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Catalytic Asymmetric Addition of Aldehydes to Oxocarbenium Ions: A Dual Catalytic System for the Synthesis of Chromenes

Magnus Rueping,* Chandra M. R. Volla, and Iuliana Atodiresei

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

magnus.rueping@rwth-aachen.de

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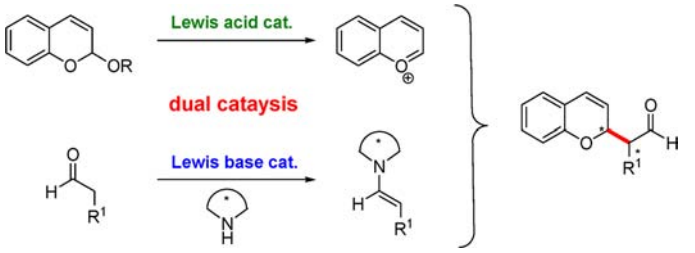
ABSTRACT



A synergistic catalytic system for the first asymmetric addition of aldehydes to in situ generated prochiral oxocarbenium ions has been developed. The dual catalytic protocol allows the simultaneous activation of both electrophile and nucleophile and provides access to a variety of valuable chiral 2*H*-chromenes with excellent enantioselectivities.

Reactions involving in situ generated highly reactive oxocarbenium ions are attracting attention due to their usefulness in the synthesis of complex natural products and bioactive molecules. Whereas Lewis acid mediated diastereoselective addition reactions to oxocarbenium ions are known, catalyzed enantioselective addition reactions to prochiral oxocarbenium ions are less explored.[1−5] The ability to generate oxocarbenium ions and use them in enantioselective catalysis offers numerous possibilities in the asymmetric synthesis of biologically relevant molecules.

These features have been recently successfully explored in the enantioselective synthesis of chromene and isochromane derivatives. In particular, Jacobsen and co-workers designed an elegant chiral anion binding approach for the thiourea catalyzed asymmetric addition of enoxysilanes to chloroisochromans.[2a]

Interesting reports came from the group of Schaus, who developed a catalytic system consisting of a chiral Brønsted acid and an achiral Lewis acid for the addition of boronate esters to oxonium ions derived from chromene acetals.[3] More recently, Watson and co-workers reported the asymmetric addition of alkynes to oxocarbenium ions derived

(1) The first example of a Lewis acid catalyzed enantioselective allylation of oxocarbenium ions: (a) Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514. Lewis acid catalyzed enantioselective addition of metal enolates to oxocarbenium ions, see: (b) Evans, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 10506. For the enantioselective Lewis acid catalyzed addition of β-keto esters to oxocarbenium ions, see: (c) Umebayashi, N.; Hamashima, Y.; Hashizume, D.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4196. For the enantioselective Lewis acid catalyzed addition of silyl enol ethers to oxocarbenium ions, see: (d) Kobayashi, S.; Arai, K.; Yamakawa, T.; Chen, Y. –J.; Slater, M. M.; Yamashita, Y. *Adv. Synth. Catal.* **2011**, *353*, 1927.

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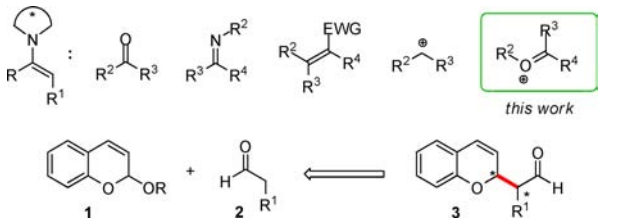
from isochroman acetals by employing chiral copper bisoxazoline complexes.[4]

Organocatalytic asymmetric additions of aldehydes to various electrophiles, including carbonyl derivatives, imines, activated alkenes and stabilized carbocations,[6] have been widely studied in recent years and the field is largely dominated by the use of chiral secondary amines, including proline, prolinol and imidazolidinone derivatives, as catalysts (Scheme 1).[7] Despite the recent developments in these two areas of research, the use of oxonium ions as electrophiles in asymmetric enamine catalysis has not been reported yet. This may be due to the intrinsic high reactivity of the oxonium ions which can lead to various undesired side reactions and byproduct formation. Especially, the development of an asymmetric method involving the addition of aldehydes to (iso)chromene or (iso)chromane acetals is of great importance as it would allow the synthesis of (iso)chromene and (iso)chromane derivatives with multiple stereogenic centers. With these considerations in mind our attention has been drawn to 2*H*-chromenes **3** (2*H*-1-benzopyrans)[8] which constitute a privileged class of structural motifs which is present in many bioactive natural products with antioxidant, antiviral, antifungal and anti-inflammatory activities. Closely related chiral chromans[9] include the lipophilic antioxidant vitamine E or rhododaurichromanic acid A which shows potent anti-HIV activity. Thus, it is desirable to develop improved procedures for the synthesis of chiral chromenes that could lead to natural products and their analogues with enhanced pharmacological features. 2*H*-Chromenes **3** might be obtained from chromene acetals which are generally stable and easily available on large scale from commercially available starting materials.

