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Organocatalytic synthesis of chiral benzopyrans

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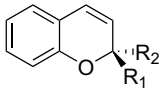
Abstract—Benzopyrans, or chromenes, are widespread in nature and are considered to be a privileged scaffold in medicinal chemistry. Herein, we report the first organocatalyzed asymmetric synthesis of chiral benzopyrans. The benzopyran unit is constructed through a domino reaction involving an oxa-Michael attack of salicylic aldehyde derivatives onto α,β-unsaturated aldehydes, activated through iminium-ion formation with the organocatalyst, followed by an intramolecular aldol reaction and subsequent elimination of water. This overall reaction sequence provides benzopyrans with aromatic C-2 substituents in up to 60% yield and 60% enantioselectivity, while C-2 aliphatic analogues can be obtained in 90% enantiomeric excess, but with only 20% yield. The role of additives, as well as the possible racemization of the benzopyran, was also investigated.

1. Introduction

The benzopyran, or chromene, structural core is a widespread element in natural products and in lead compounds with proven pharmacological activities.[1] Certain benzopyrans have also received attention due to their photochromic and thermochromic properties.[2] Many of the biologically active benzopyrans reported to date belong to the 2,2-dimethyl-2*H*-benzopyrans family **1**, that is, they lack a stereogenic center in the pyran ring, while others possess a stereogenic center at C-2, that is, **2**:



1 $R_1 = R_2 = Me$
2 $R_1 \neq R_2$

Chiral benzopyrans have been prepared by kinetic resolution,[3a] dehydrogenation of chromane,[3b] cyclization of an α,β-unsaturated sulfoxide,[3c] and most recently through Ru-catalyzed metathesis.[3d,e] The most recent methodology for the preparation of non-chiral benzopyrans is based on base-catalyzed condensation of 2-hydroxybenzaldehydes with α,β-unsaturated aldehydes as reported by Bräse et al.[4]

The latter procedure relies on a substoichiometric amount (0.5 equiv) of a non-secondary base for increasing the nucleophilicity of the hydroxybenzaldehyde. We figured that this synthetic sequence should benefit from an organocatalytic activation of the α,β-unsaturated aldehyde through iminium-ion catalysis,[5,6] which would allow a novel entry to C-2 chiral benzopyrans if a chiral catalyst were to be used. This synthetic sequence would open an alternative route toward these highly attractive targets, which in turn will help unravel the stereochemical influence on these molecules' biological activity.

2. Results and discussion

We envisaged a reaction sequence in which the iminium-ion intermediate **4** is first formed through the reaction of a secondary amine catalyst and the α,β-unsaturated aldehyde **3** (Scheme 1). This highly electrophilic compound then undergoes a domino reaction involving an oxa-Michael addition with the hydroxy-aldehyde, leading to enamine **5**, followed by an intramolecular aldol reaction giving β-hydroxy-aldehyde **6**. Although valuable per se, this compound is expected to readily undergo elimination leading to the conjugated benzopyran system **7**.

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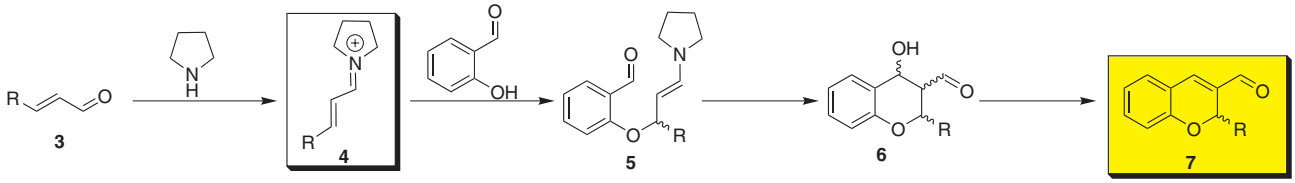
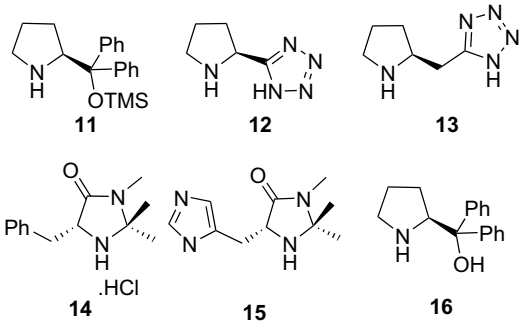


Scheme 1. Proposed organocatalytic synthesis of benzopyrans.

