DOI: 10.1002/adsc.201300920

Enantioselective Synthesis of Azaflavanones Using Organocatalytic 6-*endo* Aza-Michael Addition

Shuanghua Cheng,[a] Lili Zhao,[a] and Shouyun Yu[a,*]

[a] State Key Laboratory of Analytical Chemistry for Life Science, Institute of Chemical Biology and Drug Innovation, School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing 210093, People's Republic of China
E-mail: yushouyun@nju.edu.cn

Received: October 16, 2013; Revised: December 24, 2013; Published online: March 12, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300920.

Abstract: A method to prepare highly enantioenriched azaflavanones using an organocatalytic 6-*endo* aza-Michael addition has been described. A variety of 2-aryl-, 2-vinyl- and 2-methylazaflavanones were prepared in good yields (53–84%) and excellent enantioselectivities (97.6:2.4 to 99.3:0.7 *er*).

Keywords: azaflavanones; dihydroquinolinones; enantioselectivity; Michael addition; organocatalysis

Azaflavanones, which are also known as dihydroquinolinones, have been characterized as one of the "privileged structures" in drug development.[1] Due to their ability to provide ligands for more than one type of receptor or enzyme targets, they exhibit important biological activities, such as cytotoxic activity against a panel of human tumor cell lines,[2] antimalarial activity[3] and potent cross-species microRNA inhibitors.[4] They also serve as key intermediates in total synthesis of biologically active natural products, including martinelline and martinellic acid.[5] Additionally, it was reported that the two enantiomers of azaflavanones displayed distinctly different activities.[2] Consequently, the enantioselective synthesis of these compounds is highly desirable.

There are two major known strategies to access enantioenriched azaflavanones (Figure 1).[6–10] One is the asymmetric intermolecular 1,4-conjugated addition of organometalllic reagents to 4-quinolones.[7] Only 2-arylazaflavanones could be accessed using this approach assisted by organometallic catalysts. The other is the 6-*endo*-trig cyclization of aminoalkylidene β-keto esters.[8] The β-ester must be introduced before cyclization and removed after cyclization, which makes this approach not step- and atom-economical. Recently, Rueping and co-workers reported the chiral Brønsted acid-catalyzed intramolecular aza-Michael addition of aminochalcone derivatives for the synthesis of 2-arylazaflavanones.[9] However, the enantioselectivity of this reaction was not satisfactory (74.5:25.5 to 81.5:18.5 *er*) and no 2-alkylazaflavanones were prepared using this method.

The organocatalytic intramolecular aza-Michael addition has emerged as a powerful tool to prepare enantioenriched nitrogen hetereocycles.[11] Significant progress has been achieved in the *exo*-type aza-Michael addition.[12] The *endo*-type aza-Michael addition turned out to be a challenging task.[8,9] As a part of our ongoing projects on intramolecular aza-Michael additions and their application in the total synthesis of alkaloids,[13] we would like to report a highly enantioselective 6-*endo* aza-Michael addition of aminochalcone derivatives using a trifunctional organocatalyst.

We chose the tosyl-protected aminochalcone **1a** for the initial investigation (Table 1). Firstly, we tried a series of organocatalysts, which have been successfully used in *exo*-type aza-Michael additions, including phase-transfer catalysts, aminocatalysts and chiral Brønsted acids. However, none of these catalysts gave

