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Transition metal-free diastereospecific synthesis of (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines by reaction of (*Z*)-1,2-dibromo-3-aryl-2-propenes with catechols

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Graphical Abstract

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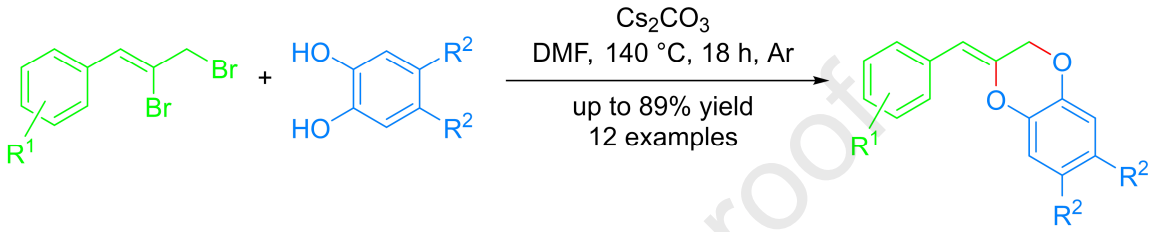

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ABSTRACT

A transition metal-free, diastereospecific reaction between substituted (*Z*)-1,2-dibromo-3-phenyl-2-propenes and substituted catechols using Cs_2CO_3 as a base at 140 °C for 18 hours delivers exclusively substituted (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines in yields up to 89%. Experiments as well as quantum chemical calculations support the assumption that the one pot transformation proceeds as an intermolecular *O*-allylation/intramolecular *O*-vinylation.

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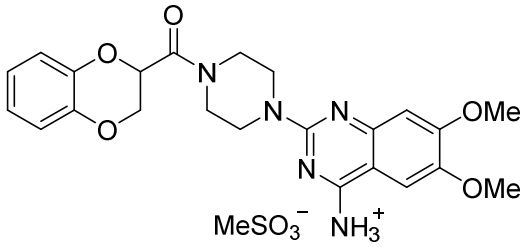
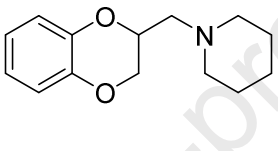
1. Introduction

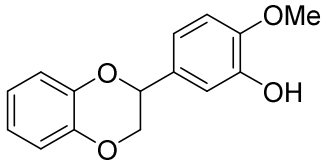
Benzo[1,4]dioxines and 2,3-dihydro[1,4]benzodioxines are important oxygen containing heterocycles since they exhibit a wide range of biological and pharmaceutical properties [1]. Among the most prominent examples are the mesylate of doxazosin (CARDURA®) (**A**), which is used as an antihypertensive agent [2], piperoxan (**B**) being a potent α-adrenergic blocking agent [3] and fluparoxan (**C**) with antidepressant effects [4] (Fig. 1). A number of 2,3-dihydro[1,4]benzodioxines like **D**, which are derived from isovanillin, are known for their strong sweetening properties [5]. In addition, there is also a number of naturally occurring 2,3-dihydro[1,4]benzodioxines [6]. The most popular are the diastereomeric flavolignans silybin A (**E**) and silybin B (**F**), isolated from *silybum marianum*, which are known for their antihepatotoxic activities [7].



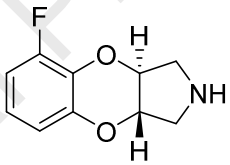
Doxazosin (CARDURA®) **A**



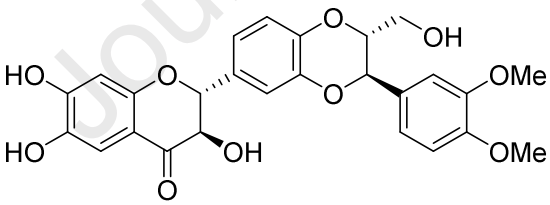
Piperoxan **B**



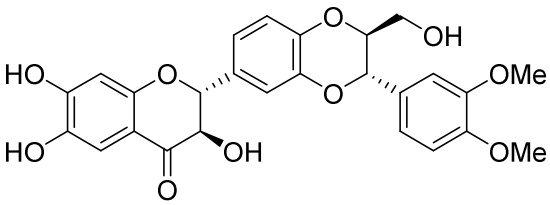
Isovanillin-based sweeting agent **D**



Fluparoxan **C**



Silybin A **E**

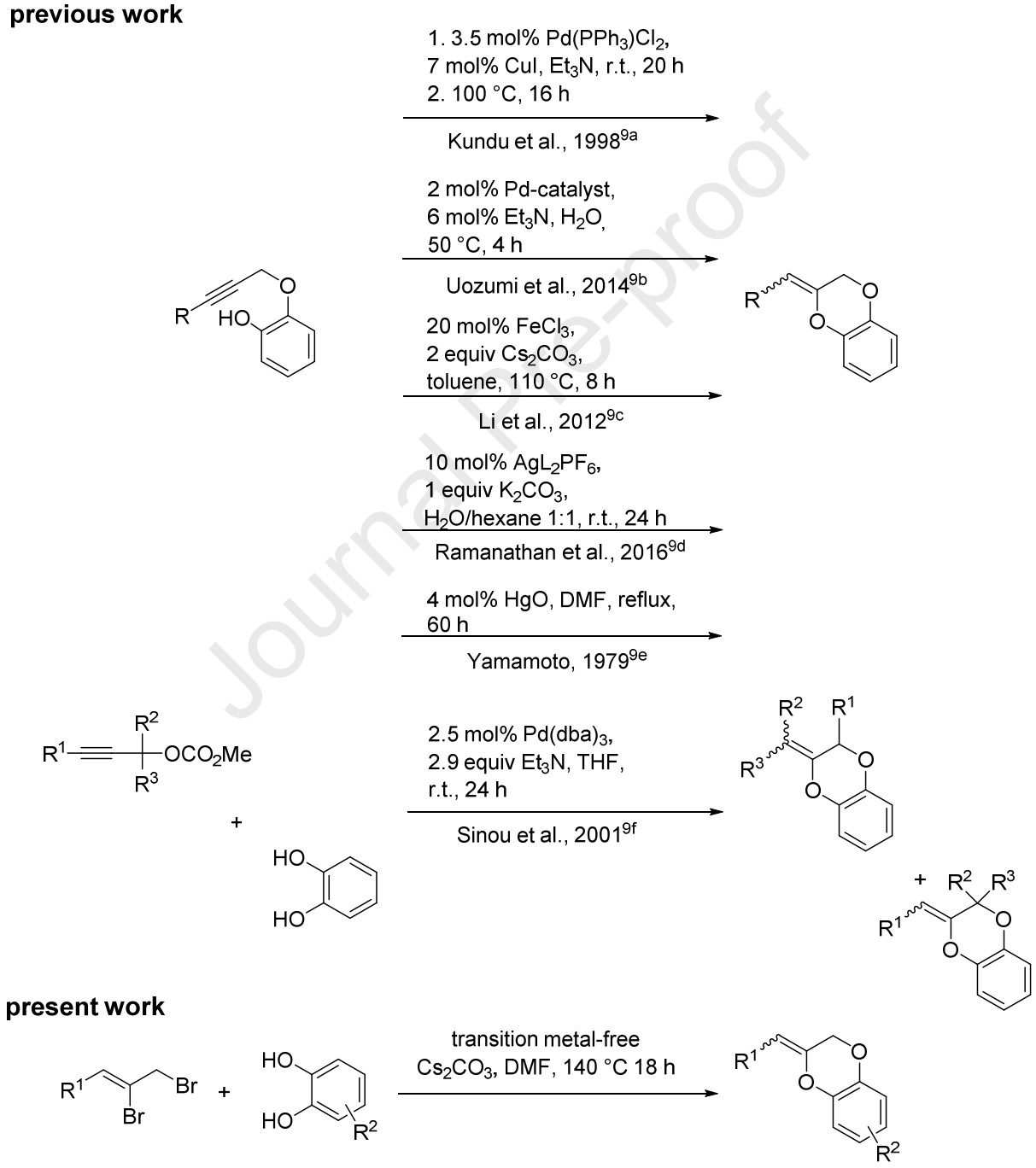


Silybin B **F**

Fig. 1. Examples of biologically active benzo[1,4]dioxine derivatives.

Due to the marked interest in biological active benzo[1,4]-dioxines and 2,3-dihydrobenzo[1,4]dioxines, a number of synthetic methods for their preparation has been developed [1,8]. In contrast, the number of synthetic approaches to 2-(ylidene)-2,3-dihydrobenzo[*b*][1,4]dioxines is rather limited (Scheme 1) [9]. Most of them are based on transition metal-catalyzed 6-*exo*-dig-type cyclizations of 2-[(3-arylprop-2-yn-1-

yl)oxy]phenols (Scheme 1). As catalysts, palladium [9a,b], iron [9c], silver [9d] and even mercury [9e] compounds have found application. Most of them deliver the corresponding cyclization products with (*Z*)-configuration around the newly formed exocyclic double bond. The 2-[(3-arylprop-2-yn-1-yl)oxy]phenols can be synthesized either by Sonogashira coupling using monoprop-2-ynylated catechols and aryl halides as substrates [9a,e] or by propargylation of a catechol with the corresponding aryl-substituted propargyl halide under basic conditions [9b,d,e]. In addition, the palladium-catalyzed reaction between substituted propargyl carbonates and catechols has also been developed for the synthesis of 2-(ylidene)-2,3-dihydrobenzo[*b*][1,4]dioxines [9f] (Scheme 1).



Scheme 1. Different approaches for the synthesis of 2-ylidene-2,3-dihydrobenzo[*b*][1,4]dioxines.

Cu(I)-catalyzed cross-couplings between bisfunctionalized substrates have proven extremely valuable for the synthesis of a plethora of heterocyclic as well as carbocyclic systems [10]. We could successfully demonstrate that Cu(I)-catalyzed reactions of aromatic biselectrophiles such as 1,2-dihalobenzenes and *ortho*-halobenzyl halides with bisnucleophiles allow access to several carbo- and heterocyclic skeletons [11]. However, Cu(I)-catalyzed cross-couplings are not restricted to reactions with aryl halides but can also be performed with vinyl halides as electrophilic substrates [12]. As an example, we reported the Cu(I)-catalyzed reaction between 1,2-dihalo-2-propenes and 1,3-dicarbonyls which produces trisubstituted furans in a highly selective and efficient way [13]. Against this background, it was planned to develop a new approach for the efficient synthesis of 2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxines **3** based on a Cu(I)-catalyzed intermolecular *C*-allylation/*O*-vinylation process using 1,2-dihalo-2-propenes **1** and catechols **2** as substrates. Herein, we disclose our results on the diastereospecific synthesis of (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3** by reaction of (*Z*)-1,2-dibromo-3-aryl-2-propenes (*Z*)-**1** with substituted catechols **2**.

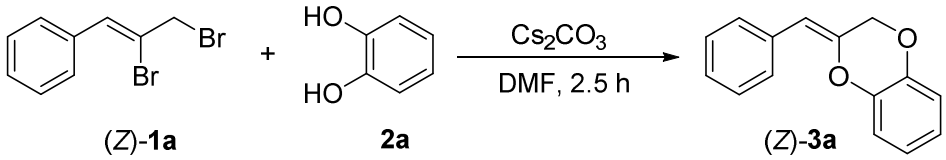
2. Results and discussion

2.1. Synthesis

As a model reaction, the transformation between (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] [14] and catechol (**2a**) was chosen. In a first attempt, (*Z*)-**1a** and **2a** were reacted under conditions that have been proven successful in a Cu(I)-catalyzed domino intermolecular *C*-allylation/*O*-vinylation reaction established in our laboratory [13]. Accordingly, 1 equiv (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] and 6 equiv of catechol (**2a**) were reacted in the presence of 10 mol% CuI under basic conditions (4 equiv of Cs_2CO_3) in DMF at 120 °C for 2.5 h (Table 1, entry 1).

Table 1

Initial experiments for the formation of benzodioxine (*Z*)-**3a** under different conditions.[a]



(*Z*)-**1a** **2a** (*Z*)-**3a**

Entry	**2a** (equiv)	Catalyst	Cs_2CO_3 (equiv)	T (°C)	Yield (*Z*)-**3a** (%)
1	6	CuI (10 mol%)[b]	4[c]	120	50
2	6	–	4[c]	120	67
3	6	–	4[c]	100	29
4	6	–	4[c]	75	7
5	6	–	4[c]	50	–
6	6	–	2[c]	120	67
7	6	–	2[d]	120	36

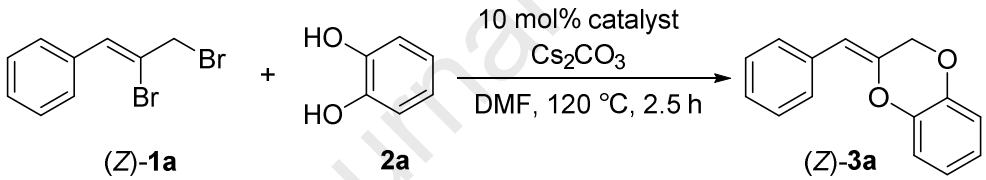
[a] All reactions were performed with 1 mmol (*Z*)-**1a** in 10 mL DMF under argon.

[a] The purity of CuI was > 98%.
[c] The purity of Cs_2CO_3 was 99%.
[d] The purity of Cs_2CO_3 was 99.99%.

To our delight, (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a**] was formed exclusively in 50% yield under these conditions. Encouraged by this finding the model reaction was optimized. To verify the role of the CuI as a catalyst, the reaction was run in the absence of Cu(I) salt. Surprisingly, (*Z*)-**3a** was also formed as the sole product and with an even better yield (67%) (Table 1, entry 2). Next, the impact of the temperature on the yield of (*Z*)-**3a** was studied. For this purpose, the copper-free reaction was run at 100 °C, 75 °C and 50 °C (Table 1, entries 3–5). It could be established that the yields of (*Z*)-**3a** decrease dramatically with decreasing temperatures: at 50 °C, the formation of (*Z*)-**3a** could not be observed. The experiment given in Table 1, entry 6 clearly demonstrated that the excess of Cs_2CO_3 could be reduced from 4 equiv to 2 equiv without affecting the yield. To identify possible effects of transition metal impurities in the Cs_2CO_3 (99% purity) used, the transformation was repeated with Cs_2CO_3 of 99.99% purity (Table 1, entry 7). Since the yield of (*Z*)-**3a** dropped to 36%, it was decided to run the model reaction in the presence of 10 mol% of several transition metal reagents using 2 equiv of Cs_2CO_3 of 99.99% purity as a base. The results are given in Table 2.

Table 2

The influence of different transition metal catalysts on the yield of (*Z*)-**3a**.[a]



(*Z*)-**1a** **2a** (*Z*)-**3a**

Entry	Catalyst	Yield (*Z*)-**3a** (%)
1	CuI	35
2	CuBr	36
3	$Cu(acac)_2$	53
4	$Cu(OAc)_2$	37
5	$CrCl_3 \times 6\ H_2O$	35
6	$Cr(NO_3)_3 \times 9\ H_2O$	25
7	Cr_2O_3	49
8	$CoCl_2 \times 6\ H_2O$	35
9	$CoCl_3 \times 6\ H_2O$	29
10	$Co(acac)_2$	traces
11	Fe	39
12	$FeCl_2 \times 4\ H_2O$	31
13	$FeCl_3 \times 6\ H_2O$	4
14	$Fe(C_2O_4) \times 2\ H_2O$	9
15	$FeSO_4 \times 7\ H_2O$	30
16	$NiCl_2$	30

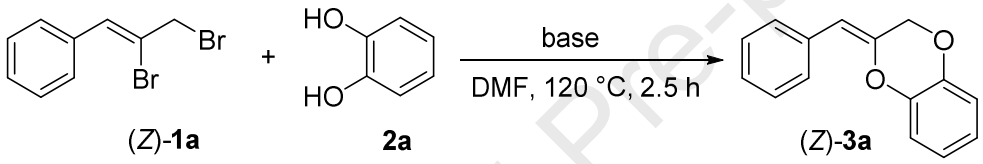
17	$Pd(OAc)_2$	41
18	$Pd(PPh_3)_4$	38

[a] All reactions were performed with 1 mmol (*Z*)-**1a**, 6 mmol **2a** and 2 mmol Cs_2CO_3 (99.99%) in 10 mL DMF under argon.

