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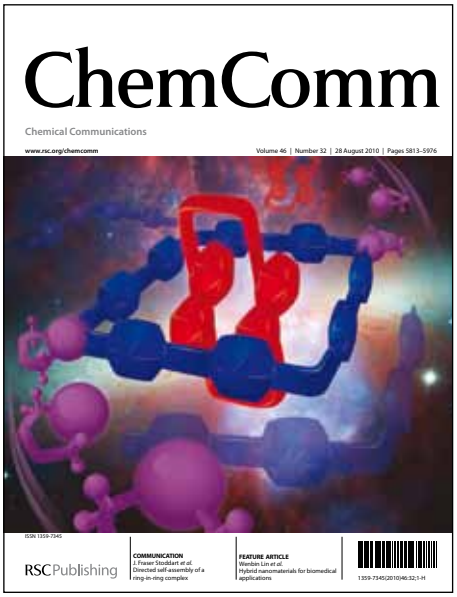

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COMMUNICATION

Asymmetric Synthesis of *trans*-Dihydroarylfurans in a Friedel-Crafts/Substitution Domino Reaction under Squaramide Catalysis

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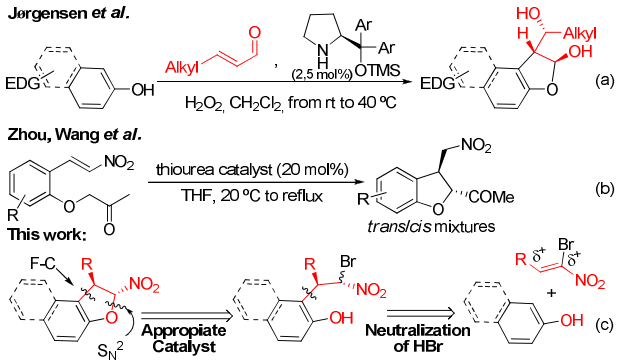
Dihydroarylfurans skeletons are efficiently synthesized from (*Z*)-bromonitroalkenes and naphthol derivatives in good yields and excellent enantioselectivities by using squaramide catalysis.

The dihydrobenzofurans (DHBs) and dihydronaphthofurans skeletons are common members in many important natural and pharmaceutical products,[1] especially those found to treat arteriosclerosis, hepatopathy and some central nervous system (CNS) disorders.[2] For example, bicunningine A and B[3] were recently isolated from *cunningamia lanceolata* or ε-Viniferin,[4] which is an important dimeric framework from resveratrol, obtusafuran (potent inductor of the anticarcinogenic marker of quinone reductase)[5] and variabilin (a novel inhibitor of phospholipase A2).[6] The importance of these structures is reflected by the publication of multiple synthetic strategies.[7-10] However, the asymmetric preparation of DHBs, especially in a catalytic manner, remains less explored and is limited to the use of some transition metal catalysis. Among them, Ru,[7a] Pd[7b] and Ir-catalyzed[7c] asymmetric hydrogenations of benzofurans are used along with other metal catalyzed reactions with Ti (IV),[8] Ag,[9] and Rh.[10] However, few examples for the synthesis of these structures *via* organocatalysis have been reported.

In the last decade, organocatalysis has emerged as a pivotal tool in organics synthesis.[11] Thus, two asymmetric organocatalytic approaches for the synthesis of dihydroarylfurans have recently appeared in the literature. Jørgensen *et al*[12] have presented the synthesis of different hemiacetal derivatives in good ee´s and moderate yields under aminocatalysis in a one-pot process (equation a, Scheme 1). More recently, Wang and Zhou[13] have reported an intramolecular Michael reaction under amino-thiourea catalysis to give furan derivatives in good ee´s but mixtures of *cis*/*trans* diastereoisomers were found (equation b, Scheme 1). Therefore, due to their inherent importance and scarcity of organocatalytic methods reported for these structures, new organocatalytic methodologies to prepare these substrates are highly desirable. (*Z*)-Bromonitroalkenes have emerged as a new bi-electrophilic synthon in organocatalysis[14] because they are electrophilic species at the α and β positions. In this paper, we propose the asymmetric synthesis of *trans*-dihydroarylfurans using (*Z*)-bromonitroalkenes under hydrogen-bonding catalysis. Thus, a Michael Friedel-Crafts (F-C) reaction followed by a nucleophilic substitution on the bromide carbon might allow the assembly of the desirable dyhydroarylfurans (equation c, Scheme 1). However, two potential problems must be solved. The first is related to the formation of hydrogen bromide during the substitution reaction, which may protonate the basic nitrogen of the catalyst and inhibits the first step (F-C reaction). The second, and more critical, is the search for an appropriate catalyst for the Michael-Friedel-Crafts reaction, as it has shown to have a limited reactivity for the nitroalkenes (4 days reaction[15a] and in some cases moderate enantioselectivities[15b]).

