DOI: 10.1002/adsc.200800371

From Mono-Triazolium Salt to Bis-Triazolium Salt: Improvement of the Asymmetric Intermolecular Benzoin Condensation

Yajun Ma,[a] Siping Wei,[a] Jie Wu,[a] Fei Yang,[a] Bo Liu,[a] Jingbo Lan,[a] Shengyong Yang,[a] and Jingsong You[a,*]

[a] Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, People's Republic of China
Fax: (+86)-28-8541-2203; e-mail: jsyou@scu.edu.cn

Received: June 13, 2008; Revised: August 31, 2008; Published online: October 16, 2008

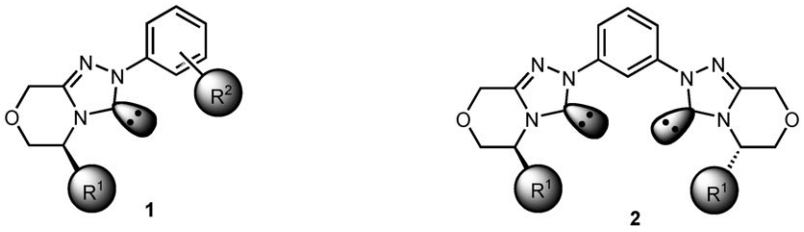
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800371.

Abstract: A solution to the long-standing challenge of developing a highly effective method for the enantioselective intermolecular benzoin condensation of aromatic aldehydes is described. The chiral bis-bicyclic triazolium salt – 1,3-bis{(*S*)-5-benzyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*][1,2,4]triazol-2-ium-2-yl}benzene dichloride [(*S*)-**5a-1**] is currently the most efficient precatalyst for the asymmetric variant of the benzoin condensation.

Keywords: asymmetric benzoin condensation; chiral bis-bicyclic triazolium salts; N-heterocyclic carbene; organocatalysis

Introduction

Optically active benzoin-type 2-hydroxy ketones are not only important structural subunits in many biologically active compounds, but also valuable synthons for stereoselective syntheses.[1] In 1966, Sheehan and co-workers reported the first asymmetric variant of the benzoin condensation employing a chiral thiazolium salt as catalyst precursor that delivered negligible enantiomeric excess (as low as 22% *ee*).[2] In the following three decades, a number of chiral thiazolium salts were synthesized and investigated for this type of asymmetric condensation. Regrettably, these catalysts performed poorly and afforded acyloin products with only moderate optical enrichment.[3] Finally in 1996, Enders et al. broke the ice using a chiral triazolium salt as precatalyst for the enantioselective benzoin reaction, which was able to be extended for the first time to a variety of aromatic aldehydes in 22–72% yields with *ee* values of 20–86%.[4] Later, Leeper et al. developed bicyclic chiral triazolium salts and documented their application to the benzoin condensation with comparable enantioselectivities (yields: 11–50%, 20–82.5% *ee*),[5] which were further improved by Enders et al. with another bicyclic chiral triazolium salt.[6] The acyloin product from benzaldehyde was isolated in 83% yield with 90% *ee*, which was the highest value recorded for a non-enzyme-dependent, catalyzed benzoin reaction in terms of chemical yield and enantioselection. A keen reader might interject that these asymmetric intermolecular benzoin condensations of aromatic aldehydes reported so far have generally suffered from low yields of acyloins which limit the scope of substrates[1d,4–9] despite considerable advances in the intramolecular asymmetric aldehyde-ketone benzoin reactions.[10] Furthermore, these results have demonstrated that it is difficult to improve this type of asymmetric reaction by increasing the loadings of triazolium precatalyst because the higher concentration of bicyclic triazolylidene with its characteristic basic properties could lead to a partial racemization of acyloin product.[4–7] Clearly, one of the key issues to overcome this problem is to develop a class of chiral triazolylidene catalysts that display high catalytic activity with essentially low catalyst loadings, minimizing a racemization of acyloins. However, in the last six years the challenging enantioselective intermolecular benzoin reactions met with limited success although a series of chiral triazolium salts annulated by aliphatic cyclic skeletons were prepared using a modification of Knight and Leeper's synthesis[10g,11] and exhibited remarkable umpolung asymmetric organocatalysis.[12]



Scheme 1. Design of the bis-bicyclic triazolylidenes **2** from their parent mono-bicyclic triazolylidenes **1**.

