Tetrahedron 67 (2011) 10287–10290

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chiral dihydrobenzo[1,4]oxazines as catalysts for the asymmetric transfer-hydrogenation of α,β-unsaturated aldehydes

Christian Ebner, Andreas Pfaltz *

Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

ARTICLE INFO

Article history:
Received 10 August 2011
Received in revised form 10 October 2011
Accepted 12 October 2011
Available online 20 October 2011

Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

Keywords:
Asymmetric catalysis
Organocatalysis
Hantzsch ester
Acrylaldehydes
Transfer-hydrogenation

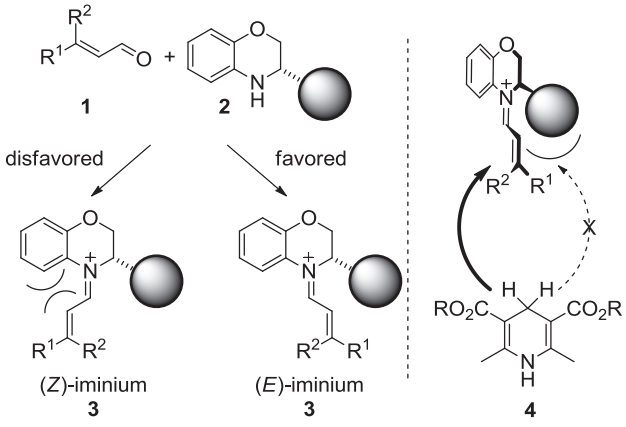
ABSTRACT

A new class of organocatalysts based on the structure of 2,3-dihydrobenzo[1,4]oxazine was prepared and applied in the enantioselective transfer-hydrogenation of α,β-unsaturated aldehydes with Hantzsch ester as hydride donor. These catalysts proved to be particularly effective for the conjugate reduction of β,β-diaryl-substituted acrylaldehydes leading to saturated aldehydes bearing a stereogenic center with two different aryl groups with enantioselectivities of up to 91% ee.

1. Introduction

Organocatalyzed asymmetric transfer-hydrogenation has emerged as a mild and very selective method for the conjugate reduction of α,β-unsaturated aldehydes or ketones.[1] The catalyst, typically a chiral pyrrolidine or imidazolidinone derivative with a stereogenic center next to the N atom, activates the aldehyde by forming an iminium ion, while the substituent at the stereogenic center shields one of the enantiotopic faces of the substrate. With dihydropyridines such as Hantzsch esters as the hydrogen source the method mimics enzymatic reductions with NADH or $FADH_2$ as cofactors.[2] Its scope is often complementary to that of analogous metal-catalyzed transformations. Especially for the conjugate reduction of α,β-unsaturated aldehydes this methodology has proved to be of great value since metal-catalyzed reductions often lead to the corresponding alcohols rather than to the saturated aldehydes.[3]

To date only a limited number of catalysts have been applied in this reaction, namely MacMillan's imidazolidinones,[1b,c,e,h] proline derivatives,[1f,g] and a catalyst system introduced by List and co-workers[1d] based on amino acid esters in combination with chiral phosphoric acids. In connection with our work on mass spectrometric screening of organocatalysts[4] we had become interested in chiral 2,3-dihydrobenzo[1,4]oxazines **2**. Based on the generally accepted mechanism[2] of asymmetric transfer-hydrogenation we thought that compounds of this type could be a useful extension to the known catalysts for this reaction (Scheme 1).



Scheme 1. Mode of stereoinduction.

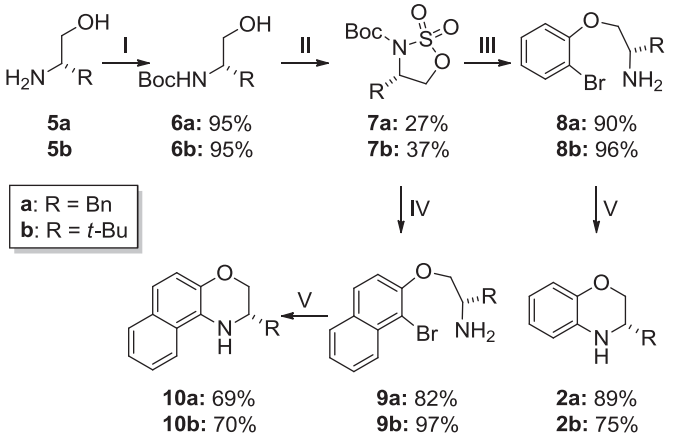
* Corresponding author. Tel.: +41 61 2671108; fax: +41 61 2671103; e-mail address: andreas.pfaltz@unibas.ch (A. Pfaltz).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.051