In a first set, the reaction was run in the presence of some other Cu(I) and Cu(II) reagents (Table 2, entries 1–4). Interestingly, the best yield was obtained when the reaction was done in the presence of 10 mol% $Cu(acac)_2$. With this Cu(II) reagent, (*Z*)-**3a** was isolated in 53% (Table 2, entry 3). Apart from Cu-based reagents, the model reaction was also performed with a number of Cr(III) reagents (Table 2, entries 5–7), Co(II) and Co(III) reagents (Table 2, entries 8–10) as well as with elemental iron, Fe(II) and Fe(III) reagents (Table 2, entries 11–15). In addition, $NiCl_2$ (Table 2, entry 16), $Pd(OAc)_2$ and $Pd(PPh_3)_4$ (Table 2, entries 17, 18) were tried as catalysts. However, under no circumstances the yield of the model reaction under transition metal-free conditions could be improved by running the reaction in the presence of 10 mol% of a transition metal catalyst.

Table 3

Impact of different bases on the outcome of the model reaction under catalyst-free conditions.[a]



(*Z*)-**1a** **2a** (*Z*)-**3a**

Entry	Base	Yield (*Z*)-**3a** (%)
1	Cs_2CO_3	67[b]
2	K_2CO_3	39[c]
3	Na_2CO_3	12[d]
4	K_3PO_4	traces[e]
5	KOH	—[f]

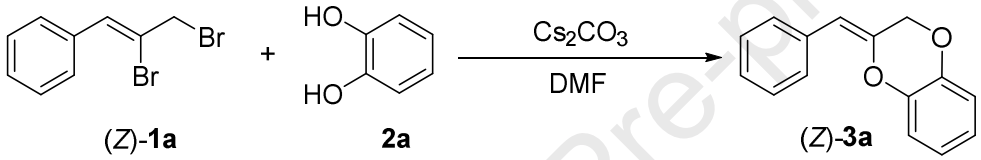
[a] All reactions were performed with 1 mmol (*Z*)-**1a**, 2 mmol base and 6 mmol **2a** in 10 mL DMF under argon.
[b] The purity of Cs_2CO_3 was 99%.
[c] The purity of K_2CO_3 was 99%.
[d] The purity of Na_2CO_3 was 99.5%.
[e] The purity of K_3PO_4 was 99.5%.
[f] The purity of KOH was 85%.

In a next step, the influence of different bases, such as K_2CO_3, Na_2CO_3, K_3PO_4 and KOH, on the outcome of the model reaction under metal-free conditions was figured out (Table 3). It was established that Cs_2CO_3 is by far the best base to facilitate this reaction (Table 3, entry 1; see also Table 1, entry 2). Finally, the influence of the molar ratio between (*Z*)-**1a** and **2a**, the amount of Cs_2CO_3 and the reaction conditions like reaction time and temperature on the yield of the model reaction was addressed. First, 1 equiv of (*Z*)-**1a** was reacted with 2 equiv of **2a** and 2 equiv Cs_2CO_3 at different reaction times and reaction temperatures. When the reaction

was run at 120 °C for 2.5 h, (*Z*)-**3a** was obtained in 59% (Table 4, entry 1). A gradual increase of reaction time and reaction temperature resulted in an improvement of the yield (Table 4, entries 1–4). The highest yield (77%) was obtained when the transformation was done at 140 °C for 18 h (Table 4, entry 4). The same yield was achieved when the amounts of **2a** and Cs_2CO_3 were doubled (Table 4, entry 5). Next, we performed some reactions between 1 equiv (*Z*)-**1a**, 3 equiv **2a** and 2 equiv of the base at different reaction temperatures and reaction times. It was established that the yields of (*Z*)-**3a** dramatically decreased with decreasing temperatures and increasing reaction time (Table 4, entries 6–10). In a final attempt, the model reaction was run with 2 equiv **2a** and 4 equiv Cs_2CO_3 at 140 °C for 18 h. Under these conditions, (*Z*)-**3a** was isolated in 89% as a single product in diastereomerically pure form. (Table 4, entry 11).

Table 4

Influence of the molar ratio between (*Z*)-**1a** and **2a**, the amount of Cs_2CO_3 and the reaction conditions on the model reaction.[a]



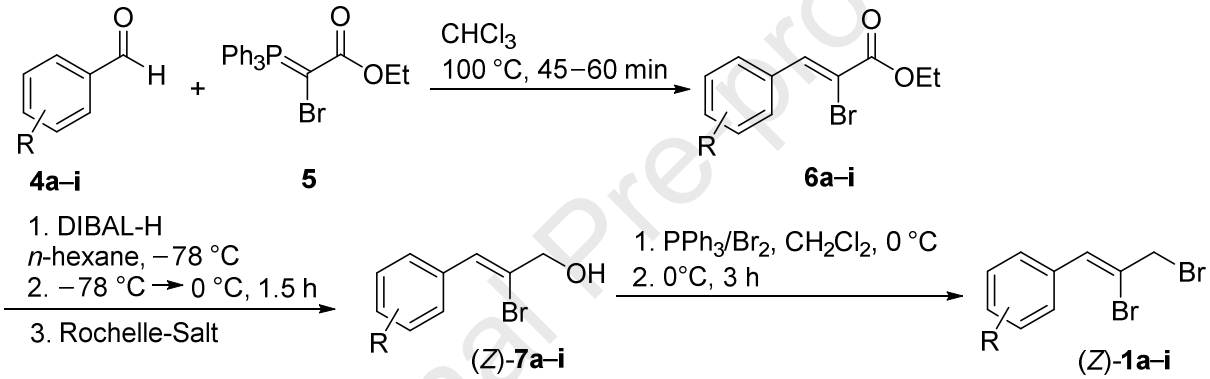
(*Z*)-**1a** **2a** (*Z*)-**3a**

Entry	**2a** (equiv)	Cs_2CO_3 (equiv)	Time (h)	T (°C)	Yield (*Z*)-**3a** (%)
1	2	2	2.5	120	59
2	2	2	2.5	140	65
3	2	2	6	140	74
4	2	2	18	140	77
5	4	4	18	140	77
6	3	2	2.5	140	66
7	3	2	2.5	120	62
8	3	2	4	100	71
9	3	2	6	90	43
10	3	2	7	70	21
11	2	4	18	140	89

[a] All reactions were performed with 1 mmol (*Z*)-**1a** in 10 mL DMF under argon. The purity of Cs_2CO_3 was 99%.

Encouraged by this result, we embarked on studying scope and limitations of the new method for the diastereospecific synthesis of (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3**. For this purpose, a number of different (*Z*)-1,2-dibromo-3-aryl-2-propenes (*Z*)-**1** were reacted with catechols **2**. While the catechols **2a–d** were commercially available, the (*Z*)-1,2-dibromo-3-aryl-2-propenes (*Z*)-**1a–i** had to be synthesized. The preparation of the dibromo compounds (*Z*)-**1a–i** was achieved by a three-step sequence starting from the commercially available, corresponding aldehydes **4a–i** (Scheme 2). Reaction of the aldehydes **4a–i** with the phosphorane **5** [15a,b] according to Thiemann *et al.* [15c] delivered the corresponding Wittig

products **6a–i** with yields between 75 and 96%. The Wittig reaction produced predominantly the α-bromoarylacrylates with (*Z*)-configuration (*Z*:*E* ≥ 4:1). The (*Z*)- and (*E*)-diastereomers can easily be distinguished by ^{1}H NMR spectroscopy. For the (*Z*)-compounds, 3-H resonates at chemical shifts δ >8 ppm, while for the (*E*)-compounds the resonance signal for 3-H is found at chemical shifts δ <8 ppm [15c]. The diastereomers also differ with respect to the values of their $^{3}J_{C=O,\ 3\text{-}H}$ coupling constants which could be determined by HSQMBC experiments. For the (*Z*)-compounds the coupling constants range between 3 and 5 Hz and for the (*E*)-isomers the coupling constants are between 7 and 13 Hz [16]. Then, the diastereomeric mixtures of the α-bromoarylacrylates **6a–i** were subjected to reduction to the corresponding 3-substituted 2-bromopropen-1-ols **7a–i** using DIBAL-H as reductant [15d]. At this stage, minor amounts of the *E*-isomers of **7a–i** were removed by repeated column chromatography on SiO_2. Finally, the diastereomerically pure (*Z*)-alcohols (*Z*)-**7a–i** were converted into the (*Z*)-1,2-dibromo-3-aryl-2-propenes (*Z*)-**1a–i** with yields up to 91% by using PPh_3/Br_2 as reagents [14].



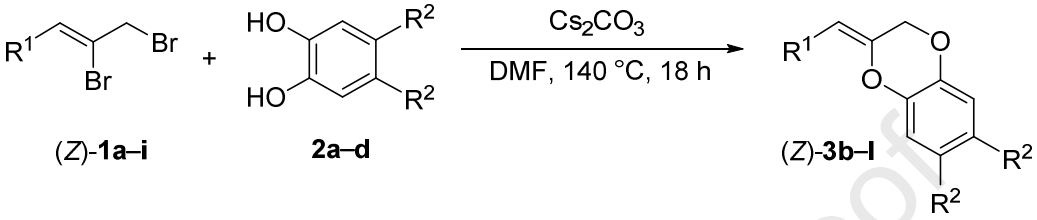
Scheme 2. Synthesis of the substituted 1,2-dibromo-3-aryl-2-propenes (*Z*)-**1a–i**.

With the substrates in hand, (*Z*)-**1b–i** were reacted with catechols **2** under optimized conditions. The reaction of the *p*-alkylaryl substituted (*Z*)-1,2-dibromo-2-propenes (*Z*)-**1b–d** with catechol (**2a**) delivered the corresponding (*Z*)-2-(4-alkylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3b–d** in diastereomerically pure form. Best yields were obtained with (*Z*)-1,2-dibromo-3*p*-tolyl-2-propene [(*Z*)-**1b**] (88%) (Table 5, entry 1), followed by (*Z*)-1,2-dibromo-3-(4-ethylphenyl)-2-propene [(*Z*)-**1c**] (77%) (Table 5, entry 2) and (*Z*)-1,2-dibromo-3-(4-isopropylphenyl)-2-propene [(*Z*)-**1d**] (68%) (Table 5, entry 3) as substrates. It seems that the size of the *p*-alkyl substituent has an influence on the yield. Next, the 3-(4-haloaryl)-substituted 1,2-dibromo-2-propenes (*Z*)-**1e–g** were reacted to deliver the (*Z*)-2-(4-halobenzylidene)-2,3-dihydrobenzo[*b*][1,4]benzodioxines (*Z*)-**3e–g** with yields between 53 and 63% (Table 5, entries 4–6). When the 3-(*m*-bromophenyl)-substituted compound (*Z*)-**1h** was employed as substrate, the product (*Z*)-**3h** was isolated in comparable yield (55%) than (*Z*)-**3g** (Table 5, entries 6 and 7). The 3-(*m*-methoxyphenyl)-substituted derivate (*Z*)-**1i** delivered the corresponding product (*Z*)-**3i** in 65% yield (Table 5, entry 8). Finally, (*Z*)-**1a** was reacted successfully with 3,4-dichlorocatechol (**2b**), 3,4-dibromocatechol (**2c**) and 2,3-dihydroxynaphthalene (**2d**) to provide the 6,7-dihalo-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3j,k** and the 2,3-dihydronaptho[2,3-*b*][1,4]dioxine [(*Z*)-**3l**]. It was demonstrated that a range of (*Z*)-1,2-dibromo-3-aryl-substituted-2-propenes (*Z*)-**1a–i** could be reacted with catechol (**2a**) and some catechol derivatives (**2b–d**) under basic, transition metal-free conditions to give the

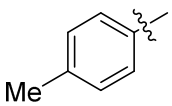
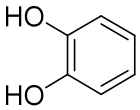
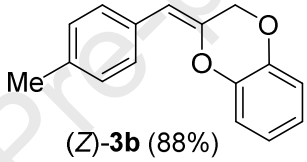
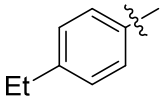
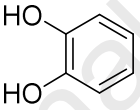
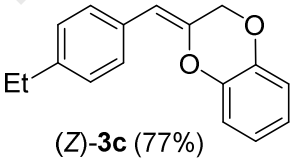
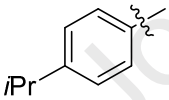
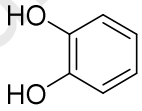
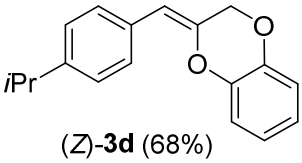
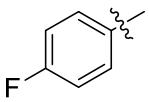
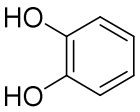
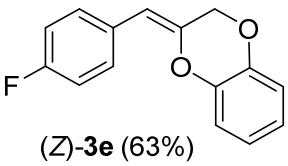
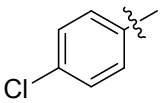
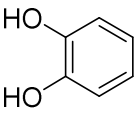
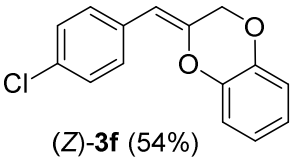
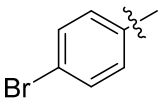
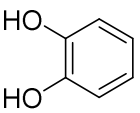
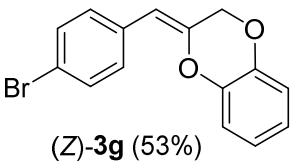
pure (*Z*)-2-(arylidene)-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3a–l** with yields in the range between 49 and 89%. When (*Z*)-**1a** was treated with 1,2-ethanediol as bisnucleophile under standard conditions, no transformation could be observed.

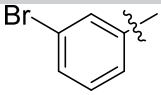
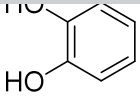
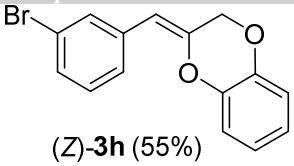
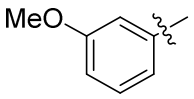
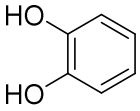
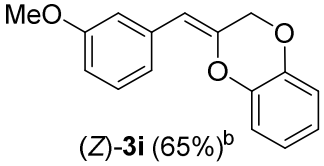
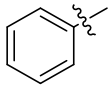
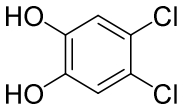
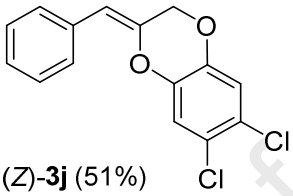
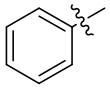
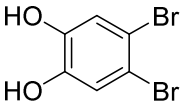
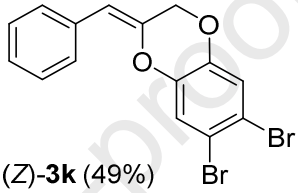
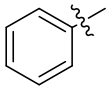
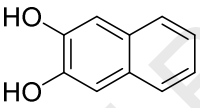
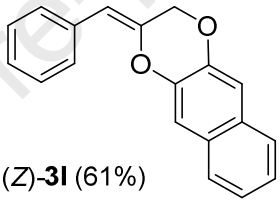
Table 5

Substrate scope of the reaction of (*Z*)-**1a–i** with **2a–d** to the corresponding (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3b–l** under optimized, transition metal-free conditions.[a]



(*Z*)-**1a–i** **2a–d** (*Z*)-**3b–l**

Entry	R^1	**2**	Yield (*Z*)-**3** (%)
1	 (*Z*)-**1b**	 **2a**	 (*Z*)-**3b** (88%)
2	 (*Z*)-**1c**	 **2a**	 (*Z*)-**3c** (77%)
3	 (*Z*)-**1d**	 **2a**	 (*Z*)-**3d** (68%)
4	 (*Z*)-**1e**	 **2a**	 (*Z*)-**3e** (63%)
5	 (*Z*)-**1f**	 **2a**	 (*Z*)-**3f** (54%)
6	 (*Z*)-**1g**	 **2a**	 (*Z*)-**3g** (53%)

7		(*Z*)-**1h**		**2a**		(*Z*)-**3h** (55%)
8		(*Z*)-**1i**		**2a**		(*Z*)-**3i** (65%)[b]
9		(*Z*)-**1a**		**2b**		(*Z*)-**3j** (51%)
10		(*Z*)-**1a**		**2c**		(*Z*)-**3k** (49%)
11		(*Z*)-**1a**		**2d**		(*Z*)-**3l** (61%)

[a] All reactions were performed with 1 mmol (*Z*)-**1**, 2 mmol **2** and 4 mmol Cs_2CO_3 (99%) in 10 ml DMF under argon.

