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FULL PAPER

Asymmetric synthesis of 2,3-dihydrobenzofurans via a (4+1) annulation between ammonium ylides and in situ generated ortho-quinone methides

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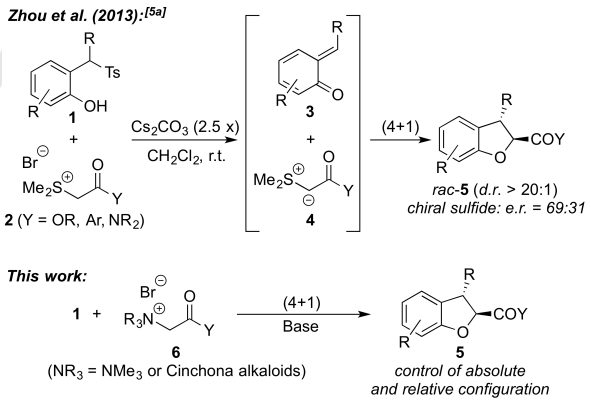
Abstract: A highly enantio- and diastereoselective (4+1)-annulation between in situ generated ammonium ylides and ortho-quinone methides for the synthesis of a variety of 2,3-dihydrobenzofurans was developed. The key factors controlling the reactivity and the stereoselectivity were systematically investigated by experimental and computational means and the hereby obtained energy profiles provide a deeper insight into the mechanistic details of this reaction.

Introduction

The 2,3-dihydrobenzofuran skeleton represents an important motif in a variety of natural products and biologically active molecules.[1] Accordingly the development of new methods for the synthesis of these important target molecules has attracted considerable recent interest and several complementary strategies have been introduced to access them in either a racemic or even in a stereoselective fashion.[2-6]

A highly valuable approach to access chiral carbo- or heterocycles is the use of onium ylides for (n+1) annulation reactions.[7] These versatile reagents have found widespread applications for (2+1) annulations to access (chiral) epoxides, aziridines, and cyclopropanes.[7-10] More recently, these compounds were also successfully employed for (4+1) annulations[11] by reacting them with different vinylogous acceptor molecules.[4-6,12,13]

One particularly powerful methodology for the generation of carbocyclic and heterocyclic targets in (4+n) annulation approaches relies on the use of *in situ* generated ortho-quinone methides or analogous aza-*ortho*-quinone methides.[14,15] Recently, the first example of the use of *in situ* generated o-quinone methides **3** (precursor **1**) for (4+1) annulation reactions with *in situ* generated carbonyl-stabilized sulfur ylides **4** (obtained from sulfonium salts **2**) to access 2,3-dihydrobenzofurans **5** have been reported by Zhou et al. (Scheme 1).[5a] High yields and excellent diastereoselectivities were obtained for different carbonyl-stabilized sulfur ylides. However, the use of a known camphor-derived chiral sulfonium ylide resulted in moderate enantiocontrol only (*e.r.* = 69:31). In addition, Yang and Xiao very recently reported the moderately enantioselective reaction of achiral sulfur ylides with in situ generated ortho-quinone methides in the presence of chiral urea catalysts.[5d]



Scheme 1. Zhou's recently developed sulfur ylide **4** addition to *ortho*-quinone methides **3** and targeted use of (chiral) ammonium salts **6** to control the absolute and the relative configuration of 2,3-dihydrobenzofurans **5**.

