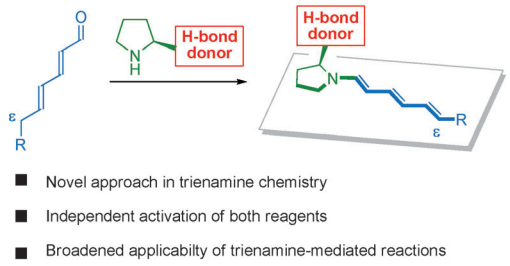
Asymmetric Catalysis

DOI: 10.1002/anie.201204790

Enantioselective H-Bond-Directing Approach for Trienamine-mediated Reactions in Asymmetric Synthesis**

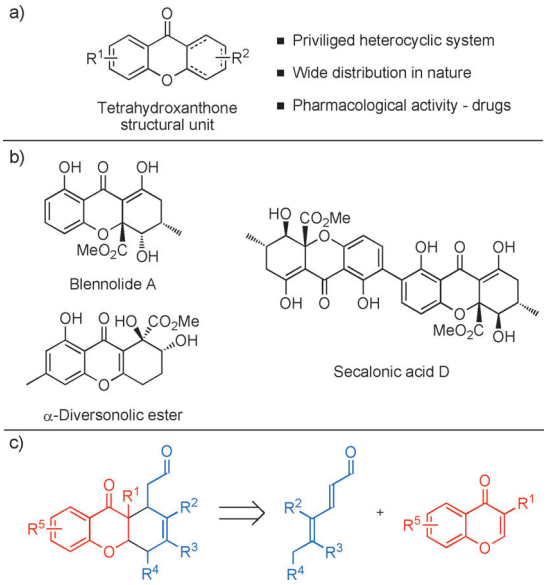
*Łukasz Albrecht, Fabio Cruz Acosta, Alberto Fraile, Anna Albrecht, Jannie Christensen, and Karl Anker Jørgensen**

Control of remote stereocenters constitutes an important challenge in modern organic synthesis.[1,2] Despite limited generality, asymmetric strategies enabling such functionalizations have found important applications in target-oriented synthesis, thereby indicating their potential.[1e,2] In recent years, dienamine- and trienamine-mediated reactions have emerged as new tools that enable stereoselective functionalizations of unsaturated aldehydes at the remote γ- or ε-positions, respectively.[3,4] In this context, trienamine-based strategies that allow stereocontrolled reactions at the carbon atom seven bonds away from the stereocenter of the catalyst are notable.[4] Classically, such aminocatalytic transformations are realized using the steric shielding principle for stereochemical induction.[5] However, important restrictions related to the dienophile scope still exist. One solution to this problem might rely on the application of H-bond-directing aminocatalysts in trienamine chemistry (Scheme 1). Benefits of such strategies relate not only to the dual activation of the reaction partners, which positions them correctly in space, thereby providing a well-defined stereochemical environment; more importantly, such strategies open the possibility of accessing new reactivities and reaction profiles resulting in further development of this field of chemistry.



Scheme 1. Remote functionalizations through H-bond-directed trienamine chemistry.

Development of new synthetic strategies that lead to pharmacologically active structural units is of high importance for the chemical community and constitutes an important part of the drug discovery process. The tetrahydroxanthone structural unit (Scheme 2a) is often encountered in nature and among pharmacologically active compounds.[6]



Scheme 2. a) Importance of the tetrahydroxanthone structural unit, b) natural products containing this unit, and c) novel enantioselective approach to this class of compounds.

Blennolide A, secalonic acid D, and α-diversonolic ester (Scheme 2b) constitute representative examples of a rich family of natural products containing the tetrahydroxanthone unit. These compounds were isolated from fungi, bacteria, and lichens and are well-recognized for their antibiotic activity.[6,7]

Given the biological properties of optically active tetrahydroxanthone derivatives and their wide occurrence in nature, studies on a synthetic methodology that offers a general and stereoselective access to this class of compounds were initiated. It was anticipated that such an approach for the preparation of tetrahydroxanthone derivatives could rely on the trienamine-mediated reaction between chromones and 2,4-dienals (Scheme 2c).