[b] Reaction was performed with 0.89 mmol (*Z*)-**1i**, 1.78 mmol **2a** and 3.56 mmol Cs_2CO_3 (99%) in 10 ml DMF under argon.

2.2. Structure elucidation

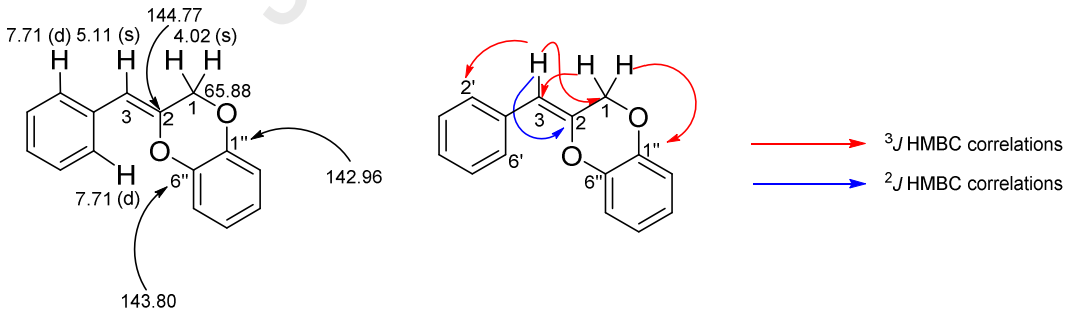


Fig. 2. Some important ^{1}H- and ^{13}C NMR chemical shifts [ppm], ^{2}J- and ^{3}J HMBC correlations from 1-H_2 and 3-H of (*Z*)-**3a**.

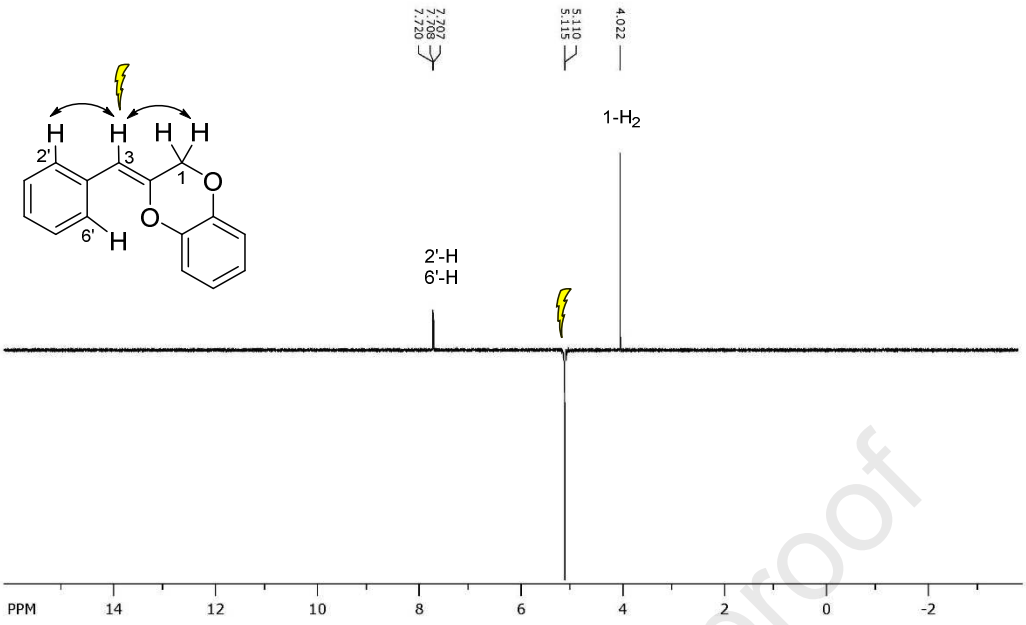


Fig. 3. [1]D-NOESY spectrum obtained by selective excitation of the signal at δ = 5.51 ppm of (*Z*)-**3a**.

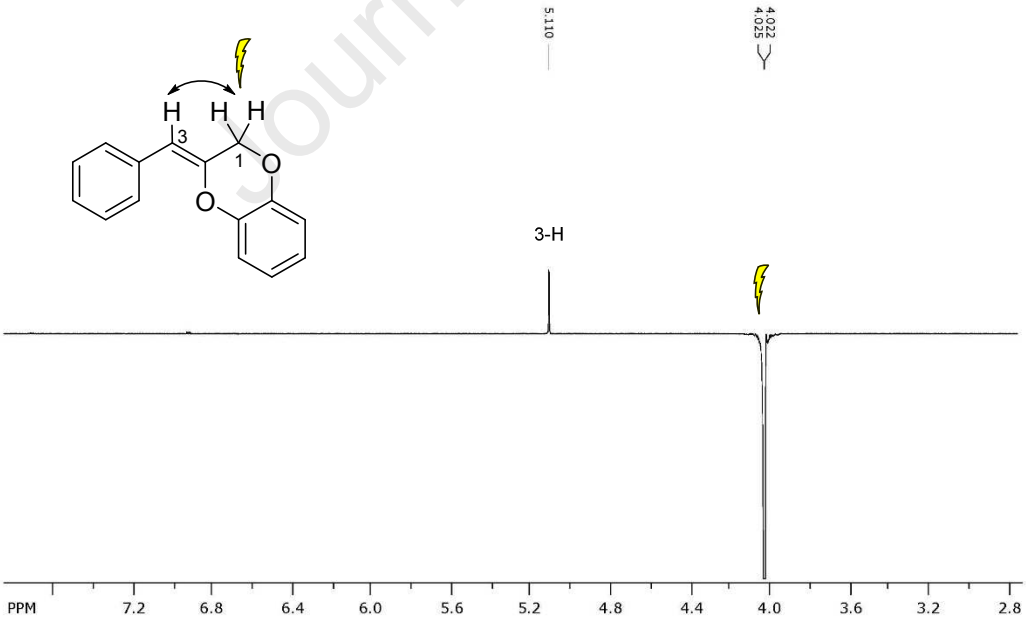


Fig. 4. [1]D-NOESY spectrum obtained by selective excitation of the signal at δ = 4.02 ppm of (*Z*)-**3a**.

All substrates (*Z*)-**1** and all (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3** were characterized by IR-, ^{1}H- and ^{13}C NMR spectroscopy as well as mass spectrometry. The structure elucidation of (*Z*)-**3a–l** is mainly based on NMR experiments, including COSY-, HMBC-, HSQC-, HSQMBC- and ^{1}D NOESY experiments. As an example, signals at δ = 65.88, 144.77, 142.96 and 143.80 ppm in the ^{13}C NMR spectrum of (*Z*)-**3a**, which are assigned unambiguously to C-1, C-2, C-1'' and C-6'', respectively, are in accordance with a 2,3-dihydrobenzo[*b*][1,4]dioxine structure with an exocyclic double bond at C-2 (Fig. 2). This is supported by the chemical shifts for the allylic protons attached to C-1 and the vinylic proton at C-3, which resonate as singlets at δ = 4.02 ppm and at δ = 5.11 ppm, respectively. In case of a 2-benzylbenzo[*b*][1,4]dioxine with an endocyclic double bond and a benzyl substituent the protons would be expected to resonate around $\delta \approx$ 5.6 ppm (vinylic proton) and $\delta \approx$ 3.2 ppm (benzylic protons) [8f]. Unambiguous evidence for the (*Z*)-configuration of the exocyclic double bond was provided by ^{1}D NOESY experiments (Figs. 3 and 4). Selective excitation of the proton attached to C-3 at δ = 5.11 ppm results in an intensity increase of the signals at δ = 4.02 ppm (1-H_2) and δ = 7.71 ppm (2'-H, 6'-H). As expected, excitation of the two protons attached to C-1 at δ = 4.02 ppm resulted in a strong enhancement of the signal intensity at δ = 5.11 ppm (3-H). In case of an (*E*)-configuration no NOE effect between the protons attached to C-1 and the proton at C-3 would be expected. Strong evidence for the (*Z*)-geometry of the exocyclic double bonds came also from the size of the coupling constants $^{3}J_{\text{C-1, 3-H}}$. For double bonds with (*Z*)-configuration the values of this coupling constant are smaller than 5 Hz while for the corresponding (*E*)-isomer the values exceed 7 Hz [17]. In all (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3a–l**, the size of the coupling constants $^{3}J_{\text{C-1, 3-H}}$ was in the range between 3.5 and 4.5 Hz, which clearly proves the (*Z*)-geometry of all products.

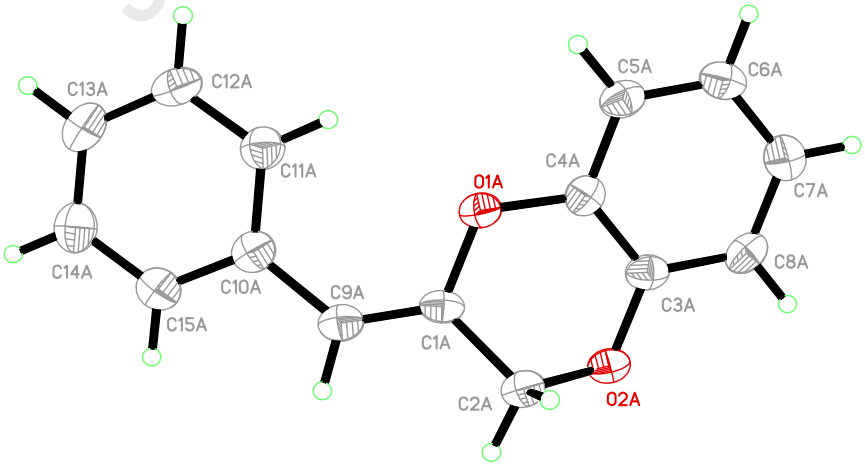
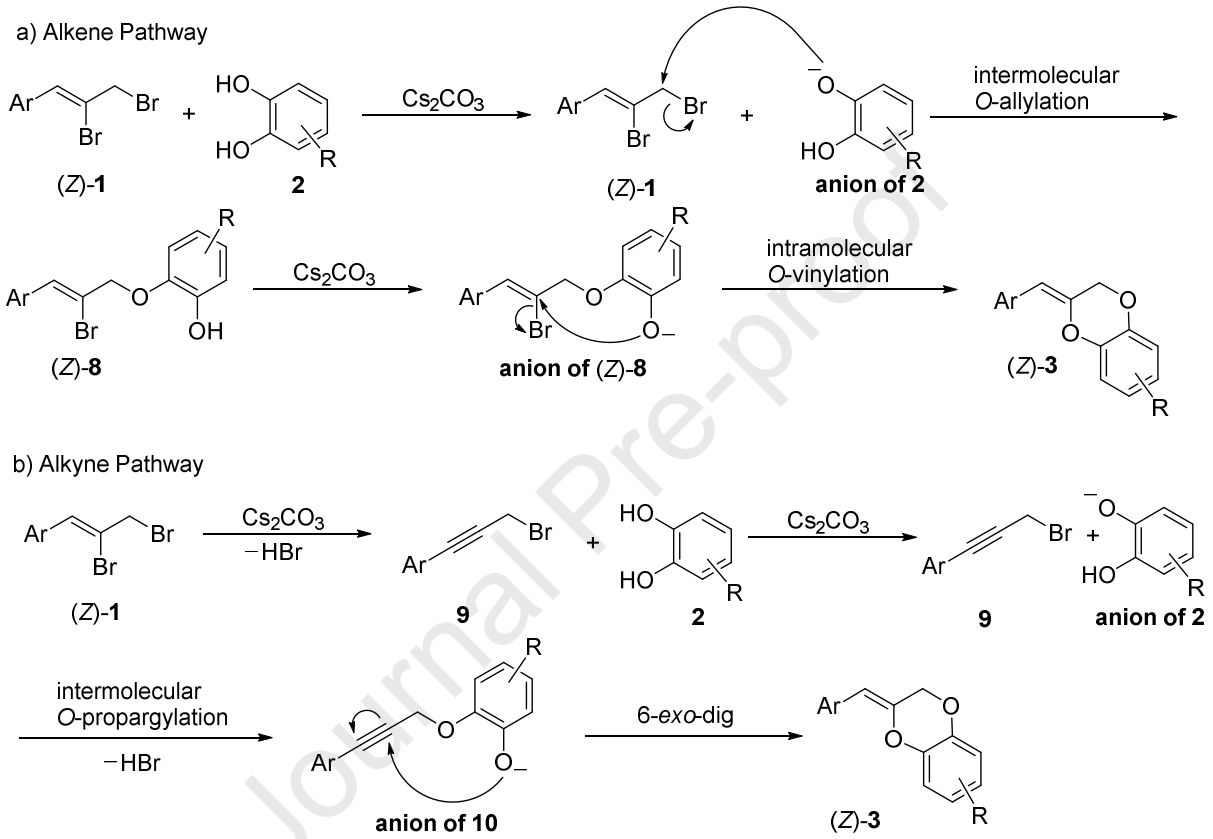


Fig. 5. Structure of (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a**], as derived from X-ray crystal structure analysis.

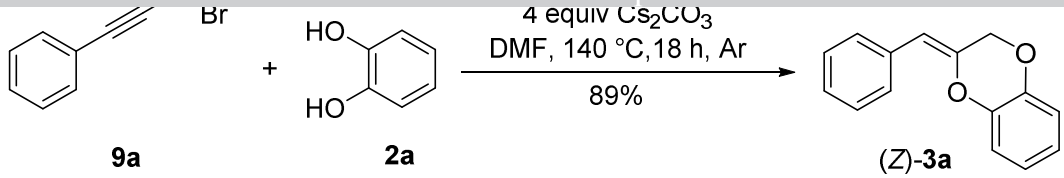
Unequivocal evidence for the structure of (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a**] came from single crystal X-ray diffraction (Fig. 5). The title compound crystallizes with two independent molecules in the asymmetric unit of the acentric space group $P2_1$. Both conformers show a *Z*-isomer. The C1-C9 double bond could be clearly identified in both molecules characterized by distances of 1.325(4) Å and 1.324(4) Å, respectively.

2.3. Reaction mechanism



Scheme 3. Two possible reaction mechanisms: a) the alkene pathway and b) the alkyne pathway.

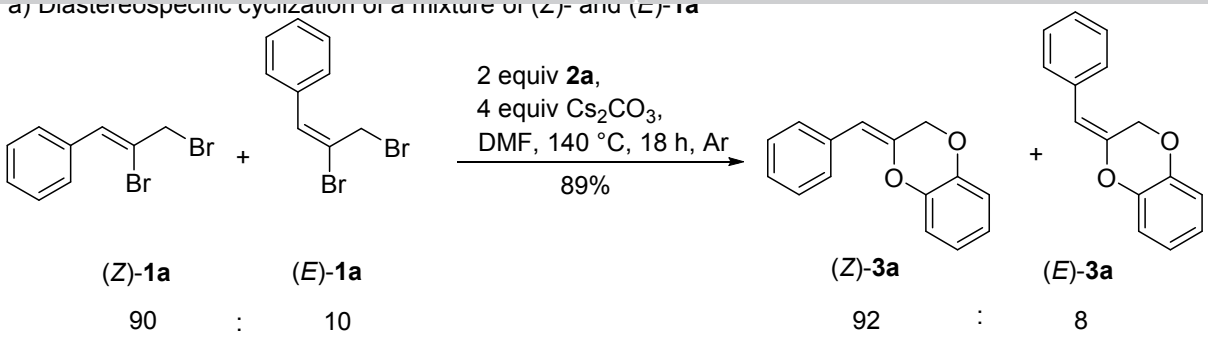
With regard to the reaction mechanism it is assumed, that the reaction sequence starts with an intermolecular *O*-allylation between a 3-aryl-substituted 1,2-dibromo-2-propene (*Z*)-**1** and a catechol **2** to deliver the corresponding allyl aryl ether (*Z*)-**8** (Scheme 3a). After a second deprotonation an intramolecular *O*-vinylation takes place, which results in the highly diastereospecific formation of the cyclization product, a (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxine (*Z*)-**3**. This requires, that the cyclization proceeds with retention of the configuration of the double bond in (*Z*)-**1**. It is also conceivable that under basic reaction conditions the reaction sequence starts with elimination of HBr from (*Z*)-**1** to form the aryl propargyl bromide **9** as an intermediate (Scheme 3b). This is followed by an intermolecular *O*-propargylation between **9** and a deprotonated catechol **2**. After subsequent deprotonation, the resulting anionic aryl propargyl ether **anion of 10** undergoes an intramolecular 6-*exo*-dig cyclization which delivers the (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxine **3** with (*Z*)-configuration around the exocyclic double bond [18].