Based on our recent research focus on ammonium ylide-mediated asymmetric annulation reactions[10] and (4+1) annulations using ylides,[12d] we now became interested in testing the potential of *in situ* generated achiral and chiral ammonium ylides (by starting from ammonium salts **6**) to access 2,3-dihydrobenzofurans with control of both the relative and the absolute configuration. Besides the development of the first

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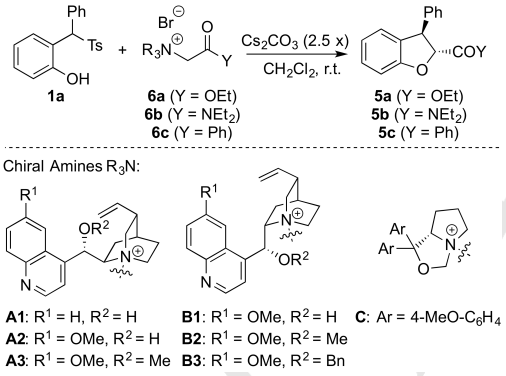
(highly) asymmetric ammonium ylide-based protocol which will overcome the so far observed less satisfactory enantioselectivity when using sulfur ylides, we also became interested in investigating this reaction in more detail by computational means to reveal the key-factors for this ylide-mediated (4+1) annulation reaction.[16]

Results and Discussion

Development of an Enantioselective Reaction Protocol.
First attempts were made using the achiral trimethyl ammonium salts **6a**-**6c** to investigate the influence of the nature of the carbonyl group on the reaction with o-quinone methide precursor **1a** (Table 1). Trimethylamine was chosen as the amine group because of its superior leaving group ability as compared to other achiral tertiary amines.[16] In an initial screening of a variety of different solvent/base combinations we found that the use of 2.5 eq. of Cs_2CO_3 in CH_2Cl_2 at room temperature is the most satisfying system when using the achiral trimethylamine containing ammonium salts **6a**-**6c**. Under these conditions, the ester-containing ammonium salt **6a** gave the corresponding dihydrobenzofuran **5a** with high *trans*-selectivity, but in only moderate yield (39%, no significant improvement by varying the conditions or stoichiometry could be achieved). Interestingly, the less stabilized amide-based ammonium ylide derived from **6b** did not give any product at all (just formation of unidentified side products), while the acetophenone-based salt **6c** could be used to access **5c** in an excellent 95% yield and with almost complete *trans* diastereoselectivity under the optimized reaction conditions (entries 1-3).

Table 1. Screening of different chiral and achiral ammonium salts **6** for the synthesis of 2,3-dihydrobenzofurans **5**.



A1: R^1 = H, R^2 = H **B1**: R^1 = OMe, R^2 = H **C**: Ar = 4-MeO-C_6H_4
A2: R^1 = OMe, R^2 = H **B2**: R^1 = OMe, R^2 = Me
A3: R^1 = OMe, R^2 = Me **B3**: R^1 = OMe, R^2 = Bn

Entry[a]	6	Amine	t (h)	Yield (%)[b]	*trans*:*cis*[c]	e.r. (*trans*)[d]
1	**6a**	Me_3N	20	39	> 95:5	--
2	**6b**	Me_3N	20	n.r.[e]	--	--
3	**6c**	Me_3N	20	95	> 95:5	--
4	**6c**	**A1**	20	37[f]	> 95:5	94:6
5	**6c**	**A2**	20	65	> 95:5	99:1
6	**6c**	**A3**	20	53	> 95:5	97:3
7	**6c**	**B1**	20	62	> 95:5	8:92
8	**6c**	**B2**	20	52	> 95:5	16:84
9	**6c**	**B3**	20	43	> 95:5	34:66
10	**6c**	**C**	20	63	90:10	30:70
11	**6c**	**A2**	72	85	> 95:5	99:1