Scheme 1. Electrophiles Used in the Enamine Catalysis



We herein demonstrate the first asymmetric addition of aldehydes to catalytically generated oxocarbenium ions. The key to the success of the reaction is to find a compatible set of two different catalysts capable of activating independently both reaction partners, chromene acetals and aldehydes in a synergetic fashion.[10,11] Lewis or Brønsted acid catalysis was envisaged for the in situ generation of oxocarbenium ions and the addition of aldehydes was hoped to be achieved with a chiral amine catalyst. However, obstacles including the addition of the amine catalyst to the oxocarbenium ions, the formation of water and resulting side reactions needed to be addressed.

The reaction of propionaldehyde **2a** with 2-ethoxy-2*H*-chromene **1a** which is available in a two step procedure starting from coumarin, was chosen for the initial studies. The aldehyde product **3a** was converted into the corresponding alcohol **4a** by reduction with sodium borohydride.[12] Initial attempts to apply a chiral amine base/achiral Brønsted acid dual catalytic system were not successful. No product was obtained using either proline **A** or prolinol **B** as the chiral base catalyst in combination with various Brønsted acids catalysts[13a] including carbonic, sulfonic or phosporic acids. Traces of the desired product were observed with the imidazolidinone salt **C** as catalyst.[14] Hence our attention turned to a Lewis base/Lewis acid dual catalytic system. After extensive examinations we were delighted to find that use of catalytic amounts of $Yb(OTf)_3$[13b] and TFA imidazolidinone salt **C** gave a clean reaction in DCM at room temperature, affording the product **4a** in 94% yield and moderate enantiomeric excess (Table 1, entry 3). Gratifyingly, we found that using the free amine **D** instead of the corresponding trifluoroacetate salt has a tremendous effect on the selectivity of the reaction. Using catalytic amounts of $Yb(OTf)_3$ in combination with the free amine **D** led to the desired product in 84% yield and 89:11 er (Table 1, entry 6). A higher enantioselectivity (er = 98:2) was observed when the reaction was performed at 0 °C (Table 1, entry 9).

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(12) The stable alcohol products allowed the easier analysis.

(13) (a) Proline **A** and prolinol **B** were tested in combination with benzoic acid, *p*-nitro benzoic acid, *p*-toluenesulfonic acid and diphenyl phosphoric acid as catalysts. (b) The use of scandium and indium triflate resulted in lower yields. For $Yb(OTf)_3$ in enamine catalysis: Mase, N.; Tanaka, F.; Barbas, C. F, III *Org. Lett.* **2003**, *5*, 4369.

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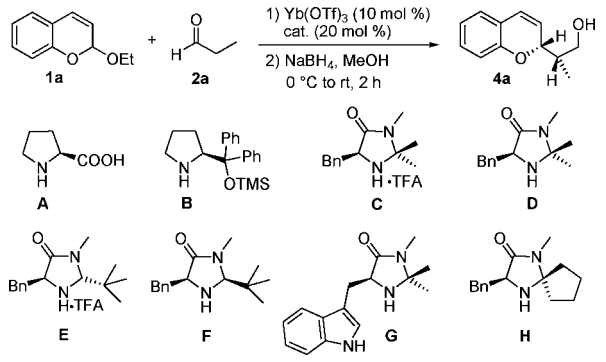
Other secondary amines such as **F**−**H** gave similar results except for the *trans* catalyst **E**, which gave the product in only 7% ee. Evaluation of different solvents led to the conclusion that chlorinated solvents are better in terms of yield. Although the selectivity was slightly better (er = 98.5:1.5) by further lowering the temperature to −10 °C, the reaction became very slow (Table 1, entry 16).