Scheme 4. Preparation of (*Z*)-**3a** by reaction of (3-bromoprop-1-yn-1-yl)benzene (**9a**) with catechol (**2a**) under optimized conditions.

The reaction mechanism via the alkyne **9** (Scheme 3b) cannot be excluded a priori, which was demonstrated by the outcome of the reaction between phenyl propargyl bromide (**9a**) and catechol (**2a**). When the transformation was run under the conditions optimized for the reaction between (*Z*)-**1a** and **2a**, the cyclization product (*Z*)-**3a** was isolated as pure (*Z*)-diastereomer in 89% yield (Scheme 4). It needs to be highlighted that this experiment clearly proves that the cyclization of 2-[(3-arylprop-2-yn-1-yl)oxy]phenols can easily be achieved under transition metal-free conditions (for transition metal-catalyzed cyclizations, see Scheme 1). To decide, whether the reaction proceeds via the alkene pathway (Scheme 3a) or the alkyne pathway (Scheme 3b) a number of experiments were performed.

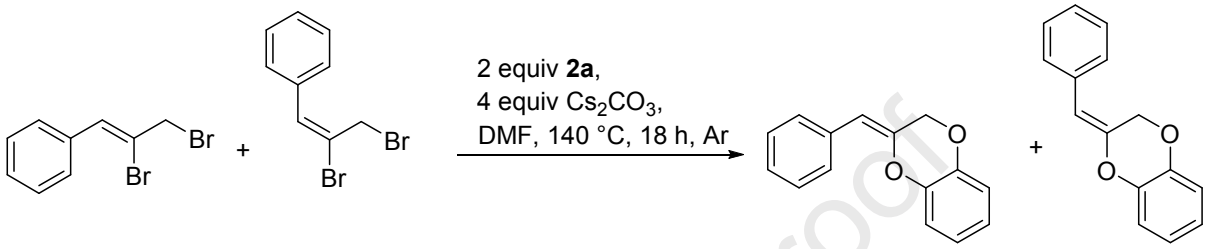
a) Diastereospecific cyclization of a mixture of (*Z*)- and (*E*)-**1a**



(*Z*)-**1a** (*E*)-**1a** (*Z*)-**3a** (*E*)-**3a**

90 : 10 92 : 8

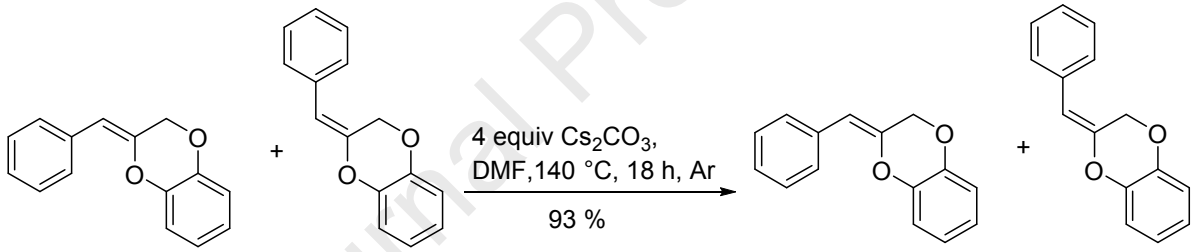
b) Diastereospecific cyclization of pure (*E*)-**1a**



(*Z*)-**1a** (*E*)-**1a** (*Z*)-**3a** (*E*)-**3a**

1 : 99 0 : 100

c) Isomerization experiment of pure (*Z*)-**3a** and a mixture of (*Z*)- and (*E*)-**3a**



(*Z*)-**3a** (*E*)-**3a** (*Z*)-**3a** (*E*)-**3a**

100 : 0 100 : 0

92 : 8 92 : 8

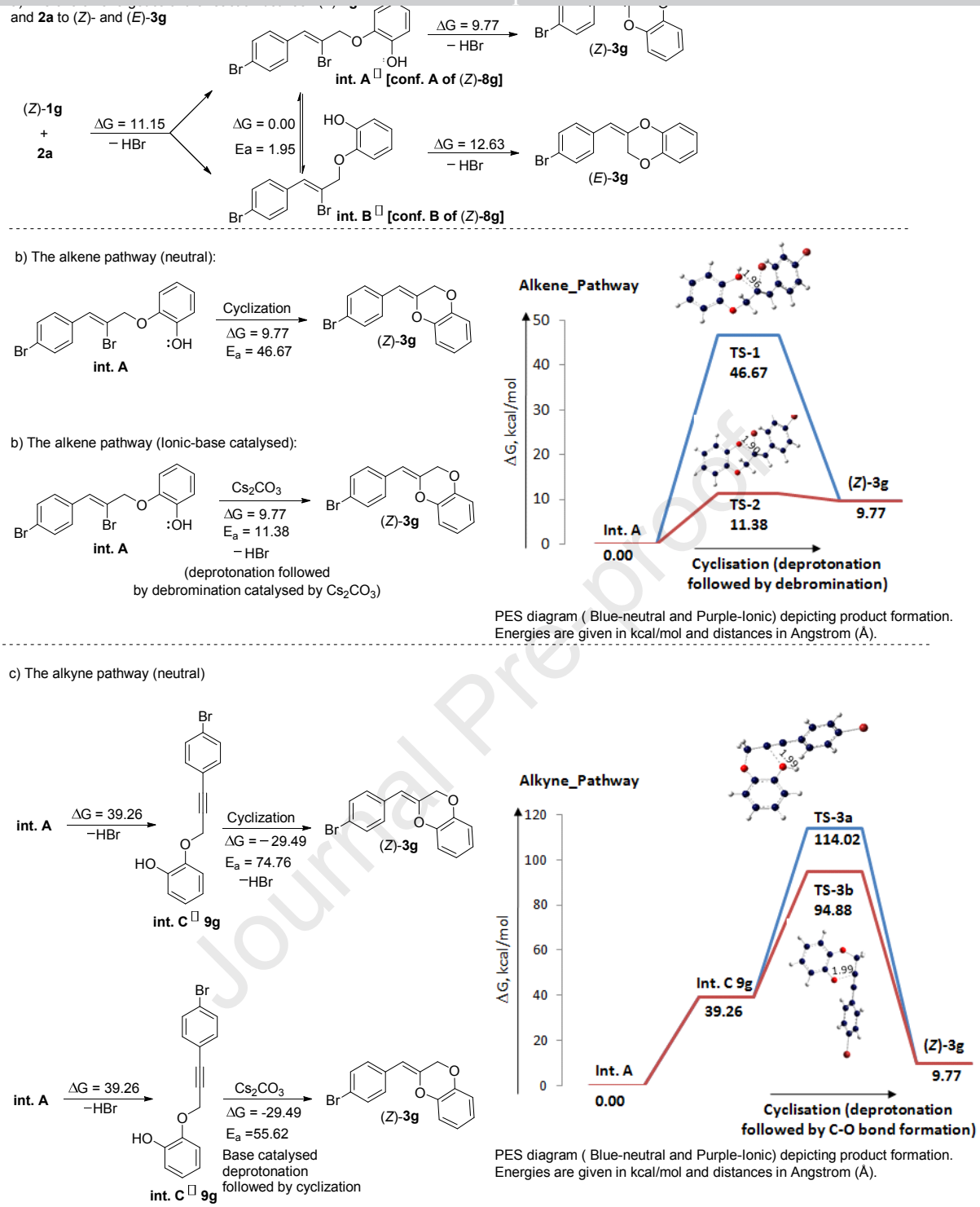
Scheme 5. a) Diastereospecific cyclization of a mixture of (*Z*)- and (*E*)-**1a**; b) diastereospecific cyclization of pure (*E*)-**1a**; c) isomerization experiment of pure (*Z*)-**3a** and a mixture of (*Z*)- and (*E*)-**3a**.

First, a 9:1 mixture of (*Z*)- and (*E*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a** and (*E*)-**1a**] [19] was reacted under standard conditions (Scheme 5a). This experiment delivered 89% of a 92:8 mixture of (*Z*)- and (*E*)- 2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a** and (*E*)-**3a**]. This outcome supports that the cyclization of the substrates with (*Z*)-configuration proceeds diastereospecifically via the alkene pathway (Scheme 3a) with retention of the configuration of the double bond. Obviously, this result offers also the opportunity to synthesize diastereoselective pure (*E*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*E*)-**3** by employing the corresponding substrates **1** with (*E*)-configuration. To prove this hypothesis, it was decided to synthesize diastereomerically pure (*E*)-**1a** and to react it under standard conditions. For this purpose, pure (*Z*)-**1a** was subjected to an iodine-catalyzed double bond isomerization

as described in the literature [20]. After chromatography, the (*E*)-isomer of **1a** was obtained in diastereomerically pure form (*Z*:*E* = 1:99). The structure was proven by NMR spectroscopy [21]. Then, (*E*)-**1a** was reacted with **2a** using our optimized protocol. It was found that the reaction of diastereomerically pure (*E*)-**1a** delivers diastereomerically pure **3a** exclusively. The structure of **3a** has unequivocally been determined by NMR spectroscopy. Due to the deshielding effect of one of the ring oxygens in the benzodioxine the vinylic proton of (*E*)-**3a** is expected to resonate at lower field (δ = 6.42 ppm) than the vinylic proton of (*Z*)-**3a** (δ = 5.11 ppm). This is in full accordance with the literature [9a]. To exclude a subsequent isomerization of the products with (*Z*)- and (*E*)-configuration, pure (*Z*)-**3a** as well as a 92:8 mixture of (*Z*)-**3a** and (*E*)-**3a** were subjected to reaction conditions (Scheme 5c). Under these conditions no isomerization occurred. It can be concluded that the reaction between (*Z*)-**1a** and **2** proceeds diastereospecifically via the alkene pathway as depicted in Scheme 3a.

2.4. DFT-calculations

Further studies concerning the exclusive formation of products **3** with (*Z*)-configuration included quantum chemical calculations which were carried out at the B3LYP/6-31+G(d) level of theory. The reaction between (*Z*)-**1g** and **2a** was taken as an example. The calculations reveal that the overall product formation is endergonic in nature by 21.37 kcal/mol (11.15 + 9.77) (Scheme 6a) for (*Z*)-**3g** and 23.78 kcal/mol (11.15 + 12.63) for (*E*)-**3g**. The endergonic character supports the necessity of harsh reaction conditions for the product formation on a relative scale. The (*Z*)-isomer **3g** is more stable by 2.41 kcal/mol, and hence, the (*E*)-isomer **3g** is expected to be formed in minor amounts.



Scheme 6. a) The overall energetics of the reaction between (*Z*)-**1g** and **2a** to form (*Z*)- and (*E*)-**3g**; b) the alkene pathway; c) the alkyne pathway. All energies are given in kcal/mol and distances in Å. Corresponding pathways involving intermediate B (**int. B**) are depicted in ESI (Scheme S1). The potential energy diagram is included.

It is assumed that the reaction starts with the loss of HBr in the presence of a base like K_2CO_3, leading to (*Z*)-**8g**. This step is endergonic by 11.15 kcal/mol. (*Z*)-**8g** can adopt two conformational states: **int. A** and **int. B**. There is no energy difference between these two states, one conformer produces the *Z*-isomer of **3g** and the other results in the *E*-isomer of **3g**. The rotational barrier between the two conformers amounts to 1.95 kcal/mol which is less

than 3 kcal/mol. Since the quantum chemical calculations revealed that the energy difference between the two isomers of the key intermediate is zero, it was concluded that the product formation is largely governed by steric factors. To understand the mechanism of the cyclization step, two pathways have been considered: the alkene and the alkyne pathways. Along the alkene pathway (Scheme 6b), **int. A** can undergo an intramolecular cyclization by nucleophilic addition. The cyclization may start either from the neutral or the anionic form of **int. A**. Starting from **int. A** in the neutral form the E_a for the cyclization, which proceeds via **TS-1**, has been found to be 46.67 kcal/mol. On the other hand, the E_a for the anionic pathway starting from the anion of **int. A** and proceeding via **TS-2** amounts to 11.38 kcal/mol. Remarkably, the activation barrier for the anionic path is considerably lower than that for the pathway starting with the neutral **int. A**. The activation barrier values suggest that the cyclization process can be considered as a base-catalyzed cyclization. In the alkyne pathway (Scheme 6c), **int. A** initially undergoes a base-catalyzed abstraction of HBr to form the alkyne **int. C**. The formation of **int. C** is endergonic by 39.26 kcal/mol. Like in the alkene pathway, the cyclization can also start either from the neutral **int. C** or the anion of **int. C**. In case of the neutral **int. C**, the cyclization proceeds via **TS-3a** with an activation barrier of 74.76 kcal/mol. Starting from the anionic form of **int. C**, the activation barrier amounts to 55.62 kcal/mol via **TS-3b**. As a result, the alkyne pathway is also accompanied with a reduction of the activation barrier in the presence of a base. Thus, in the cyclization starting from **int. A** (alkene pathway) as well as the cyclization starting from **int. C** (alkyne pathway) the base could function as a catalytic agent. However, it can be concluded, that the alkene pathway is preferred over the alkyne pathway.

3. Conclusions

To summarize, a new and efficient one pot process of the synthesis of (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3** with yields up to 89% has been established. Reaction of a range of diastereomerically pure (*Z*)-1,2-dibromo-2-propenes (*Z*)-**1** with catechols **2** under transition metal-free conditions using Cs_2CO_3 as a base delivers the diastereomerically pure (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxines (*Z*)-**3**. It is assumed that the reaction starts with an intermolecular *O*-allylation, which is followed by an intramolecular *O*-vinylation. The reaction mechanism is supported by experiments as well as by DFT calculations. Our study has also revealed that the reaction of (*E*)-1,2-dibromo-2-propene (*E*)-**1a** with catechol (**2a**) delivers (*E*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*E*)-**3a**] and that the reaction between (3-bromoprop-1-yn-1-yl)benzene (**9a**) and catechol (**2a**) yields the (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4] dioxine [(*Z*)-**3a**] under transition metal-free conditions. The structures of all products were elucidated unequivocally by NMR spectroscopy.

4. Experimental section

4.1 General

All commercially available reagents were used without further purification. Catechol (**2a**) was recrystallized from toluene prior to use. DMF used in reactions was distilled prior to use and stored under argon over molecular sieves 4 Å. Other solvents used in reactions and solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperatures. Thin-layer chromatography (TLC) was performed on precoated aluminum plates (silica gel Macherey-Nagel ALUGRAM® Xtra SIL G/UV_{254}) and visualized by UV light (254 nm) and/or by immersion in an ethanolic vanillin solution followed by heating. Products were purified by flash chromatography on silica gel (MN 60, 0.04–0.063 mm; Marcherey-Nagel or by preparative thin layer chromatography (Merck PLC Silica gel 60 F□□□, 2 mm). Melting points were determined on a Büchi melting point apparatus B-545 and are uncorrected. IR spectra were measured on a Bruker Alpha FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 500 MHz on Varian Unity Inova spectrometers and at 600 MHz on a Bruker Avance III HD spectrometer using $CDCl_3$, C_6D_6 or pyridine-d_5 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.02 ($CDCl_3$), δ H/C 7.16/128.39 (C_6D_6) and δ H/C 8.74/150.35 (pyridine-d_5) relative to TMS as internal standard. COSY-, HSQC-, HMBC-, HSQMBC- and ^{1}D NOESY-spectra were recorded on Bruker Avance III HD spectrometer at 600 MHz. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet) and ovl (overlapped). Low-resolution electron impact mass spectra [MS (EI)] and high-resolution mass electron impact mass spectra [HRMS (EI)] were obtained at 70 eV using a double focusing sector field mass spectrometer Finnigan MAT 95. High resolution spectra [HRMS (APCI)] were recorded in the solvent system 0.2 % formic acid in water (solvent A) and acetonitrile + 0.2 % formic acid in water (solvent B) using Agilent 1290-APCI (Q Exactive plus, Thermo Fisher Scientific, APCI, pos) with the following gradient program: 0.00 (min), 0.30 (mL/min), A:B = 90:10; 10.00 (min), 0.30 (mL/min), A:B = 30:70; 15.00 (min), 0.30 (mL/min), A:B = 10:90; 20.00 (min), 0.30 (mL/min), A:B = 90:10; 25.00 (min), 0.30 (mL/min), A:B = 90:10. Intensities are reported as percentages relative to the base peak (I = 100%).

