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Structural Insights into the TES/TFA Reduction of Differently Substituted Benzofurans: Dihydrobenzofurans or Bibenzyls?

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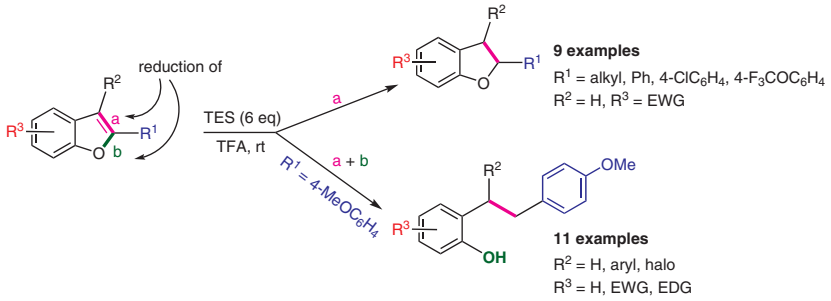

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Abstract Various polysubstituted benzofurans were reduced by using triethylsilane in trifluoracetic acid. 2,3-Dihydrobenzofurans or bibenzyl compounds were obtained in high yields, depending on the nature of the substituents at C2 and on the benzene ring of the core structure. A *p*-anisole substituent at C2 of benzofurans always led to the corresponding bibenzyls.

Key words benzofurans, dihydrobenzofurans, bibenzyls, triethylsilane, trifluoroacetic acid, reduction

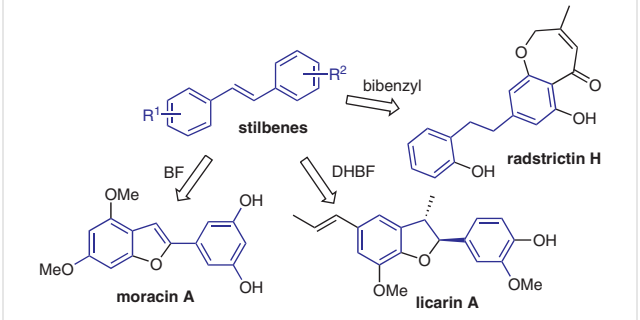

Figure 1 Examples of natural stilbenoids

2,3-Dihydrobenzofuran-based compounds as well as derivatives of bibenzyl (1,2-diarylethanes) are found in a range of natural products. Stilbenoids and benzofurans have become of particular interest for their various biological and pharmacological activities (Figure 1). 2,3-Dihydrobenzofurans exhibit antiviral, antibacterial, antiinflammatory, antiangiogenic, and antimitotic activities,[1] whereas bibenzyls show other biological and agrochemical activities,[2] and are also used as starting materials for the synthesis of drug molecules.[3] This has triggered substantial research efforts into the development of efficient methods for the preparation of dihydrobenzofurans, both in racemic and enantioenriched forms,[4] and for a more direct preparation of bibenzyls.

The hydrogenation of benzofurans represents, in principle, the most direct and most straightforward approach to 2,3-dihydrobenzofurans, but it is widely considered as unattractive, and few examples have been described.[5] The catalytic hydrogenation of benzofuran under harsh reaction conditions is often accompanied by partial cleavage of the furan ring and the formation of 2-ethylcyclohexanol and 2-cyclohexylethanol, thereby restricting its practical application. However, reductive methods have been used for the preparation of symmetric and nonasymmetric bibenzyl derivatives in good yields.[6]

In the last decade, reports have been published on asymmetric hydrogenations under medium to high pressures of hydrogen by using various catalytic systems, for example, Ru,[7] Rh,[8] or Ir[9] complexes.

Catalytic hydrogenation was used in the synthesis of (±)-ampelopsin B and (±)-ε-viniferin.[10] Either Pd-catalyzed hydrogenation or a combination of NH_4 and Mg in methanol has been used on a range of 2-aryl-3-(alkoxycarbonyl)benzofurans, affording *cis*- or *trans*-2,3-dihydrobenzofurans, respectively.[1c] However, all such methods for the direct reduction of variously substituted benzofurans appear to be substrate-dependent and, consequently, developing a general and selective reductive method to access 2,3-dihydrobenzofurans remains a challenge.