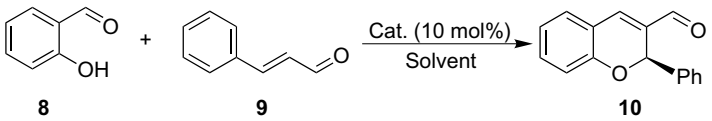
Initially, we set out to investigate the addition of salicylaldehyde **8** and *trans*-cinnamaldehyde **9** to yield chiral 2-phenyl-2*H*-chromene-3-carbaldehyde **10** (Table 1). A selected number of organocatalysts, that is, **11**–**16**, were tested for this benchmark reaction:



Jørgensen[7] et al. have repeatedly shown that the TMS protected prolinol derivative **11** is useful for activating α,β-unsaturated aldehydes for Michael addition reactions, and the results presented in Table 1 confirm this. Despite the fact that this catalyst was employed as a free base, considerable turnover and promising levels of enantioselectivity were observed in dichloromethane (entry 1), while other solvents gave slower reactions (entries 2–4). Neither of the tetrazole catalysts **12**[8] and **13**[9] gave any product, nor did the MacMillan[5a] catalyst **14**. The novel imidazole catalyst **15**, successful in activating α,β-unsaturated aldehydes for nucleophilic attack by nitroalkanes,[10] did not provide any product. The lack of reactivity for the archetypal iminium-ion catalysts **14** and **15** suggests that these are too bulky to successfully bring about this intramolecular domino reaction.

The effect of acid and base additives on the reaction is outlined in Table 2. The addition of base was expected to increase the nucleophilicity of the salicylic aldehyde and also promote the final elimination of water, which resulted in formation of the conjugated benzopyran structure. The use of imidazole (Table 2, entry 1) decreased the rate of conversion significantly but increased the ee by 9%. Although the most successful reagent for the non-asymmetric substoichiometric reaction explored by Bräse, DABCO decreased the yield and enantioselectivity of the iminium-catalyzed reaction, possibly by promoting an unwanted vinylogous aldol reaction leading to tri-cyclic hemiacetal formation.[4a] Likewise, the addition of *trans*-2,5-dimethylpiperazine led to a decrease in yield (entry 3). The addition of acid on the other hand was expected to facilitate the formation of the activated iminium-ion. Surprisingly, the use of strong acids such as TFA or *p*-toluenesulfonic acid more or less completely inhibited the reaction (entries 4 and 5), while a weaker acid, such as *p*-chlorobenzoic acid, yielded the product with a 12%

Table 1. Screening of catalysts for the organocatalyzed reaction between salicylaldehyde **8** and *trans*-cinnamaldehyde **9** yielding 2-phenyl-2*H*-chromene-3-carbaldehyde **10**



Entry	Catalyst	Time (h)	Solvent	Conversion (%)[b]	ee (%)[c]
1	**11**	48	CH_2Cl_2	90	60
2	**11**	64	DMF	20	35
3	**11**	45	Toluene	19	nd
4	**11**[a]	45	CH_2Cl_2	6	nd
5	**12**	67	CH_2Cl_2	0	—
6	**12**	67	DMF	0	—
7	**13**	67	CH_2Cl_2	5	nd
8	**13**	67	DMF	0	—
9	**14**	67	CH_2Cl_2	0	—
10	**14**	67	DMF	0	—
11	**15**	64	DMF	0	—
12	**16**	66	CH_2Cl_2	20	22

All reactions were carried out using **8** (1 equiv) and **9** (0.5 equiv) with catalyst (0.05 equiv) at ambient temperature.

[a] 0 °C.

[b] Determined by ^{1}H NMR.

