Asymmetric Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201503370
Internationale Ausgabe: DOI: 10.1002/anie.201503370

Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans**

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Abstract: *A novel asymmetric organocatalytic 1,6-addition/1,4-addition sequence to 2,4-dienals is described. Based on a 1,6-Friedel–Crafts/1,4-oxa-Michael cascade, the organocatalyst directs the reaction of hydroxyarenes with a vinylogous iminium-ion intermediate to give only one out of four possible regioisomers, thus providing optically active chromans in high yields and 94–99% ee. Furthermore, several transformations are presented, including the formation of an optically active macrocyclic lactam. Finally, the mechanism for the novel reaction is discussed based on computational studies.*

The enantioselective synthesis of small chiral molecules, containing biologically relevant frameworks, by a general and efficient strategy is an important goal in modern organic chemistry. One such class of molecules is the chiral chromans, which are encountered in nature and have been found as core elements commonly present in synthetic and natural compounds possessing broad and interesting biological activities (Figure 1).[1]

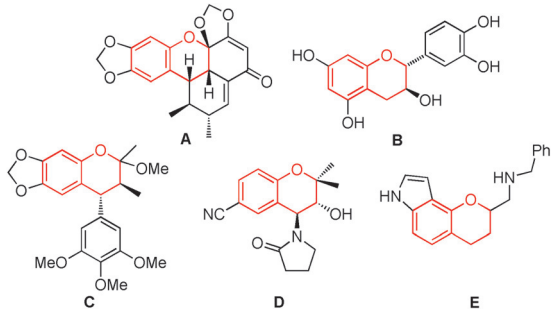

Figure 1. Structures containing a chiral chroman core. Carpanone (**A**; natural product). Catechin (**B**; antitumor agent). NCS 381582 (**C**; podophyllotoxin analogue, antimitotic agent). Cromakalim (**D**; potassium channel opener). Dopamine D_2 partial agonist (**E**).

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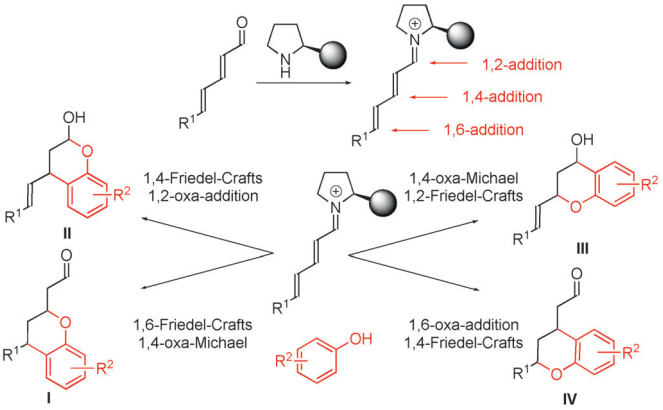
[**] This work was made possible by support from Aarhus University and Carlsberg Foundation. K.S.F. and B.M.P. thank the CAPES Brazilian Foundation (BEX 14224/13-5 and BEX 952513-0) for financial support. We also thank Magnus E. Jensen for performing X-ray analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503370.

Given the intriguing properties of chiral chroman derivatives, we decided to investigate the feasibility of a novel organocatalytic asymmetric cascade reaction between hydroxyarenes and 2,4-dienals through vinylogous iminium-ion activation,[2] thus giving rise to the chroman core structure. However, several challenging issues have to be addressed for such an approach. The regioselectivity has to be taken into account as both electrophile and nucleophile have multiple reaction sites (Scheme 1). First, the competition



Scheme 1. The four different regioselective approaches of hydroxyarenes to the vinylogous iminium-ion.

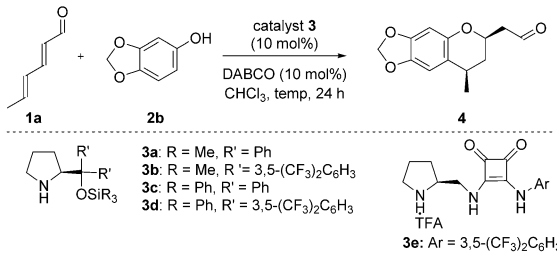
between 1,6- versus 1,4-addition of the first nucleophilic attack is crucial. Experimental and computational studies have shown that the organocatalytic 1,4-addition is frequently favored over the 1,6-addition.[3] Except for one single example[4] in which unbiased aliphatic 2,4-dienals were used, all previous studies of regio- and enantioselective 1,6-additions to 2,4-dienals have relied on sterically blocking the 4-position to suppress the competing 1,4-addition.[5] Second, the hydroxyarene can react either through the hydroxy group or a Friedel–Crafts-type reaction in the first step (Scheme 1). Furthermore, the control of stereoselectivity is another equally important challenge which must be addressed as the initial stereocenter is formed at the 6-position of the aldehyde, six bonds away from the stereocenter of the catalyst. Finally, both the diastereo- and enantioselectivities of the product have to be controlled. The four different regioselective approaches of the hydroxyarene to the vinylogous iminium-ion intermediate are outlined in Scheme 1.