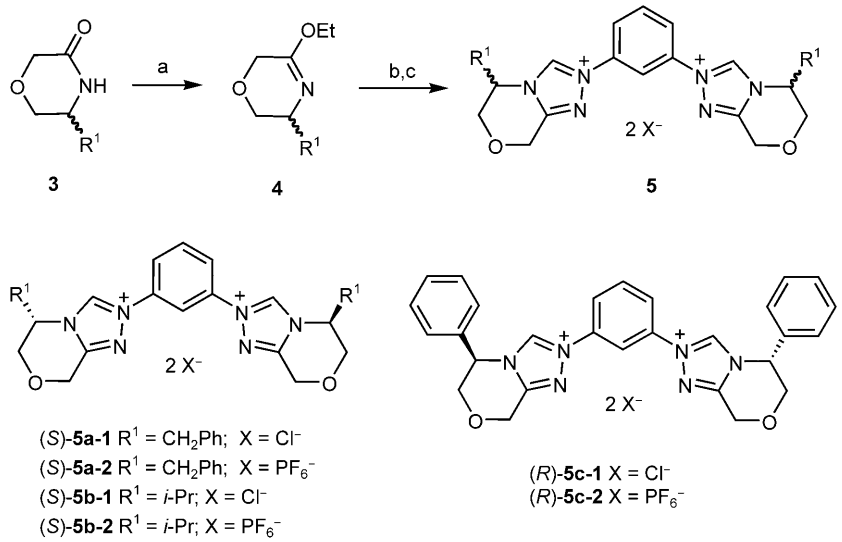
The key step in the NHC-catalyzed nucleophilic acylation of aldehydes involves the attack of the carbene at the carbonyl group of aldehydes to form the so-called "Breslow intermediate".[13] It has been realized that several structural factors (e.g., the steric bulkiness around the carbene carbon, and the presence of electron-withdrawing groups in the N-heterocyclic backbone or in *N*-aryl substituents, etc.) may have dramatic effects on the electronic property, reactivity and stability of carbenes.[12,14] It may be noteworthy that stereoselective control and catalytic activity have been proven to vary strongly with slight structural changes in the substitution pattern of the triazolium systems.[5–6,10g,11a,12] The electronic nature of the phenyl ring at the triazolium 2-N position has been demonstrated to be one of the decisive factors in the catalyst design. The introduction of either electron-withdrawing groups [e.g., fluorine, trifluoromethyl group(s), etc.] or electron-donating substituents (e.g., methoxy group, etc.) on the *N*-phenyl group (R^2) is significantly capable of influencing the performance of bicyclic triazolium salts (Scheme 1).[15–17] These results beg the question: *can the highly active chiral triazolium catalysts for the intermolecular asymmetric benzoin couplings be achieved by subtle electronic and conformational modulation?*

Results and Discussion

From molecular modeling inspection based on the first principle density functional theory (DFT),[18] we have learned that the bis-triazolylidenes **2** have a larger conjugation interaction over the Leeper-type mono-triazolylidenes **1**.[7a,19] Thus, it is reasonable to assume that the bis-triazolylidenes **2** are much more stable than their parent **1**, leading to a higher concentration of active species that may facilitate higher turnover numbers in organocatalysis. On the other hand, one should not ignore another important factor that the increased number of active centers of **2** may also be expected to enhance the catalytic efficiency. Furthermore, we have found that the two triazolylidene rings and the phenyl ring are perfectly coplanar, which may provide an attractive chiral environment (see Supporting Information for computational details). Therefore, we rationalize that this novel type of chiral bis-triazolium salts should give rise to the improved catalytic performance in asymmetric organocatalysis. In this paper, we have synthesized of a series of enantiopure bis-triazolium salts **5a–c** and wish to describe here our results in their application for highly enantioselective benzoin condensations with a number of aromatic aldehydes.

As shown in Scheme 2, the synthesis of bis-bicyclic triazolium salts **5a–c** is a straightforward process according to Leeper's synthesis with an appropriate modification starting from the corresponding morpholin-3-one **3**, which arose from readily available amino alcohols.[5] Ethylation of **3** with Meerwein's reagent yielded the imino ether **4**. *m*-Phenylenedihydrazine dihydrochloride then reacted with **4** to afford the amidrazone hydrochloride, followed by cyclization with triethyl orthoformate to give the final products **5** (51–64% overall yields from **3**). These salts are air- and water-stable solids with melting points around 300 °C. The structure of (*S*)-**5a-2** was confirmed by X-ray crystallographic analysis (Figure 1).[20]

Our initial exploration for the triazolylidene-catalyzed enantioselective benzoin condensation focused on the coupling of benzaldehyde. After screening a variety of bases, we found that *t*-BuOK was clearly the best choice in terms of yield (95%) and enantioselectivity (95% *ee*) in the presence of 1 mol% of (*S*)-**5a-1** and 2 mol% of base in THF [i.e., K_2CO_3 (91% yield, 93% *ee*); DBU (43% yield, 74% *ee*); Et_3N (15% yield, 78% *ee* in THF; 83% yield, 90% *ee* in CH_3OH); DIPEA (trace amounts of benzoin)]. Other solvents (i.e., MeOH, EtOH, CH_2Cl_2, and toluene) were also investigated, but were found to be inferior to THF. The results from the triazolium precatalyst **5a–c** survey in combination with *t*-BuOK are summarized in Table 1. The results demonstrated that the catalytic performance (activity and enantioselectivity) of the ligands was largely dependent on the R^1 substituents of the morpholine ring. Of the six chiral bis-bicyclic triazolium salts with the illustrated absolute configurations, the phenylalanine-derived (*S*)-**5a-1** with a benzyl group at the morpholine ring proved to be the ligand of choice (entry 3), while (*R*)-**5c-1** with a phenyl group gave rise to moderate yield and enantioselectivity and (*S*)-**5b-1** with an isopropyl group deliv-