In line with our interest in designing suitable benzofurans[11] and 2,3-dihydrobenzofurans[12] for the synthesis of natural products, we report the direct reduction of various substituted benzofurans by using a triethylsilane/trifluoroacetic acid (TES/TFA) system, in an attempt to understand how substituents affect the reduction of benzofurans.

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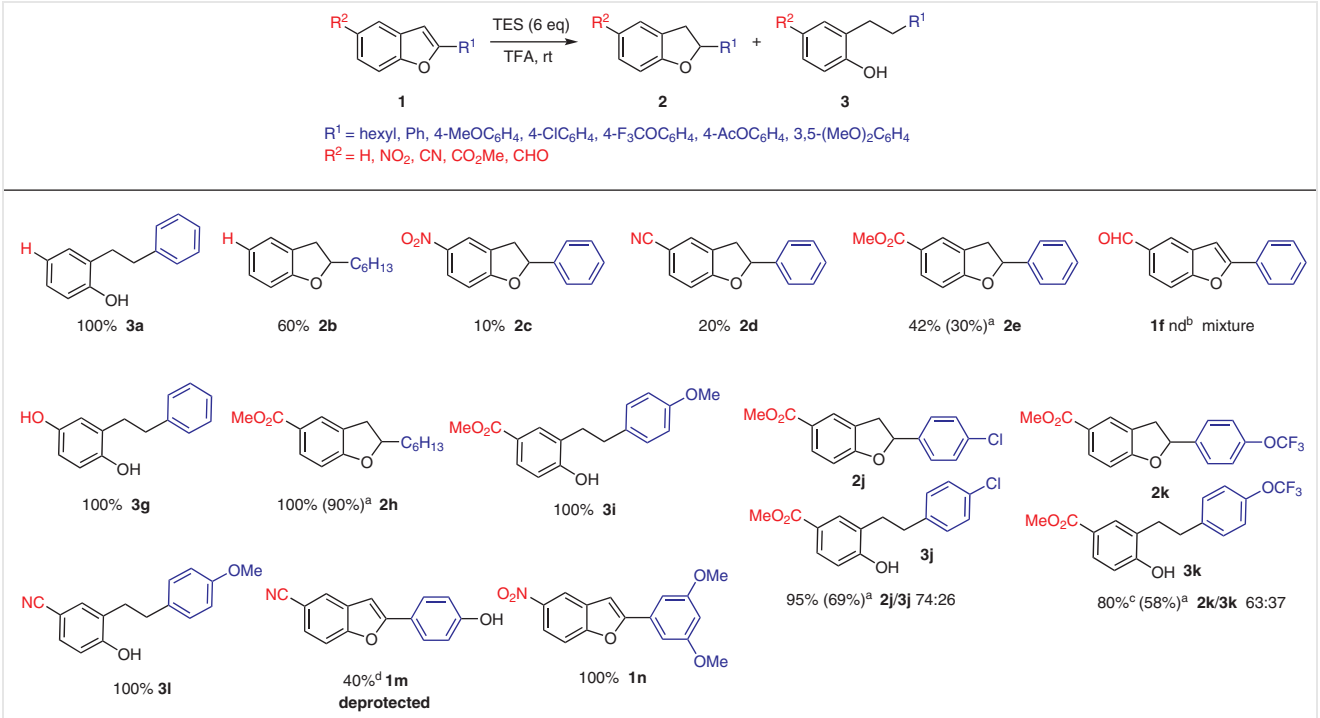
There has been only one report on the reduction of 2,3-diarylbenzofurans by using TES/TFA,[13] whereas several examples of reductions of 2,3-dialkylbenzofurans have been described.[14]