Herein, we present a new, enantioselective approach to biologically relevant tetrahydroxanthone derivatives based on a novel trienamine-mediated [4+2] cycloaddition with

[*] Dr. Ł. Albrecht, F. Cruz Acosta, Dr. A. Fraile, Dr. A. Albrecht, J. Christensen, Prof. Dr. K. A. Jørgensen
Center for Catalysis, Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

[**] This work was made possible by grants from Aarhus University, OChemSchool, Carlsberg Foundation, and FNU. F.C.A. thanks CSIC for predoctoral JAE grant. We thank Dr. Jacob Overgaard for performing X-ray analysis.

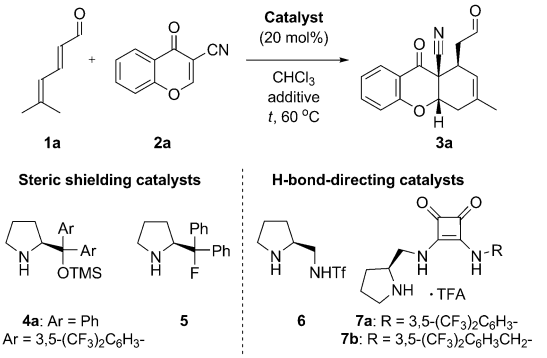
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204790.

activated chromones as dienophiles. Furthermore, the possibility to control the stereochemical outcome of organocatalytic trienamine-mediated reactions by an H-bond-directing aminocatalyst is demonstrated.

Initial experiments identified the presence of the cyano group in the 3-position of the starting chromone as a crucial factor ensuring high reactivity, and more importantly, high diastereoselectivity of the tested cycloaddition. Accordingly, optimization studies were initiated using 5-methyl-2,4-hexadienal **1a** and 3-cyanochromone **2a**[8] as model substrates (Table 1; for full screening results, see the Supporting Information). Disappointingly, when classical sterically demanding catalysts **4** or **5** were applied (Table 1, entries 1–3), moderate enantioselectivities (45–60% *ee*) were obtained. To overcome these difficulties we turned our attention to an H-bond-directed catalytic approach.[4f,9] It was reasoned that additional activation of **2a** through hydrogen bonding should lead to an increase in its reactivity and provide a well-defined stereochemical environment resulting in enhanced enantioselectivity. To our delight, application of the H-bond-directing catalysts **6** or **7** (Table 1, entries 4–6) led to a significant improvement of the enantioselectivity (76–87% *ee*) with squaramide-based organocatalyst **7a** being the most effective (Table 1, entry 5). It should be noted, that for catalysts **7a**,**b** the use of *N*,*N*-diethylacetamide (DEA) was necessary to achieve good catalytic activity. Further screening concerning the effect of concentration (Table 1, entries 5, 7, 8) revealed that higher dilutions were beneficial for the reaction outcome. Finally, the amount of additive was screened (Table 1, entries 8–11), and the results indicate the significant influence of the amount of additive on both reactivity and enantioselectivity of the reaction.

After having established the optimal reaction conditions for the H-bond-directed [4+2] cycloaddition, we turned the attention to the scope of the methodology (Table 2). Delightfully, the developed reaction proved general, as both electron-rich (Table 2, entries 2–4) and electron-poor chromones (Table 2, entries 5–7) could be applied to afford the target products **3b–g** in good yields (59–98%) and with high enantioselectivities (88–91% *ee*). Furthermore, in all of the cases, complete diastereoselectivity was observed. Longer reaction times were required to achieve full conversion for chromones **2b–d** and **2g**, thus indicating the influence of both

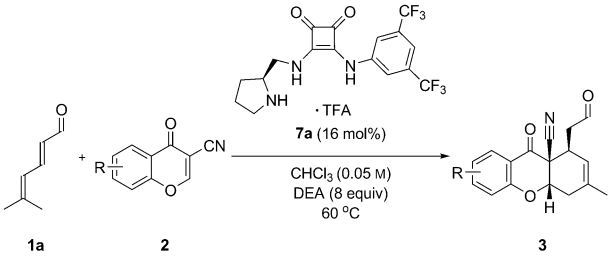
Table 1: Enantioselective synthesis of tetrahydroxanthone **3a**: optimization studies.[a]

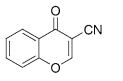
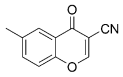
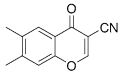
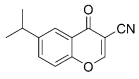
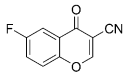
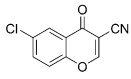
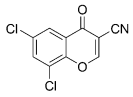