Herein, we present the first asymmetric Friedel–Crafts reaction[6,7] of hydroxyarenes with aliphatic and aromatic 2,4-

dienals, followed by a ring-closing oxa-Michael reaction[8] in a 1,6-addition/1,4-addition cascade. This novel reaction concept is based on the regio- and stereoselective Friedel–Crafts 1,6-addition reaction of hydroxyarenes to a vinylogous iminium-ion intermediate and subsequent oxa-Michael 1,4-addition to the iminium-ion formed in the first step (Scheme 1, lower left). This organocatalytic cascade proceeds with full regioselectivity in the two addition steps and the chiral chroman products are formed with excellent enantioselectivity and good to high diastereoselectivity. Importantly, no substituents on the 2,4-dienal are required to ensure complete remote selectivity in the first step.

We initiated our studies of the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction by performing the reaction between (*E*,*E*)-2,4-hexadienal (**1a**) and sesamol (**2b**; Table 1). The

Table 1: Organocatalytic asymmetric 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction: Screening results.[a]



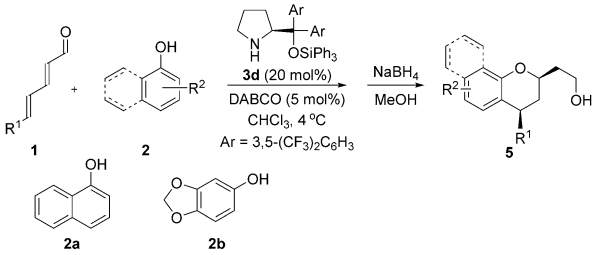
Entry	**1a**/**2b**	**3**	Solvent	*T* [°C]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	3:1	**3a**	$CHCl_3$	RT	87	1:1.2	34
2	3:1	**3b**	$CHCl_3$	RT	41	2.7:1	87
3	3:1	**3c**	$CHCl_3$	RT	15	1.2:1	63
4	3:1	**3d**	$CHCl_3$	RT	40	6.0:1	98
5	3:1	**3e**	$CHCl_3$	RT	–	–	–
6	3:1	**3d**	$CHCl_3$	40	49	4.5:1	97
7	3:1	**3d**	CH_2Cl_2	40	50	3.1:1	93
8	3:1	**3d**	MTBE	40	–	–	–
9	3:1	**3d**	toluene	40	19	1.6:1	69
10	1:2	**3d**	$CHCl_3$	RT	83	3.3:1	93
11[e]	1:2	**3d**	$CHCl_3$	4	71	4.9:1	98

[a] Reactions were performed on a 0.1 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess was determined by UPC^2 (ultra performance convergence chromatography) (see the Supporting Information). [e] 20 mol% of **3d** and 5 mol% of DABCO applied. DABCO = 1,4-diazobicyclo [2.2.2] octane, MTBE = methyl *tert*-butyl ether, TFA = trifluoroacetic acid.

reaction was conducted in the presence of 10 mol% of the TMS-protected diphenylprolinol catalyst **3a**[9] and 10 mol% of DABCO in $CHCl_3$ at room temperature. Delightfully, only one product, **4**, corresponding to the 1,6-Friedel–Crafts/1,4-oxa-Michael reaction, was observed, albeit with poor stereocontrol (1:1.2 d.r. and 34% *ee*). The screening of a series of catalysts revealed that the catalyst **3d**, possessing both CF_3-disubstituted aryl groups and a triphenylsilyl-protecting group, led to improvements in both enantio- and diastereoselectivity (entry 4). The hydrogen-bond directing catalyst **3e** was unable to catalyze the reaction (entry 5). The reaction was very solvent dependent, while an increase in temperature to 40 °C resulted in decreased stereoselectivity and did not improve the conversion (entries 6–9). A higher conversion was obtained by applying an excess of **2b**, but resulted in decreased diastereoselectivity (entry 10). This decrease in diastereoselectivity was solved by lowering the temperature to 4 °C and using 20 mol% of **3d** and 5 mol% of DABCO (entry 11; for further screening results see the Supporting Information).

