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Asymmetric synthesis of polysubstituted chiral chromans *via* an organocatalytic oxa-Michael-nitro-Michael domino reaction†‡

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A catalytic asymmetric method for the synthesis of polysubstituted chromans *via* an oxa-Michael-nitro-Michael reaction has been developed. The squaramide-catalyzed domino reaction of 2-hydroxynitrostyrenes with *trans*- β -nitroolefins produced chiral chromans with excellent enantioselectivities (up to 99% ee), diastereoselectivities (up to >20 : 1 dr), and moderate to good yields (up to 82%).

Chromans play an essential role in natural products and pharmaceutical molecules (Fig. 1).¹ Given the biological relevance and diverse applications of this indispensable structural motif, numerous valuable methods for building chiral chromans have been developed.² Rapid, direct, and highly atom-economical asymmetric strategies to construct optically active chromans are the first choice.

In the past several years, considerable effort has been made to build chiral chroman derivatives with multichiral centers *via* asymmetric domino reactions³ catalyzed by aminocatalysts,⁴ thiourea organocatalysts⁵ squaramide organocatalysts,⁶ and other organocatalysts.⁷ Among these approaches, the addition to nitroolefins is a simple but highly efficient route to obtain

chiral chromans containing nitro-group, and the nitro group can often lead to changes in chemical and physical properties.^{4d-h,4j,5b-d} In 2013, Zhu *et al.* reported the organocatalytic oxa-Michael-Michael cascade strategy for the construction of spiro [chroman/tetrahydroquinoline-3,3'-oxindole] scaffolds from 2-hydroxynitrostyrenes and N-Boc-protected methyleneindolinones using a squaramide-cinchona bifunctional catalyst.^{6a} Peng *et al.* disclosed the highly efficient synthesis of polysubstituted 4-amino-3-nitrobenzopyrans from 2-hydroxyaryl-substituted α -amido sulfones and nitroolefins mediated by chiral squaramides.^{6b} Furthermore, Yan and Wang's group developed the squaramide-catalyzed cascade reaction of 2-hydroxychalcones with β -CF₃-nitroolefins to yield CF₃-containing heterocyclic compounds with a quaternary stereocenter.^{6c} Notably, a general strategy for the synthesis of chiral chromans bearing two nitro moieties was never reported, especially for 2-alkyl-substituted chromans. In 2003, an easy and efficient method for the synthesis of 3-nitrochromans *via* the reaction of 2-hydroxynitrostyrenes and *trans*- β -nitroolefins in the presence of DABCO was reported.⁸ Motivated by our previous work concerning the asymmetric synthesis of chromans,^{4e,9} this paper presents a highly efficient asymmetric method for the synthesis of polysubstituted chiral chroman derivatives, especially 2-alkyl-substituted chiral types, from 2-hydroxynitrostyrenes and *trans*- β -nitroolefins using a chiral bifunctional squaramide organocatalyst.^{10,11}

Given these considerations and previous work, the organocatalytic oxa-Michael-nitro-Michael reaction was performed with 2-hydroxynitrostyrene **1a** and aliphatic *trans*- β -nitroolefin **2a** as model substrates to examine the feasibility of our approach. Different parameters (Table 1), such as the catalyst and solvent, were studied. Efficient bifunctional squaramide organocatalysts possessing both H-bonding (thiourea, squaramide) and basic/nucleophilic moieties (tertiary amine), which act cooperatively, have been developed by several research

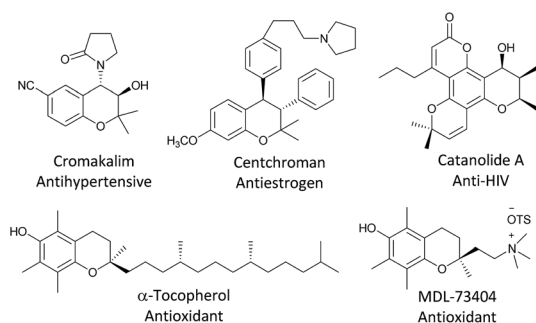


Fig. 1 Selected biologically active compounds.

