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Catalytic Asymmetric Mannich–Ketalization Reaction: Highly Enantioselective Synthesis of Aminobenzopyrans

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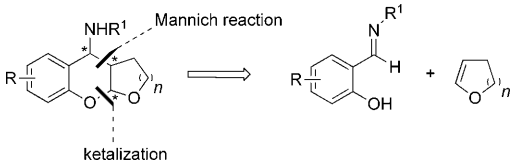
The benzopyran structure is present in a number of naturally occurring products with interesting biological activities,[1] including antihypertensive and anti-ischemic behavior.[2] 4-Aminobenzopyran derivatives can also be used as modulators of potassium channels affecting cardiac activity of the blood pressure.[3] Owing to the importance of the benzopyran framework, their synthesis has attracted considerable attention.[4] Although several Lewis acids have been employed as catalysts to afford benzopyran derivatives, to the best of our knowledge, there is no report of a direct catalytic asymmetric method for the synthesis of optically active 4-aminobenzopyran derivatives.[5] Thus, the development of a new catalytic asymmetric method for their preparation attracted our interest.

Over the past few years, asymmetric organocatalysis has emerged as a powerful tool for a variety of organic transformations. In this context, organocatalytic domino reactions are of particular interest as more than one stereocenter can be formed in a single reaction sequence.[6] Thus we decided to examine the enantioselective domino reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2*H*-pyran (DHP) and 2,3-dihydro-2*H*-furan (DHF). This would not only be the first example of a direct asymmetric catalytic variant of such a reaction but more importantly it would give direct and ready access to enantiomerically enriched 4-aminobenzopyran and derivatives.

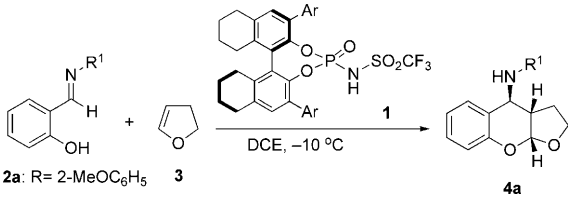
Herein we report the first catalytic asymmetric synthesis of 4-aminobenzopyranes and derivatives through an enantioselective Mannich[7]–ketalization reaction (Scheme 1).

On the basis of our previous work in the field of chiral counterion and domino catalysis, we initially started our investigation with the exploration of various metal free catalysts in the Mannich–ketalization reaction of *o*-methoxybenzaldimine with 2,3-dihydro-2*H*-furan. The best results with regard to reactivity and selectivity were obtained with the highly acidic *N*-triflylphosphoramides (Table 1).[8] These had earlier been introduced by Yamamoto et al.[9a] but have surprisingly not yet been widely applied in asymmetric catalysis.[9]



Scheme 1. A Mannich–ketalization reaction for the synthesis of 4-aminobenzopyrans.

Table 1. Evaluation of chiral *N*-triflylphosphoramide catalysts in the enantioselective domino Mannich–ketalization reaction.



2a: R= 2-MeOC$_6$H$_5$ **3** **4a**

Entry[a]	Ar	Yield [%][b]	d.r.[c]	e.r.[d]
1	phenyl (**1a**)	88	1.1:1	60:40
2	1-naphthyl (**1b**)	85	1.5:1	80:20
3	2-naphthyl (**1c**)	75	1:1	60:40
4	4-F-C$_6$H$_4$ (**1d**)	85	1:1	59:41
5	4-OMe-C$_6$H$_4$ (**1e**)	90	1.1:1	60:40
6	9-anthracenyl (**1f**)	69	1.3:1	79:21
7	9-phenanthryl (**1g**)	78	1.15:1	86:14
8[e]	9-phenanthryl (**1h**)	80	1.2:1	12:88

[a] Reaction conditions: **2a**, **3** (5.0 equiv), **1** (5 mol%), 0.25 M solution in 1,2-dichloroethane (DCE) at −10 °C. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] Use *S* enantiomer of **1g** yields in the opposite enantiomer **4a′**.

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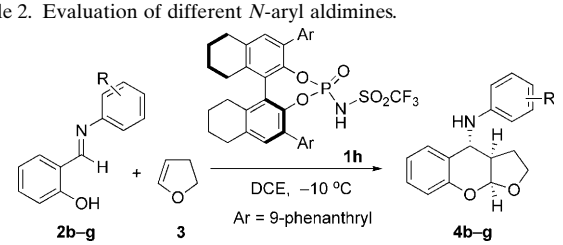
The best results with regard to diastereo- and enantioselectivity were obtained with catalytic amounts of **1g** (5 mol%) providing 4-aminobenzopyran (**4a**) with an enantiomeric ratio of 86:14 in favor of the *cis*-isomer (Table 1, entry 7). Applying chiral *N*-triflylphosphoramide (**1h**) derived from (*S*)-BINOL as the catalyst resulted in the product with the opposite configuration.