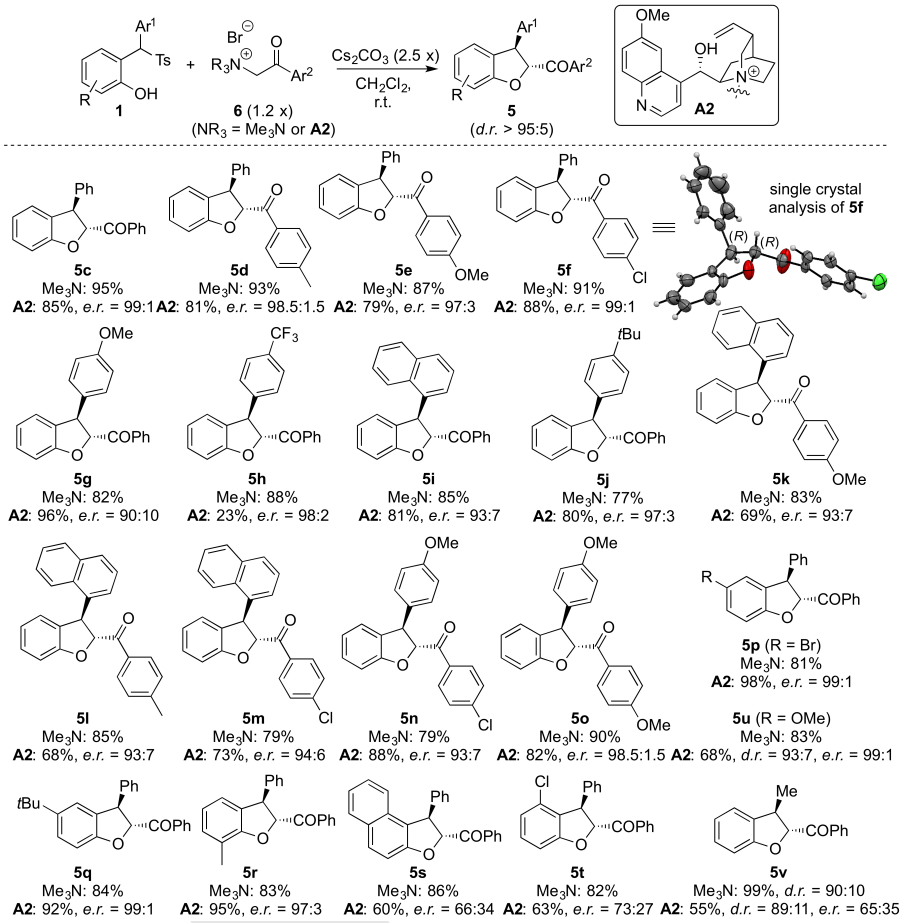
[a] Typical conditions: **1a** (0.1 mmol), **6** (0.12 mmol), Cs_2CO_3 (0.25 mmol) in CH_2Cl_2 at r.t.; [b] Isolated yield; [c] Determined by ^1H NMR of the crude product; [d] Determined by HPLC using a chiral stationary phase and given as ratio (2R,3R):(2S,3S); X-ray analysis of the chlorine-containing product **5f** (see Scheme 2) confirmed a (2R,3R)-configuration for this derivative and **5c** was assigned in analogy; [e] Full consumption and formation of unidentified side-products of **1** and **6b**; [f] Incomplete conversion of **6**.