The iminium intermediate can adopt a cis or a trans conformation and discrimination between these two isomers by the catalyst is crucial for achieving high enantioselectivity, because in the (*E*)- and (*Z*)-isomer the opposite faces of the π-system are shielded. Assuming a planar conformation of the unsaturated iminium π-system the (*E*) isomer should be strongly favored due to the steric repulsion between the olefinic H atom and the benzene ring. Thus the reaction is expected to proceed via the (*E*) isomer and hydride attack from the less hindered side, making benzoxazines of this type attractive catalyst candidates.

2. Results and discussion

Synthesis of different dihydrobenzooxazines **2** and dihydronaphthooxazines **10** was achieved starting from commercially available amino alcohols **5** (Scheme 2).[5] These were *N*-Boc protected and converted to the cyclic sulfamidates **7a**,**b**. Subsequent reaction with 2-bromophenol followed by acidic *N*-Boc deprotection yielded the benzoxazine precursors **8a**,**b**, which were then cyclized to the desired organocatalysts **2a,b** by Buchwald–Hartwig amination.[6] Naphthyl derivatives **10a**,**b** were obtained by nucleophilic cleavage of sulfamidates **7a**,**b** with 2-bromonaphthalen-2-ol and subsequent palladium-catalyzed ring closure (for details, see Supplementary data).

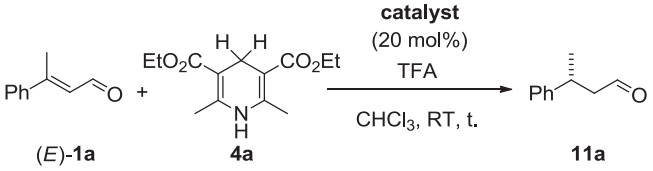


Scheme 2. Catalyst syntheses. Conditions: I: Boc_2O, NEt_3, THF, rt, 1.5 h; II: (1) $SOCl_2$, imidazole, NEt_3, DCM, 0 °C→rt, 18 h; (2) $NaIO_4$, $RuO_2 \cdot H_2O$, H_2O/EtOAc, 0 °C, 1 h; III: (1) 2-bromophenol, NaH, DMF, RT, 18 h; (2) concd H_2SO_4, dioxane/H_2O, 1 h; IV: (1) 1-bromonaphthalen-2-ol, NaH, DMF, rt, 18 h; (2) concd H_2SO_4, dioxane/H_2O, 1 h; V: $Pd(OAc)_2$, Xantphos, *t*-BuONa, toluene, 100 °C, 18 h.

For initial experiments β-methyl cinnamaldehyde ((*E*)-**1a**) was chosen as model substrate. When catalyst **2a** was applied at room temperature we were pleased to find full conversion to the desired product **11a** already after 15 min (Table 1, entry 1). Furthermore we found an ee of 61% in favor of the (*R*)-enantiomer. Catalyst screening showed that benzyl-substituted derivatives induced higher enantioselectivities than the *tert*-butyl analogues. Catalyst **10b** showed only low activity resulting in less than 10% conversion even after 24 h (entry 5).

Next, different reaction conditions were evaluated (Table 2). The nature of the solvent had only a small influence on the enantioselectivity (entries 1–5). The best result was obtained in Et_2O yielding **11a** with full conversion after 30 min and 69% ee. However, when the reaction in Et_2O was carried out at lower temperature, it did not reach completion anymore. The reaction in $CHCl_3$ was faster and could be carried out at low temperature. We found that the ee increased with decreasing temperature but it did not exceed 67% ee (entry 7). The steric demand of the Hantzsch ester had essentially no effect on the ee as shown in the reaction with the di-*tert*-butyl ester (entry 8). The results show that dihydrobenzoxazine derivatives are very reactive catalysts. However, the enantioselectivities in the reduction of substrate **1a** are lower than those reported for the best catalysts.