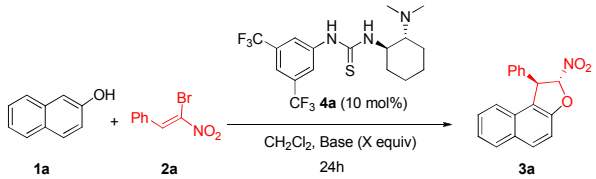


Scheme 1. Other approaches and our retrosynthetic approach to *trans*-dihydroarylfurans using (*Z*)-bromonitroalkenes

In order to identify the optimal reaction conditions, we evaluated the reactivity of the naphthol **1a** and (*Z*)-bromonitrostyrene **2a** under 10 mol% of Takemoto's catalyst **4a** (entry 1, Table 1). As it was expected, only 10% conversion was found since the generated HBr, during the first catalytic cycle, protonated the basic nitrogen of the catalyst **4a.** Interestingly, a promising 50% enantiomeric excess was obtained. Stimulated with this initial result, we supposed that delivered HBr at end of process could be neutralized by a stequiometric amount of appropriated base. Thus, we tested several bases in order to increase the conversion and to preserve the obtained 50% ee (see ESI for full screening). Different organic bases (Et_3N, DBU, DMAP) in sub- and stoichiometric amounts were found beneficial for the final conversion. However, slightly lower enantioselectivities (50% ee) were obtained in all cases, indicating that the background reaction had occurred with these organic bases (entries 2-4). The change to 1.0 equiv. of an inorganic base such as NaOAc provoked an increase in the conversion, and more interestingly, the enantioselectivity was maintained (50% ee), indicating that the background reaction was

not occurring with this base (entry 5, table 1). Other bases were found less active in the conversion and in the final enantiomeric excess (see ESI). With these results in hand, we began to study other catalysts (thioureas[16] and squaramides[17]) to improve the enantioselectivity (Table 2).

Table 1. Screening of different bases.



Entry	Base	Base (equiv.)	Conversion (%)	Ee (%)
1	-	-	10	50
2	Et_3N	1.0	100	28
3	DMAP	0.5	67	45
4	DBU	0.5	77	43
5	**NaOAc**	**1.0**	**81**	**50**

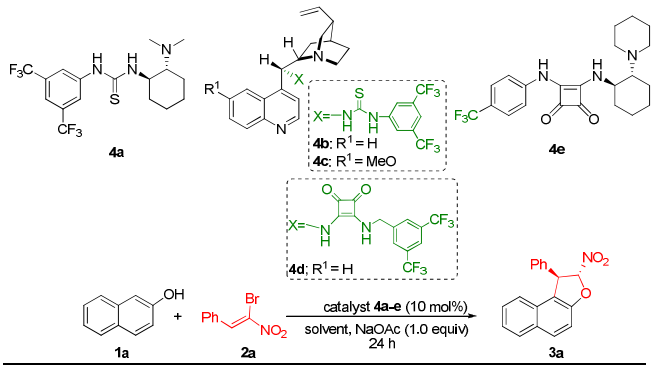
[a] All the reactions were performed in 0.2 mmol scale of **2a** in 0.4 mL of dry CH_2Cl_2 using 1.8 equiv. of 2-naphthol.

To our delight, we observed that the use of alkaloid thiourea **4b** in CH_2Cl_2 for 48 h at rt led to the furan derivative **3a** in 69% conversion and 76% ee (entry 2). The quinine thiourea **4c** gave a lower enantioselectivity (entry 3). Then, we focused on the squaramide catalysts (**4d** and **4e**), since they have been used for the activation of nitroalkenes with excellent results for different reactions.[17] Catalyst **4d** did not improve the results (entry 4). However, the use of catalyst **4e**,[17b] analogous to Takemoto´s catalyst **4a**, provoked a dramatic change from 50% to 82% ee under the same reaction conditions (compare entries 1 and 5). Next, we studied other solvents, such as toluene, xylene, benzene, Et_2O and $CHCl_3$ (entries 6-10). $CHCl_3$ was found to be the best solvent giving excellent conversion and good enantioselectivity (entry 10). We also studied the effect of the temperature, and when the reaction was carried out at 0 ºC, the obtained enantioselectivy was quite similar (93%), although with slightly lower conversion (entry 11). To improve this conversion and the efficiency of the catalyst (released from HBr), we increased the amount of NaOAc to 1.5 equiv. at the same temperature, and we found an excellent 98% ee, good conversion and good isolated yield (entry 12).