Table 1. Optimization of the Aldehyde Addition to Oxocarbenium Ions



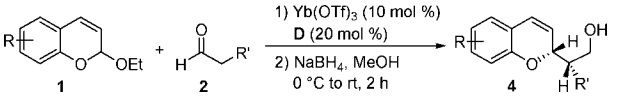
entry	cat.	solvent	temp (°C)	time (h)	dr	yield[a] (%)	er[b]
1	**A**	CH_2Cl_2	rt	24			
2	**B**	CH_2Cl_2	rt	24			
3	**C**	CH_2Cl_2	rt	3	50:50	94	76:24
4[e]	**C**	CH_2Cl_2	rt	24		traces	
5	-	CH_2Cl_2	rt	24			
6	**D**	CH_2Cl_2	rt	24	52:48	85	89:11
7	**E**	CH_2Cl_2	rt	2	50:50	67	53.5:46.5
8	**C**	CH_2Cl_2	0	24	52:48	89	80:20
9	**D**	CH_2Cl_2	0	48	68:32	84	98:2
10	**F**	CH_2Cl_2	0	48	51:49	78	94.5:5.5
11	**G**	CH_2Cl_2	0	48	68:32	76	98:2
12	**H**	CH_2Cl_2	0	48	68:32	74	97.5:2.5
13[d]	**D**	$CHCl_3$	0	48	52:48	58	95.5:4.5
14[d]	**D**	Toluene	0	48	50:50	27	97.5:2.5
15[e]	**D**	CH_2Cl_2	0	72		traces	
16	**D**	CH_2Cl_2	−10	72	68:32	35	98.5:1.5

[a] Yield for the two diastereomers after column chromatography. [b] Enantiomeric ratios were determined by HPLC analysis. [c] Reaction without $Yb(OTf)_3$. [d] Reaction was not complete. [e] 4 Å MS was added to the reaction.

With the optimized conditions in hand, we explored the substrate scope of this transformation by employing differently substituted chromene acetals and aldehydes (Table 2).

Use of methyl acetal instead of the ethyl acetal gave similar results (Table 2, entry 2 vs 1). Furthermore, when the reaction was conducted on 0.5 g scale, the product was isolated in 78% yield with a good enantiomeric excess of 95:5 er (Table 2, entry 3). In addition to propanal, various other aldehydes were tested in the reaction (Table 2, entries 4−9). Less reactive aldehydes reacted sluggishly with the chromene acetal at 0 °C. Pleasingly, we found that slightly increasing the temperature to 5 °C allows a clean reaction with the acetal.

Table 2. Scope of the Reaction Using Different Chromene Acetals and Aldehydes



entry[a]	R	R′	4	dr	yield[b] (%)	er[c]
1	H	Me	**4a**	68:32	84	98:2
2[d]	H	Me	**4a**	68:32	82	98.5:1.5
3[e]	H	Me	**4a**	67:33	78	95:5
4	H	Et	**4b**	66:34	82	97.5:2.5
5	H	*n*-Pr	**4c**	73:27	69	94.5:5.5
6	H	*n*-Bu	**4d**	68:32	76	94.5:5.5
7	H	Bn	**4e**	64:36	72	93.5:6.5
8	H	8-nonenyl	**4f**	65:35	72	92.5:7.5
9	H	OBn	**4g**	59:41	89	86:14
10	6-Br	Me	**4h**	67:33	78	98:2
11	6-Me	Me	**4i**	64:36	84	97:3
12	6-Me	*n*-Pr	**4j**	69:31	73	87.5:12.5
13	7-Me	Me	**4k**	68:32	81	97:3
14	7-Me	Et	**4l**	74:26	78	90:10
15	7-MeO	Me	**4m**	64:36	74	97.5:2.5

[a] Addition reactions were performed at 5 °C and in the case of propanal (R′ = Me) at 0 °C for 48 h. [b] Yield for the two diastereomers after column chromatography. [c] Enantiomeric ratios were determined by HPLC analysis. [d] Methyl chromene acetal was used in the reaction. [e] Reaction was performed on a larger scale (0.5 g **1a**).

In general the scope of this transformation was found to be relatively wide as different substituents on the chromenes led to products in good yields and excellent enantioselectivities (Table 2, entries 10−15). The bromine substituted coumarin derivative (Table 2, entry 10) is particularly interesting as the product can be further functionalized by transition metal-catalyzed carbon−carbon cross-coupling reactions, alkoxylations, or aminations. The synthetic utility of the addition products was illustrated by converting the carbonyl group into other useful functionalities (Scheme 2). As described above, aldehyde **3a** can easily be reduced by sodium borohydride to afford the appropriate alcohol **4a** (Scheme 2, top). Enal esters are useful building blocks in organic synthesis because of their excellent electrophilic character. Treatment of aldehyde **3a** with 1.2 equivalents of commercially available phosphorane in DCM gave the product **5a** in 92% yield after 2 h (Scheme 2, middle). Aliphatic carboxylic acids can also be prepared by employing sodium chlorite as the stoichiometric oxidant (Scheme 2, bottom).

By a combination of theoretical studies and CD- and NMR-spectroscopy, the absolute configuration of the two diastereomeric alcohol products **4a** has been determined to be as *S*,*R* and *S*,*S* for the major and minor diastereomers, respectively.[15,16] A model explaining the stereoselective addition of aldehydes to the oxonium ions is depicted in Scheme 3.