[c] Determined by Daicel AS-H column, hexane–isopropanol (97:3), flow = 0.8 ml min^{-1}.

Table 2. Investigation into how basic or acidic additives affect the reaction between **8** and **9** catalyzed by **11**

Entry	Time (h)	Additive	Conversion (%)[a]	ee (%)[b]
1	67	Imidazole	10	69
2	67	DABCO	43	43
3	67	*trans*-2,5-Dimethylpiperazine	34	7
4	67	TFA	10	nd
5	67	*p*-TsOH	0	nd
6	40	*p*-Chlorobenzoic acid	29	72
7	67	*p*-Chlorobenzoic acid	52	72

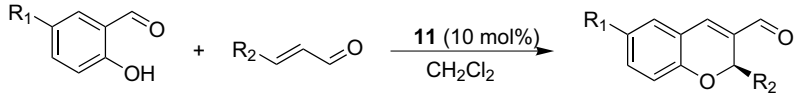
All reactions were carried out using 1 equiv of the additive with respect to the catalyst (10% as compared to the limiting reagent).
[a] Determined by ^{1}H NMR.
[b] Determined by Daicel AS-H column, hexane–isopropanol (97:3), flow = 0.8 ml min^{-1}.

increase in enantioselectivity, albeit with lower yield. The use of *p*-chlorobenzoic acid not only decreased the rate of formation of **10** as monitored by ^{1}H NMR, but also decreased the rate of conversion of **9** into unwanted side products. The effect of additives suggests that there is a fine balance between promoting and obstructing the various reaction steps involved in the desired domino reaction and in the reactions pathways leading to unwanted side products.

Bräse has already shown that an increased yield can be obtained by using the more electron rich 5-methoxy salicylaldehyde **17** instead of salicylaldehyde **8** as the nucleophile in the oxa-Michael addition.[4a] This led us to investigate the use of derivatives of the reactants that would favor the oxa-Michael addition. We found that the use of 5-methoxy salicylaldehyde **17** resulted in a much faster reaction, with higher isolated yields but at the expense of enantioselectivity (Table 3, entries 1 and 2). Surprisingly, the use of nitro-substituted cinnamaldehydes **18** and **19**, which would be expected to be better Michael acceptors than cinnamaldehyde **9**, led to a decrease in both isolated yields and enantioselectivity. The use of the aliphatic substrate 2-hexenal **20** resulted in very poor yields; however, the product was isolated in excellent enantiomeric excess (90%). We also tried to increase the yield by making the salicylaldehyde **8** the limiting reagent; however, this led to by-product formation (possibly through self-condensation) especially when aliphatic aldehyde **20** was used. We then performed the reaction by adding 4 equiv of 2-hexenal **20** in 20 portions over 24 h (entry 9). This not only increased the yield slightly, but also decreased the product's ee.

Concerning the mechanism of this reaction, we failed to observe intermediates **5** and **6** via NMR. However, we were able to detect the rapid formation of iminium-ion **4**. Consequently, we do not expect the iminium-ion formation to be rate determining in this reaction, as suggested by the lack of rate enhancement in the presence of an acid (Table 2). Thus, it appears that the oxa-Michael reaction is the

Table 3. Scope of the organocatalyzed synthesis of chiral benzopyrans



8 R_1 = H
17 R_1 = OMe

9 R_2 = Phenyl
18 R_2 = *p*-Nitrophenyl
19 R_2 = *o*-Nitrophenyl
20 R_2 = propyl

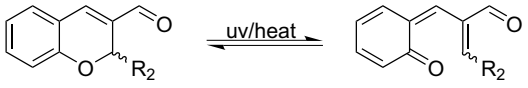
	R1	R2
10	H	Phenyl
21	OMe	Phenyl
22	H	*p*-Nitrophenyl
23	H	*o*-Nitrophenyl
24	OMe	*o*-Nitrophenyl
25	H	propyl
26	OMe	propyl

Entry	Product	Time (h)	Isolated yield (%)	ee (%)
1	**10**	48	63	60
2	**21**	36	70	44
3	**22**	48	36	48
4	**23**	48	28	27
5	**24**	36	54	29
6	**25**	16	14	77
7[a]	**25**	24	25	69
8	**26**	16	15	90
9[b]	**26**	16	21	90