Subsequently, we examined different reaction parameters by varying reactant concentrations, solvents, temperatures and the influence of the aldimine protecting group in order to improve the enantioselectivity.[10] For instance, several *N*-aryl-aldimine derivatives were prepared and tested in the enantioselective domino Mannich–ketalization reaction. The results are summarized in Table 2. In general excellent enantiomeric ratios were obtained irrespective of the aryl group used (Table 2, entry 2–7). The highest enantiomeric ratios (e.r. 96:4) were obtained with phenyl- and *p*-methoxyphenyl-protected aldimine derivatives.

Table 2. Evaluation of different *N*-aryl aldimines.

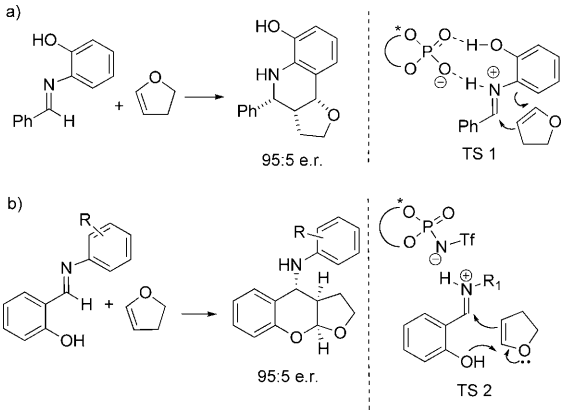


2b–g 3 4b–g

Entry[a]	R	*t* [h]	Yield [%][b]	d.r.[c]	e.r.[d]
1	2-OMe	24	80 (**4a**)	1.2:1	88:12
2[e]	H	36	81 (**4b**)	2.7:1	96:4
3[f]	4-OMe	72	51 (**4c**)	2.5:1	96:4
4	4-Cl	60	84 (**4d**)	2.3:1	95:5
5	4-F	52	76 (**4e**)	2.1:1	95:5
6	4-Br	50	86 (**4f**)	2.3:1	94:6
7	4-Me	55	74 (**4g**)	2.6:1	95:5

[a] Reaction conditions: **2**, **3** (5.0 equiv), **1h** (5 mol%), 0.25 M solution in DCE at −10 °C. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] The reaction was carried out at −20 °C. [f] 10 equiv of **3**.

The latter observation is particularly interesting if compared to the recently reported chiral phosphoric acid[11,12]-catalyzed reverse electron-demanding aza-Diels–Alder reaction by Akiyama and co-workers.[13] The activation of the aldimine in this transformation is believed to proceed through a bifunctional activation via a nine-membered hydrogen-bonded transition state TS 1 which results in the formation of the 8-hydroxytetrahydroquinolines (Scheme 2a). In contrast, our newly developed *N*-triflylphosphoramide catalyzed Mannich–ketalization reaction selectively yields 4-aminofuranobenzopyrans and is most likely to proceed through the formation of an intermediary chiral iminium ion pair transition state (Scheme 2b). Compared to the tetrahydroquinoline synthesis the difference in regioselectivity must be due to the nucleophilicity of the benzaldimine hydroxyl group which leads to a faster ketalization reaction.



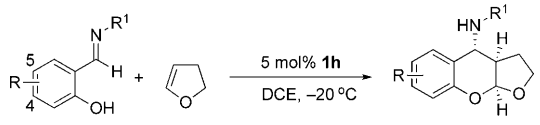
Scheme 2. Brønsted acid catalyzed reaction of aldimines with dihydrofuranes leads depending on the hydroxyl substitution to either formation of a) tetrahydroquinolines or b) furanobenzopyranes.

With the optimized conditions in hand, we decided to explore the scope of this new asymmetric domino Mannich–ketalization reaction yielding tricyclic furanobenzopyrans with control of three stereocenters. In general differently substituted *o*-hydroxybenzaldimines (Table 2) with various *N*-aryl residues (Tables 2 and 3) can be effectively reacted with 2,3-dihydro-2*H*-furan to give the desired products in good yields and with excellent enantioselectivities.

The molecular structure of the products was determined by X-ray analysis of **6h** (Figure 1). The absolute configuration of the major diastereomer was assigned to be 3*R*,4*R*,9*S*.

Encouraged by these results we proceeded to examine additionally the use of 3,4-dihydro-2*H*-pyran (**8**) in this new catalytic asymmetric Mannich–ketalization reaction.[14] This

Table 3. Scope of the Brønsted acid catalyzed enantioselective domino Mannich–ketalization reaction.