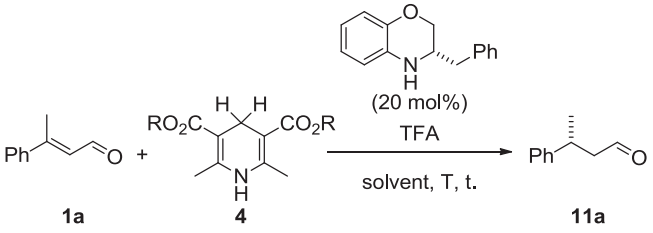
Table 1
Catalyst screening



Entry	Catalyst	*t* [h]	Conv.[a] [%]	ee[b] [%] (config.)
1	**2a**	0.25	>99	61 (*R*)
2	**2b**	0.75	>99	40 (*R*)
3	**10a**	0.5	>99	59 (*R*)
4	**10b**	4	<10	26 (*R*)
5	**10b**	24	<10	25 (*R*)

TFA=trifluoro acetic acid.
[a] Determined by GC analysis of the reaction mixture.
[b] Determined by GC analysis (Chiraldex G-TA).

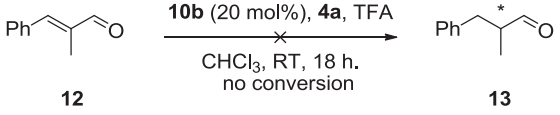
Table 2
Optimization studies



Entry	Solvent	*T* [°C]	*t* [h]	R	Conv.[a] [%]	ee[b] [%] (config.)
1	$CHCl_3$	25	0.25	Et	>99	61 (*R*)
2	CH_2Cl_2	25	0.25	Et	>99	57 (*R*)
3	Toluene	25	0.25	Et	>99	56 (*R*)
4	Et_2O	25	0.50	Et	>99	69 (*R*)
5	Dioxane	25	1.25	Et	>99	63 (*R*)
6	$CHCl_3$	−25	15	Et	>99	66 (*R*)
7	$CHCl_3$	−50	3	Et	>99	67 (*R*)
8	$CHCl_3$	25	1	*t*-Bu	>99	59 (*R*)

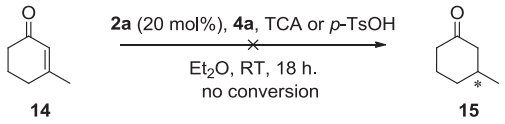
TFA=trifluoroacetic acid.
[a] Determined by GC analysis of the reaction mixture.
[b] Determined by GC analysis (Chiraldex G-TA).

We also examined α-substituted acrylaldehydes **12** as substrates. However, catalysts **2a**,**b** and **10a**,**b** proved to be unreactive and no reduction product was detected even after 18 h (Scheme 3). These results were consistent with ESI-MS studies, which we carried out to evaluate the tendency of the catalysts to form an iminium intermediate with the substrate. As expected, the sterically demanding *tert*-butyl-substituted catalysts **2b** and **10b** did not form iminium salts. With the more reactive benzyl-substituted catalysts signals of iminium salts were detected but the intensity was very low. Interestingly, the dihydronaphthoxazine derivative **10a** showed the strongest iminium signal in the MS, although the signal ratio of the iminium salt to the free catalyst was still very low (1:24) compared to the ratios measured for the more reactive substrate **1a**.[7]



Scheme 3. Attempted transfer-hydrogenation of α-methyl cinnamaldehyde (TFA=trifluoroacetic acid).

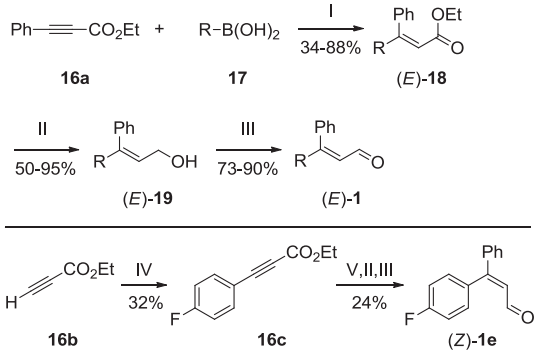
β-Methyl cyclohexanone (**14**) proved to be unreactive as well. When we applied the same conditions as reported in literature for a different catalyst system,[1e] no conversion was observed (Scheme 4). As expected, no iminium signals could be detected by ESI-MS in this case.



Scheme 4. Attempted transfer-hydrogenation of β-methyl cyclohexanone (TCA=trichloroacetic acid, *p*-TsOH=*p*-toluenesulfonic acid).