Entry	Cat.	Conc. [M]	Additive (equiv)	*t* [h]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	0.33	–	20	85	>20:1	46[e]
2	**4b**	0.33	–	20	60	>20:1	60[e]
3	**5**	0.33	–	20	85	>20:1	45[e]
4	**6**	0.33	–	20	67	>20:1	76
5	**7a**[f]	0.33	DEA(4)	20	75	>20:1	87
6	**7b**[f]	0.33	DEA(4)	20	73	>20:1	82
7	**7a**[f]	0.1	DEA(4)	48	92	>20:1	89
8	**7a**[f]	0.05	DEA(4)	48	74	>20:1	n.d.
9	**7a**[f]	0.05	DEA(8)	48	92 (91)	>20:1	90
10	**7a**[f]	0.05	DEA(16)	48	87	>20:1	89
11	**7a**[f]	0.05	DEA(32)	48	>95	>20:1	86

[a] Reactions performed on a 0.1 mmol scale (see the Supporting Information for details). Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid. [b] Conversion of **2a** as determined by ^{1}H NMR spectroscopy. The yield of isolated product **3a** is given in parentheses. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined after Ramirez olefination by HPLC using a chiral stationary phase. [e] *ent*-**3a** was obtained. [f] 16 mol% of catalyst applied.

Table 2: Enantioselective synthesis of tetrahydroxanthones **3**: 3-cyanochromone scope.[a]

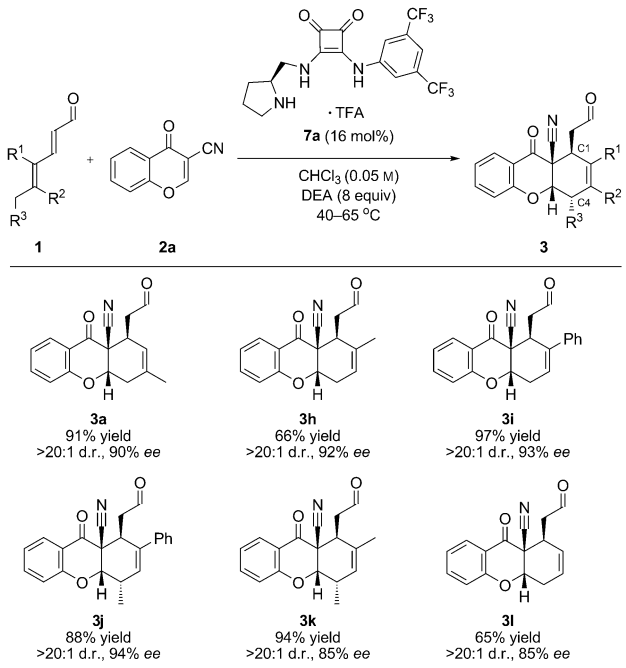


Entry	**2**		Reaction time [h]	**3**: Yield [%]	d.r.[b]	*ee* [%][c]
1		**2a**	48	**3a**: 91	>20:1	90
2		**2b**	96	**3b**: 98	>20:1	90
3		**2c**	96	**3c**: 80	>20:1	90
4		**2d**	2 weeks	**3d**: 87	>20:1	88
5		**2e**	48	**3e**: 96	>20:1	91
6		**2f**	48	**3f**: 98	>20:1	90
7		**2g**	96	**3g**: 59	>20:1	89

[a] Reactions were performed on a 0.2 mmol scale (see the Supporting Information for details). [b] Determined by ^{1}H NMR spectroscopy. [c] Determined after Ramirez olefination by HPLC using a chiral stationary phase.

electronic and steric factors on the reactivity of the 3-cyanochromones.

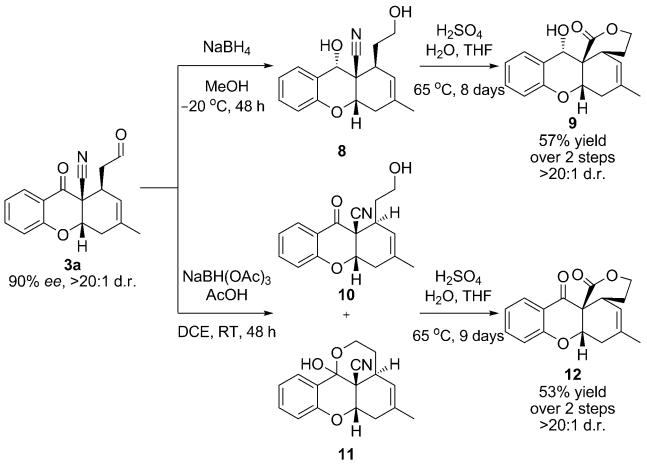
In further studies, the possibility to utilize differently substituted 2,4-dienals **1** in the developed H-bond-directed [4+2] cycloaddition was evaluated (Scheme 3). To our delight, different substituents could be present in the starting



Scheme 3. Enantioselective synthesis of tetrahydroxanthones **3**: 2,4-dienal scope (see the Supporting Information for details).