5a–l 3 6a–l

Entry[a]	R	R^1	Yield [%][b]	d.r.[c]	e.r.[d]
1	5-Cl	Ph	83 (**6a**)	1.9:1	96:4
2	5-Br	Ph	87 (**6b**)	2.2:1	96:4
3	5-OMe	Ph	81 (**6c**)	1.7:1	96:4
4	5-Me	Ph	89 (**6d**)	1.9:1	95:5
5[e]	4,6-$(Cl)_2$	Ph	88 (**6e**)	-[h]	98:2
6[e]	4-OMe	Ph	46 (**6f**)	1.8:1	92:8
7[e]	3-OEt	Ph	87 (**6g**)	2.1:1	87:13
8[e]	5-Cl	*p*-Cl-C_6H_4	78 (**6h**)	2.2:1	93:7
9[e,f]	5-OMe	PMP	53 (**6i**)	1.2:1	95:5
10[f,g]	5-Cl	PMP	51 (**6j**)	1.15:1	94:6
11[f,g]	5-Br	PMP	59 (**6k**)	1.5:1	94:6
12[f,g]	5-Me	PMP	55 (**6l**)	1.3:1	91:9

[a] Reaction conditions: **5**, **3** (5.0 equiv), **1h** (5 mol%), 0.25 M solution in DCE at −20 °C for 30–72 h. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR-spectroscopy. [d] Determined by HPLC analysis. [e] At −10 °C. [f] 10 equiv of **3**. [g] At 0 °C. [h] Only *syn* isomer detected.

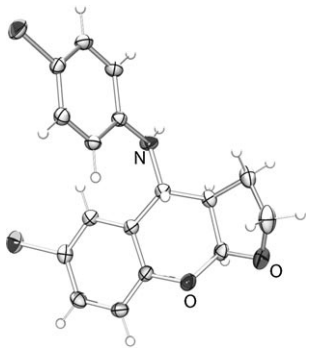
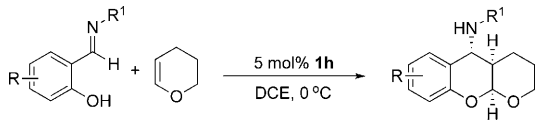


Figure 1. Molecular structure of furanobenzopyran **6h**.

would be the first example of the catalytic enantioselective synthesis of optically pure 4-amino pyranobenzopyrans. Again diverse *o*-hydroxy benzaldimines with electron-withdrawing and electron-donating substituents underwent the enantioselective domino Mannich–ketalization reaction to give the desired products **9a–g** in good yields with high enantiomeric ratios (Table 4).

Table 4. Brønsted acid catalyzed enantioselective synthesis of pyrano benzopyrans.



2b, 5a–e, 5h **8** **9a–g**

Entry[a]	R	R^1	Yield [%][b]	d.r.[c]	e.r.[d]
1	H	Ph	65 (**9a**)	6.8:1	95:5
2	5-Cl	Ph	66 (**9b**)	7.5:1	94:6
3	5-Br	Ph	63 (**9c**)	4.3:1	94:6
4	5-OMe	Ph	69 (**9d**)	4.8:1	94:6
5	5-Me	Ph	59 (**9e**)	6.3:1	93:7
6	4,6-$(Cl)_2$	Ph	71 (**9f**)	33:1	97.5:2.5
7	H	*p*-Cl-C_6H_4	65 (**9g**)	21:1	93:7

[a] Reaction conditions: **2b** or **5**, **8** (10.0 equiv), **1h** (5 mol%), 0.25 M solution in DCE at 0 °C. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.[14]

In summary, we have developed the first enantioselective domino Mannich–ketalization reaction of *o*-hydroxy benzaldimines with electron-rich alkenes. The new reaction sequence provides an easy and direct access to optically pure 4-aminobenzopyrans in good yields with excellent enantiomeric ratios (up to e.r. 98:2). Our newly developed reaction nicely complements Akiyama's previously reported Brønsted acid catalyzed reaction of aldimines with dihydrofurans and dihydropyrans which lead to tetrahydroquinolines. However, our reaction results in the enantioselective synthesis of biologically relevant furanobenzopyrans and pyranobenzopyrans. The reaction sequence proceeds under mild reaction conditions in the presence of an air-stable chiral *N*-triflylphosphoramide catalyst and represent a first example of a Mannich–ketalization reaction in asymmetric domino catalysis.

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Keywords: Brønsted acid · chromene · domino reactions · ion pairs · organocatalysis

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