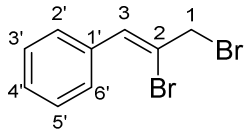
*4.2 Synthesis and characterization of starting materials [(Z)-**1a–i**]*

*General procedure I for the synthesis of starting materials (Z)-**1a–i** [14]*

A solution of bromine (1.09 equiv) in dichloromethane (1.63 mL/mmol bromine) was added dropwise to a stirred solution of a 2-bromo-2-propen-1-ol (*Z*)-**7** (1.0 equiv) and triphenylphosphine (1.10 equiv) in dichloromethane (3 mL/mmol alcohol) at 0 °C. After stirring for 3 h at 0 °C the reaction mixture was allowed to warm to room temperature and the mixture was applied to reduced pressure until a small residue of solvent was left (≈ 5 mL/20 mmol alcohol). The residue was subjected to precipitation with *n*-pentane (60 mL) and was

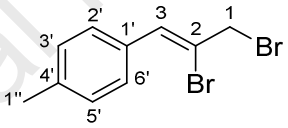
kept overnight at −25 °C. The solid triphenylphosphine oxide was filtered over silica and the filter cake was washed thoroughly with *n*-pentane (3 × 100 mL). The filtrate was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel using *n*-pentane as eluent to afford the corresponding 1,2-dibromo-3-aryl-2-propene (*Z*)-**1** in analytically pure form.

*4.2.1 (Z)-1,2-Dibromo-3-phenyl-2-propene [(Z)-**1a**] [21]*



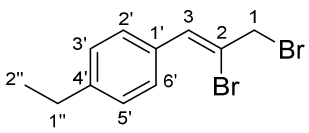
According to general procedure I, 2-bromo-3-phenyl-prop-2-en-1-ol [(*Z*)-**7a**] (2.01 g, 9.43 mmol), triphenylphosphine (2.72 g, 10.38 mmol) in dichloromethane (28 mL) and a solution of bromine (0.53 mL, 1.66 g, 10.38 mmol) in dichloromethane (17 mL) were reacted for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] was obtained as a pale yellow oil in 91% yield (2.38 g, 8.60 mmol, *Z*:*E* ≥ 95:5); R_f 0.41 (*n*-pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (s, 2H, 1-H), 7.13 (s, 1H, 3-H), 7.36–7.38 (m, 3H, arom. H), 7.66–7.64 (m, 2H, arom. H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.65 (C-1), 120.75 (C-3), 128.25 (arom. C), 128.70 (arom. C), 129.06 (arom. C), 132.20 (arom. C), 134.58 (arom. C); MS (EI, 70 eV) *m/z* (%) 275 (9) $[M]^+ \triangleq [C_9H_8Br_2]^+$, 195 (30) $[M–Br]^+ \triangleq [C_9H_8Br]^+$, 115 (100) $[M–2 \times Br]^+ \triangleq [C_9H_8]^+$.

*4.2.2 (Z)-1,2-Dibromo-3-*p*-tolyl-2-propene [(Z)-**1b**] [21]*



According to general procedure I, 2-bromo-3-(*p*-tolyl)prop-2-en-1-ol [(*Z*)-**7b**] (4.74 g, 20.00 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60 mL) and a solution of bromine (1.12 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-*p*-tolyl-2-propene [(*Z*)-**1b**] was obtained as a pale yellow oil in 30% yield (1.71 g, 5.88 mmol, *Z*:*E* ≥ 95:5); R_f 0.43 (*n*-pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3H, 1''-H), 4.44 (s, 2H, 1-H), 7.09 (s, 1H, 3-H), 7.19 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 7.5 Hz, 2H, 3'-H and 5'-H), 7.55 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 7.6 Hz, 2H, 2'-H and 6'-H);^{13}C NMR (125 MHz, $CDCl_3$) δ 21.38 (C-1''), 41.04 (C-1), 119.80 (C-2), 128.97 (C-2' and C-6'), 129.03 (C-3' and C-5'), 131.67 (C-1'), 132.20 (C-3), 138.96 (C-4'); MS (EI, 70 eV) *m/z* (%) 289 (9) $[M]^+ \triangleq [C_{10}H_{11}Br_2]^+$, 210 (31) $[M–Br]^+ \triangleq [C_{10}H_{11}Br]^+$, 130 (100) $[M–2 \times Br]^+ \triangleq [C_{10}H_{11}]^+$, 115 (49), 64 (10).

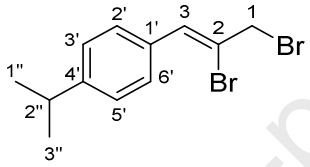
*4.2.3 (Z)-1,2-Dibromo-3-(4-ethylphenyl)-2-propene [(Z)-**1c**]*



According to general procedure I, (*Z*)-2-bromo-3-(4-ethylphenyl)prop-2-en-1-ol [(*Z*)-**7c**] (4.82 g, 20.00 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60mL) and a solution of bromine (1.12 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred

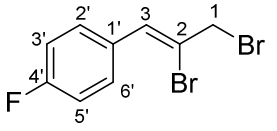
for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(4-ethylphenyl)-2-propene [(*Z*)-**1c**] was obtained as a pale yellow oil in 57% yield (3.44 g, 11.32 mmol, *Z*:*E* ≥ 95:5); R_f 0.46 (*n*-pentane); IR (ATR) *v* 2962, 2929, 2870, 1607, 1509, 1454, 1413, 1285, 1206, 1184, 1131, 1071, 1019, 899, 870, 819, 619, 533 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, ^3J(2''-H, 1''-H) = 7.5 Hz, 3H, 2''-H), 2.68 (q, ^3J(1''-H, 2''-H) = 7.5 Hz, 2H, 1''-H), 4.46 (s, 2H, 1-H), 7.12 (s, 1H, 3-H), 7.24 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.0 Hz, 2H, 3'-H and 5'-H), 7.62 (d like ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.0 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.27 (C-2''), 28.70 (C-1''), 41.08 (C-1), 119.75 (C-2), 127.75 (C-3' and C-5'), 129.11 (C-2' and C-6'), 131.86 (C-1'), 132.19 (C-3), 145.24 (C-4'); MS (EI, 70 eV) *m/z* (%) 303 (11) $[M]^+$ ≙ $[C_{11}H_{13}Br_2]^+$, 223 (41) $[M–Br]^+$ ≙ $[C_{11}H_{13}Br]^+$, 144 (100) $[M–2 \times Br]^+$ ≙ $[C_{11}H_{13}]^+$, 129 (92), 115 (38), 105 (15), 79 (29); HRMS (EI, M^+) calculated for $[C_{11}H_{12}Br_2]^+$ 303.9286 found 303.9347.

*4.2.4 (Z)-1,2-Dibromo-3-(4-isopropylphenyl)-2-propene [(Z)-**1d**]*



According to general procedure I, (*Z*)-2-bromo-3-(4-isopropylphenyl)prop-2-en-1-ol [(*Z*)-**7d**] (5.10 g, 20.00 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60 mL) and a solution of bromine (1.12 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(4-isopropylphenyl)-2-propene [(*Z*)-**1d**] was obtained as a light yellow oil in 47% yield (3.01 g, 9.45 mmol, *Z*:*E* ≥ 95:5); R_f 0.50 (*n*-pentane); IR (ATR) *v* 2958, 2867, 1607, 1508, 1458, 1414, 1278, 1206, 1052, 1017, 899, 870, 818, 620, 556, 499, 431 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.25 (d, ^3J(1''-H, 2''-H) = ^3J(3''-H, 2''-H) = 6.9 Hz, 6H, 1''-H and 3''-H), 2.91 (sep, ^3J(2''-H, 1''-H) = ^3J(2''-H, 3''-H) = 6.9 Hz, 1H, 2''-H), 4.44 (s, 2H, 1-H), 7.09 (s, 1H, 3-H), 7.23 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.2 Hz, 2H, 3'-H and 5'-H), 7.61 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.2 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.77 (C-1'' and C-3''), 33.99 (C-2''), 41.13 (C-1), 119.72 (C-2), 126.35 (C-3' and C-5'), 129.15 (C-2' and C-6'), 131.99 (C-1'), 132.18 (C-3), 149.87 (C-4'); MS (EI, 70 eV) *m/z* (%) 317 (14) $[M]^+$ ≙ $[C_{12}H_{15}Br_2]^+$, 237 (27) $[M–Br]^+$ ≙ $[C_{12}H_{15}Br]^+$, 194 (43), 157 (71) $[M–2 \times Br]^+$ ≙ $[C_{12}H_{15}]^+$, 143 (100), 128 (80), 115 (68), 91 (14) ≙ $[C_7H_7]^+$; HRMS (EI, M^+) calculated for $[C_{12}H_{14}Br_2]^+$ 317.9442 found 317.9468.

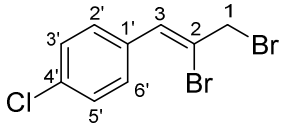
*4.2.5 (Z)-1,2-Dibromo-3-(4-fluorophenyl)-2-propene [(Z)-**1e**] [21]*



According to general procedure I, (*Z*)-2-bromo-3-(4-fluorophenyl)prop-2-en-1-ol [(*Z*)-**7e**] (1.16 g, 5 mmol), triphenylphosphine (1.58 g, 6.00 mmol) in dichloromethane (15 mL) and a solution of bromine (0.31 mL, 0.96 g, 6.00 mmol) in dichloromethane (10 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(4-fluorophenyl)-2-propene [(*Z*)-**1e**] was obtained as a light yellow oil in 77% yield (1.13 g, 3.82 mmol, *Z*:*E* ≥

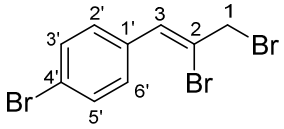
95:5); R_f 0.41 (*n*-pentane); ^{1}H NMR (600 MHz, C_6D_6) δ 3.77 (s, 2H, 1-H), 6.32 (s, 1H, 3-H), 6.70 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.0 Hz, 2H, 3'-H and 5'-H), 7.19 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.5 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 40.10 (C-1), 115.0 (d, ^2J(4'-F, C-3') = ^2J(4'-F, C-5') = 21.9 Hz, C-3' and C-5'), 120.77 (C-2), 130.62 (d, ^4J(4'-F, C-1') = 3.3 Hz, C-1'), 130.73 (C-3), 130.90 (d, ^3J(4'-F, C-2') = ^3J(4'-F, C-6') = 8.7 Hz, C-2' and C-6'), 162.64 (d, ^1J(4'-F, C-4') = 250.1 Hz, C-4'); MS (EI, 70 eV) *m/z* (%) 293(14) $[M]^+ \triangleq [C_9H_7Br_2F]^+$, 212 (47) $[M–Br]^+ \triangleq [C_9H_7BrF]^+$, 134 (100) $[M–2 \times Br]^+ \triangleq [C_9H_7F]^+$.

*4.2.6 (Z)-1,2-Dibromo-3-(4-chlorophenyl)-2-propene [(Z)-**1f**] [21]*



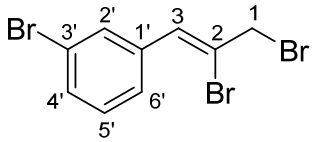
According to general procedure I, (*Z*)-2-bromo-3-(4-chlorophenyl)prop-2-en-1-ol [(*Z*)-**7f**] (4.95 g, 20 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60 mL) and a solution of bromine (0.31 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(4-chlorophenyl)-2-propene [(*Z*)-**1f**] was obtained as a light yellow oil in 61% yield (3.76 g, 12.12 mmol, *Z*:*E* ≥ 95:5); R_f 0.44 (*n*-pentane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (s, 2H, 1-H), 7.08 (s, 1H, 3-H), 7.34 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.0 Hz, 2H, 3'-H and 5'-H), 7.57 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.5 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.26 (C-1), 121.49 (C-2), 128.50 (C-3' and C-5'), 130.31 (C-2' and C-6'), 130.94 (C-3), 132.98 (C-1'), 134.59 (C-4'); MS (EI, 70 eV) *m/z* (%) 309 (12) $[M]^+ \triangleq [C_9H_7Br_2Cl]^+$, 230 (44) $[M–Br]^+ \triangleq [C_9H_7BrCl]^+$, 150 (69) $[M–2 \times Br]^+ \triangleq [C_9H_7Cl]^+$, 115 (100) $\triangleq [C_9H_7]^+$.

*4.2.7 (Z)-1,2-Dibromo-3-(4-bromophenyl)-2-propene [(Z)-**1g**]*



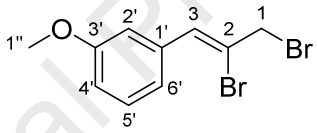
According to general procedure I, (*Z*)-2-bromo-3-(4-bromophenyl)prop-2-en-1-ol [(*Z*)-**7g**] (5.84 g, 20 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60 mL) and a solution of bromine (0.31 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(4-bromophenyl)-2-propene [(*Z*)-**1g**] was obtained as a light yellow oil in 47% yield (3.36 g, 9.46 mmol, *Z*:*E* ≥ 95:5); R_f 0.50 (*n*-pentane); IR (ATR) ν 2921, 2851, 1615, 1584, 1484, 1398, 1275, 1199, 1123, 1071, 1006, 902, 880, 809, 674, 636, 611, 557, 514, 498, 429 cm^{-1}; ^{1}H NMR (600 MHz, pyridine-d_5) δ 6.81 (s, 1H, 1-H), 7.49 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.5 Hz, 2H, 2'-H and 6'-H), 7.70 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.0 Hz, 2H, 3'-H and 5'-H), 8.82 (s, 1H, 3-H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 68.48 (C-1), 117.59 (C-2), 131.28 (C-2' and C-6'), 131.58 (C-3' and C-5'), 133.47 (C-1'), 135.63 (C-3), 136.84 (C-4'); MS (EI, 70 eV) *m/z* (%) 353 (13) $[M]^+ \triangleq [C_9H_7Br_3]^+$, 274 (34) $[M–Br]^+ \triangleq [C_9H_7Br_2]^+$, 193 (71) $[M–2 \times Br]^+ \triangleq [C_9H_7Br]^+$, 115 (100) $[M–3 \times Br]^+ \triangleq [C_9H_7]^+$, 69 (11); HRMS (APCI, 5 kV, $[M+H]^+$) calculated for $[C_9H_7Br_3]^+$ 352.8171 found 352.8170.

*4.2.8 (Z)-1,2-Dibromo-3-(3-bromophenyl)-2-propene [(Z)-**1h**]*



According to general procedure I, (*Z*)-2-bromo-3-(3-bromophenyl)prop-2-en-1-ol [(*Z*)-**7h**] (5.84 g, 20.00 mmol), triphenylphosphine (5.77 g, 22.00 mmol) in dichloromethane (60 mL) and a solution of bromine (0.31 mL, 3.52 g, 22.00 mmol) in dichloromethane (36 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(3-bromophenyl)-2-propene [(*Z*)-**1h**] was obtained as a light yellow oil in 45% yield (3.19 g, 8.98 mmol, *Z*:*E* ≥ 95:5); R_f 0.50 (*n*-pentane); IR (ATR) *ν* 2956, 2925, 1589, 1558, 1470, 1405, 1276, 1204, 1070, 995, 912, 885, 777, 679, 623, 562, 475, 436 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 4.60 (s, 2H, 1-H), 7.26 (s, 1H, 3-H), 7.44 (t like, ^3J(5'-H, 4'-H) = ^3J(5'-H, 6'-H) = 7.9 Hz, 1H, 5'-H), 7.66 (d like, ^3J(6'-H, 5'-H) = 7.9 Hz, 1H, 6'-H), 7.73 (d like, ^3J(4'-H, 5'-H) = 7.9 Hz, 1H, 4'-H), 7.98 (s, 1H, 2'-H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 39.91 (C-1), 122.31 (C-2), 122.39 (C-1'), 127.64 (C-6'), 129.77 (C-5'), 130.67 (C-3), 131.66 (C-4'), 131.79 (C-2'), 136.66 (C-3'); MS (EI, 70 eV) *m/z* (%) 353 (12) $[M]^+$ ≙ $[C_9H_7Br_3]^+$, 274 (29) $[M–Br]^+$ ≙ $[C_9H_7Br_2]^+$, 243 (10), 193 (64) $[M–2 \times Br]^+$ ≙ $[C_9H_7Br]^+$, 115 (100) $[M–3 \times Br]^+$ ≙ $[C_9H_7]^+$, 57 (12); HRMS (EI, M^+) calculated for $[C_9H_7Br_3]^+$ 353.8049 found 353.8072.