Having identified conditions that allowed for the high yielding and highly diastereoselective synthesis of racemic dihydrobenzofuran **5c**, we next focused on the identification of a suitable chiral amine leaving group to develop an enantioselective protocol of this reaction. Cinchona alkaloids are usually the chiral pool-based tertiary amines of choice for chiral ammonium enolate-based reactions and have proven their potential for ammonium ylide-mediated cyclopropanations[9a,9b] or (4+1) annulations to α,β-unsaturated imines in the past.[13b] However, these amines were found not to be suited for ammonium ylide-mediated asymmetric epoxidation reactions and it was only recently that we succeeded in developing a proline-based chiral amine (structure **C**, Table 1) to achieve that goal.[10f] We were thus very pleased to see that literally the first attempt with amine **A1** already gave **5c** in high enantiopurity (entry 4, Table 1). As shown in entry 5, the yield and enantiopurity could be improved by using quinidine (**A2**) as the chiral amine leaving group (*e.r.* = 99:1, *d.r.* > 95:5 and 65% isolated yield) and we also soon realized that Cinchona alkaloids with a free 9-OH group (**A2** and **B1**) allow for higher enantioselectivities than the analogous O-alkyl derivatives (see entries 4-9). Both enantiomers of *trans*-**5c** could readily be obtained by using either **A2** or the pseudoenantiomeric **B1** but it should be pointed out that **A2** allowed for slightly higher enantiomeric ratios than **B1**. Based on our positive recent experience with compounds **C**,[10f] we also tested this class of auxiliaries herein (entry 10), but it was clearly shown that these amines are less-suited for this (4+1) annulation than the easily available Cinchona alkaloids. Interestingly, as the conversion of amine **A2**-containing ammonium salt **6c** was still not complete after 20 h reaction time (which is in sharp contrast to the use of Me_3N), longer reaction times of up to 3 days were necessary to achieve comparable yields for the enantioselective protocol (compare entries 11 and 3).
Unfortunately, attempts to start from α-bromo acetophenone and carry out an *in situ* ammonium salt formation and ylide generation were not successful, neither using a catalytic, nor using a stoichiometric amount of quinidine. As we observed mainly decomposition of **1a** in these attempts it seems likely that ammonium salt **6c** formation is slow as compared to the generation of o-quinone methide **3** (which in the absence of a suitable nucleophilic reaction partner undergoes aforementioned decomposition reactions). Overall this obstacle makes a catalytic protocol presently not feasible. However, it should be pointed out that the amine that is liberated during the reaction can easily be recovered after work up.

10.1002/chem.201700171

FULL PAPER

Having identified the optimum conditions and the best-suited chiral amine leaving group for the first highly asymmetric and high yielding formal (4+1) annulation procedure of onium ylides to o-quinone methides, we next explored the application scope of this strategy. As can be seen in Scheme 2 a variety of differently substituted acceptors **1** and ammonium salts **6** were very well tolerated either in a racemic fashion (using Me_3N-containing ammonium salts) or in the asymmetric protocol. In all cases the *trans* products were obtained with almost exclusive diastereoselectivity and satisfying isolated yields. The major exception in this regard was the asymmetric synthesis of the CF_3-containing product **5h**, which was achieved in a low yield of 23% only, while the racemic protocol proceeded with 88%. We first reasoned that this may be attributed to a decomposition reaction between the product and the free Cinchona base that is liberated during the reaction. However, test reactions proved that product **5h** is stable in the presence of **A2** and therefore the exact reason for this striking difference remains unclear.



Scheme 2. Application scope for the asymmetric synthesis of 2,3-dihydrobenzofurans **5**. All reactions were run on 0.1 – 1 mmol scale. Racemic reactions were run for 1 day and the chiral amine-based ones for 3 days to ensure full conversion. X-ray analysis of the chlorine-containing product **5f** proved a (2*R*,3*R*)-configuration for this derivative[17] and the other products were assigned by analogy.

With respect to the influence of different aryl substituents on the enantioselectivity two cases caught our attention. While only subtle decreases were observed in most cases when we introduced either substituents on the acceptor or on the donor site, the presence of residues in position 3 of the quinone methide part resulted in a significantly lower enantioselectivity (see products **5s** and **5t**). It has been reported that the introduction of sterically demanding groups in this position leads to a preferred formation of the (*Z*)-quinone methides, while unsubstituted derivatives mainly form the (*E*)-isomers.[14] We thus rationalize that this lower selectivity may be attributed to formation of a less selective (*Z*)-quinone methide (or a (*E*)/(*Z*) mixture) in these two cases. We also tested one substrate **1** with a methyl group instead of the Ar^1 substituent which performed reasonably well in the racemic approach giving **5v** in 99% but with a slightly lower *d.r.*. However, the achieved enantioselectivity for the asymmetric protocol turned out to be lower in that case. We also carried out a gram-scale experiment for the asymmetric synthesis of **5i** which was thereby obtained with the same enantiopurity as in the 0.1 mmol scale experiment (see Scheme 2) and in 67% yield (compared to 81% on a smaller scale).