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† Dedicated to Professor Zhen-Yuan Xu on the occasion of his 80th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 1031452. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra13525d



Table 1 Screening of reaction conditions^a

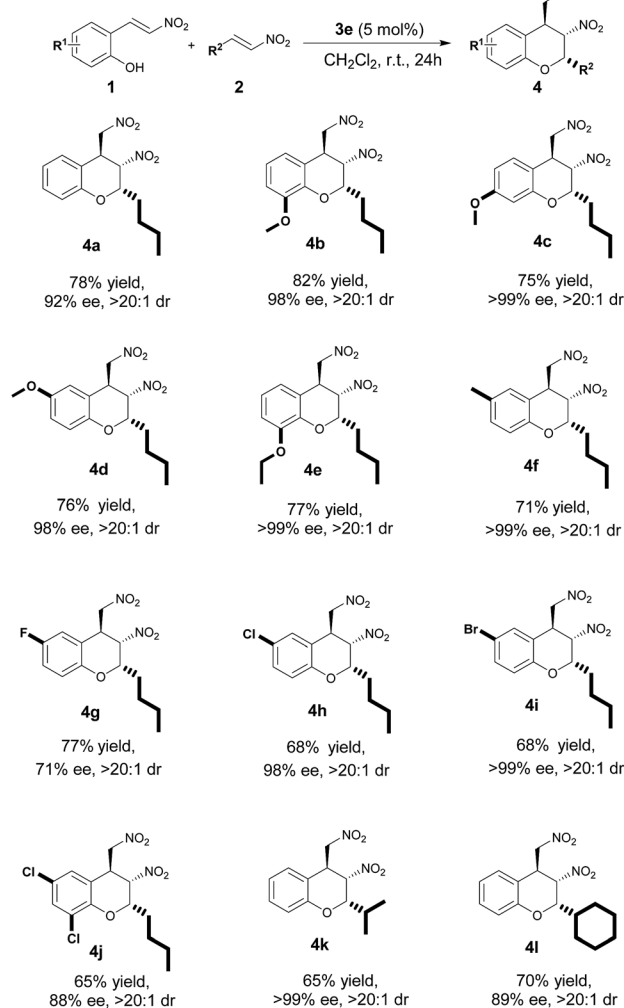
Entry	Catalyst	Solvent	Yield ^b (%)	ee ^c (%)	dr ^c
1	3a	CH ₂ Cl ₂	47	5	>20 : 1
2	3b	CH ₂ Cl ₂	Trace	N.D. ^d	N.D.
3	3c	CH ₂ Cl ₂	42	-39	>20 : 1
4	3d	CH ₂ Cl ₂	73	80	>20 : 1
5	3e	CH ₂ Cl ₂	78	92	>20 : 1
6	3f	CH ₂ Cl ₂	65	43	>20 : 1
7	3g	CH ₂ Cl ₂	71	85	>20 : 1
8	3h	CH ₂ Cl ₂	69	75	>20 : 1
9	3i	CH ₂ Cl ₂	75	79	>20 : 1
10	3j	CH ₂ Cl ₂	67	58	>20 : 1
11	3k	CH ₂ Cl ₂	68	69	>20 : 1
12	3e	CHCl ₃	65	93	>20 : 1
13	3e	ClCH ₂ CH ₂ Cl	77	88	>20 : 1
14	3e	EtOAc	71	57	>20 : 1
15	3e	THF	32	87	3 : 1
16	3e	1,4-Dioxane	Trace	N.D.	N.D.
17	3e	Et ₂ O	Trace	N.D.	N.D.
18	3e	CH ₃ CN	61	27	>20 : 1
19	3e	Toluene	77	81	8 : 1
20	3e	Cyclohexane	49	38	10 : 1