Next, we studied the scope of the reaction with different substituents at the bromonitroalkene (Table 3). The use of electron-donating groups such as *p*-Me (entry 2) or *p*-MeO (entry 3) provided products **3b** and **3c** with good enantioselectivities, but in the case of the *p*-MeO group, the obtained yield was lower due to the lower electrophilicity of the nitroalkene **2c**. In the case of halogen substituents, such as *o*-F or *p*-F (entries 4 and 5, respectively), products **3d** and **3e** were obtained with similar results. The use of *p*-Br was also compatible (entry 6), and it was possible to scale up the reaction without erosion of the final results (entry 7). An alkyl group such as *n*-butyl allowed the synthesis of the product **3g** (entry 8). However, the use of bulkier alkyl groups, such as *t*-butyl was not compatible, due to the steric hindrance of the first step. This poor reactivity was also observed for non-bromo-nitroalkenes.[15]

Then, we studied different substituted naphthols and phenols derivatives (Scheme 2). Thus, the method was compatible with different bromo substituents at 2, 6 or 7 positions in all the cases

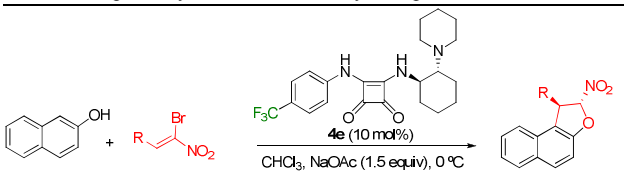
Table 2. Screening of catalysts and solvents. [a]



Entry	Catalyst (mol%)	Solvent	Conversion (%)	Ee (%)
1	**4a** (10mol%)	CH_2Cl_2	81	50
2	**4b** (10mol%)	CH_2Cl_2	69	76
3	**4c** (10mol%)	CH_2Cl_2	68	52
4	**4d** (10mol%)	CH_2Cl_2	88	45
5	**4e** (10mol%)	CH_2Cl_2	81	82
6	**4e** (10mol%)	Toluene	71(69)[d]	70
7	**4e** (10mol%)	*p*-Xylene	84(76)[d]	58
8	**4e** (10mol%)	benzene	91(55)[d]	52
9	**4e** (10mol%)	Et_2O	57(88)[d]	85
10	**4e** (10mol%)	$CHCl_3$	97 (62)[d]	92
11[b]	**4e** (10mol%)	$CHCl_3$	67 (43)[d]	93
12[b,c]	**4e (10mol%)**	**$CHCl_3$**	**84 (71)**[d]	**98**

[a] All the reactions were performed in 0.2 mmol scale of **2a** in 0.4 mL of dry CH_2Cl_2 using 1.8 equiv. of 2-napthtol. [b] The reaction was carried out at 0º C. [c] 1.5 equiv of NaOAc was used. [d] Isolated yield after flash-chromatography.

Table 3. Scope for synthesis of *trans*-dihydronaphthofurans.[a]