Computational Studies.

In order to identify the mechanism and the key factors controlling the reactivity and stereoselectivity in this (4+1) annulation, we have investigated the free energy profile of the parent reaction between trimethylamine containing ylide **6c** (R = Me_3N; Ar^2 = Ph) and the o-quinone methide generated form **1a** (Ar^1 = Ph; Fig. 1). Calculations were carried out at the B3LYP-D3/6-311+G**//B3LYP-D3/6-31G* level of theory[18] including a continuum description of dichloromethane as solvent.[19]

The mechanistic sequence involves two key- steps along each of the diastereoisomeric pathways leading to *cis*- and *trans*-2,3-dihydrobenzofurans **5**. The first is addition of the ammonium ylide onto the methylene position of the electron-deficient o-quinone methide to form a betaine intermediate (see Fig. 1).[20] This betaine can then undergo ring closure, with concomitant expulsion of the amine, to give the corresponding 2,3-dihydrobenzofuran.[21]

Despite of the sterically hindered character of the formed betaine, the initial addition step is slightly exothermic (by 2-6 kcal.mol^{-1}) due to the rearomatization of the phenolic fragment. Two diastereomeric betaines can be formed during the addition step (*trans*-**A** and *cis*-**A**; Fig. 1). *Trans*-**A** is computed to be more stable than *cis*-**A** (-6.1 and -1.7 kcal/mol, respectively) but the latter is predicted to be

10.1002/chem.201700171

formed through a lower free energy barrier (11.6 kcal.mol^{-1}) than *trans*-**A** (13.6 kcal.mol^{-1}).

Since the S_N2-type mechanism, and hence the stereospecificity, of the cyclization step, betaines *trans*-**A** and *cis*-**A** lead to the *trans*- and *cis*-2,3-dihydrobenzofurans **5**, respectively. The free energy barrier to ring closure is found to be similar for both diastereomeric betaines (13-14 kcal.mol^{-1}). In the case of *trans*-**A**, the transition state of the ring closure lies lower in free energy than the addition TS, thus indicating a non-reversible initial addition step. For the *cis* pathway, the lower stability of *cis*-**A** induces a partially reversible betaine formation. Indeed, the *cis* addition TS and *cis* elimination TS are very close in terms of free energy (11.6 and 11.7 kcal.mol^{-1}, respectively). These transition states lie however lower than the *trans* addition TS, thus predicting a *cis* selectivity, which is in disagreement with the observed high *trans* selectivity (*trans*/*cis* > 95/5).

We reasoned that this contrast between computational predictions and experiment could be explained by a faster *cis*-2,3-dihydrobenzofuran **5c** formation (kinetic selectivity) followed by epimerization of this latter. In order to test this hypothesis, we isolated *cis*-**5c** and put it back under reaction conditions. A slow isomerization into the more stable *trans*-**5c** isomer was observed by NMR which led to complete epimerization after 15 h (*d.r.* > 95/5). Monitoring of the (4+1) annulation reaction over time revealed however that the >95/5 diastereomeric ratio in favour of the *trans*-2,3-dihydrobenzofuran is observed throughout and even in the first few minutes. Given its slow kinetic, epimerization of *cis*-2,3-dihydrobenzofuran can thus not account by itself for the observed high *trans* selectivity.