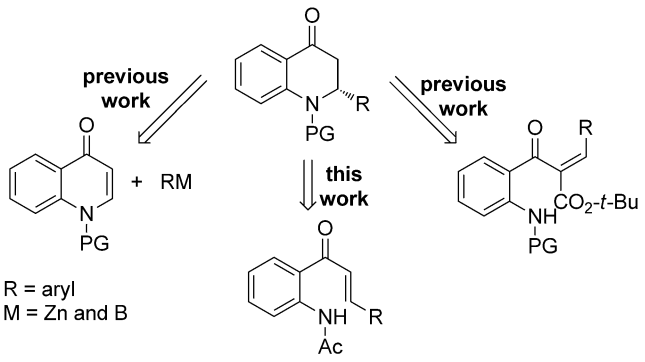
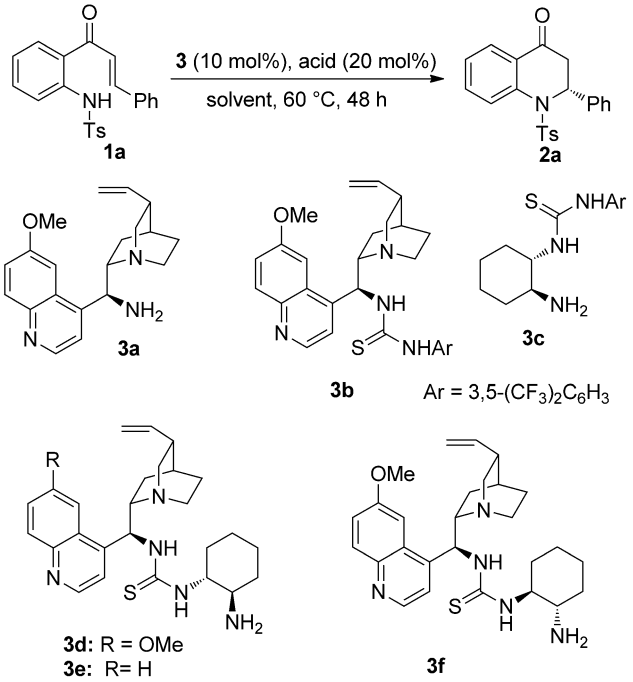


Figure 1. Synthetic approaches to azaflavones.

Table 1. Catalyst screening.[a]



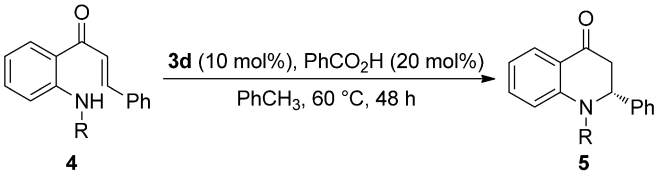
Entry	3	Acid	Solvent	Yield [%][b]	*er*[c]
1	**3a**	TFA	THF	0	–
2	**3b**	$PhCO_2H$	$PhCH_3$	0	–
3	**3c**	$PhCO_2H$	$PhCH_3$	23	32:68
4	**3d**	$PhCO_2H$	$PhCH_3$	87	89:11
5	**3e**	$PhCO_2H$	$PhCH_3$	79	84:16
6	**3f**	$PhCO_2H$	$PhCH_3$	23	36:64
7	**3d**	$PhCO_2H$	CH_2Cl_2	50	83:17
8	**3d**	$PhCO_2H$	CH_3CN	33	83:17
9	**3d**	$PhCO_2H$	THF	25	78:22
10	**3d**	4-$NO_2C_6H_4CO_2H$	$PhCH_3$	80	89:11
11	**3d**	4-$MeOC_6H_4CO_2H$	$PhCH_3$	94	82:18
12	**3d**	CH_3CO_2H	$PhCH_3$	92	86:14
13	**3d**	(*S*)-Boc-Pro	$PhCH_3$	69	85:15

[a] *Reaction conditions:* a solution of **1a** (0.1 mmol), **3** (0.01 mmol) and acid (0.02 mmol) in indicated solvent (1 mL) was stirred at 60 °C for 48 h.
[b] Isolated yield.
[c] The *ee* value was determined by HPLC on a chiral stationary phase.

us promising results (not shown). We next turned our attention to multifunctional organocatalysts. Quinine-derived primary amine **3a**[14] and thiourea **3b**[15] could not promote this transformation either (entries 1 and 2). *trans*-1,2-Diaminocyclohexane-derived thiourea **3c**[16] could catalyze this reaction assisted by $PhCO_2H$ at 60 °C, but only with 23% yield and 32:68 *er* (entry 3). To our delight, the quinine-derived trifunctional catalyst **3d**[17] combined with $PhCO_2H$ was a suitable catalyst system to give the desired product **2a** with 87% yield and 89:11 *er* (entry 4). Cinchonidine-derived catalyst **3e** could not give improved results (entry 5). (1*S*,2*S*)-*trans*-1,2-Diaminocyclohexane proved to be mismatched with the quinine-derived amine (entry 6). Further solvent and acid screening could not give superior results (entries 7–11).