The scope of the organocatalytic asymmetric cascade reaction was then explored for various 2,4-dienals (**1**) reacting with either 1-naphthol (**2a**) or sesamol (**2b**) in the presence of **3d** as the catalyst (Table 2). The results show that both

Table 2: Aldehyde scope for the organocatalytic asymmetric 1,6-Friedel–Crafts/1,4–oxa-Michael cascade reaction.[a]

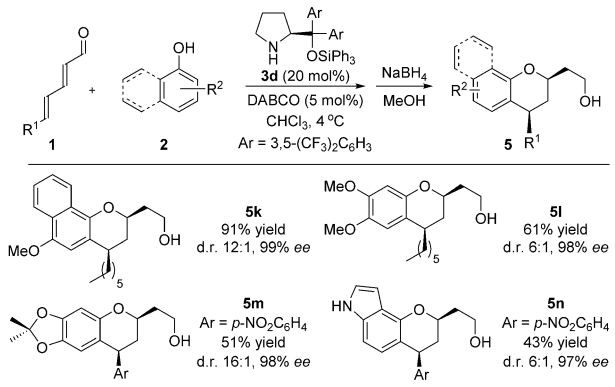


Entry	R^1	**2**	Yield [%]	d.r.[b]	*ee* [%][c]
1	Me (**1a**)	**2a**	**5a**: 72	4:1	96
2	*n*-hexyl (**1b**)	**2a**	**5b**: 82	6:1	98
3	cyclohexyl (**1c**)	**2a**	**5c**: 63	16:1	99
4	*o*-$NO_2C_6H_4$ (**1d**)	**2a**	**5d**: 70	16:1	99
5	*p*-$NO_2C_6H_4$ (**1e**)	**2a**	**5e**: 67	7:1	99
6	*p*-BrC_6H_4 (**1f**)	**2a**	**5f**: 66	6:1	96
7	*p*-$CF_3C_6H_4$ (**1g**)	**2a**	**5g**: 77	13:1	99
8	*n*-hexyl (**1b**)	**2b**	**5h**: 54	5:1	96
9	*o*-$NO_2C_6H_4$ (**1d**)	**2b**	**5i**: 66	6:1	98
10	*p*-$NO_2C_6H_4$ (**1e**)	**2b**	**5j**: 69	5:1	94

[a] Reactions were performed on a 0.1 mmol scale. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Enantiomeric excess was determined by UPC^2 (ultra performance convergence chromatography) (see the Supporting Information).

aliphatic and aromatic 2,4-dienals react smoothly in the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction with **2a** and the optically active chromans are obtained in 63–82% yield with excellent enantioselectivity (96–99% *ee*) and a diastereomeric ratio ranging from 4:1 to 16:1 (entries 1–7). The highest enantioselectivity is obtained for the cyclohexyl-substituted 2,4-dienal **1c** and the majority of the aromatic 2,4-dienals (**1d**,**e**,**g**), while the highest diastereoselectivity is found for the cyclohexyl- and *ortho*-nitrophenyl-substituted 2,4-dienals, **1c** and **1d**, respectively. The reaction for the various 2,4-dienals also proceeds with the same excellent enantioselectivity for **2b**, but the diastereoselectivity is slightly lower compared to the results obtained for **2a**.

Scheme 2 shows that applying a more nucleophilic hydroxyarene, such as 4-methoxy-1-naphthol, leads to an increase in both yield and diastereo- and enantioselectivity for the chroman **5k** compared to those for 1-naphthol

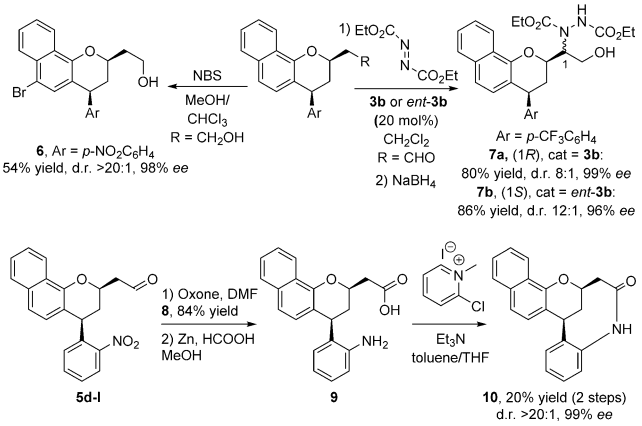


Scheme 2. Reaction of different nucleophiles in the organocatalytic asymmetric 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction.