2,4-dienals **1**, hereby further increasing the structural diversity of the obtained products **3**. Moreover, the introduction of an additional stereogenic center in the 4-position of the target tetrahydroxanthones proved possible. Notably, the reactions proceeded with a very high and unprecedented[4] *trans*-relationship between the C1 and C4 stereogenic centers in **3j**,**k** that originate from the starting 2,4-dienals **1** (for a discussion of the stereochemical outcome of the reaction, see Scheme 6). Importantly, less reactive and more challenging, linear substrates could also be employed as demonstrated for 2,4-hexadienal **1f** (**1** with $R^1 = R^2 = R^3 = H$ in Scheme 3) providing **3l**.

After the successful development of an H-bond-directed approach for trienamine-mediated reactions, the possibilities of synthetic utilization of the obtained cycloadducts **3** were investigated. We were particularly interested in the application of the densely functionalized molecular scaffold of **3** for the construction of various polycyclic structures. Initially we investigated the possibility to introduce a δ-lactone ring system to the target products in a sequence of reactions that involves reduction of the aldehyde moiety and a subsequent hydrolytic cyclization onto the inherent cyano group. When tetrahydroxanthone **3a** was subjected to $NaBH_4$ reduction, both carbonyl groups in **3a** were reduced (Scheme 4). Importantly, the diastereoselectivity of this process could be

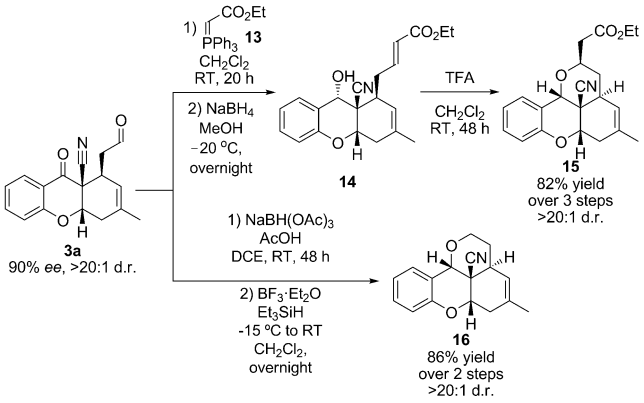


Scheme 4. Enantioselective synthesis of tetrahydroxanthones **9** and **12** that contain δ-lactone rings. DCE = dichloroethane.

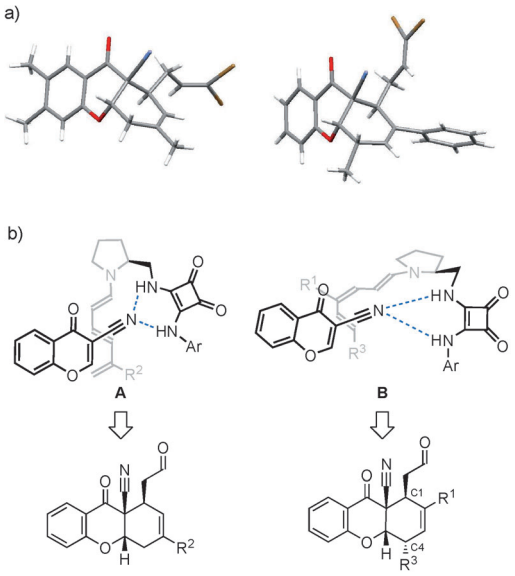
fully controlled by decreasing the reaction temperature to −20 °C, thereby affording **8** as a single diastereoisomer. Interestingly, when $NaBH(OAc)_3$ was employed as the reducing agent, chemoselective reduction of the aldehyde moiety could be achieved, thereby affording **10** in a mixture with its corresponding hemiacetal **11** in a 3:1 ratio. Subsequently, the crude reaction mixtures were subjected to hydrolytic cyclization under acidic conditions. In such a manner, the δ-lactone ring was furnished affording **9** and **12** in good overall yields and as single diastereoisomers.