In order to improve the enantioselectivity further, we next evaluated the nitrogen protecting groups using **3d** (10 mol%) as catalyst and $PhCO_2H$ (20 mol%) as additive. As shown in Table 2, a variety of sulfonamide-based substrates were tested (entries 1–5). Disappointingly, none of them gave better results. Carbamates turned out to be less efficient protecting groups (entries 6 and 7). The methyl group also proved be a poor protecting group. The protecting group-free substrate could not go through this transformation at all (entry 9). Finally, we were pleased to find that the acetyl group was a more promising protecting group with moderate yield (42%) and excellent enantioselectivity (97:3 *er*) (entry 10). The yield could be improved to 73% without any loss of enantioselectivity when 20 mol% catalyst and 40 mol% acid were used at 90 °C (entry 11). A higher *er* value (99:1) could be obtained with slightly less yield when less acid (20 mol%) was em-

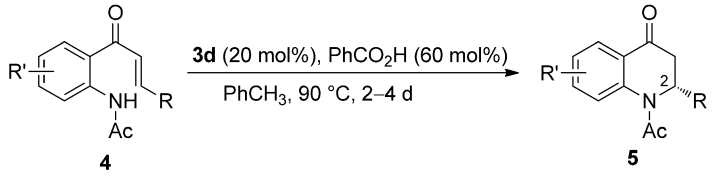
Table 2. Nitrogen protecting group screening.[a]

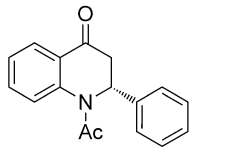


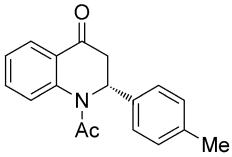
Entry	R	Yield [%][b]	*er*[c]
1	4-$MeOC_6H_4SO_2$	46	87:17
2	4-$NO_2C_6H_4SO_2$	92	65:35
3	$PhSO_2$	69	85:15
4	Ms	84	79:21
5	Tf	28	70:30
6	Cbz	10	89:11
7	MeOCO	14	98:2
8	Me	11	89:11
9	H	0	–
10	Ac	42	97:3
11[d,e]	Ac	73	97:3
12[d,f]	Ac	70	99:1
13[d,g]	**Ac**	**84**	**98:2**
14[d,h]	Ac	36	99:1

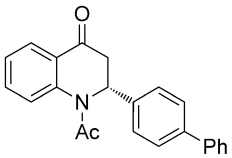
[a] *Reaction conditions:* a solution of **1** (0.1 mmol), **3d** (0.01 mmol) and $PhCO_2H$ (0.02 mmol) in $PhCH_3$ (1 mL) was stirred at 60 °C for 48 h.
[b] Isolated yield.
[c] The *er* value was determined by HPLC on chiral stationary phase.
[d] 20 mol% **3d** were used at 90 °C.
[e] 40 mol% $PhCO_2H$ were used.
[f] 20 mol% $PhCO_2H$ were used.
[g] 60 mol% $PhCO_2H$ were used.
[h] 100 mol% $PhCO_2H$ was used.