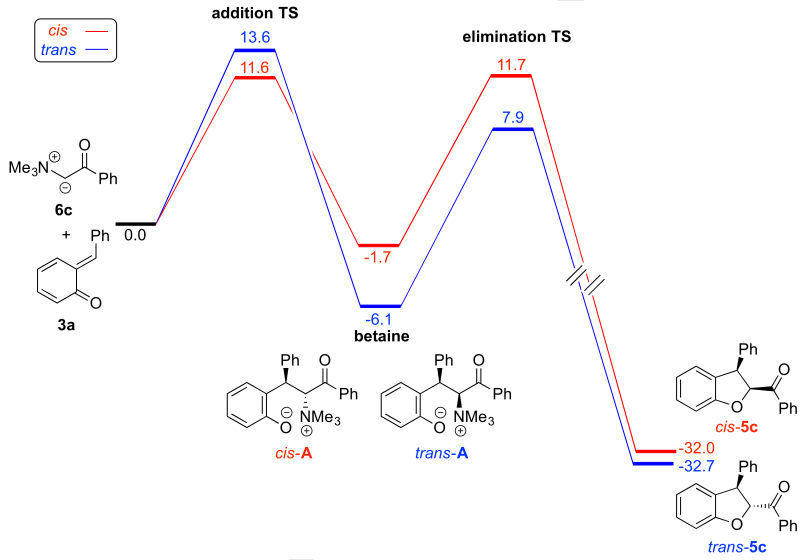


Figure 1. Computed free energy profiles (kcal.mol^{-1}) for the formation of *cis*- and *trans* 2,3-dihydrobenzofurans **5c** from ammonium ylide **6c**.

Another potential explanation involves the epimerization of the betaine intermediate **A** by a deprotonation/protonation mechanism such as previously observed by Aggarwal et al. in sulfur ylide-mediated cyclopropanation reactions.[22] Indeed, the computed relative free energy of **B** (0.7 kcal.mol^{-1}) indicates a facile proton transfer, and hence epimerization, in *cis*-**A** (see SI for full details). The observed high *trans*-selectivity can thus be accounted for by selective *cis*-**A** formation followed by rapid epimerization into *trans*-**A**, which then undergoes ring closure to give the *trans*-2,3-dihydrobenzofurans (Fig. 2). This also rationalizes why the two less enantioselective examples **5s** and **5t** were still obtained with very high *trans*-selectivities, even when quinone methide-formation proceeds with low diastereoselectivity only.

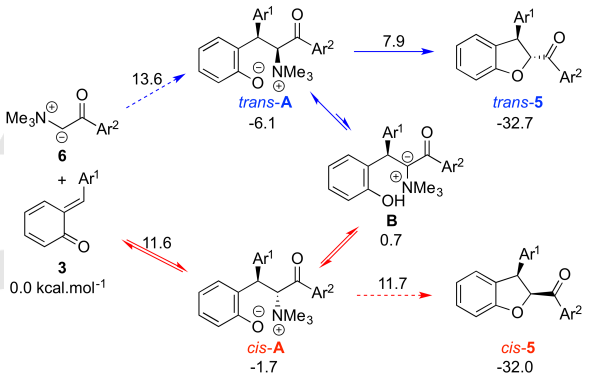


Figure 2. Mechanism and rationale for the observed high trans selectivity in (4+1)-annulation reactions between ketone-stabilized ammonium ylides and ortho-quinone methides (Relative free energies are in kcal.mol^{-1}).

Interestingly, the computed free energy profile (see Figure 1) allows also a rationalization for the low (or no) yield in **5** with ester- and amide-based ammonium ylides derived from **6a** and **6b**, respectively (see entries 1-2 in Table 1): Due to a lower stabilization of the ylide, addition should be more favoured, and more exothermic, in these cases as compared to ketone-based ylides. But for the elimination step, that is the reverse as the free energy barrier is expected to be increased with ester and amide derivatives.[23] In addition, isomerization of betaine by deprotonation/protonation should also be less favoured herein and the poor yields in these cases can thus probably be explained by a longer lifetime of betaine intermediates favouring side reactions.