Further application studies were focused on the utilization of the carbonyl groups of **3** for the introduction of an additional tetrahydropyrane ring in the target products. Two complementary routes enabling such functionalization were elaborated. The first was initiated by a Wittig reaction of tetrahydroxanthone **3a** with stabilized ylide **13** followed by chemo- and diastereoselective reduction of the ketone moiety (Scheme 5). A subsequent, TFA-mediated, intramolecular oxa-Michael reaction of **14** afforded the target product **15** in a high 82% overall yield. Notably, the developed reaction sequence allows the introduction of two new stereogenic centers in a fully diastereoselective manner. In the second approach, chemoselective reduction of the aldehyde moiety of **3a** was performed as the first step. Hereafter, Lewis acid mediated reductive etherification of the originally formed mixture of alcohol **10** and its hemiacetal **11** using triethylsilane as a reducing agent was performed, and enabled stereoselective construction of the tetrahydropyrane ring in **16** (Scheme 5). Importantly, both developed reaction sequences consisting of either two or three steps could be performed without purification of the intermediates, thereby underlining the high practicality of the developed synthetic strategies.

The absolute configuration of the products was unambiguously assigned by using single-crystal X-ray analysis of the corresponding Ramirez olefination products derived from **3c** and **3j** (Scheme 6a).[10] The absolute configuration of the remaining products **3a**, **b**, **d**–**i**, **k**, **l** was assigned by analogy. The relative configuration of the newly introduced stereogenic centers in products **9**, **15**, and **16** was assigned by 1D



Scheme 5. Introduction of a tetrahydropyrane ring into tetrahydroxanthone **3a**.



Scheme 6. Configurational assignments and rationalization for the stereochemical outcome of the H-bond-directed trienamine-mediated cycloadditions. a) Crystal structures of the products of the Ramirez olefination of **3c** (right) and **3j** (left). Blue N; red O, white H; gray C, brown Br. b) Transition state models for the H-bond-directed trienamine-mediated cycloadditions and the corresponding products.

NOE experiments. Based on the configurational assignments, transition state models rationalizing the observed absolute and relative stereochemistry of the products **3** were proposed (Scheme 6b). It is postulated that the 3-cyanochromone interacts with the squaramide moiety of the catalyst through the electron-rich cyano group[11] rather than the carbonyl group. Secondary orbital overlap with participation of the chromone carbonyl group as well as π-stacking interactions between the aromatic ring of the chromone system and the conjugated π system of the corresponding trienamine might further support such an alignment of the dienophile. Importantly, the reaction pathway strongly depends on the substitution pattern of the starting 2,4-dienal **1**. When there is no substituent in the 4-position of the starting aldehyde **1**, the reaction is proposed to proceed through transition state **A**. Accordingly, it is assumed that the corresponding trienamine intermediate reacts in the *s-cis*-(C3=C4−C5=C6) and *s-cis*-(C1=C2−C3=C4) conformation and the reaction occurs across the remote diene system. However, for steric reasons, the presence of a substituent in the 4-position of **1** forces the reaction to proceed through transition state **B**. In this case, the sterically demanding R^1 substituent positions itself away from the first double bond of the trienamine system as well as from the C2 substituent of the pyrrolidine catalyst. This reactive conformation of the diene can account for the unprecedented *trans* relationship between the C1 and C4 stereogenic centers of **3**. In both cases, proper alignment of the reactive diene system with respect to the chromone dienophile is postulated to be the crucial factor determining the stereochemistry of the product. Nonetheless, the obtained results suggest that the mechanism(s) of trienamine-mediated reactions can be a rather complex issue and might be highly dependent on the structure of the starting dienal. Computational studies in an attempt to understand H-bond-directed trienamine-mediated reactions are currently in progress.

In summary, the first H-bond-directed trienamine-mediated [4+2] cycloaddition was developed, thereby demonstrating the viability of such an activation strategy. The reaction between diversely substituted 2,4-dienals and 3-cyanochromones proceeded smoothly and in a highly stereoselective manner in the presence of a squaramide-containing aminocatalyst. Furthermore, it was demonstrated that the obtained cycloadducts can be chemo- and diastereoselectively transformed into polycyclic products with high molecular and stereochemical complexity that possess up to five stereogenic centers. An unexpected stereochemical outcome of the reaction was observed and a rationalization of the results was provided.