As these catalysts showed no activity in the reduction of enones or α-substituted acrylaldehydes but were able to reduce β-disubstituted acrylaldehydes with high activity, we focused our attention on β,β-diaryl-acrylaldehydes. The resulting saturated aldehydes with a diaryl-substituted stereogenic center in the β position are of interest as potential precursors for the synthesis of bioactive natural products or drugs such as tolteridine,[8] mimosifoliol[9] or arpromidine.[10] Only very few examples of enantioselective conjugate reductions of 1-acceptor-substituted 2,2-diarylalkenes can be found in literature.[10,11] However, no such reactions of β,β-diaryl-acrylaldehydes have been reported yet.

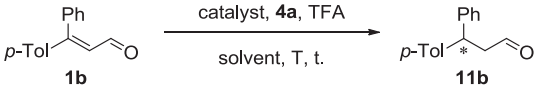
Synthesis of the required substrates was accomplished following known literature procedures.[12] Starting from commercially available ethyl 3-phenylpropiolate (**16a**), ethyl acrylates (*E*)-**18** were obtained by copper-catalyzed conjugate addition of the corresponding arylboronic acids **17** with perfect *E*/*Z* selectivity. Reduction to the allylic alcohols (*E*)-**19** with $NaBH_4$ and subsequent oxidation with MnO_2 afforded the desired acrylaldehydes (*E*)-**1** (Scheme 5). In a similar fashion substrate (*Z*)-**1e** was obtained from 3-(4-fluorophenyl)-propiolate (**16c**), which was prepared by a ligand-free copper(I)-catalyzed Sonogashira-type coupling[13] of (4-fluorophenyl)boronic acid with ethyl propiolate (**16b**) (for detailed synthetic procedures and scope, see Supplementary data).



Scheme 5. Substrate synthesis. Conditions: I: Cu(I)OAc, MeOH, rt, 18 h; II: $NaBH_4$, $ZnCl_2$, NEt_3, THF, reflux, 3 h; III: MnO_2, $CHCl_3$, rt, 2 d; IV: 4-F–C_6H_4–$B(OH)_2$, CuI, Ag_2O, Cs_2CO_3, DCE, 80 °C, 36 h; V: Ph–$B(OH)_2$, Cu(I)OAc, MeOH, rt, 18 h.

Initial experiments with these substrates gave very promising results. Subsequent optimization studies were carried out using substrate (*E*)-**1b** (Table 3). In the reaction with catalyst **2a** $CHCl_3$ proved to be the best solvent yielding the corresponding saturated aldehyde in 76% ee with full conversion after 15 min (entry 1). As observed before in the reduction of 2-methylcinnamaldehyde (**1a**) the reaction times were remarkably short, allowing us to lower the reaction temperature to −20 °C. Under these conditions conversion was still complete within 1 h while the ee increased to 78% (entry 4). When the temperature was further decreased to −50 °C the reaction did not go to completion anymore (entry 5). Among the four catalysts tested, benzoxazines **2a** and **2b** gave better results in terms of reactivity than naphthoxazines **10a** and **10b**. Dihydrobenzoxazine **2a** emerged as the catalyst of choice for this reaction, as it was the only catalyst that gave full conversion, although the *tert*-butyl derivative **2b** induced slightly higher enantioselectivity (entry 6).