(Table 2, entry 2). The increase in stereoselectivity might be due to the more sterically demanding nucleophile having a methoxy substituent, rather than a hydrogen atom. A similar increase in stereoselectivity is also observed for the dimethyl-substituted sesamol (**5m**). 3,4-Dimethoxy phenol also reacts smoothly and the product **5l** is obtained in good yield and diastereoselectivity with 98% *ee*. An interesting nucleophile is the one derived from indole, which provides the chroman **5n** with similar results. Notably, the developed methodology could be scaled up while maintaining the high selectivity; the product *ent*-**5k** was obtained in 69% yield (0.7 g), 14:1 d.r. and 99% *ee* when performing the reaction on a 3.0 mmol scale.

The absolute configuration of the chiral chromans obtained was unambiguously assigned by X-ray analysis of the carboxylic acid derivative of **5f** (see the Supporting Information).

It has been observed that hydroxyarenes having electron-withdrawing substituents are not reactive under the present reaction conditions.[10] However, optically active chromans, in which the hydroxyarene is substituted with a bromine, can be obtained by bromination of **5e**, thus providing **6** in 54% yield,



Scheme 3. Selective bromination of the aromatic moiety in the chroman (top left), diastereoselective α-amination of the aldehyde (top right), and formation of a macrocyclic lactam (bottom). DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide.

> 20:1 d.r., and 98% *ee* (Scheme 3). The optically active chroman aldehydes can also be selectively functionalized at the α-position of the aldehyde, thereby adding an additional step to the cascade sequence. However, this step requires the less sterically hindered catalyst **3b**, and by using both enantiomers of **3b** access to both diastereomeric forms of the α-aminated aldehydes **7a**,**b** is achieved in good yields and excellent stereoselectivities (Scheme 3); thus a new stereocenter is introduced. Furthermore, the synthesis of the macrocyclic lactam chroman core structure **10**[11] is shown (Scheme 3).

The four different regioselective approaches of a hydroxyarene to the vinylogous iminium-ion intermediate are outlined in Scheme 1. The complete regioselectivity of the 1,6-Friedel–Crafts/1,4-oxa-Michael cascade reaction observed is in sharp contrast to what has been found in the other investigations involving linear 2,4-dienals, as the 1,4-addition is normally favored compared to the 1,6-addition.[3,5b,c] The 1,4-selectivity has, for example, been accounted for by computational studies which show that C4 in the vinylogous iminium-ion intermediate has both a higher positive charge and orbital coefficient in the LUMO, compared to C6.[3] We have performed calculations, which support these results. To change the reaction course from a 1,4-addition to a selective 1,6-addition, previous work on regio- and enantioselective 1,6-additions to 2,4-dienals relied on sterically blocking the 4-position to suppress the competing 1,4-addition.[5] The remarkable selectivity of the 1,6-addition/1,4-addition cascade in the present development encouraged us to try to elucidate the origin of this selectivity.

Scheme 1 shows the four possible products (**I**-**IV**) of the cascade reaction, but only **I** is observed. Based on DFT-calculations (wB97XD/pcseg-1 using the $CHCl_3$ IEFPCM solvent model[12]) for the model reaction of 2,4-hexadienal with 1-naphthol, the relative energies of **I**/**II**/**III**/**IV** are 5:36:57:0 kJ mol^{-1}. To probe the reaction mechanism we have located transition structures for the four possible addition reactions corresponding to either the Friedel–Crafts (C-addition) or oxa-Michael (O-addition) addition at the 4-position and 6-position of a vinylogous iminium-ion, formed from pyrrolidine and 2,4-hexadienal. The 1-naphthol reagent was modelled either as the free 1-naphtolate, as a 1-naptholate-1-naphthol complex,[13] or as 1-naphthol interacting with DABCO, acting as a base. The conformational degrees of freedom were sampled using the MMFF force field followed by full optimizations at the DFT level mentioned above. All transition structures were confirmed by frequency calculations and the conformational lowest energy transition structure was characterized by following the IRC to both sides.