Conclusions

We herein succeeded in the development of the first highly asymmetric (4+1) annulation protocol between *in situ* generated ammonium ylides and *ortho*-quinone methides to access chiral 2,3-dihydrobenzofuran derivatives. Key to success was the use of an easily available Cinchona alkaloid as the chiral leaving group, which resulted in an operationally simple and highly enantio- and diastereoselective synthesis strategy. Detailed computational studies support a mechanistic scenario where the high *trans*-selectivity of this procedure originates from a rapid isomerization of the *cis*-betaine intermediate to the *trans*-betaine intermediate, thus resulting in high diastereoselectivities for a broad application scope.

Experimental Section

General details can be found in the online supporting information. This document contains detailed synthesis procedures of starting materials and products and analytical data of novel compounds and reaction products as well as copies of NMR spectra and HPLC traces. The supporting information also includes the details of the computational investigations.

General asymmetric (4+1) annulation procedure: Compound **1** (1 equiv.), ammonium salt **6** (1.2 equiv.) and Cs_2CO_3 (2.5 equiv.) are dissolved in DCM (15 mL per mmol **1**). The reaction mixture is stirred at room temperature for 3 days and afterwards extracted with DCM and brine. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness. The crude products are purified by column chromatography (silica gel, heptane:EtOAc). Purification by column chromatography (gradient of heptanes and EtOAc) gives the corresponding 2,3-dihydrobenzofurans in the reported yields and enantiopurities.

Product 5c. Obtained as a white residue in 85% yield on 1 mmol scale (*e.r.* = 99:1). $[\alpha]_D^{20}$= -8.8 (c = 0.2, DCM, *e.r.* = 99:1); 1H NMR (700 MHz, δ, $CDCl_3$, 298 K): 4.99 (d, *J* = 6.5 Hz, 1H), 5.82 (d, *J* = 6.4 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.98 (m, 2H), 7.24 – 7.20 (m, 3H), 7.30 – 7.28 (m, 1H), 7.35 – 7.33 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H) ppm. 13C NMR (176 MHz, δ, CDCl3, 298 K): 51.0, 90.7, 110.1, 121.8, 125.5, 127.6, 128.3, 128.8, 129.0, 129.1, 129.5, 133.9, 134.6, 142.4, 159.2, 194.8 ppm. HRMS (ESI): *m/z* calculated for $C_{21}H_{16}O_2$: 323.1043 $[M+Na]^+$; found: 323.1040. The enantioselectivity was determined by HPLC (YMC Cellulose-SB, eluent: hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{major} (2R,3R) = 15.7 min, t_{minor} (2S,3S) = 17.0 min).

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Keywords: Ylides • Quinone Methides • Stereoselectivity • Chiral Auxiliary • DFT Calculations

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21 The betaine can ring close according to two different pathways: by attack of the C2 of the aromatic ring or of the phenolic oxygen to yield either a spirocyclic cyclopropane or a 2,3-dihydrobenzofuran, respectively. The exclusive formation of 2,3-dihydrobenzofuran and the non-observation of cyclopropane derivatives can, in part, be explained by the loss of aromaticity of the phenolic fragment that formation of the latter would cause. See SI for details.

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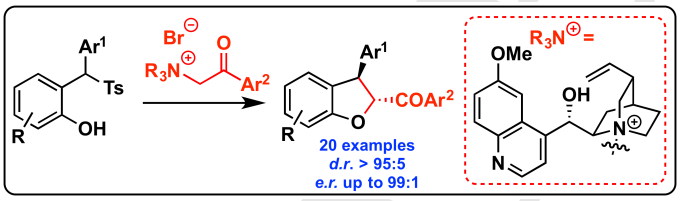

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Page No. – Page No.

Asymmetric synthesis of 2,3-dihydrobenzofurans via a (4+1) annulation of ammonium ylides and in situ generated *ortho*-quinone methides

The first highly enantio- and diastereoselective (4+1) annulation protocol between *in situ* generated ammonium ylides and *ortho*-quinone methides has been developed. This protocol gives access to highly functionalized chiral 2,3-dihydrobenzofuran derivatives.