Table 3
Optimization studies

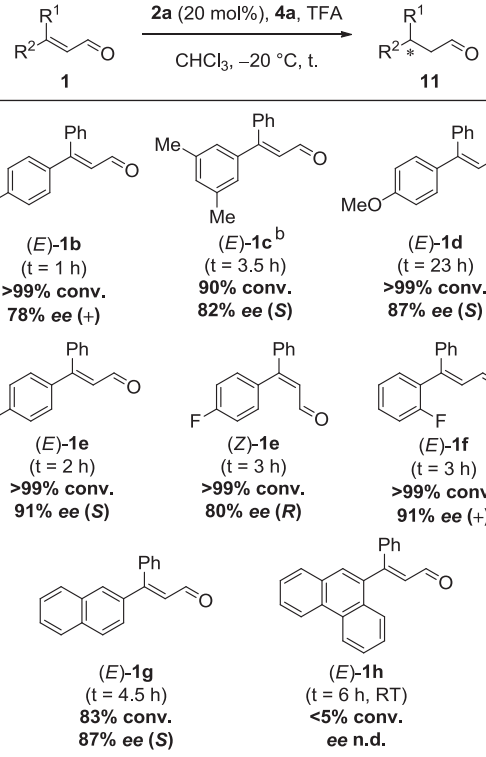


Entry	Catalyst	Solvent	*T* [°C]	*t* [min]	Conv.[a] [%]	ee[b] [%] (config.)
1	**2a**	$CHCl_3$	25	15	>99	76 (+)
2	**2a**	Et_2O	25	30	>99	63 (+)
3	**2a**	CH_2Cl_2	25	60	>99	72 (+)
4	**2a**	$CHCl_3$	−20	45	>99	78 (+)
5	**2a**	$CHCl_3$	−40	210	50	n.d.
6	**2b**	$CHCl_3$	25	60	75	79 (+)
7	**10a**	$CHCl_3$	25	120	40	73 (+)
8	**10b**	$CHCl_3$	25	300	<10	n.d.

TFA=trifluoroacetic acid; n.d. denotes 'not determined'.
[a] Determined by GC analysis of the reaction mixture.
[b] Determined by HPLC analysis (Daicel Chiracel AD-H) of the corresponding alcohol after reduction with $NaBH_4$.

Having found the optimal reaction conditions (Table 3, entry 4) we examined the substrate scope (Table 4). Catalyst **2a** showed high activity and enantioselectivities between 78% and 91% ee for a range of β,β-diaryl-acrylaldehydes with different steric and

Table 4
Scope of the reaction[a]



TFA=trifluoroacetic acid; n.d. denotes 'not determined'.
[a] Screening reactions were carried out on a 0.1 mmol scale. Conversion determined by GC analysis of the reaction mixture, ee determined by HPLC analysis of the corresponding alcohol on a chiral stationary phase after reduction with $NaBH_4$. When given, the absolute configuration was determined by comparison of the sign of optical rotation of the saturated aldehyde with literature data.[14]
[b] When the reaction was carried out on a 10-fold scale (1 mmol), 81% yield (89% conv.) and 82% ee (*S*) were obtained.

electronic properties. Both electron-donating (substrate **1d**) and electron-withdrawing (**1e** and **1f**) aryl groups were tolerated. With the more sterically demanding substrates **1c** and **1g** incomplete conversions were observed, while the enantioselectivities were still at 82% and 87% ee, respectively. The phenanthrene derivative **1h** proved to be unreactive. Apparently, the phenanthrenyl group induced too much steric hindrance, so only traces of product were formed.

For comparison we also tested MacMillan's (*S*)-2-(*tert*-butyl)-3-methylimidazolidin-4-one under the conditions reported for the hydrogenation of substrate (*E*)-**1a**.[1c] The conversion of substrate (*E*)-**1e** after 2 h was only 26%. After 18 h the conversion reached 65% but did not further increase from there on. The hydrogenation product **11e** was formed in 62% ee.

The absolute configuration of the major enantiomers produced in these reactions is in agreement with the model of stereoinduction shown in Scheme 1. Sterically controlled *Re*-facial hydride transfer to the (*E*)-iminium salt derived from (*E*)-**1c**, for example, should lead to (*S*)-**11c** and indeed, this was the major enantiomer found. Experiments with the cis/trans isomers (*Z*)-**1e** and (*E*)-**1e** showed that the sense of chiral induction depends on the configuration of the C=C bond. Reduction of (*E*)-**1e** resulted in (*S*)-**11e** with 91% ee while (*Z*)-**1e** gave the opposite enantiomer (*R*)-**11e** with 80% ee.

In this respect, the stereochemical course differs from that reported for the reduction of the β-methyl-substituted acrylaldehyde **1a** and related β-alkyl derivatives.[1] For β-alkyl-substituted substrates a stereoconvergent pathway was observed, which leads to the same product enantiomer starting either from the (*E*)- or the (*Z*)-isomer. This stereoconvergence has been rationalized by rapid cis/trans isomerization via a dienamine intermediate under the reaction conditions. Obviously, such an isomerization reaction is not possible for β,β-diaryl-substituted acrylaldehydes and therefore (*E*)- and (*Z*)-isomers are converted to opposite enantiomers. According to the model for the enantioselective step shown in Scheme 1, it is the interaction of the catalyst with the less substituted α-C atom rather than the prochiral β-CAr^1Ar^2 unit that dictates enantioselectivity. Consequently, it is possible to achieve high enantioselectivity even with sterically and electronically very similar aryl substituents, provided that the substrate is available as pure (*E*)- or (*Z*)-isomer.