Received: June 19, 2012
Published online: August 7, 2012

Keywords: asymmetric synthesis · organocatalysis · synthetic methods · tetrahydroxanthones · trienamines

[1] For selected reviews, see: a) H. Sailes, A. Whiting, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1785; b) K. Mikami, M. Shimizu, H.-C. Zhang, B. E. Maryanoff, *Tetrahedron* **2001**, *57*, 2917; c) J. Clayden, N. Vassiliou, *Org. Biomol. Chem.* **2006**, *4*, 2667; d) E. J. Thomas, *Chem. Rec.* **2007**, *7*, 115; e) J. Clayden, *Chem. Soc. Rev.* **2009**, *38*, 817.

[2] For selected recent examples, see: a) K. Tatsuta, S. Hosokawa, *Chem. Rev.* **2005**, *105*, 4707; b) S. Sezer, D. Özdemirhan, E. Şahin, C. Tanyeli, *Tetrahedron: Asymmetry* **2006**, *17*, 2981; c) K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem.* **2008**, *120*, 5911; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827; d) C. A. Lewis, J. L. Gustafson, A. Chiu, J. Balsells, D. Pollard, J. Murry, R. A. Reamer, K. B. Hansen, S. J. Miller, *J. Am. Chem. Soc.* **2008**, *130*, 16358.

[3] For a recent review on dienamine chemistry, see: a) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865; for selected examples, see: b) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; c) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685; d) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M.

Christmann, *Org. Lett.* **2011**, *13*, 70; e) J.-L. Li, S.-L. Zhou, P.-X. Chen, L. Dong, T.-Y. Liu, Y.-C. Chen, *Chem. Sci.* **2012**, *3*, 1879; f) Ł. Albrecht, G. Dickmeiss, F. Cruz Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543; g) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem.* **2012**, *124*, 4180; *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

[4] For a highlight on trienamine chemistry, see: a) E. Arceo, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 5384; *Angew. Chem. Int. Ed.* **2012**, *51*, 5290; for examples, see b) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; c) H. Jiang, B. Gschwend, Ł. Albrecht, S. G. Hansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 9032; d) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem.* **2011**, *123*, 8797; *Angew. Chem. Int. Ed.* **2011**, *50*, 8638; e) Y.-K. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212; f) Y. Liu, M. Nappi, E. C. Escudero-Adán, P. Melchiorre, *Org. Lett.* **2012**, *14*, 1310.

[5] For general reviews on applications of steric shielding aminocatalysts in aminocatalysis, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79; b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922; c) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243; d) L. Z. Zimmer, C. Sparr, R. Gilmaur, *Angew. Chem.* **2011**, *123*, 12062; *Angew. Chem. Int. Ed.* **2011**, *50*, 11860; e) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248.

[6] a) K.-S. Masters, S. Bräse, *Chem. Rev.* **2012**, *112*, 3717; b) R. N. Kharwar, A. Mishra, S. K. Gond, A. Stierle, D. Stierle, *Nat. Prod. Rep.* **2011**, *28*, 1208.

[7] a) R. Andersen, G. Buechi, B. Kobbe, A. L. Demain, *J. Org. Chem.* **1977**, *42*, 352; b) K. C. Nicolaou, A. Li, *Angew. Chem.* **2008**, *120*, 6681; *Angew. Chem. Int. Ed.* **2008**, *47*, 6579; c) M. E. Maier, *Nat. Prod. Rep.* **2009**, *26*, 1105.

[8] For examples of the application of 3-cyanochromones in Diels–Alder reaction, see: a) R. P. Hsung, *J. Org. Chem.* **1997**, *62*, 7904; b) S. J. Degen, H. C. Shen, G. M. Golding, C. A. Zificsak, R. P. Hsung, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 973.

[9] For recent reviews on H-bond-directed catalysis, see: a) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330; b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890; for the seminal report on squaramide-based catalysts in enantioselective synthesis, see: c) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416.

[10] See the Supporting Information for the crystal structures. CCDC 886343 and 886348 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968; for a review on H-bond strengths, see: b) T. Steiner, *Angew. Chem.* **2002**, *114*, 50; *Angew. Chem. Int. Ed.* **2002**, *41*, 48.