All reactions were carried out with **8/17** (2 equiv), the α,β-unsaturated aldehyde (1 equiv) and catalyst **11** (10 mol %) at room temperature for a maximum of 48 h or until 100% conversion of the limiting reagent. See Ref. 12 for a typical procedure.
[a] Cat. amount of *p*-chlorobenzoic acid added.
[b] 2-Hexenal (4 equiv) was added portionwise.

rate-determining step in this reaction. This assumption is supported by NMR and GC–MS investigations of the reaction mixture showing that the amount of salicylaldehyde is conserved either as starting material or product throughout the reaction, while the α,β-unsaturated aldehyde is consumed in some type of self-condensation (presumably via a vinylogous aldol reaction) and/or hemiacetal formation that inhibits an efficient activation through reaction with the catalyst.

Benzopyrans are known to undergo photochemical and thermal racemization via opening and closing of the bicyclic framework (Scheme 2).[2,3e] This racemization has also been proposed to account for the finding that many naturally occurring benzopyrans are isolated as racemates.[3e] To investigate whether photoinduced racemization was a problem under the reaction conditions employed in the present investigation, we subjected benzopyran **25** to white light and heat from a desk lamp for 48 h. The solution turned from light green to light orange and the enantiomeric excess of the product dropped from 90% to 71%. This is quite a modest drop in enantiomeric excess, when compared to the fast racemization observed by Wipf et al. for a benzopyran lacking C-3 substitution.[3e] We suspect that the photoinduced racemization of **25** is efficiently inhibited by the carbonyl group at C-3. Similarly slow racemization was observed by Malinakova et al. for benzopyrans with ester-substitution at both C-2 and C-3.[11] These results show that no racemization of these products occurs during normal work-up and isolation, but that some precautions should be taken if the products are to be further transformed.



Scheme 2. Photochemical and thermal excitation are known to cause racemization of unsubstituted benzopyrans. The carbonyl group at the C-3 position apparently slows this process down.

3. Conclusion

In conclusion, we have shown that chiral benzopyrans, also known as chromenes, can be successfully synthesized through an organocatalytic domino reaction sequence consisting of iminium-ion activation of an α,β-unsaturated aldehyde, followed by intermolecular oxa-Michael addition of a salicylic aldehyde derivative. The intermediate enamine thus formed undergoes an intramolecular aldol reaction, which upon elimination of water leads to the desired benzopyran core containing a chiral center at C-2. These products contain several functionalities that allow further transformations into even more complex entities, but are also highly valuable molecules themselves, due to their widespread occurrence in Nature and as privileged scaffolds in medicinal chemistry. Although the present organocatalytic route has limitations in terms of yields and stereoselectivities, it still measures up as one of the most efficient methods around for constructing C-2 chiral benzopyrans from readily available starting material. Moreover, the preliminary studies on the reaction mechanism, and the findings concerning the stereochemical integrity of the benzopyran suggest that an even more effectual process may be obtained by careful optimization of the reaction conditions involved.

Acknowledgments

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12. Typical reaction conditions. Salicylaldehyde (1 mmol), cinnamaldehyde (0.5 mmol), and catalyst (0.05 mmol) in dry DCM (0.5 ml) were stirred at ambient temperature for the required time. Pure product was obtained after chromatography (silica gel, diethyl ether–pentane). All the products are light green in color and their migration through the column can be easily monitored. The following is a list of solvent systems used for flash chromatography given in the ratio of diethyl ether–pentane. Compounds **15** and **21** (0.5:9.5), **22**–**24** (1:1), **25** and **26** (0.25:9.75). Enantioselectivities were determined using a Chiralpak AS-H column (0.46 cm × 25 cm), flow of 0.8 ml min^{-1}; compounds **15**, **21**, **25**, and **26** required a mobile phase of 97:3 hexane–isopropanol and **22**–**24** required a mobile phase of 80:20 hexane–isopropanol for separation.