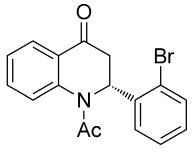
Table 3. Scope of the aza-Michael additions.[a]

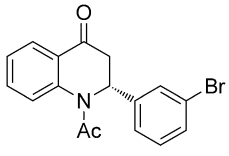


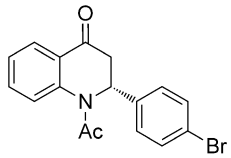

5a, 84%, 98.1:1.9 *er*

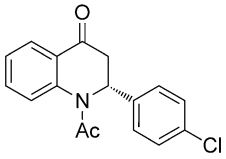

5b, 77%, 98.8:1.2 *er*

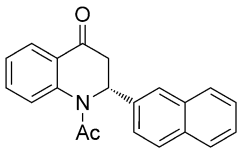

5c, 77%, 98.2:1.8 *er*

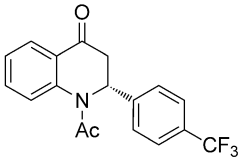

5d, 67%, 98.8:1.2 *er*

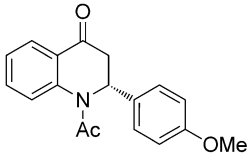

5e, 78%, 99.1:0.9 *er*

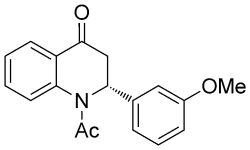

5f, 75%, 97.8:2.2 *er*

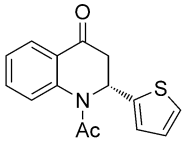

5g, 79%, 98.4:1.6 *er*

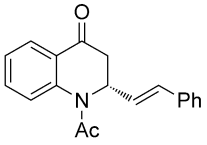

5h, 83%, 98.9:1.1 *er*

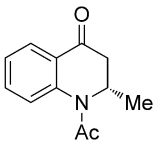

5i, 79%, 99.2:0.8 *er*

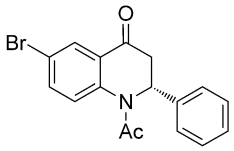

5j, 80%, 97.7:2.3 *er*


5k, 83%, 98.6:1.4 *er*


5l, 67%, 97.6:2.4 *er*


5m, 62%, 99.3:0.7 *er*


5n, 53%, 99.1:0.9 *er*


5o, 77%, 98.0:2.0 *er*

[a] *Reaction conditions:* a solution of **4** (0.1 mmol), **3d** (0.02 mmol) and $PhCO_2H$ (0.06 mmol) in $PhCH_3$ (1 mL) was stirred at 90 °C for 2–4 days. The yields given are for isolated products. The *er* values were determined by HPLC on a chiral stationary phase.

ployed (entry 12) while slightly higher *er* value (98:2) and significantly higher yield (84%) were observed when more acid (60 mol%) was used (entry 13). Further increasing the amount of the acid (100 mol%) led to significant lower yield (36%, entry 14).

With optimal conditions established, the scope of the reaction was surveyed using an assay of substituted acetyl-protected aminochalcones as shown in Table 3. Pleasingly, a variety of 2-arylazaflavanones (**5a–l**, **5o**) could be prepared with satisfactory yields (67–84%) and excellent enantioselectivities (97.6:2.4 to 99.2:0.8 *er*) using this 6-*endo* aza-Michael addition. The electronic property and position of the substitutions did not affect the outcome of this reaction. Remarkably, 2-vinylazaflavanone **5m** and 2-methylazaflavanone **5n** could also be accessed with acceptable yields and excellent enantioselectivities using our stategy.

In order to account for the high stereoinduction, a well-defined transition state model is proposed as shown in Figure 2. All of the three functional groups of the catalyst play cooperative roles in the transition state. The primary amine moiety of catalyst interacts with ketone group of the substrate to generate an iminium ion,[18] which is protonated by acid. The benzoic acid anion is believed to bind to the thiourea motif to provide a chiral counterion of the iminium ion.[19] The tertiary amine in quinine interacts with the amide hydrogen of the substrate through hydrogen bonding,[20] which directs the conjugate addition from the *Si* face of the double bond. The absolute configuration of the desired product could be predicted as "*R*" by this