^a All the reactions were conducted with **1a** (0.2 mmol), **2a** (0.24 mmol), and solvent (2 mL) in the presence of 5 mol% organocatalyst **3** at room temperature with vigorous stirring for 24 h. ^b Isolated yield of **4a**. ^c Determined by chiral HPLC using an OJ-H column. ^d N.D. = Not determined.

groups for a broad range of enantioselective transformations.^{5c,d} An appropriate basic/nucleophilic moiety is critical to this kind of reaction. Under this consideration, chiral 1,2-diphenylethylenediamine, cyclohexanediamine, and quinine were selected as scaffolds. After a preliminary study, the quinine scaffold revealed excellent stereoinduction for the asymmetric synthesis of the chiral chroman **4a** when paired with the squaramide unit (Table 1, entries 1–4). Therefore, the influence of the quinine-derived catalysts should be studied systematically. Among the quinine-derived thiourea and squaramide organocatalysts **3d**–**3k**, the squaramide catalyst **3e** could promote the efficient formation of **4a** with increased enantioselectivities (up to 92% ee) (entries 4–11). A series of solvents was tested, and the performance of dichloromethane was satisfactory to afford **4a** in 78% yield, 92% ee, and >20 : 1 dr (Table 1, entries 5 and 12–20).

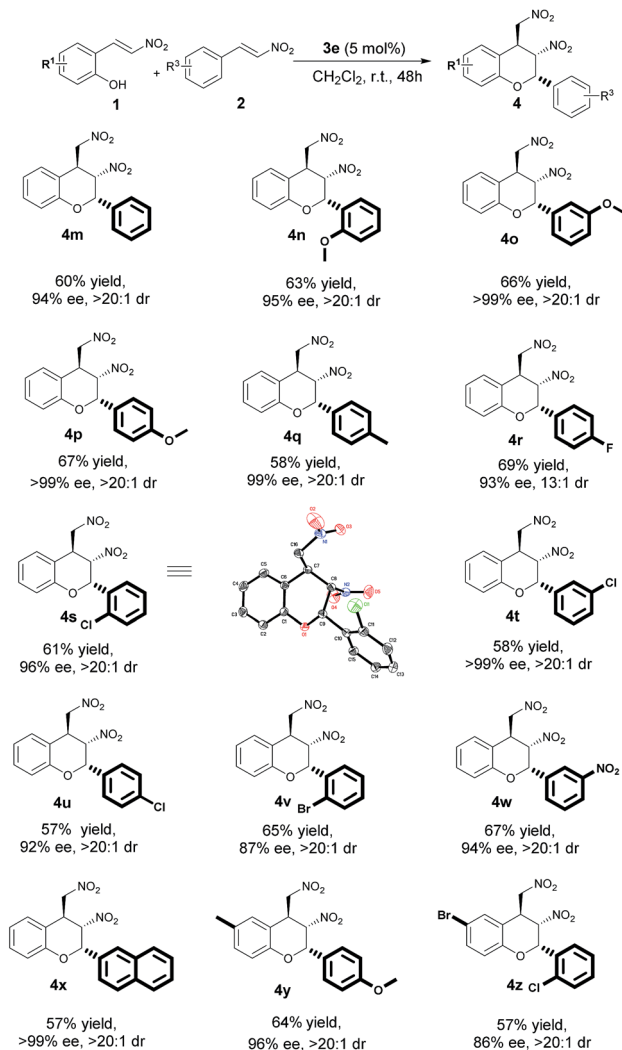
Consequently, the best conditions were found with 5 mol% of catalyst **3e** loading in CH₂Cl₂ at room temperature.