*4.2.9 (Z)-1,2-Dibromo-3-(3-methoxyphenyl)-2-propene [(Z)-**1i**]*



According to general procedure I, (*Z*)-2-bromo-3-(3-methoxyphenyl) prop-2-en-1-ol [(*Z*)-**7i**] (0.73 g, 3.00 mmol), triphenylphosphine (0.87 g, 3.30 mmol) in dichloromethane (9 mL) and a solution of bromine (0.17 mL, 0.53 g, 3.30 mmol) in dichloromethane (5.5 mL) were stirred for 3 h at 0 °C. After work-up and purification, (*Z*)-1,2-dibromo-3-(3-methoxyphenyl)-2-propene [(*Z*)-**1i**] was obtained as a light yellow oil in 47% yield (0.15 g, 1.41 mmol, *Z*:*E* ≥ 95:5); R_f 0.35 (*n*-pentane); IR (ATR) *ν* 3000, 2956, 2935, 2832, 1596, 1575, 1485,1454, 1421, 1320, 1260, 1208, 1039, 940, 865, 778, 688, 624, 479, 456 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 3.83 (s, 3H, 1''-H), 4.43 (s, 2H, 1-H), 6.89 (d like, ^3J(4'-H, 5'-H) = 7.6 Hz, 1H, 4'-H), 7.11 (s, 1H, 3-H), 7.17 (d like, ^3J(6'-H, 5'-H) = 7.6 Hz, 1H, 6'-H), 7.25 (s, 1H, 2'-H), 7.28 (t like, ^3J(5'-H, 4'-H) = ^3J (5'-H, 6'-H) = 7.6 Hz, 1H, 5'-H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 40.61 (C-1), 55.29 (C-1''), 114.13 (C-2'), 114.67 (C-4'), 120.91 (C-2), 121.77 (C-6'), 129.26 (C-5'), 132.09 (C-3), 135.82 (C-1'), 159.35 (C-3'); MS (EI, 70 eV) *m/z* (%) 305 (14) $[M]^+$ ≙ $[C_{10}H_{10}Br_2O]^+$, 224 (36) $[M–Br]^+$ ≙ $[C_{10}H_{10}BrO]^+$, 146 (100) $[M–2 \times Br]^+$ ≙ $[C_{10}H_{10}O]^+$, 131 (31) ≙ $[C_9H_7O]^+$, 103 (40) ≙ $[C_8H_7]^+$, 77 (14) $[C_6H_5]^+$; HRMS (EI, M^+) calculated for $[C_9H_7Br_3]^+$ 305.9046 found 305.9073.

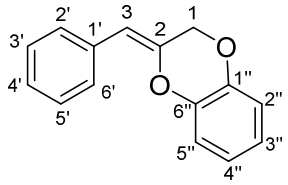
*4.3 Synthesis and characterization of products [(Z)-**3a–l**]*

*General procedure II for the synthesis of (Z)-**3a–l***

A two-necked round-bottom flask was charged with a 1,2-dibromo-3-aryl-2-propene (*Z*)-**1** (1 mmol, 1 equiv), a catechol **2** (2 mmol, 2 equiv), Cs_2CO_3 (4 mmol, 4 equiv) and DMF (10 mL) under argon. The reaction mixture was vigorously stirred for 18 h at 140 °C. After cooling to

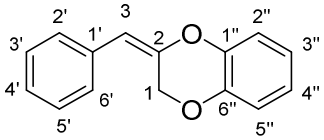
100 °C, the reaction mixture was quenched with 2 M HCl (2.5 mL) and then allowed to cool to room temperature. The reaction mixture was diluted with H_2O (25 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using mixtures of *n*-hexane and ethyl acetate as eluents to afford the corresponding 2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine (*Z*)-**3** in pure form.

*4.3.1 (*Z*)-2-Benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3a**] [9a-d,f]*



According to general procedure II, (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] (276 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a**] was obtained as a white solid in 89% yield (199 mg, 0.89 mmol, *Z*:*E* ≥ 95:5); R_f 0.40 (*n*-hexane:ethyl acetate = 49:1); ^{1}H NMR (600 MHz, C_6D_6) δ 4.02 (s, 2H, 1-H), 5.11 (s, 1H, 3-H), 6.67–6.69 (m, 1H, 3''-H), 6.69–6.71 (m, 1H, 4''-H), 6.91–6.92 (m, 1H, 2''-H), 6.92–6.93 (m, 1H, 5''-H), 7.09 (t like, ^3J(4'-H, 3'-H) = ^3J(4'-H, 5'-H) = 7.4 Hz, 1H, 4'-H), 7.25 (t like, ^3J(3'-H, 2'-H) = ^3J(3'-H, 4'-H) = ^3J(5'-H, 4'-H) = ^3J(5'-H, 6'-H) = 7.4 Hz, 2H, 3'-H and 5'-H), 7.71 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 7.4 Hz, 2H, 2'-H and 6'-H; ^{13}C NMR (125 MHz, C_6D_6) δ 65.88 (C-1), 107.30 (C-3), 116.99 (C-2''), 117.74 (C-5''), 122.46 (C-3''), 122.86 (C-4''), 127.12 (C-4'), 128.61 (C-3' and C-5'), 129.32 (C-2' and C-6'), 134.88 (C-1'), 142.96 (C-1''), 143.80 (C-6''), 144.77 (C-2); HRMS (APCI, 5 kV, $[M+H]^+$) calculated for $[C_{15}H_{13}O_2]^+$ 225.0917 found 225.0916.

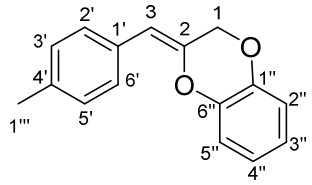
*4.3.2 (*E*)-2-Benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*E*)-**3a**] [9e]*



According to general procedure II, (*E*)-1,2-dibromo-3-phenyl-2-propene [(*E*)-**1a**] (25 mg, 90 µmol), catechol (**2a**) (20 mg, 180 µmol) and Cs_2CO_3 (117 mg, 360 µmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by preparative thin layer chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*E*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*E*)-**3a**] was obtained as a white solid in 35% yield (7 mg, 31 µmol, *Z*:*E* = 0:100); R_f 0.42 (*n*-hexane:ethyl acetate = 49:1); ^{1}H NMR (600 MHz, C_6D_6) δ 4.44 (s, 2H, 1-H), 6.42 (s, 1H, 3-H), 6.67–6.69 (m, 1H, arom. H), 6.69–6.71 (m, 1H, arom. H), 6.82–6.86 (m, 2H, arom. H), 6.90–6.94 (m, 1H, arom. H), 6.97–7.06 (m, 4H, arom. H). ^{13}C NMR (125 MHz, C_6D_6) δ 59.67 (C-1), 108.54 (C-3), 115.58 (arom. C), 116.44 (arom. C), 121.28 (arom. C), 121.44 (arom. C), 125.78 (arom. C), 127.54 (arom. C), 127.98 (arom. C), 133.35 (arom. C), 142.22 (arom. C),

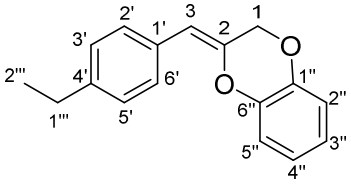
143.63 (arom. C), 144.91 (arom. C), HRMS (APCI, 3 kV, $[M+H]^+$) calculated for $[C_{15}H_{13}O_2]^+$ 225.0917 found 225.0916.

*4.3.3 (Z)-2-(4-Methylbenzylidene)-2,3-dihydrobenzo[b][1,4]dioxine [(Z)-**3b**] [9a,c,d]*



According to general procedure II, (*Z*)-1,2-dibromo-3-*p*-tolyl-2-propene [(*Z*)-**1b**] (290 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane: ethyl acetate = 49:1) (*Z*)-2-(4-methylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3b**] was obtained as a white solid in 88% yield (213 mg, 0.89 mmol, *Z*:*E* ≥ 95:5); R_f 0.42 (*n*-hexane:ethyl acetate = 49:1); ^{1}H NMR (600 MHz, C_6D_6) δ 2.16 (s, 3H, 1'''-H), 4.05 (s, 2H, 1-H), 5.15 (s, 1H, 3-H), 6.67–6.68 (m, 1H, 3''-H), 6.68–6.69 (m, 1H, 4''-H), 6.93–6.94 (m, 1H, 2''-H), 6.94–6.95 (m, 1H, 5''-H), 7.10 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 7.5 Hz, 2H, 3'-H and 5'-H), 7.67 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 7.6 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 20.07 (C-1'''), 64.82 (C-1), 106.26 (C-3), 115.83 (C-3''), 116.62 (C-4''), 121.28 (C-2''), 121.62 (C-5''), 128.20 (C-2' and C-6'), 128.22 (C-3' and C-5'), 130.98 (C-1'), 135.57 (C-4'), 141.93 (C-2), 142.04 (C-6''), 143.68 (C-1''); MS (EI, 70 eV) *m/z* (%) 238 (100) $[M]^+$ ≙ $[C_{16}H_{14}O_2]^+$, 223 (22) $[M–CH_3]^+$ ≙ $[C_{15}H_{12}O_2]^+$, 129 (98) ≙ $[C_6H_5O]^+$, 105 (58), 91 (15), 79 (10).

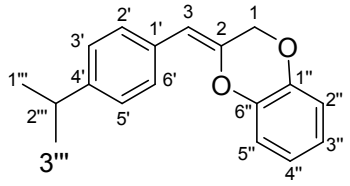
*4.3.4 (Z)-2-(4-Ethylbenzylidene)-2,3-dihydrobenzo[b][1,4]dioxine [(Z)-**3c**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(4-ethylphenyl)-2-propene [(*Z*)-**1c**] (304 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-(4-ethylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3c**] was obtained as a white solid in 77% yield (194 mg, 0.77 mmol, *Z*:*E* ≥ 95:5); mp 97–98 °C; R_f 0.46 (*n*-hexane:ethyl acetate = 49:1); IR (ATR) ν 2962, 1678, 1593, 1490, 1460, 1374, 1347, 1258, 1168, 1104, 1027, 995, 925, 853, 768, 744, 571, 528, 474 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 1.11 (t, ^3J(2'''-H, 1'''-H) = 8.0 Hz, 3H, 2'''-H), 2.48 (q, ^3J(1'''-H, 2'''-H) = 8.0 Hz, 2H, 1'''-H), 4.06 (s, 2H, 1-H), 5.17 (s, 1H, 3-H), 6.67–6.69 (m, 1H, 3''-H), 6.69–6.71 (m, 1H, 4''-H), 6.92–6.95 (m, 1H, 2''-H), 6.96–6.99 (m, 1H, 5''-H), 7.13 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.2 Hz, 2H, 3'-H and 5'-H), 7.70 (d

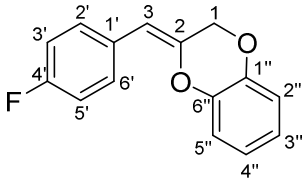
like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.2 Hz, 2H, 2'-H and 6'-H), ^{13}C NMR (125 MHz, C_6D_6) δ 15.73 (C-2'''), 28.96 (C-1'''), 65.96 (C-1), 107.43 (C-3), 116.97 (C-2''), 117.77 (C-5''), 122.43 (C-3''), 122.78 (C-4''), 128.16 (C-3' and C-5'), 129.44 (C-2' and C-6'), 132.37 (C-1'), 143.22 (C-4'), 144.10 (C-6''), 143.10 (C-2), 143.08 (C-1''); MS (EI, 70 eV) *m/z* (%) 252 (100) $[M]^+ \triangleq [C_{17}H_{16}O_2]^+$, 205 (14), 151 (10), 144 (65), 129 (70) $\triangleq [C_6H_5O]^+$, 97 (37), 95 (40), 85 (51), 83 (54), 71 (78), 57 (88); HRMS (EI, M^+) calculated for $[C_{17}H_{16}O_2]^+$ 252.1150 found 252.1152.

*4.3.5 (Z)-2-(4-isopropylbenzylidene)-2,3-dihydrobenzo[b][1,4]dioxine [(Z)-**3d**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(4-isopropylphenyl)-2-propene [(*Z*)-**1d**] (304 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-(4-isopropylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**1d**] was obtained as a white solid in 68% yield (194 mg, 0.77 mmol, *Z*:*E* ≥ 95:5); mp 96–97 °C; R_f 0.49 (*n*-hexane:ethyl acetate = 49:1); IR (ATR) ν [cm^{-1}] 2957, 2865, 1680, 1593, 1489, 1461, 1346, 1307, 1278, 1256, 1169, 1104, 1053, 1028, 992, 925, 854, 767, 745, 574, 486, 402; ^{1}H NMR (600 MHz, C_6D_6) δ 1.17 (d, ^3J(1''-H, 2''-H) = ^3J(3'''-H, 2'''-H) = 6.9 Hz, 6H, 1'''-H and 3'''-H), 2.75 (sep, ^3J(2'''-H, 1'''-H) = ^3J(2'''-H, 3'''-H) = 6.9 Hz, 1H, 2'''-H), 4.06 (s, 2H, 1-H), 5.17 (s, 1H, 3-H), 6.69–6.71 (m, 1H, 3''-H), 6.71–6.73 (m, 1H, 4''-H), 6.92–6.95 (m, 1H, 5''-H), 6.96–7.01 (m, 1H, 2''-H), 7.13 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.2 Hz, 2H, 3'-H and 5'-H), 7.70 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.2 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 24.05 (C-1''' and C-3'''), 34.21 (C-2'''), 65.95 (C-1), 107.42 (C-3), 116.96 (C-3''), 117.99 (C-4''), 122.43 (C-2''), 122.78 (C-5''), 126.70 (C-3' and C-5'), 129.46 (C-2' and C-6'), 132.50 (C-1'), 143.09 (C-1''), 143.23 (C-2), 144.82 (C-6''), 147.72 (C-4'); MS (EI, 70 eV) *m/z* (%) 266 (100) $[M]^+ \triangleq [C_{18}H_{18}O_2]^+$, 251 (72), 223 (14), 158 (27), 143 (73), 128 (33), 115 (38), 91 (51) $\triangleq [C_7H_7]^+$; HRMS (EI, M^+) calculated for $[C_{18}H_{18}O_2]^+$ 266.1306, found 266.1307.

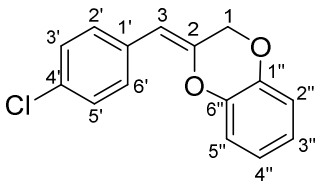
*4.3.6 (Z)-2-(4-Fluorobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxine [(Z)-**3e**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(4-fluorophenyl)-2-propene [(*Z*)-**1e**] (294 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-(4-fluorobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3e**] was obtained as a pale yellow oil in 63% yield (153 mg, 0.63 mmol, *Z*:*E* ≥ 95:5); R_f 0.51 (*n*-hexane:ethyl acetate = 29:1); IR (ATR) ν 3042, 2852, 1682, 1599, 1490, 1463, 1347, 1306, 1258, 1225, 1159, 1106, 1029, 997, 928, 842, 746, 572,

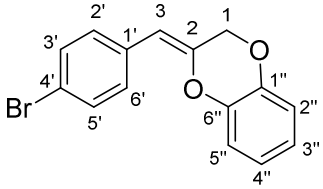
524, 480, 419 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 4.00 (s, 2H, 1-H), 4.96 (s, 1H, 3-H), 6.68–6.69 (m, 1H, 3''-H), 6.69–6.70 (m, 1H, 4''-H), 6.86–6.90 (ovl, m, 1H, 5''-H), 6.86–6.90 (ovl, m, 2H, 3'-H and 5'-H), 6.92–6.93 (m, 1H, 2''-H), 7.45–7.49 (m, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 65.79 (C-1), 106.05 (C-3), 115.44 (d, ^2J(4'-F, C-3') = ^2J(4'-F, C-5') = 21.2 Hz, C-3' and C-5'), 116.92 (C-5''), 117.79 (C-2''), 122.50 (C-3''), 122.97 (C-4''), 130.89 (d, ^3J(4'-F, C-2') = ^3J(4'-F, C-6') = 7.8 Hz, C-2' and C-6'), 130.95 (C-1'), 142.84 (C-6''), 143.40 (d, ^6J(4'-F', C-2) = 2.0 Hz, C-2), 144.73 (C-1''), 162.00 (d, ^1J(4'-F, C-4') = 246.5 Hz, C-4'); MS (EI, 70 eV) *m/z* (%) 242 (100) $[M]^+ \triangleq [C_{15}H_{11}O_2F]^+$, 134 (68), 121 (10); HRMS (EI, M^+) calculated for $[C_{15}H_{11}O_2F]^+$ 242.0738 found 242.0725.