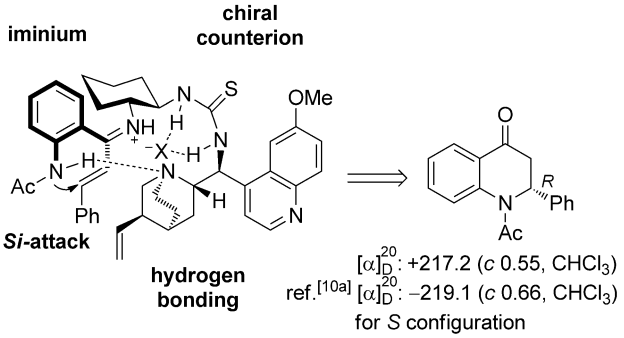


Figure 2. Proposed transition state.

model, which was confirmed by comparison of the specific optical rotation with the literature value of the known enantiomer.[10a]

In summary, we have described a highly enantioselective 6-*endo* aza-Michael addition of aminochalcone derivatives, which leads to highly enantioenriched azaflavanones. A variety of 2-aryl-, 2-vinyl and 2-methylazaflavanones were prepared in good yields (53–84%) and excellent enantioselectivities (97.6:2.4 to 99.3:0.7 *er*). Studies on the synthetic applications of this reaction are underway and will be reported in due course.

Experimental Section

Representative Procedure for the Intramolecular Aza-Michael Addition of Azaflavanones 5

To a reaction vial, *N*-protected 2-aminochalcone **4a** (27.0 mg, 0.1 mmol), organocatalyst **3d** (9.9 mg, 20 mol%), $PhCO_2H$ (7.3 mg, 60 mol%) and toluene (1 mL) were sequentially added at room temperataure. The resultant solution was stirred at 90 °C for 2 d. After the reaction was completed (as indicated by TLC analysis), the crude reaction mixture was subjected to flash chromatography on silica gel with mixtures of hexanes and ethyl acetate as eluent to afford the desired product **5a** as a yellowish solid; yield: 22.6 mg (84%).

Acknowledgements

This work was supported by 863 program (2013AA092903), National Natural Science Foundation of China (21102072 and 21272113) and Research Fund for the Doctoral Program of Higher Education of China (20110091120008).

References

[1] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. Dipardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235.

[2] a) Y. Xia, Z.-Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, T. Hackl, K.-H. Lee, *J. Med. Chem.* **1998**, *41*, 1155; b) S.-X. Zhang, J. Feng, S.-C. Kuo, A. Brossi, E. Hamel, A. Tropsha, K.-H. Lee, *J. Med. Chem.* **2000**, *43*, 167.

[3] A. Patti, S. Pedotti, T. Grassi, A. Idolo, M. Guido, A. De Donno, *J. Organomet. Chem.* **2012**, *716*, 216.

[4] S. Chandrasekhar, S. N. C. V. L. Pushpavalli, S. Chatla, D. Mukhopadhyay, B. Ganganna, K. Vijeender, P. Srihari, C. R. Reddy, M. J. Ramaiah, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 645.

[5] a) D. Ma, C. Xia, J. Jiang, J. Zhang, *Org. Lett.* **2001**, *3*, 2189; b) D. Ma, C. Xia, J. Jiang, J. Zhang, W. Tang, *J. Org. Chem.* **2003**, *68*, 442.

[6] For a review on asymmetric synthesis of azaflavanones and related compounds, see: A. E. Nibbs, K. A. Scheidt, *Eur. J. Org. Chem.* **2012**, 449.

[7] a) R. Shintani, T. Yamagami, T. Kimura, T. Hayashi, *Org. Lett.* **2005**, *7*, 5317; b) X. Zhang, J. Chen, F. Han, L. Cun, J. Liao, *Eur. J. Org. Chem.* **2011**, 1443.

[8] a) Z. Feng, Q. L. Xu, L. X. Dai, S. L. You, *Heterocycles* **2010**, *80*, 765; b) X. Liu, Y. Lu, *Org. Lett.* **2010**, *12*, 5592; c) X. Xiao, X. Liu, S. Dong, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2012**, *18*, 15922.

[9] M. Rueping, S. A. Moreth, M. Z. Bolte, *Z. Naturforsch. B* **2012**, 67, 1021.