The reaction scope was determined under the optimal conditions. To investigate the versatility of the catalytic system, we first explored the universality of 1-nitro-1-hexene **2a** in this squaramide-catalyzed domino reaction. The reaction was tolerant to a range of substituents, such as OMe, OEt, Me, F, Cl, and Br, on the aromatic ring of 2-hydroxynitrostyrenes. The results revealed that the current transformation was a general and efficient strategy for the asymmetric synthesis of *n*-Bu group-substituted chiral chromans in the 2-position with three contiguous stereogenic centers. More specifically, when the substrates bore electron-donating groups (R¹ = OMe, OEt, Me) or electron-withdrawing groups (R¹ = F, Cl, Br) at the 6-, 7-, and 8-positions of the benzene ring, the target products achieved 68–82% yields with excellent diastereoselectivities (>20 : 1 dr) and enantioselectivities (71–99% ee). The targeted products with electron-donating groups resulted in high yields (Scheme 1, **4b**, **4c**, **4d**, **4e**, **4f** versus **4g**, **4h**, **4i**, **4j**). In particular, other aliphatic nitroolefins substituted by branched chain aliphatic group (R² = *i*-Pr) and cycloaliphatic group (R² = cyclohexyl) were further explored,



Scheme 1 Scope of 2-alkyl chromans.

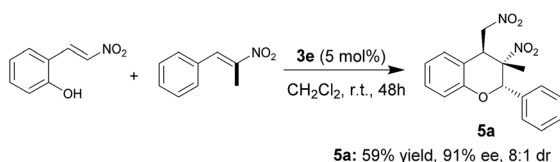




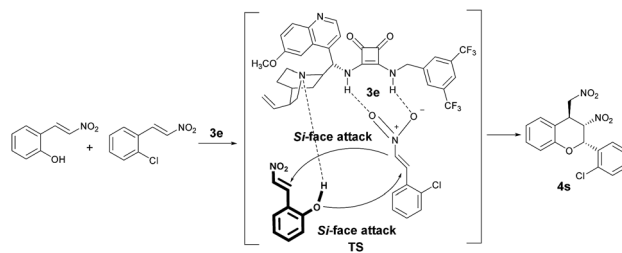
Scheme 2 Scope of 2-aryl chromans.

and these compounds delivered products with good asymmetric inductions (99% and 89% ee, >20 : 1 dr).

In-depth study of the current situation revealed that the enantioselectivities and diastereoselectivities of the chromans with 2-alkyl substituted groups were satisfactory. Therefore, further exploration of aromatic nitroolefins in the oxa-Michael-nitro-Michael domino reaction was necessary. Scheme 2 shows that nitroolefins incorporating electron-withdrawing groups and electron-donating groups at the aryl substituents in the 2-position could be successfully employed under these conditions, resulting in final adducts with high to excellent enantioselectivities (86–99% ee), high-to-excellent diastereoselectivities (up to >20 : 1 dr),



Scheme 3 Further investigation of the substrate scope.



Scheme 4 Proposed transition state for this reaction.

and moderate yields (57–69%). In general, nitroolefins with OMe and Me as substituent R³ groups yielded products in excellent 95–99% ee (Scheme 2, 4n–4q, 4y), which were superior to nitroolefins incorporating electron-withdrawing groups (R³ = F, Cl, Br, NO₂). However, product 4t was an interesting special case with 99% ee. The absolute configuration of product 4s was determined to be (2*S*, 3*S*, 4*S*) by single-crystal X-ray diffraction analysis (Scheme 3).¹²

To further demonstrate the synthetic utility of this reaction, we tested *trans*- α -Me- β -nitroolefin. As listed in Scheme 4, *trans*- α -Me- β -nitroolefin was suitable for this reaction and afforded the product 5a with an all-carbon quaternary stereocenter in the 3-position in 59% yield, 91% ee, and 8 : 1 dr.

On the basis of the X-ray crystallographic analysis of the absolute configuration of adduct 4s, we proposed a transition state model (Scheme 4). 2-Chloro-nitroolefin was activated well through the hydrogen-bonding interaction between the nitro group of 2-chloro-nitroolefin and the N–H of squaramide catalyst 3e. Meanwhile, 2-hydroxynitroolefin was activated through a hydrogen-bonding interaction between the hydroxyl group of 1a and the basic/nucleophilic moiety of 3e. Therefore, the hydroxyl group of 1a attacked the β -carbon of the activated 2-chloro-nitroolefin from the Si face under the control of the catalyst 3e. Subsequently, the α -carbon of activated 2-chloro-nitroolefin attacked the β -carbon of 1a from the Si face to yield the major stereoisomer of chiral chroman 4s with the configuration of (2*S*, 3*S*, 4*S*).