*4.3.7 (Z)-2-(4-Chlorobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3f**] [9c,d]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(4-chlorophenyl)-2-propene [(*Z*)-**1f**] (310 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-(4-chlorobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3f**] was obtained as a white solid in 54% yield (141 mg, 0.54 mmol, *Z*:*E* ≥ 95:5); R_f 0.53 (*n*-hexane:ethyl acetate = 19:1); ^{1}H NMR (600 MHz, C_6D_6) δ 3.96 (s, 2H, 1-H), 4.90 (s, 1H, 3-H), 6.67–6.79 (m, 1H, 3''-H), 6.69–6.71 (m, 1H, 4''-H), 6.86–6.88 (m, 1H, 2''-H), 6.91–6.93 (m, 1H, 5''-H), 7.20 (d like, ^3J(3'-H, 2'-H) = ^3J(5'-H, 6'-H) = 8.2 Hz, 2H, 3'-H and 5'-H), 7.41 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.2 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 65.72 (C-1), 105.90 (C-3), 116.92 (C-2''), 117.77 (C-5''), 122.55 (C-4''), 123.07 (C-3''), 128.76 (C-3' and C-5'), 130.47 (C-2' and C-6'), 132.68 (C-4'). 133.27 (C-1'), 142.74 (C-6''), 144.23 (C-2), 144.68 (C-1''); MS (EI, 70 eV) *m/z* (%) 258 (100) $[M]^+ \triangleq [C_{15}H_{11}O_2Cl]^+$, 223 $[M–Cl]^+ \triangleq [C_{15}H_{11}O_2Cl]^+$ (14), 150 (60), 129 (15), 115 (89), 97 (11), 63 (10).

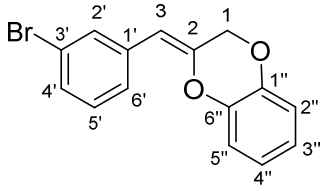
*4.3.8 (Z)-2-(4-Bromobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3g**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(4-bromophenyl)-2-propene [(*Z*)-**1g**] (355 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-(4-bromobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3g**] was obtained as a white solid in 53% yield (161 mg, 0.53 mmol, *Z*:*E* ≥ 95:5); mp 90–91 °C; R_f 0.56 (*n*-hexane:ethyl acetate = 29:1); IR (ATR) ν 3056, 2839, 1672, 1594, 1482, 1401, 1343, 1304, 1279, 1262, 1189, 1106, 1068, 995, 867, 853, 824, 766, 741, 657, 568, 509, 469 cm^{-1}; ^{1}H NMR (600 MHz, pyridine-d_5) δ 4.64 (s, 2H, 1-H), 5.65 (s, 1H, 3-H), 6.97–6.99 (m, 1H, 3''-H), 6.99–7.02 (m, 1H, 4''-H), 7.08–7.11 (m,

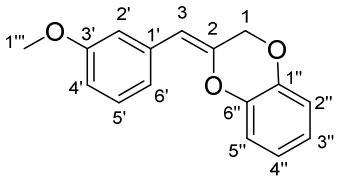
1H, 2''-H), 7.21–7.23 (m, 1H, 3''-H), 7.39 (d like, ^3J(3''-H, 2''-H) = ^3J(3''-H, 6''-H) = 8.5 Hz, 2H, 3'-H and 5'-H), 7.71 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 8.5 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 65.99 (C-1), 106.00 (C-3), 117.18 (C-2''), 117.92 (C-6''), 120.78 (C-1'), 122.82 (C-3''), 123.82 (C-4''), 131.09 (C-3' and C-5'), 131.89 (C-2' and C-6'), 134.10 (C-4'). 142.78 (C-6''), 142.89 (C-2), 144.89 (C-1''); MS (EI, 70 eV) *m/z* (%) 301 (100) $[M]^+ \triangleq [C_{15}H_{11}O_2Br]^+$, 223 $[M–Br]^+ \triangleq [C_{15}H_{11}O_2Br]^+$ (19), 193 (34), 115 (66); HRMS (EI, M^+) calculated for $[C_{15}H_{11}O_2Br]^+$ 301.9937 found 301.9924.

*4.3.9 (Z)-2-(3-Bromobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3h**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-(3-bromophenyl)-2-propene [(*Z*)-**1h**] (355 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-(3-bromobenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3h**] was obtained as a white solid in 55% yield (168 mg, 0.55 mmol, *Z*:*E* ≥ 95:5); mp 90–91 °C; R_f 0.56 (*n*-hexane:ethyl acetate = 29:1); IR (ATR) ν 3001, 2857, 1673, 1585, 1492, 1461, 1417, 1353, 1269, 1171, 1105, 1073, 1029, 994, 937, 878, 839, 824, 779, 748, 717, 675, 581, 500, 451, 435, 411 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 3.93 (s, 2H, 1-H), 4.83 (s, 1H, 3-H), 6.64–6.67 (m, 1H, 3''-H), 6.67–6.69 (m, 1H, 4''-H), 6.84 (t like ^3J(5'-H, 4'-H) = ^3J(5'-H, 6'-H) = 7.8 Hz, 1H, 5'-H), 6.85–6.87 (m, 1H, 2''-H), 6.89–6.91 (m, 1H, 5''-H), 7.19 (d like, ^3J(4'-H, 5'-H) = 7.8 Hz, 1H, 4'-H), 7.44 (d like, ^3J(2'-H, 3'-H) = 7.8 Hz, 1H, 6'-H), 7.87 (s, 1H, 2'-H); ^{13}C NMR (125 MHz, C_6D_6) δ 65.32 (C-1), 105.24 (C-3), 116.69 (C-2''), 117.38 (C-5''), 122.31 (C-3''), 122.54 (C-1'), 122.78 (C-4''), 127.25 (C-6'), 129.61 (C-5'), 129.70 (C-4'), 131.78 (C-2'), 136.65 (C-3'), 142.33 (C-6''), 144.30 (C-1''), 144.57 (C-2); MS (EI, 70 eV) *m/z* (%) 301 (100) $[M]^+ \triangleq [C_{15}H_{11}O_2Br]^+$, 223 $[M–Br]^+ \triangleq [C_{15}H_{11}O_2]^+$ (14), 194 (34), 147 (10), 115 (68); HRMS (EI, M^+) calculated for $[C_{15}H_{11}O_2Br]^+$ 301.9937 found 301.9913.

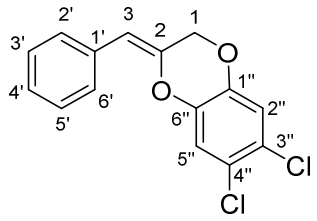
*4.3.10 (Z)-2-(3-Methoxybenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3i**]*



According to general procedure 4, (*Z*)-1,2-dibromo-3-(3-methoxyphenyl)-2-propene [(*Z*)-**1i**] (355 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-(3-methoxybenzylidene)-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3i**] was obtained as a white solid in 65% yield (147 mg, 0.55 mmol, *Z*:*E* ≥ 95:5); mp 85–86 °C; R_f 0.54 (*n*-hexane:ethyl acetate = 49:1); IR (ATR) ν 2997, 2910, 1674, 1594, 1488, 1459, 1349, 1300, 1254, 1206, 1170, 1103, 1037, 998, 949, 906, 863, 784, 772, 746, 688, 627, 507, 456, 410 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 3.41 (s,

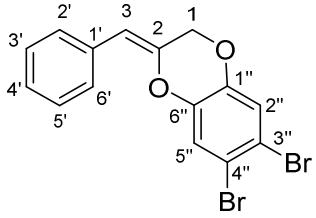
3H, 1‘‘-H), 4.02 (s, 2H, 1-H), 5.11 (s, 1H, 3-H), 6.66–6.69 (m, 1H, 3‘‘-H), 6.69–6.71 (m, 1H, 4‘‘-H), 6.75 (d like, ^3J(4’-H, 5’-H) = 7.6 Hz, 1H, 4’-H), 6.90–6.92 (m, 1H, 2‘‘-H), 6.92–6.94 (m, 1H, 5‘‘-H), 7.19 (t like, ^3J(5’-H, 4’-H) = ^3J(5’-H, 6’-H) = 7.6 Hz, 1H, 5’-H), 7.31 (d like, ^3J(2’-H, 3’-H) = 7.6 Hz, 1H, 6’-H), 7.49 (s, 1H, 2’-H); ^{13}C NMR (125 MHz, C_6D_6) δ 54.66 (C-1‘‘‘), 65.88 (C-1), 107.33 (C-3), 112.91 (C-4’), 114.98 (C-2’), 116.96 (C-3‘‘), 117.73 (C-4‘‘), 121.97 (C-6’), 122.47 (C-2‘‘), 122.88 (C-5‘‘), 129.51 (C-5’), 136.14 (C-1’), 142.92 (C-6‘‘), 143.93 (C-2), 144.74 (C-1‘‘), 160.19 (C-3’); HRMS (APCI, 5 kV, $[M+H]^+$) calculated for $[C_{16}H_{15}O_3]^+$ 255.1016 found 255.1013.

*4.3.11 (Z)-2-Benzylidene-6,7-dichloro-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3j**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] (276 mg, 1 mmol), 4,5-dichlorocatechol (**2b**) (358 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-benzylidene-6,7-dichloro-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3j**] was obtained as a white solid in 51% yield (148 mg, 0.55 mmol, *Z*:*E* ≥ 95:5); mp 99–100 °C; R_f 0.51 (*n*-hexane:ethyl acetate = 29:1); IR (ATR) ν 2997, 2920, 1681, 1579, 1486, 1470, 1389, 1369, 1351, 1315, 1281, 1180, 1165, 1110, 1018, 999, 957, 902, 871, 853, 809, 744, 685, 670, 634, 598, 547, 517, 462, 444, 385 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 3.80 (s, 2H, 1-H), 5.06 (s, 1H, 3-H), 6.82 (s, 1H, 2‘‘-H), 6.83 (s, 1H, 5‘‘-H), 7.11 (t like, ^3J(4’-H, 3’-H) = ^3J(4’-H, 5’-H) = 7.4 Hz, 1H, 4’-H), 7.26 (t like, ^3J(3’-H, 2’-H) = ^3J(3’-H, 4’-H) = ^3J(5’-H, 4’-H) = ^3J(5’-H, 6’-H) = 7.4 Hz, 2H, 3’-H and 5’-H), 7.58 (d like, ^3J(2’-H, 3’-H) = ^3J(6’-H, 5’-H) = 7.4 Hz, 2H, 2’-H and 6’-H); ^{13}C NMR (125 MHz, C_6D_6) δ 65.64 (C-1), 108.50 (C-3), 118.24 (C-2‘‘), 118.95 (C-5‘‘), 125.32 (C-3‘‘), 125.73 (C-4‘‘), 127.62 (C-4’), 128.69 (C-3’ and C-5’), 129.39 (C-2’ and C-6’), 134.15 (C-1’), 142.61 (C-6‘‘), 143.63 (C-2), 144.44 (C-1‘‘); MS (EI, 70 eV) *m/z* (%) 292 (50) $[M]^+$ ≙ $[C_{15}H_{10}Cl_2O_2]^+$, 272 (10), 193 (11), 178 (20), 116 (100), 57 (11); HRMS (EI, M^+) calculated for $[C_{15}H_{10}Cl_2O_2]^+$ 292.0052 found 292.0049.

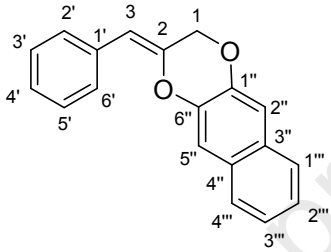
*4.3.12 (Z)-2-Benzylidene-6,7-dibromo-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3k**]*



According to general procedure II, (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] (276 mg, 1 mmol), 4,5-dibromocatechol (**2c**) (536 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 29:1) (*Z*)-2-benzylidene-6,7-dibromo-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3k**] was obtained as a white solid in 49% yield (185 mg, 0.55 mmol, *Z*:*E* ≥ 95:5); mp 100–101 °C; R_f 0.55 (*n*-hexane:ethyl acetate = 29:1); IR (ATR) ν

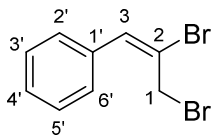
3023, 2914, 1678, 1574, 1474, 1349, 1314, 1276, 1178, 1162, 1097, 1015, 995, 943, 908, 872, 851, 803, 747, 686, 630, 590, 541, 483, 461, 441 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 3.78 (s, 2H, 1-H), 5.05 (s, 1H, 3-H), 7.03 (s, 1H, 2''-H), 7.04 (s, 1H, 5''-H), 7.10 (t like, ^3J(4'-H, 3'-H) = ^3J(4'-H, 5'-H) = 7.4 Hz, 1H, 4'-H), 7.25 (t like, ^3J(3'-H, 2'-H) = ^3J(3'-H, 4'-H) = ^3J(5'-H, 4'-H) = ^3J(5'-H, 6'-H) = 7.4 Hz, 2H, 3'-H and 5'-H), 7.56 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 7.4 Hz, 2H, 2'-H and 6'-H; ^{13}C NMR (125 MHz, C_6D_6) δ 65.29 (C-1), 108.24 (C-3), 116.19 (C-3''), 116.69 (C-4''), 120.99 (C-2''), 121.77 (C-5''), 127.30 (C-4'), 128.39 (C-3' and C-5'), 129.08 (C-2' and C-6'), 133.82 (C-1'), 141.88 (C-1''), 141.97 (C-2), 143.92 (C-6''); MS (EI, 70 eV) *m/z* = 381 (63) $[M]^+ \triangleq [C_{15}H_{10}Br_2O_2]^+$, 303 (12), 116 (100); HRMS (EI, M^+) calculated for $[C_{15}H_{10}Br_2O_2]^+$ 381.9022 found 381.0009.

*4.3.13 (Z)-2-Benzylidene-2,3-dihydronaphtho[2,3-b][1,4]dioxine [(Z)-**3l**] [9a]*



According to general procedure II, (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] (276 mg, 1 mmol), 2,3-dihydroxynaphthalene (**2d**) (321 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-benzylidene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine [(*Z*)-**3l**] was obtained as a white solid in 61% yield (181 mg, 0.66 mmol, *Z*:*E* ≥ 95:5); R_f 0.51 (*n*-hexane:ethyl acetate = 49:1); ^1H NMR (600 MHz, pyridine-d_5) δ 4.72 (s, 2H, 1-H), 5.77 (s, 1H, 3-H), 7.29 (t like, ^3J(4'-H, 3'-H) = ^3J(4'-H, 5'-H) = 7.4 Hz, 1H, 4'-H), 7.36–7.39 (m, 1H, 2'''-H), 7.39–7.42 (m, 1H, 3'''-H), 7.45 (t like, ^3J(3'-H, 2'-H) = ^3J(3'-H, 4'-H) = ^3J(5'-H, 4'-H) = ^3J(5'-H, 6'-H) = 7.4 Hz, 2H, 3'-H and 5'-H), 7.51 (s, 1H, 2''-H), 7.65 (s, 1H, 5''-H), 7.77 (d like, ^3J(2'''-H, 3'''-H) = 8.0 Hz, 1H, 2'''-H), 7.84 (d like, ^3J(5'''-H, 4'''-H) = 8.0 Hz, 1H, 5'''-H), 7.90 (d like, ^3J(2'-H, 3'-H) = ^3J(6'-H, 5'-H) = 7.4 Hz, 2H, 2'-H and 6'-H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 66.08 (C-1), 107.15 (C-3), 112.75 (C-5''), 113.27 (C-2''), 125.01 (C-4'''), 125.19 (C-3'''), 126.92 (C-2'''), 127.02 (C-5'''), 127.19 (C-4'), 128.69 (C-3' and C-5'), 129.27 (C-2' and C-6'), 130.14 (C-6'''), 130.30 (C-1'''), 134.71 (C-1'), 142.68 (C-6''), 144.05 (C-2), 144.67 (C-1''); MS (EI, 70 eV) *m/z* (%) 274 (100) $[M]^+$, 115 (53).