[10] For other catalytic enantioselective syntheses of azaflavanones, see: a) B.-L. Lei, C.-H. Ding, X.-F. Yang, X.-L. Wan, X.-L. Hou, *J. Am. Chem. Soc.* **2009**, *131*, 18250; b) K. Kanagaraj, K. Pitchumani, *J. Org. Chem.* **2013**, *78*, 744; c) H. Zheng, Q. Liu, S. Wen, H. Yang, Y. Luo, *Tetrahedron: Asymmetry* **2013**, *24*, 875.

[11] For recent reviews on asymmetric aza-Michael addition, see: a) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991; b) L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem.* **2005**, 633; c) J. L. Vicario, D. Badía, L. Carrillo, J. Etxebarria, E. Reyes, N. Ruiz, *Org. Prep. Proced. Int.* **2005**, *37*, 513; d) J. L. Vicario, D. Bada, L. Carrillo, *Synthesis* **2007**, 2065; e) P. R. Krishna, A. Sreeshailam, R. Srinivas, *Tetrahedron* **2009**, *65*, 9657; f) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058; g) S. Fustero, M. Sánchez-Roselló, C. del Pozo, *Pure Appl. Chem.* **2010**, *82*, 669; h) A. Y. Rulev, *Russ. Chem. Rev.* **2011**, *80*, 197; i) J. Wang, P. F. Li, P. Y. Choy, A. S. C. Chan, F. Y. Kwong, *ChemCatChem* **2012**, *4*, 917; j) Z. Amara, J. Caron, D. Joseph, *Nat. Prod. Rep.* **2013**, *30*, 1211.

[12] For organocatalytic *exo*-type aza-Michael additions, see: a) K. Takasu, S. Maiti, M. Ihara, *Heterocycles* **2003**, *59*, 51; b) S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283; c) E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett, R. G. Carter, *J. Org. Chem.* **2008**, *73*, 5155; d) S. Fustero, J. Moscardó, D. Jiménez, M. D. Pérez-Carrión, M. Sánchez-Roselló, C. del Pozo, *Chem. Eur. J.* **2008**, *14*, 9868; e) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem.* **2010**, *122*, 8848; *Angew. Chem. Int. Ed.* **2010**, *49*, 8666; f) Q. Gu, S.-L. You, *Chem. Sci.* **2011**, *2*, 1519; g) J.-D. Liu, Y.-C. Chen, G.-B. Zhang, Z.-Q. Li, P. Chen, J.-Y. Du, Y.-Q. Tu, C.-A. Fan, *Adv. Synth. Catal.* **2011**, *353*, 2721; h) S. Fustero, C. del Pozo, C. Mulet, R. Lazaro, M. Sánchez-Roselló, *Chem. Eur. J.* **2011**, *17*, 14267; i) R. Miyaji, K. Asano, S. Matsubara, *Org. Lett.* **2013**, *15*, 3658.

[13] a) C. Zeng, H. Liu, M. Zhang, J. Guo, S. Jiang, S. Yu, *Synlett* **2012**, *23*, 2251; b) H. Liu, C. Zeng, J. Guo, M. Zhang, S. Yu, *RSC Adv.* **2013**, *3*, 1666.

[14] Y.-C. Chen, *Synlett* **2008**, 1919.

[15] a) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; c) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, *4*, 603.

[16] a) X.-J. Zhang, S.-P. Liu, J.-H. Lao, G.-J. Du, M. Yan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 1451;

b) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286.
[17] P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302.
[18] For a comprehensive review about iminium catalysis, see: A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.
[19] For reviews about asymmetric counterion-directed catalysis, see: a) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nature Chem.* **2012**, *4*, 603; b) M. mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540; *Angew. Chem. Int. Ed.* **2013**, *52*, 518; c) K. Brak, E. N. Jacobsen, *Angew. Chem.* **2013**, *125*, 558; *Angew. Chem. Int. Ed.* **2013**, *52*, 534.
[20] For selected reviews about hydrogen bonding catalysis, see: a) M. S. Taylaor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.