In conclusion, the first enantioselective, organocatalytic oxa-Michael-nitro-Michael domino reaction of 2-hydroxynitrostyrenes with *trans*- β -nitroolefins was successfully demonstrated. The new domino reaction provided an easy and efficient approach to construct 2-alkyl-substituted chiral chroman derivatives bearing three contiguous stereogenic centers with two nitro moieties. This strategy was also suitable for the asymmetric synthesis of 2-aryl-substituted chiral derivatives. Furthermore, this methodology could be used to construct chiral chromans with an all-carbon quaternary stereocenter in the 3-position. Further applications of this organocatalytic system are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 (a) G. W. Burton and K. U. Ingold, *Acc. Chem. Res.*, 1986, **19**, 194; (b) J. Martin Grisar, M. A. Petty, F. N. Bolkenius, J. DOW, J. Wagner, E. R. Wagner, K. D. Haegele and W. De Jong, *J. Med. Chem.*, 1991, **34**, 257; (c) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (d) J.-M. Zingg and A. Azzi, *Curr. Med. Chem.*, 2004, **11**, 1113; (e) J. Lal, *Contraception*, 2010, **81**, 275; (f) C. M. Starks, R. B. Williams, V. L. Norman, S. M. Rice, M. O'Neil-Johnson, J. A. Lawrence and G. R. Eldridge, *Phytochemistry*, 2014, **98**, 216; (g) S. Khan, S. Shukla, S. Sinha, A. D. Lakra, H. K. Bora and S. M. Meeran, *Int. J. Biochem. Cell Biol.*, 2015, **58**, 1; (h) M. Fridén-Saxin, T. Seifert, M. Malo, K. S. Andersson, N. Pemberton, C. Dyrager, A. Friberg, K. Dahlén, E. A. A. Wallén, M. Grötl and M. Luthman, *Eur. J. Med. Chem.*, 2016, **114**, 59.
- 2 (a) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (b) H. C. Shen, *Tetrahedron*, 2009, **65**, 3931; (c) T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210; (d) W.-J. Bai, J. G. David, F.-Z. Feng, M. G. Weaver, K.-L. Wu and T. R. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655; (e) T. Netscher, *Angew. Chem., Int. Ed.*, 2014, **53**, 14313; (f) N. Majumdar, N. D. Paul, S. Mandal, B. Bruin and W. D. Wulff, *ACS Catal.*, 2015, **5**, 2329; (g) N. Hu, K. Li, Z. Wang and W. Tang, *Angew. Chem., Int. Ed.*, 2016, **55**, 5044.
- 3 For selected reviews on organocatalytic domino reactions, see: (a) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (b) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (c) L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278; (d) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (e) F. Lv, S. Liu and W. Hu, *Asian J. Org. Chem.*, 2013, **2**, 824; (f) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442; (g) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (h) Y. Wang, H. Lu and P.-F. Xu, *Acc. Chem. Res.*, 2015, **48**, 1832.
- 4 For selected examples of the synthesis of chiral chromans by aminocatalysis, see: (a) P. Kotame, B.-C. Hong and J.-H. Liao, *Tetrahedron Lett.*, 2009, **50**, 704; (b) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **7**, 1627; (c) D. B. Ramachary and R. Sakthidevi, *Chem.-Eur. J.*, 2009, **15**, 4516; (d) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259; (e) D. Enders, C. Wang, X. Yang and G. Raabe, *Adv. Synth. Catal.*, 2010, **352**, 2869; (f) B.-C. Hong, P. Kotame, C.