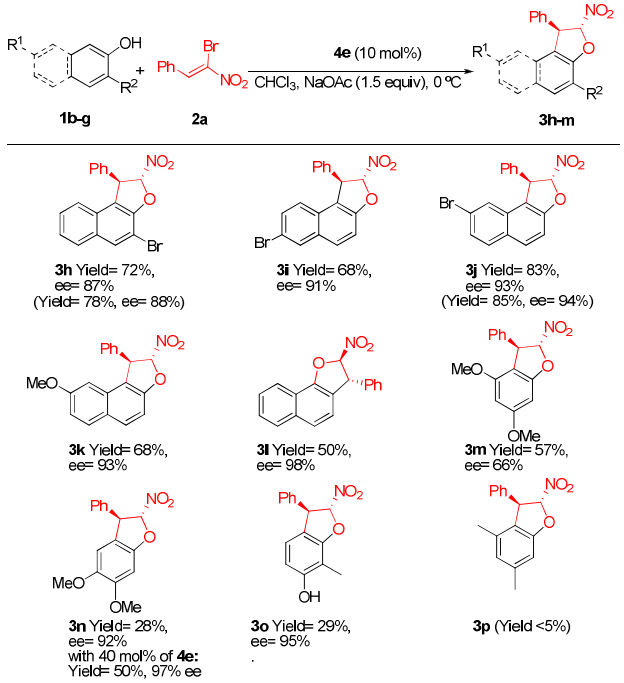


Entry	R-starting material	Reaction Time (h)	Yield (%)-Product	Ee (%)
1	Ph-**2a**	16	71-**3a**	98
2	*p*-MeC_6H_4-**2b**	62	85-**3b**	94
3	*p*-$MeOC_6H_4$-**2c**	62	45-**3c**	94[b]
4	*o*-FC_6H_4-**2d**	16	94-**3d**	88
5	*p*-FC_6H_4-**2e**	16	59-**3e**	97
6	*p*-Br C_6H_4-**2f**	16	78-**3f**	92
7[b]	*p*-Br C_6H_4-**2f**	48	72-**3f**	92
8	*n*-Bu-**2g**	7d	55-**3g**	91
9	*t*-Bu-**2h**	24	n.r.	-

[a] All the reactions were performed in 0.2 mmol scale of **2a-h** in 0.4 mL of dry CH_2Cl_2 using 1.8 equiv. of β-napthol. [b] The reaction was carried out in 1.0 mmol scale. [c] The reaction was carried out at -10 ºC.

with excellent enatioselectivities and good yields. The reaction was carried out in a 2.0 mmol scale without erosion in the enantioselectivity for compounds **3h** and **3j** (results in brackets).

The reaction was compatible with electrondonating groups (MeO), with a similar efficiency (middle-left). The 1-naphthol can be also used in the same reaction to obtain an excellent enantioselectivity but a lower yield (**3l**, 50%). Other aryl groups, such as 3,5-dimethoxyphenol gave a lower yield and enantioselectivities (bottom-right). Interestingly, the use of 3,4-dimethoxyphenol and 2-methylresorcinol gave an excellent enantioselectivity but a moderate yield were found for both cases (**3n** and **3o**). The yield of **3n** was improved to 50% by using 40 mol% of catalyst **4e**. Finally, a less activated phenol ring, such as 3,5-dimethylphenol, did not gave the reaction, and only traces of the expected product **3p** can be found in the crude mixture.



Scheme 2. All the reactions were performed in 0.2 mmol scale (Results in brackets carried out at 2.0 mmol scale).

The absolute configuration was unequivocally determined by X-ray diffraction analysis from crystals of compounds **3h** and **3j**,† which allowed us to assign their absolute configuration as (1*S*,2*S*) in both cases (Figure 1). This assignment was then used for the remainder of the compounds **3** depicted in Table 3 and Scheme 2.

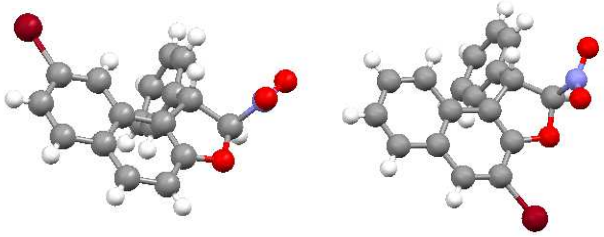


Figure 1. X- Ray analysis of compounds **3h** (left) and **3j** (right).

In conclusion we have found that chiral *trans*-dihydroarylfuran derivatives can be efficiently synthesized from (*Z*)-bromonitroalkenes and naphthol or phenol derivatives from moderated to good yield and excellent ee´s by using a squaramide catalysis. The key of this catalytic system is the neutralization of the generated HBr by a stequiometric co-base.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental Procedure for synthesis of compounds **3** and X-ray data of compound **3h** and **3j** (CCDC 902091 and 902092). See DOI: 10.1039/b000000x/

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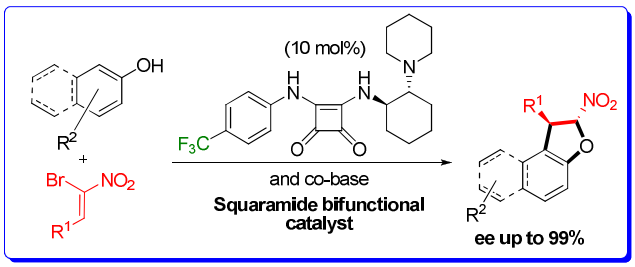

Abstract