A series of 2-aryl (or 2-alkyl) 5-substituted benzofurans were prepared from the parent *p*-substituted *o*-halophenols and terminal alkynes by Pd-catalyzed cyclization.[15] Our initial investigations on the conversion of benzofurans into 2,3-dihydrobenzofurans were carried out by using 2-phenyl-1-benzofuran (**1a**) and 2-hexyl-1-benzofuran **1b** (Scheme 1). The reaction of **1a** (0.5 mmol) with TES (3 mmol) in TFA (7.5 mL) at room temperature for 18 hours led to the ring-opened product **3a** without any trace of 2-phenyl-2,3-dihydro-1-benzofuran (**2a**),[16] whereas the same reaction on **1b** (0.5 mmol) with TES (3 mmol) in TFA (7.5 mL) at room temperature for six hours led to 2-hexyl-2,3-dihydro-1-benzofuran (**2b**) exclusively, with 60% conversion. The reaction was then performed on some 2,5-disubstituted benzofurans. 2-Phenyl-1-benzofurans **1c–e**, bearing an electron-withdrawing group at C5, reacted slowly (with conversions of up to 42%) and gave dihydrobenzofurans **2c–e** exclusively. The formyl group in compound **1f** was not tolerated, leading to the formation of many degradation products.

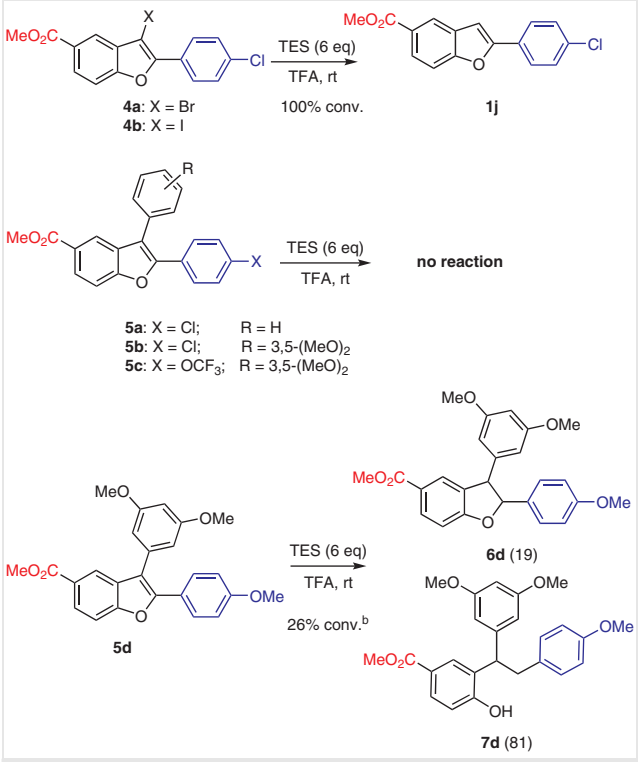
Reduction of 5-hydroxy-2-phenyl-1-benzofuran (**1g**) led to the ring-opened product **3g** exclusively. Compound **1h**, bearing an alkyl substituent at C2, as in compound **1b**, gave the 2,3-dihydrobenzofuran **2h**, whereas methyl 2-(4-methoxyphenyl)-1-benzofuran-5-carboxylate (**1i**), with an electron-donating group on the 2-aryl substituent, gave the over-reduction product **3i**. The presence of a weakly inductively electron-withdrawing *para*-chloro group on the 2-aryl substituent made substrate **1j** reactive toward reduction, with over-reduction occurring after an extended reaction time. Switching to a *para*-trifluoromethyl group on the 2-aryl substituent in **1k**, where the trifluoromethyl group decreased the electron-releasing effect of the oxygen, resulted in slow reduction to give **2k**. Benzofuran **1l**, with an electron-withdrawing group at C5 and an electron-donating *para*-methoxy group on the 2-aryl substituent, underwent slow over-reduction to product **3l**, without any trace of the corresponding dihydrobenzofuran **2l**. Compound **1m**, with a *para*-acetoxy group on the 2-aryl substituent, gave the deacetylated derivative **1m′** as the sole product, and no reduced product was observed, despite the electron-donating nature of the hydroxy group. This suggested a probable transesterification reaction leading to an intermediate trifluoroacetoxy derivative that was incapable of being reduced and underwent subsequent hydrolysis on workup. Benzofuran **1n** bearing an electron-withdrawing group on C5 and a 3,5-dimethoxyphenyl group on C2 proved unreactive under the reduction conditions.