-W. Tsai and J.-H. Liao, *Org. Lett.*, 2010, **12**, 776; (g) C. Wang, X. Yang, G. Raabe and D. Enders, *Adv. Synth. Catal.*, 2012, **354**, 2629; (h) Z.-C. Geng, S.-Y. Zhang, N.-K. Li, N. Li, J. Chen, H.-Y. Li and X.-W. Wang, *J. Org. Chem.*, 2014, **79**, 10772; (i) A.-B. Xia, C. Wu, T. Wang, Y.-P. Zhang, X.-H. Du, A.-G. Zhong, D.-Q. Xu and Z.-Y. Xu, *Adv. Synth. Catal.*, 2014, **356**, 1753; (j) P. H. Poulsen, K. S. Feu, B. M. Paz, F. Jensen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 8203.
- 5 For selected examples of the synthesis of chiral chromans by thiourea organocatalysis, see: (a) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 8379; (b) D. B. Ramachary, R. Sakthidevi and K. S. Shruthi, *Chem.-Eur. J.*, 2012, **18**, 8008; (c) Z.-X. Jia, Y.-C. Luo, X.-N. Cheng, P.-F. Xu and Y.-C. Gu, *J. Org. Chem.*, 2013, **78**, 6488; (d) P. Saha, A. Biswas, N. Molleti and V. K. Singh, *J. Org. Chem.*, 2015, **80**, 11115; (e) W. Zheng, J. Zhang, S. Liu, C. Yu and Z. Miao, *RSC Adv.*, 2015, **5**, 91108; (f) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104.
- 6 For selected examples of the synthesis of chiral chromans by squaramide organocatalysis, see: (a) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng and C. Zhu, *Org. Lett.*, 2013, **15**, 4062; (b) B. Zheng, W. Hou and Y. Peng, *ChemCatChem*, 2014, **6**, 2527; (c) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, S. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang and R. Wang, *Org. Lett.*, 2015, **17**, 3826.
- 7 (a) M. Rueping and M.-Y. Lin, *Chem.-Eur. J.*, 2010, **16**, 4169; (b) M. Rueping, U. Uria, M.-Y. Lin and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732; (c) M. J. Climent, S. Iborra, M. J. Sabater and J. D. Vidal, *Appl. Catal., A*, 2014, **481**, 27.
- 8 C.-F. Yao, Y.-J. Jang and M.-C. Yan, *Tetrahedron Lett.*, 2003, **44**, 3813.
- 9 (a) D.-Q. Xu, Y.-F. Wang, S.-P. Luo, S. Zhang, A.-G. Zhong, H. Chen and Z.-Y. Xu, *Adv. Synth. Catal.*, 2008, **350**, 2610; (b) S.-P. Luo, Z.-B. Li, L.-P. Wang, Y. Guo, A.-B. Xia and D.-Q. Xu, *Org. Biomol. Chem.*, 2009, **7**, 4539; (c) A.-B. Xia, D.-Q. Xu, S.-P. Luo, J.-R. Jiang, J. Tang, Y.-F. Wang and Z.-Y. Xu, *Chem.-Eur. J.*, 2010, **16**, 801; (d) A.-B. Xia, G.-J. Pan, C. Wu, X.-L. Liu, X.-L. Zhang, Z.-B. Li, X.-H. Du and D.-Q. Xu, *Adv. Synth. Catal.*, 2016, **358**, 3155.
- 10 For selected reviews on the hydrogen bonding organocatalysis, see: (a) R. Ian Storer, C. Aciroa and L. H. Jones, *Chem. Soc. Rev.*, 2011, **40**, 2330; (b) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem.-Eur. J.*, 2011, **17**, 6890; (c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, *Adv. Synth. Catal.*, 2015, **357**, 253; (d) F. E. Held and S. B. Tsogoeva, *Catal. Sci. Technol.*, 2016, **6**, 645.
- 11 For selected examples catalyzed by hydrogen bonding, see: (a) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416; (b) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2010, **49**, 153; (c) M. Rombola, C. S. Sumaria, T. D. Montgomery and V. H. Rawal, *J. Am. Chem. Soc.*, 2017, **139**, 5297.
- 12 CCDC 1031452 contains the supplementary crystallographic data for the compound **4s**.[†]