(15) See Supporting Information for further details.
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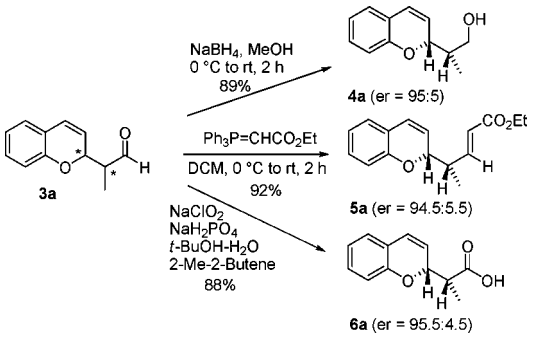
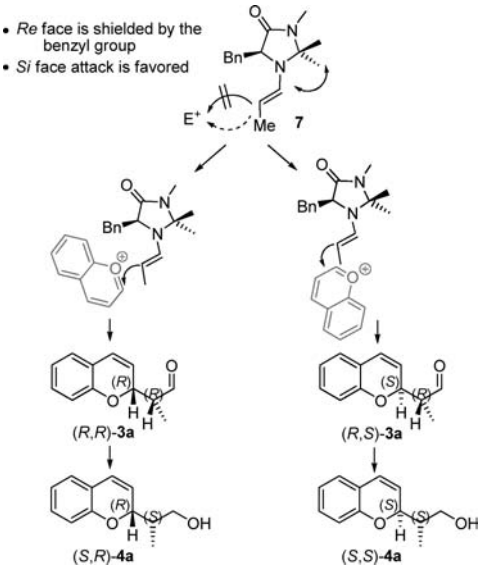
Scheme 2. Functionalization of the Addition Products



Scheme 3. Stereochemical Model for the Addition of Propanal to the Oxonium Ion



The aldehyde reacts with the imidazolidinone catalyst to form enamine **7**, which possesses the stable *E*-configured carbon−carbon double bond facing away from the geminal dimethyl groups.[17−19] The bulky benzyl group present on the top face controls the addition of the enamine to the oxonium ion. The benzyl group of the catalyst shields the *Re* face of the enamine and subsequently the oxonium ion will be attacked from the enamine *Si* face,[20] leading to the (*R*)-configuration at the center bearing the aldehyde for both diastereomers. The configuration at the second chiral center of the two diastereomeric products is given by the attack on either *Si* or *Re* face of the planar oxonium ion and has been established by comparing the measured and theoretically calculated CD-spectra for the corresponding alcohols **4a** with spectra of known members from the same class of compounds.[15,16]

In summary, we have developed the first asymmetric addition of aldehydes to prochiral oxocarbenium ions yielding valuable chiral 2H-chromene derivatives. Given the difficulties that typically arise from the in situ formation of highly reactive oxocarbenium ions and the side reactions that can occur, the results presented here are very encouraging. A catalytic system consisting of an achiral Lewis acid and a chiral imidazolidinone catalyst which simultaneously activates the electrophile and nucleophile, was key to afford the products with excellent enantioselectivities. The resulting optically active aldehydes can be subjected to different functional group transformations to form the corresponding alcohols, enal esters and acids. The stereochemical outcome of this combined metal and organocatalyzed reaction provides the basis for further extensions. Together with previously reported amine catalyzed additions of aldehydes to imines, carbonyl groups, and carbocations, the addition to oxocarbenium ions presented here not only expands the repertoire of Lewis base catalysis but also provides fast and ready access to valuable chromenes and chromans in a highly enantioselective fashion. It is anticipated that this new mode of activation will find application in related reactions of oxocarbenium ions and is the focus of ongoing research.

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Supporting Information Available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(18) For the use of imidazolidinone **D** as chiral auxiliary, see: (a) Solodin, I.; Goldberg, Y.; Zelčāns, G.; Lukevics, E. *J. Chem. Soc., Chem. Commun.* **1990**, 1321. (b) Solodin, I. *Monatsh. Chem.* **1992**, *123*, 565. For selected structural and spectroscopic studies on the iminium ions derived from imidazolidinone **D**, see: (c) Brazier, J. B.; Evans, G.; Gibbs, T. J. K.; Coles, S. J.; Hursthouse, M. B.; Platts, J. A.; Tomkinson, N. C. O. *Org. Lett.* **2009**, *11*, 133. (d) Grošelj, U.; Schweizer, W. B.; Ebert, M.-O.; Seebach, D. *Helv. Chim. Acta* **2009**, *92*, 1. (e) Seebach, D.; Grošelj, U.; Schweizer, W. B.; Grimme, S.; Mück-Lichtenfeld, C. *Helv. Chim. Acta* **2010**, *93*, 1. (f) Um, J. M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 6001. Recent review on quantum mechanical investigations: (g) Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042.

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