formation of intense pink/violet to green colors that bleach completely in a few minutes in the dark (Scheme 124). Also, compound **63** show acidochromic properties: addition of TFA to an uncolored solution of compound **63** leads to the immediate development of an intense violet



Scheme 124 Photochromic equilibrium for 1-vinylidenenaphtho[2,1-*b*]furan **63**.

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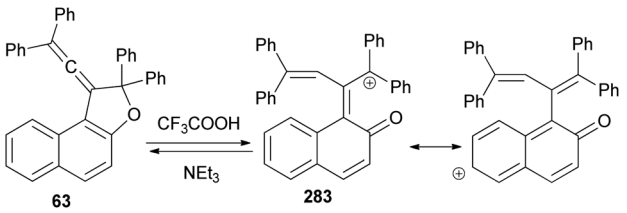
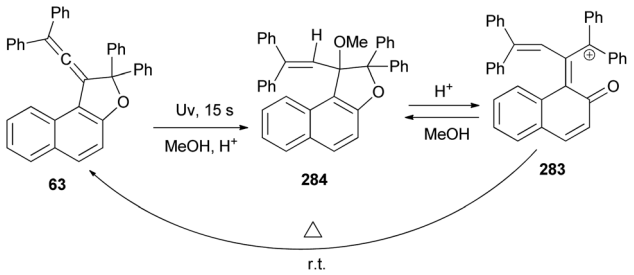


Scheme 125 Acidochromism of 1-vinylidenenaphtho[2,1-*b*]furan **63**.

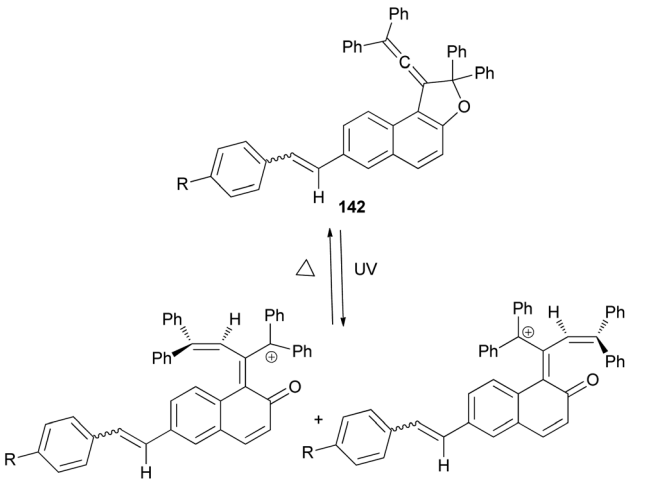


Scheme 126 Mechanism of photochromism for 1-vinylidene-naphthofuran **63**.

coloration **283** that bleaches immediately when a weak base (NEt_3) is added (Scheme 125).[15]

Vinylidene-naphthofurans **63** exhibit acidochromic properties in TFA solutions. They are converted into stable cationic species in strong acidic medium and bleach back to the uncoloured closed form upon neutralisation with Et_3N. A mechanism for their thermally reversible photochromic behaviour is proposed based on NMR analysis of UV-irradiated CH_3OD + THF-d_8 acidified solutions: the UV light promotes the addition of methanol to the naphthofuran affording non-coloured photoproduct **284**. In the presence of acid, the later is quickly converted into a cationic violet dye **283** that returns thermally to the initial closed naphthofuran in the dark. This photochromic system switches between the uncoloured and violet state after UV or sunlight exposure (15 s) and returns thermally to the initial uncoloured state in 2–8 min, in the dark, at room temperature (Scheme 126).[16]

The introduction of a styryl chain in the structure of the vinylidene-naphthofurans such as **140–142** leads to a new set of uncoloured photochromic compounds that afford grey/brown colourations upon exposure to the UV or sunlight, at room temperature and returning to the uncoloured state, in the dark, in several minutes. The photochromic properties of these smart dyes are very sensitive to the chemical environment, specially their acidity being faster in THF/HCOOH solution than in silica gel. The amount of formic acid influences the kinetics of the fading reaction as a low concentration leads to a faster system but with a lower colourability. A good compromise was obtained in THF/HCOOH (2/0.5) solutions. The substituents in the styryl group influences the kinetic of the fading process: electron-withdrawing groups like Br or CF_3 increases the fading rate leading to fast switching compounds but confers an initial yellowish colour to the solution before irradiation (Scheme 127).[17]



Scheme 127 Photochromic equilibrium for 7-styryl-1-vinylidenenaphthofurans **142**.

The photochromic properties of the ormosil materials **68** showed a strong dependence on the nature of the silanes, spacer, acid and curing conditions. The functionalization of the vinylidene-naphthofurans with a reactive siloxane group was essential to avoid their precipitation after curing. The best results were obtain using a mixture of TEOS, MTES, PTES, 1,2-ethanodiol, water, chloroacetic acid and vinylidene-naphthofurans (**68**: R = OMe) cured at 50 °C for 7 days. This uncoloured material is transparent and develops an intense green colouration, characterized by two absorption bands at 460 and 640 nm, after 2 min under UV light. When the light source is removed a mono-exponential colour decay occurs due to the spontaneously ring closure reaction that afford the initial molecule. These hybrids showed a fast thermal bleaching kinetics, losing almost their total colouration in 20 min in the dark (Fig. 4).[19]