*4.4 Synthesis of (E)-1,2-Dibromo-3-phenyl-2-propene [(E)-**1a**] [20,21]*



Iodine (25 mg, 100 µmol) was added to a solution of (*Z*)-1,2-dibromo-3-phenyl-2-propene [(*Z*)-**1a**] (276 mg, 1 mmol) in 3 mL $CHCl_3$. The mixture obtained was stirred until a light pink homogeneous solution was formed and then exposed to a daylight lamp. The isomerization

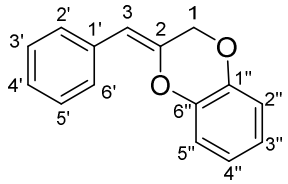
was monitored by TLC (SiO_2, *n*-pentane). After 24 h, a 2:1 mixture of [(*Z*)-**1a**] and [(*E*)-**1a**] had been formed (NMR). The solvent was removed under reduced pressure and the crude product was purified by preparative thin layer chromatography (SiO_2, *n*-pentane) to afford (*E*)-1,2-dibromo-3-phenyl-2-propene [(*E*)-**1a**] as a colorless oil in 27% yield (75 mg, 270 µmol, *Z*:*E* = 1:99). R_f 0.45 (*n*-pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (s, 2H, 1-H), 7.12 (s, 1H, 3-H), 7.33–7.36 (m, 3H, arom. H), 7.39–7.43 (m, 2H, arom. H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.20 (C-1), 122.63 (C-3), 127.99 (arom. C), 128.37 (arom. C), 128.92 (arom. C), 135.28 (arom. C), 136.78 (arom. C); MS (EI, 70 eV) *m/z* (%) 275 (9) $[M]^+ \triangleq [C_9H_8Br_2]^+$, 195 (30) $[M–Br]^+ \triangleq [C_9H_8Br]^+$, 115 (100) $[M–2 \times Br]^+ \triangleq [C_9H_8]^+$.

*4.5 Synthesis of (3-bromoprop-1-yn-1-yl) benzene (**9a**) [22]*

A stirred solution of triphenylphosphine (2.89 g, 10.00 mmol) in dichloromethane (34 mL) was cooled to 0 °C. Bromine (0.56 mL, 1.74 g, 10.90 mmol) was added dropwise at 0 °C until a yellow suspension was formed. A solution of 3-phenylprop-2-yn-1-ol in dichloromethane (17 mL) was added slowly to the suspension. The resulting yellow solution was stirred for 1 h at 0 °C. The solution was allowed to warm to room temperature and *n*-hexane (68 mL) was added. A white precipitate was formed and the reaction mixture was stirred for 30 min at room temperature. The white solid was filtered over silica and the filter cake was washed with *n*-hexane (3 × 100 mL). The organic phases were collected and the volatiles were removed under reduced pressure. The crude product was subjected to column chromatography (SiO_2, *n*-hexane/ethyl acetate = 29:1) to afford (3-bromoprop-1-yn-1-yl)benzene (**9a**) as a colorless oil in 70% yield (1.37 g, 7.00 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (s, 2H, 1-H), 7.28–7.35 (m, 3H, arom. H), 7.42–7.48 (m, 2H, arom. H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.27 (C-1), 84.19 (acetylenic C), 86.71 (acetylenic C), 122.12 (arom. C), 128.31 (arom. C), 128.85 (arom. C), 131.86 (arom. C); HRMS (APCI, 5 kV, $[M+H]^+$) calculated for $[C_9H_8Br]^+$ 194.9803 found 194.9805.

*4.6 Synthesis of (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(Z)-**3a**] [9a-d,f]*

starting from *(3-bromoprop-1-yn-1-yl) benzene (**9a**) [22]*



According to general procedure II, (3-bromoprop-1-yn-1-yl) benzene (**9a**) (195 mg, 1 mmol), catechol (**2a**) (221 mg, 2 mmol) and Cs_2CO_3 (1.31 g, 4.00 mmol) were reacted for 18 h at 140 °C in DMF. After work-up and purification by column chromatography (SiO_2, *n*-hexane:ethyl acetate = 49:1) (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine [(*Z*)-**3a**] was obtained as a white solid in 89% yield (197 mg, 0.88 mmol, *Z*:*E* ≥ 95:5).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at xxxx.

References and notes

[1] (a) For a review on benzodioxines, see: Achari B, Mandal SB, Dutta PK, Chowdhury C. Synlett 2004;(14):2449–67;
(b) Guillaumet G. 1,4-Dioxins, Oxathiins, Dithiins and their Benzo Derivatives. In: Katritzky AR, Rees CW, Scriven EFV, editors. Comprehensive Heterocyclic Chemistry II. Oxford: Pergamon; 1996. p. 447–81.

[2] (a) Fang QK, Grover P, Han Z, McConville FX, Rossi RF, Olsson DJ, Kessler DW, Wald SA, Senanayake CH. Tetrahedron Asymmetry 2001;12(15):2169–74;
(b) Guthrie RM, Siegal RL. Clin Ther 1999;21(10):1732–48;
(c) Campbell SF, Davey MJ, Hardstone JD, Lewis BN, Palmer M. J Med Chem 1987;30(1):49–57;
(d) Elliot HL, Meredith PA, Reid JL. Am J Cardiol 1987;59(14):78G–81G.

[3] (a) Zhou R, Luo G, Ewing AG. J Neurosci1994;14(4):2402–7;
(b) Nelson WL, Powell ML. J Med Chem 1979;22:1125.

[4] Pinder RM, Wieringa JH. Med Res Rev 1993;13(3):259–325.

[5] Arnoldi A, Bassoli A, Merlini L, Ragg E. J Chem Soc Perkin Trans II 1991;(9):1399–406.

[6] (a) Pilkington LI, Barker D. J Org Chem 2012;77(18):8156–66;
(b) She X, Jing X, Pan X, Chan ASC, Yang T-K. Tetrahedron Lett 1999;40(24):4567–70;
(c) Ishibashi F, Taniguchi E. Phytochemistry 1998;49(2):613–22;
(d) Afifi MSA, Ahmed MM, Pezzuto JM, Kinghornt AD. Phytochemistry 1993;34(3):839–41;
(e) Debenedetti SL, Nadinic EL, Coussio JD, De Kimpe N, Dupont, JF, Declercq JP. Phytochemistry 1991;30(8):2757–58;
(f) Arnoldi A, Merlini L. J Chem Soc Perkin Trans I 1985;2555–57;
(g) Taniguchi E, Oshima Y. Agric Biol Chem 1972;36(6):1013–25.

[7] Rouf A, Gupta P, Aga MA, Kumar B, Chaubey A, Parshad R et al. Tetrahedron: Asymmetry 2012;23(22–23):1615–23.

[8] (a) Massacret M, Lhoste P, Lakhmiri R, Parella T, Sinou D. Eur J Org Chem 1999;(10):2665–73;
(b) Massacret M, Goux C, Lhoste P, Sinou D. Tetrahedron Lett 1994;35(33):6093–6;
(c) Ruiz N, Pujol MD, Guillaumet G, Coudert G. Tetrahedron Lett 1992;33(21):2965─8;
(d) Lee HH, Denny WA. J Chem Soc Perkin Trans 1 1990;(4):1071–74;

(e) Lee TV, Leigh AJ, Chapleo CB. Synthesis 1989;1989(3):208–9;
(f) Adam W, Schmidt E, Takayama K. Synthesis 1982;1982(4):322–4;
(g) Guillaumet G, Coudert G, Loubinoux B. Tetrahedron Lett 1979;20(45):4379–82;
(h) Farina G, Zecchi G. Synthesis 1977;1977(11):755;
(i) Katritzky AR, Sewell MJ, Topsom RD. Tetrahedron; 1966;22(3):931–9.

[9] (a) Chowdhury C, Chaudhuri G, Guha S, Mukherjee A, Kundu NG. J Org Chem 1998;63(6):1863–71;
(b) Hamasaka G, Uozumi Y. Chem Commun 2014;50(93):14516–8;
(c) Liang L, Fang Q, Xu X, Li Y. Chinese J Org Chem 2012;32(2):409–12;
(d) Singh A, Ramanathan G. Asian J Org Chem 2016;5(7):865–9;
(e) Yamamoto M. J Chem Soc Perkin Trans I 1979:3161–5;
(f) Labrosse JR, Lhoste P, Sinou D. J Org Chem 2001;66(20):6634–42.

[10] For reviews on Cu(I)-catalyzed reactions for the synthesis of cyclic compounds, see:
(a) Wu X-F, Beller M. Heterocycles from Double-Functionalized Arenes: Transition Metal Catalyzed Coupling Reactions. Cambridge: The Royal Society of Chemistry; 2015;
(b) Liao Q, Yang X, Xi C. J Org Chem 2014;79(18):8507–15;
(c) Gulevich AV, Dudnik AS, Chernyak N, Gevorgyan V. Chem Rev 2013;113(5):3084–213;
(d) Lin H, Sun D. Org Prep Proced Int 2013;45(5):341–94;
(e) Ball CJ, Willis MC. European J Org Chem 2012; 2013(3):425–41;
(f) Fu H, Liu T. Synthesis 2012;44(18):2805–24;
(g) Liu Y, Wan JP. Chem Asian J 2012; 7(7):1488–501;
(h) Liu Y, Wan J-P. Org Biomol Chem 2011;9(20): 6873–94;
(i) Evano G, Blanchard N, Toumi M. Chem Rev 2008;108(8):3054–131.

[11] (a) Weischedel H, Sudheendran K, Mikhael A, Conrad J, Frey W, Beifuss U. Tetrahedron 2016;72(24):3454–67;
(b) Omar MA, Conrad J, Beifuss U. Tetrahedron 2014;70(35):5682–95;
(c) Sudheendran K, Malakar CC, Conrad J, Beifuss U. Adv Synth Catal 2013; 355(11-12):2400–16;
(d) Aljaar N, Malakar CC, Conrad J, Strobel S, Schleid T, Beifuss U. J Org Chem 2012; 77(18):7793–803;
(e) Malakar CC, Sudheendran K, Imrich H-G, Mika S, Beifuss U. Org Biomol Chem 2012; 10(19):3899–905;
(f) Malakar CC, Baskakova A, Conrad J, Beifuss U. Chem Eur J. 2012;18(29):8882–5;
(g) Malakar CC, Schmidt D, Conrad J, Beifuss U. Org Lett 2011;13(8):1972–5.

[12] For reviews of Cu(I)-catalyzed cross-couplings with vinyl halides, see:
(a) Theunissen C, Thilmany P, Lahboubi M, Blanchard N, Evano G. Org Synth 2019;96:195–213;
(b) Wu X-F, Beller M. Five-membered Heterocycle Synthesis. In: Wu X-F, Beller M, editors. Heterocycles from Double-Functionalized Arenes: Transition Metal Catalyzed Coupling Reactions. Cambridge: The Royal Society of Chemistry; 2015. p.138–40 and 143–5;
(c) Kuranaga T, Sesoko Y, Inoue M. Nat Prod Rep 2014;31(4):514–32.

For some recent examples of Cu-catalyzed cross-couplings of vinyl halides, see:
(d) Nitelet A, Thevenet D, Schiavi B, Hardouin C, Fournier J, Tamion R et al.. Chem Eur J. 2019;25(13):3262–6;
(e) Weischedel H, Schmidt D, Conrad J, Beifuss U. Tetrahedron 2018;74(44):6426–41;
(f) Lee HK, Sohn H-S, Cho CS. Synth Commun 2017;47(11):1046–51;
(g) Nitelet A, Wouters J, Dewez DF, Evano G. Org Lett 2017;19(23):6276–9;
(h) Yamaguchi K, Kawaguchi S-I, Sonoda M, Tanimori S, Ogawa A. Tetrahedron Lett 2017;58(43):4043–7;
(i) Zhao X, Zhang J, Zheng Z, Xu R. Molecules 2017;22(1):53–65;
(j) Anselmi E, Le TN, Bouvet S, Diter P, Pégot B, Magnier E. European J Org Chem 2016;2016(25):4423–8;
(k) Nitelet A, Evano G. Org Lett 2016;18(8):1904–7;
(l) Shrestha B, Thapa S, Gurung SK, Pike RAS, Giri R. J Org Chem 2016;81(3):787–802.

[13] Schmidt D, Malakar CC, Beifuss U. Org Lett 2014;16(18):4862–5.

[14] Schaefer JP, Higgins JG, Shenoy PK. Org Synth 1968;48:51.

[15] (a) Xu S, Li C, Jia X, Li J. J Org Chem 2014;79(22):11161−9;
(b) Gong X, Yang H, Liu H, Jia Y, Zhao Y, Fu H. Org Lett 2010;12(14):3128–31;
(c) Thiemann T, Tanaka Y, Ideta K, Mataka S. Cent Eur J Chem 2006;4(3):403–27;
(d) Trost BM, Donckele EJ, Thaisrivongs DA, Osipov M, Masters JT. J Am Chem Soc 2015;137(7):2776–84.

[16] (a) Hoffmann M, Miaskiewicz S, Weibel J-M, Pale P, Blanc A. RSC Adv 2015;5(47):37138−48;
(b) Olpp T, Brückner R. Synthesis 2004;2004(13):2135–52.

[17] (a) Moreau P, Al Neirabeyeh M, Guillaumet G, Coudert G. Tetrahedron Lett 1991;32(40),5525–8;
(b) Cabbiddu S, Floris C, Melis S, Sotigu F, Cerioni G. J Heterocycl Chem. 1986;23(6):1815–20.

[18] Gilmore K, Alabugin IV. Chem Rev 2011;111(11):6513–56.

[19] The 9:1 mixture of (Z)- and (E)- 1,2-dibromo-3-phenyl-2-propene [(Z)- and (E)-1a] was obtained by heating pure (Z)-1,2-dibromo-3-phenyl-2-propene [(Z)-1a] for 2h at 40 °C under reduced pressure.

[20] Gatti M, Drinkel E, Wu L, Pusterla I, Gaggia F, Dorta R. J Am Chem Soc 2010;132(43):15179–81.

[21] Laali K, Nandi GC, Bunge SD. Tetrahedron Lett 2014;55(15):2401–5.

[22] Ritter C, Nett N, Acevedo-Rocha CG, Lonsdale R, Kräling K, Dempwolff F et al. Angew Chem Int Ed 2015;54(45):13440–3.

[23] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1972851. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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Transition metal-free diastereospecific synthesis of (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines by reaction of (*Z*)-1,2-dibromo-3-aryl-2-propenes with catechols

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Significance of the work presented

Heterocycles are not only important skeletons in organic synthesis, they also play a decisive role in the fields of life and material sciences. Therefore the interest in the development of new and efficient approaches for the synthesis of heterocycles is unabated. This holds particularly true if new methods are widely applicable and expand the arsenal of the known synthetic methodology.

In this context transition metal-free cross-couplings which allow the efficient construction of *C,heteroatom* bonds play a particularly important role. Their combination with other reactions to new domino processes allows the synthesis of numerous heterocyclic systems in one-pot.

Benzo[*b*][1,4]dioxines and related heterocyclic systems are important as natural products and in medicinal chemistry. This is why the development of new approaches for the selective and efficient construction of these class of compounds is of great interest.

In this contribution we report on the first transition metal-free method for the efficient and diastereospecific preparation of (*Z*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines in a single synthetic step from easily accessible starting materials. Treatment of (*Z*)-1,2-dibromo-3-aryl-2-

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propenes with substituted catechols delivers substituted 2-arylidene-2,3-dihydrobenzo[*b*][1,4] dioxines with (*Z*)-configuration across the exocyclic double bond with yields up to 89%. It is assumed that the transformation starts with an intermolecular *O*-allylation, which is followed by an intramolecular *O*-vinylation. The reaction mechanism proposed is supported by experiments as well as by DFT calculations. Our study has also revealed that the reaction of (*E*)-1,2-dibromo-3-aryl-2-propenes with catechol produces (*E*)-2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines and that the reaction between (3-bromoprop-1-yn-1-yl)benzene and catechol gives the (*Z*)-2-benzylidene-2,3-dihydrobenzo[*b*][1,4]dioxine under transition metal-free conditions.

The advantages of our method include a) easily available substrates, b) simple experimental setup, c) simple work-up, d) product formation in a single synthetic step and e) diastereospecific formation of the 2-arylidene-2,3-dihydrobenzo[*b*][1,4]dioxines with (*Z*)-configuration across the exocyclic double bond.

We are sure that this contribution will arouse great interest among organic chemists involved in the development of new synthetic methods, in biologically active compounds as well as in heterocyclic chemistry. This is why we believe that this manuscript is suitable for publication in *Tetrahedron* as a paper.

I assure that the present manuscript is not under consideration for publication and has not been published elsewhere in any medium including electronic journals and computer databases of a public nature.

I hope that this contribution will receive your attention and remain

Yours sincerely,

Uwe Beifuss

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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