As **1j** and **1k** afforded the best reductive outcome to produce 2,3-dihydrobenzofurans, various 5-methoxycar-



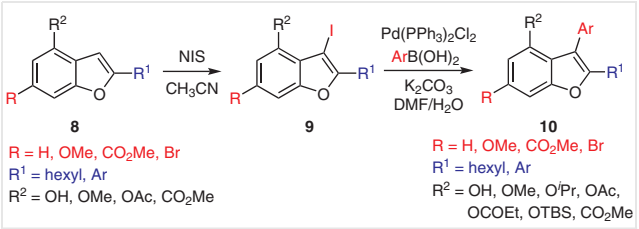
Scheme 1 Reduction of 2-substituted and 2,5-disubstituted benzofurans. *Reagents and conditions*: **1** (1 mmol), Et_3SiH (6.0 equiv), TFA (0.5 mL), rt, 2–24 h. Conversions and products ratios were determined by ^1H NMR spectroscopy. [a] Isolated yield of the main product. [b] Not determined; degradation occurred. [c] After 24 h, the mixture was warmed to 40 °C. [d] Deprotected: the phenol was recovered due to hydrolysis of the acetate group.

bonyl 2,3-disubstituted benzofurans were investigated (Scheme 2). Compounds **4a** and **4b**, obtained by halogenation of compounds **1j** and **1k** with *N*-bromosuccinimide or *N*-iodosuccinimide, respectively, were subjected to Suzuki cross-coupling to give compounds **5a–d**.[11a] 3-Halogenated, as well as 3-aryl-substituted, derivatives were tested in the reduction reaction. In the case of the 3-iodo and 3-bromo derivatives **4a** and **4b**, dehalogenation occurred first, leading to **1j** as the major product, with traces of the corresponding reduced products **2j** and **3j**. It is worth noting that when the 3-position is substituted, as in compounds **5a–c**, reduction does not readily occur and, if it does occur, the substitution of the 2-aryl group is critical. With a *para*-methoxy substituent on the 2-aryl group, reduction occurred slowly, and the main product was the open-chain derivative **7d**.



Scheme 2 Reduction of 5-methoxycarbonyl 2,3-disubstituted benzofurans. *Reagents and conditions*: **4** or **5** (1 mmol), Et_3SiH (6.0 equiv), TFA (0.5 mL), rt, 2–24 h. Conversions and products ratios were estimated by GC/MS.

Subsequently, C4- and/or C6-substituted 2-aryl and 2,3-diarylbenzofurans were studied. Starting from compounds **8**, in which R^2 at C4 was a free hydroxy group or one protected as a methyl ether or methyl ester (**8a–h**)[11a] or as an ester functionality (**8i**),[17] the iodinated compounds **9** and the corresponding 2,3-diaryl-substituted benzofurans **10** were obtained by subsequent iodination and Suzuki cross-coupling reactions, respectively (Scheme 3).