A series of photochromic vinylidene-naphthofurans **88** and **89** with extended conjugation, embedded in ormosil matrices affording solid and transparent materials that acquire different colourations (violet, green, bluish), reversibly, when exposed to the UV (sun) light, for 2 min, at room temperature. The presence of an extra phenyl ring in some positions affects both the λ_{max} of absorption of the photochromic compounds in the uncoloured closed and open coloured form. After removal of the light source the materials lose progressively their colouration returning to the initial uncoloured state in less than 15 min at

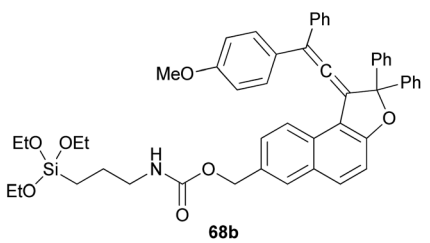


Fig. 4 Structure of vinylidene-naphthofuran **68b**.

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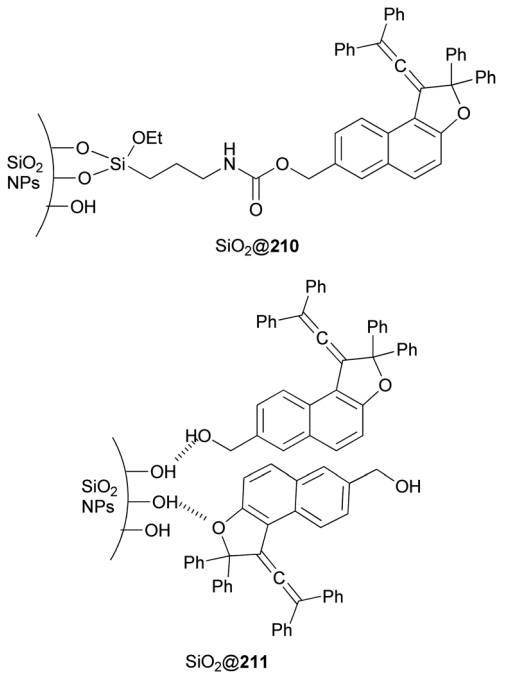
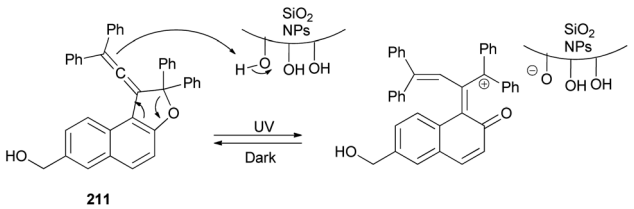


Fig. 5 Schematic representation of the vinylidene-naphthofurans **210** and **211** immobilization onto SiO_2 NPs.

room temperature. Photochromic 1-vinylidene-naphtho[2,1-*b*]furan derivatives **210** and **211** were successfully anchored onto silica nanoparticles (SiO_2 NPs) through direct adsorption (SiO_2@211) and covalent post-grafting (SiO_2@210) (Fig. 5).

SiO_2 NPs with different size and surface chemistry (pH_{pzc} in the range of 5–9) were used, offering a wide range of possibilities to fabricate tailor-made photochromic materials. The photochromic behavior of these new nanoparticles indicates that silica surface acidity and the type of vinylidene-naphthofuran immobilization strategy (adsorption *vs.* covalent grafting) were crucial factors for the occurrence of photochromism in the vinylidene-naphthofuran-based SiO_2 NPs. Upon direct UV ($\lambda = 365$ nm) or sunlight exposure during 1 min, only the SiO_2@211 nanomaterials prepared by direct vinylidene-naphthofuran adsorption onto SiO_2 NPs with $pH_{pzc} \approx 6.0$ showed direct and reversible photochromic properties, developing fast (in seconds) and intense salmon and violet coloration, with high values of total color difference and optical densities; in contrast, all nanomaterials prepared by covalent grafting of **210** onto SiO_2 NPs (SiO_2@210) did not exhibit photochromism. In the case of the photochromic SiO_2@211 NPs, the decoloration process followed a bi-exponential decay with fast rate constants, which were responsible for the loss of coloration in less than 10 min. Furthermore, they presented very good resistance to fatigue, showing reversibility between the colored/uncolored states without significant loss of their performance for at least 8 successive UV/dark cycles. Scheme 128 has been represented of the proposed mechanism responsible for the photochromic behavior of **211** onto SiO_2 NPs.[18]



Scheme 128 Proposal mechanism.

4. Conclusions

In this review, wide range of synthetic strategies of dihydronaphthofurans (DHNs) as an important class of arene ring-fused furans has been discussed. We have started with chemical, photochemical and electrochemical methods for the synthesis of DHNs, followed by presenting of their diverse biological, pharmacological activities and photochromic properties. In general, naphthol derivatives play an important role and work well in construction of DHNs. Moreover, different types of reactions such as annulation of naphthols and naphthoquinones, [3 + 2] and [4 + 1] cycloaddition, Friedel–Crafts and Diels–Alder reactions, Claisen and neophyl rearrangement, cyclization of allyl naphthols and *etc.* were demonstrated for synthesis of DHNs. We believed that the reported methods could be of interest in material science, medicinal, photochromic compounds and natural products synthesis and their use has been growing rapidly.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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