The four possible transition-state and product energies ($\mathbf{6}_C$, $\mathbf{6}_O$, $\mathbf{4}_C$, $\mathbf{4}_O$) for the three models are shown in Figure 2. Addition of 1-naphthol to the vinylogous iminium-ion gives significantly higher transition-state energies for carbon acting as nucleophile, and no stable adducts when oxygen is the nucleophile. The series shows an inverse Hammond-type relationship, with the lowest transition-state energy leading to the least stable intermediate, and vice versa. The lowest activation energy is for the 1,4-oxa-Michael addition forming

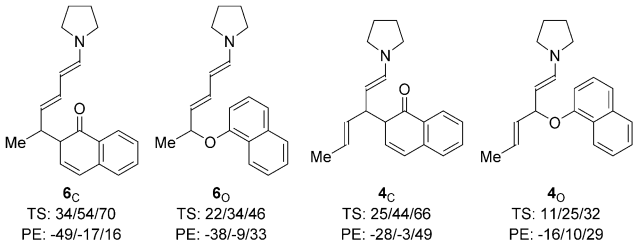
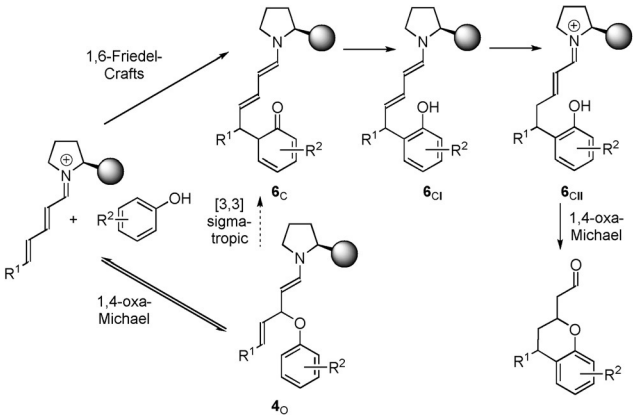


Figure 2. Transition-state (TS) and product energies (PE) (kJ mol^{-1}) for addition of 1-naphtholate, 1-naphtholate-1-naphthol, and 1-naphthol-DABCO to the vinylogous iminium-ion.

$\mathbf{4}_O$, while the highest is for the 1,6-Friedel–Crafts reaction leading to $\mathbf{6}_C$. The kinetic preference for the nucleophilic attack at C4 is in agreement with this carbon atom having both the highest positive charge and LUMO coefficient in the vinylogous iminium-ion intermediate. The relative energies of the products formed by these four different nucleophilic attacks show that the most stable intermediate is $\mathbf{6}_C$ followed by $\mathbf{6}_O$ and $\mathbf{4}_C$/$\mathbf{4}_O$. The higher stability of $\mathbf{6}_C$/$\mathbf{6}_O$ relative to $\mathbf{4}_C$/$\mathbf{4}_O$ is due to conjugation of the double bonds in the former class of products.

The energetics in Figure 2 show that activation energies decrease and product stabilities increase as the nucleophilicity of 1-naphthol is increased by complexation with DABCO or conversion into the naphtolate. All four addition reactions are predicted to be reversible under the reaction conditions, and $\mathbf{6}_C$ will thus be formed preferentially. Keto–enol tautomerization of $\mathbf{6}_C$ is calculated to be exothermic by 27 kJ mol^{-1}, thus leading to a dienamine-trapped intermediate $\mathbf{6}_{CI}$, and this effectively traps the first formed product corresponding to a 1,6-Friedel–Crafts reaction (Scheme 4). Upon protonation



Scheme 4. Proposed mechanism with intermediates.

at the γ-position of the intermediate $\mathbf{6}_{CI}$ the corresponding iminium-ion intermediate $\mathbf{6}_{CII}$ is generated. Once $\mathbf{6}_{CII}$ is formed it immediately undergoes the 1,4-oxa-Michael addition, thus leading to the observed product. The proposed overall mechanism is shown in Scheme 4. It should also be noted that no transition-state energy for the [3,3]-sigmatropic rearrangement of $\mathbf{4}_O$ leading to $\mathbf{6}_C$ was found, hence this pathway might result in higher energies than the dissociation energy of $\mathbf{4}_O$.

In summary, the first asymmetric organocatalytic 1,6-Friedel–Crafts/1,4–oxa-Michael cascade by reaction of hydroxyarenes with 2,4-dienals for the construction of chromans is described. The reaction proceeds with excellent regio- and enantioselectivities, thus giving optically active chromans in high yields and 94–99 % *ee*. The potential of the reaction concept developed is demonstrated with a series of transformations, including the formation of an optically active macrocyclic lactam. Computational studies point to a reaction sequence, involving a number of intermediates, driven by thermodynamic control of the Friedel–Crafts reaction step.

Keywords: asymmetric synthesis · heterocycles · Michael addition · organocatalysis · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8203–8207
Angew. Chem. **2015**, *127*, 8321–8325

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Received: April 14, 2015
Published online: May 26, 2015