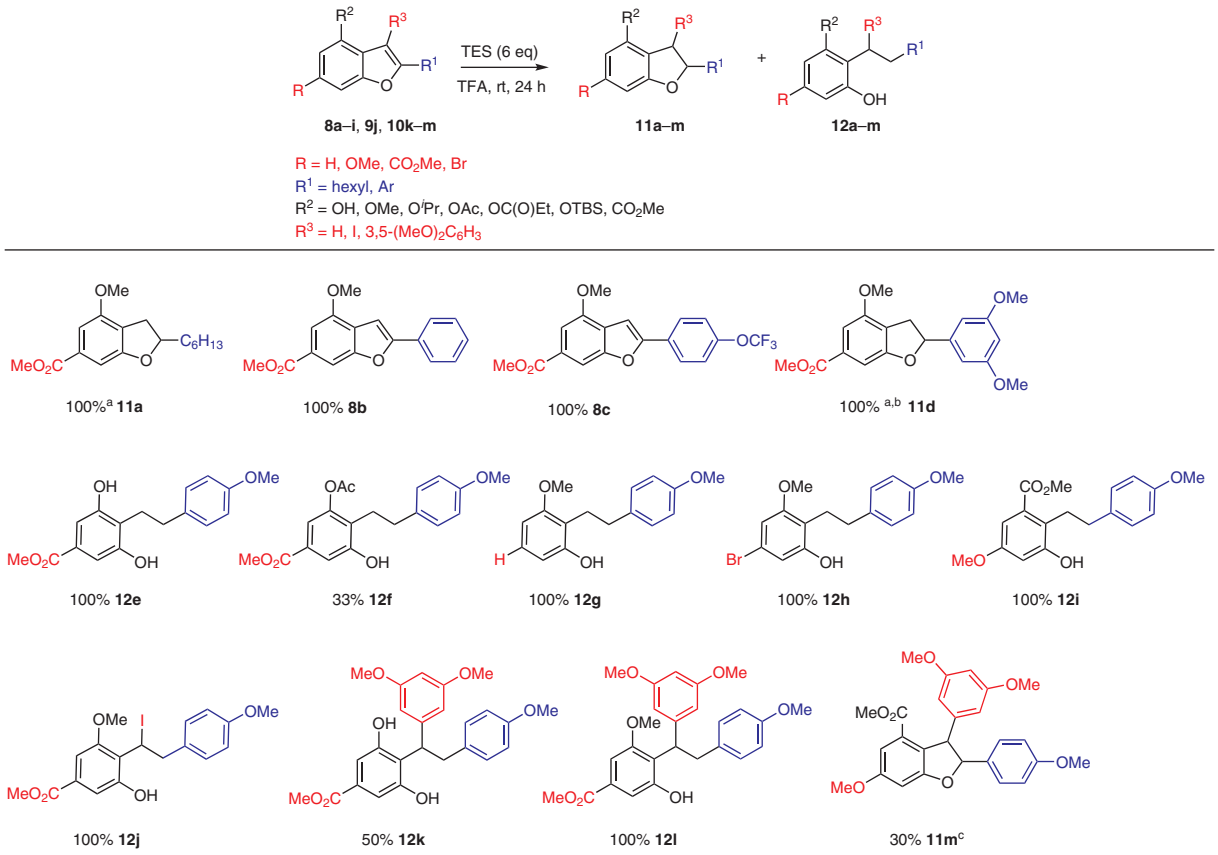


Scheme 3 Synthesis of 6-substituted 2,3-diaryl-4-alkoxy-1-benzofurans

Compounds **8**, **9**, and **10** were then subjected to the reduction conditions (Scheme 4). Compound **8a** [R = CO_2Me; R^1 = $(CH_2)_5Me$; R^2 = OMe] gave the 2,3-dihydrobenzofuran **11a** exclusively (in line with the previously examined substrates **1b** and **1h**; Scheme 1). In this case, the reaction appeared to be driven by the substituent on C2. On switching to substrates bearing an aryl ring at C2, a somewhat puzzling behavior occurred. Phenyl-substituted **8b** and *p*-(trifluoromethyl)phenyl-substituted **8c** did not undergo any reduction at all, whereas **8d**, containing a 3,5-dimethoxyphenyl group at C2, gave the corresponding 2,3-dihydrobenzofuran **11d** as the main product, and as the sole product on quenching the reaction at low temperature. With the aim of investigating the effect of an electron-releasing aryl group at C2, we tested a range of *para*-methoxyphenyl derivatives **8e–h**. In all cases, over-reduction occurred and the 2,3-dihydrobenzofurans **11e–h** were not obtained. In the case of the 4-acetoxy derivative **8f**, the conversion was low, and deesterification occurred. The ester moiety at C6 did not affect the reduction. In fact, when hydrogen (in **8g**) or bromine (in **8h**) were present, over-reduction products were also obtained. The open-chain product **12i** was also obtained when a methoxy group at C6 and an ester group at C4 were present in benzofuran **8i**.