3. Conclusion

We have shown that 2,3-dihydro-benzo[1,4]oxazines are efficient catalysts for the enantioselective transfer-hydrogenation of α,β-unsaturated aldehydes. They appear to be particularly effective for the conjugate reduction of β,β-diaryl-substituted acrylaldehydes, a reaction which has not been reported for other organocatalysts yet. The resulting saturated aldehydes bearing a stereogenic center in the β position with two different aryl groups are of interest as potential precursors for the synthesis of various bioactive natural products or drugs.

4. Experimental section

4.1. Organocatalyzed transfer-hydrogenation of substrate (*E*)-1e

To a solution of (*E*)-3-(4-fluorophenyl)-3-phenyl-acrylaldehyde ((*E*)-**1e**, 22.6 mg, 0.1 mmol, 1.00 equiv), Hantzsch ester (**4a**, 30.2 mg, 0.12 mmol, 1.20 equiv) and catalyst **2a** (4.50 mg, 0.02 mmol, 20 mol %) in $CHCl_3$ (0.5 ml, 0.2 M) was added TFA (0.456 mg, 4 μmol, 4 mol %) at −20 °C. The conversion was followed by GC analysis of an aliquot of the reaction mixture and full conversion was achieved after 2 h. After removal of the solvent under reduced pressure the residue was purified by column chromatography (SiO_2, 2×20 cm, pent/Et_2O=5:1) and the desired compound was obtained as a colorless oil (19.2 mg, 84%). The analytical data matched the literature values.[14] R_f (SiO_2, pent/Et_2O) 0.21; GC (Macherey-Nagel Optima 5 PhMeSi, 100 °C, 2 min, 10 K/min, 270 °C, 10 min): 14.2 min (**11e**), 15.3 min ((*E*)-**1e**); MS (EI, 70 eV): *m*/*z* (%)=228 (61), 210 (30), 186 (24), 185 (100), 183 (59), 170 (15), 165 (67), 121 (139), 105 (28), 104 (10), 103 (14), 101 (10), 91 (10), 77 (17), 75 (10), 63 (12), 51 (25), 50 (11). The ee was determined by HPLC analysis of the corresponding alcohol. For this purpose the aldehyde **11c** was dissolved in MeOH (1 ml) and the solution was cooled to 0 °C. Then $NaBH_4$ (15.9 mg, 0.421 mmol, 5.00 equiv) was added and the mixture was stirred for 1 h before it was quenched with satd NH_4Cl-solution. After extraction with EtOAc and drying over $MgSO_4$, the solvent was removed under reduced pressure. HPLC analysis (Daicel Chiracel OD-H, hept/*i*-PrOH=95:5, 0.5 ml/min, 40 °C, t_R=32.7 min (*R*), 37.2 min (*S*)) indicated 91% ee in favor of the (*S*)-enantiomer.

Acknowledgements

Financial support by the Swiss National Science Foundation is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.051.

References and notes

1. (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660; (b) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108; (c) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32; (d) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368; (e) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662; (f) Zhao, G.-L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 7417; (g) Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. *Org. Lett.* **2008**, *10*, 2035; (h) Hoffman, T. J.; Dash, J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 2756.
2. Lelais, G.; MacMillan, D. W. C. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley VCH: Weinheim, 2007; p 95.
3. (a) Teddy, J.; Falqui, A.; Corrias, A.; Carta, D.; Lecante, P.; Gerber, I.; Serp, P. *J. Catal.* **2011**, *278*, 59; (b) Hong, Y.-C.; Sun, K.-Q.; Zhang, G.-R.; Zhong, R.-Y.; Xu, B.-Q. *Chem. Commun.* **2011**, 1300.
4. Fleischer, I.; Pfaltz, A. *Chem.—Eur. J.* **2010**, *16*, 95.
5. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283.
6. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
7. When cinammaldehyde was mixed with catalyst **2a** in the presence of TFA, a catalyst/iminium signal ratio of 2.3:1 was found by ESI-MS analysis.
8. Paras, N. A.; Simmons, B.; MacMillan, D. W. C. *Tetrahedron* **2009**, *65*, 3232.
9. Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2004**, *69*, 9196.
10. Lee, D.; Yang, Y.; Yun, J. *Org. Lett.* **2007**, *9*, 2749.
11. (a) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W. M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855; (b) Yoo, K.; Kim, H.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 11134; (c) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881.
12. Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010.
13. Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett.* **2009**, *50*, 5044.
14. Tokunaga, N.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 607.