This type of behavior was confirmed to occur generally with 2,3-disubstituted derivatives. In the cases of the 3-iodo derivative **9j** or the 3-aryl derivatives **10k** and **10l**, over-reduction occurred exclusively, although protonation should have been more difficult. In the case of **10k**, which bore a free hydroxy group at C4, a low conversion was obtained and the over-reduction product **12k** was obtained. Notably, for the two structural isomers **10l** and **10m**, in which the two substituents at C4 and C6 were reversed, the trend of reduction was different. Compound **10l** furnished the over-reduced product **12l**, whereas compound **10m** gave the 2,3-dihydrobenzofuran **11m**, albeit in modest yield, confirming a report in the literature.[13]

Surprisingly, different protections of a hydroxy group at C4 affected the reduction (Scheme 5). The isopropyl group in **10n** was removed sufficiently fast to permit subsequent reduction (and over-reduction), affording **12k** in 25% yield after 24 hours, whereas acetyl- (**10o**), propionyl- (**10p**), or *tert*-butyl(dimethyl)silyl (**10q**)-protected derivatives were



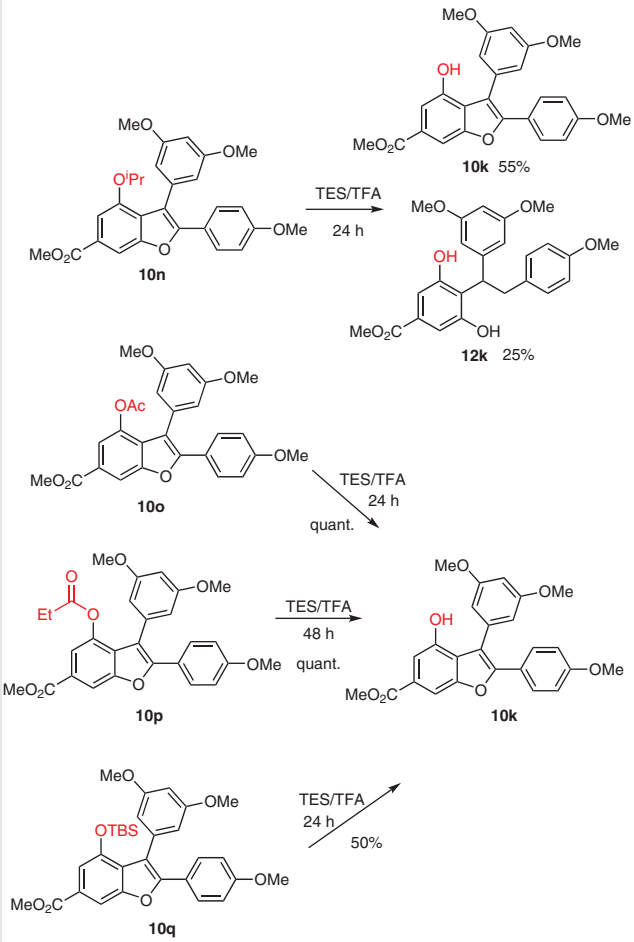
Scheme 4 Reduction of 2,3,4,6-tetrasubstituted benzofurans. [a] Isolated yield of the main product. [b] **12d** was obtained after quenching and purification on silica gel. [c] A single diastereoisomer was obtained.

unreactive toward reduction, and only deprotection occurred, slowly giving rise to compound **10k**.

We concluded that, under these conditions of hydrogenation,[18] when an alkyl group was present at C2 reduction occurred and the corresponding 2,3-dihydrobenzofuran was obtained, regardless of the substituents on the benzene ring. However, when an aryl group was present at C2, 2,3-dihydrobenzofurans or bibenzyls were obtained, depending on the nature and the position of substituents on the aryl group and on the benzofuran core.

A plausible mechanism for this reaction, depicted in Scheme 6, explains the results in terms of the relative stabilities of the intermediates that are formed. A 2-aryl substituent stabilizes the benzyl carbenium ion formed under acidic conditions by furyl ring opening, so that over-reduction can occur provided no substituent on the benzene ring slows down the over-reduction (as in the case of R = H). The mesomeric effect of substituents of the 2-aryl substituent influences the stabilization of the benzylic carbocation. Moreover, an electron-withdrawing group at the 5-position of the benzofuran ring (R = CN, NO_2, CO_2Me) favors the formation of 2,3-dihydrobenzofurans in the absence of additional stabilization of the benzyl carbocation [Ar = Ph, 4-ClC_6H_4, 4-$F_3COC_6H_4$, 3,5-$(MeO)_2C_6H_3$]. Equally, over-reduction occurs if an electron-donating group is present at the *para*-position of the 2-aryl substituent. Otherwise, if an electron-donating group is present at C5, further protonation is possible and the furan ring is opened. Other substituents at C5 do not affect the pattern of reduction. The reaction trend is directed solely by the pattern of substitution on the 2-aryl substituent.

Surprisingly, the formation of 2,3-dihydrobenzofurans occurred when a carboxy group was present at C4 of the 2,3-diaryl-substituted benzofuran **10m**, but no reduced products were observed when a hydroxy group at the same position was protected with a sterically hindered group (**10o–q**). Further investigations will be carried in an attempt to understand these outcomes. A probable acid–base Lewis-type interaction occurs between the C3 aryl substituent and the substituent at C4, which prevents protonation of the furan ring and subsequent reduction and/or over-reduction of the benzofuran. This might be an efficient method for obtaining asymmetric bibenzyls (the over-reduced products), which are useful as building blocks and are constituents of important classes of biological compounds.



Scheme 5 Reduction of benzofurans **10n–q**

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705949.

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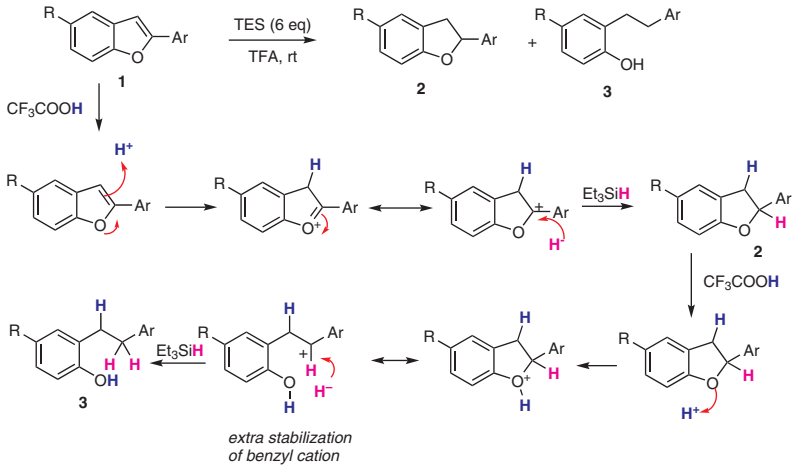

Scheme 6 Possible mechanism of reduction to 2,3-dihydrobenzofurans and 1,2-diarylethanes

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(16) Several trials were performed by changing the amount of TES (1–12 equiv), the solvent (CH_2Cl_2, toluene, AcOH, or TFA), the reducing agent ($NaBH_4$ or TES), and the temperature (0–40 °C), without any meaningful improvement in the conversion or the ratio of reduced products.
(17) Benzofuran **8i** was prepared according to the reported procedure; see: Liu, J.-t.; Do, T. J.; Simmons, C. J.; Lynch, J. C.; Gu, W.; Ma, Z.-X.; Xu, W.; Tang, W. *Org. Biomol. Chem.* **2016**, *14*, 8927.
(18) **TFA/TES Reduction: Typical Procedure**
In a round-bottomed flask under an Ar atmosphere, the appropriate benzofuran substrate (0.5 mmol) was dissolved in TFA (7.5 mL), and TES (6 equiv) was added. The reaction was monitored every hour by GC/MS. When complete, the reaction was quenched with aq $NaHCO_3$ at 0 °C until the effervescence stopped. The mixture was then extracted with EtOAc (×3), and the extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was analyzed by GC/MS or NMR. Generally, the dihydrobenzofurans had similar R_f values to those of the starting benzofurans, so purification by column chromatography on silica gel was avoided when the reaction showed a low conversion.
2-Hexyl-2,3-dihydro-1-benzofuran (2b)
Prepared by reduction of **1b** with according to the typical procedure; yield: 60% (NMR). ^{1}H NMR (500 MHz, $CDCl_3$); δ = 7.56s (s, 1 H), 7.12 (m, 2 H), 6.81 (m, 1 H), 4.75 (m, 1 H), 3.25 (m, 2 H), 2.85 (m, 2 H), 1.25 (m, 8 H), 0.81 (m, 3 H).