Scheme 2. Synthesis of triazolium salts **5a–c**. a) $Et_3O^+ \cdot BF_4^-$ (1.2 equiv.), CH_2Cl_2, room temperature, 15 h. b) *m*-Phenylenedihydrazine dihydrochloride (0.5 equiv.), MeOH, 50 °C. c) $HC(OCH_2CH_3)_3$ (5 equiv.), MeOH, 80 °C, 12 h.

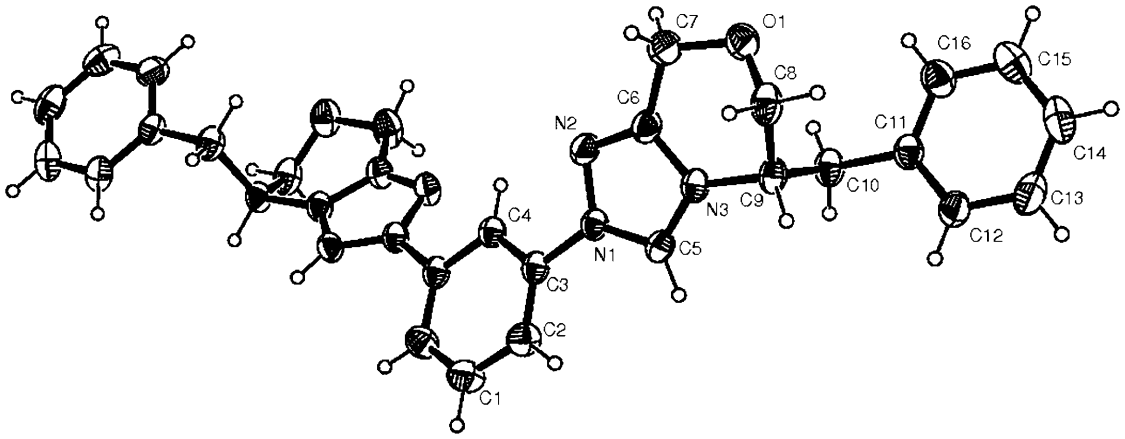
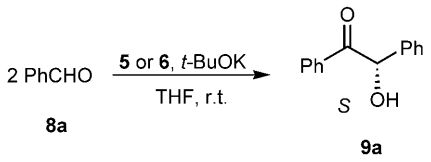


Figure 1. ORTEP drawing of the molecular structure of (*S*)-**5a-2**. Thermal ellipsoids are set at the 30% probability level. The PF_6^- anions were omitted.

ered only trace amounts of the coupling product (entries 8 and 10). In addition, the counteranions of the bis-bicyclic triazolium salts could also influence both the stereoselectivity and yield of the model reaction. Indeed, the catalytic performance of precatalysts with chloride as counteranion was superior to the corresponding hexafluorophosphates (entries 3, 7–11). Further optimization of reaction conditions revealed that an increase in the amount of *t*-BuOK or (*S*)-**5a-1** would lower the enantioselectivies although the yields could be improved, which is assumed to be attributable to a partial racemization of the product due to the higher concentration of *t*-BuOK or basic triazolylidene as mentioned above (entries 1–6).[4–6] A screening of the precatalyst/*t*-BuOK ratio indicated that a 1:2 ratio was the best choice in terms of enantioselectivity and yield, which is in good accordance with the calculated amount of base required for the complete deprotonation of the bis-bicyclic triazolium salt (*S*)-**5a-1**. Further lowering the amount of (*S*)-**5a-1** to 0.5 mol% could give an excellent enantioselectivity of up to 98% *ee*, albeit with a lower yield of 53% (entry 5). The best result was obtained in THF at room temperature (20 °C) for 20 h under N_2 using only 1 mol% of (*S*)-**5a-1** in the presence of 2 mol% of *t*-BuOK, delivering an excellent enantioselectivitiy of 95% *ee* and a high yield of 95%, which is the highest value ever reported in terms of enantioselectivitiy and yield [83% yield with 90% *ee* using 10 mol% of (*S*)-**7** at 18 °C].[6] In sharp contrast, on using 1 mol% of the corresponding parent mono-triazolium salts (*S*)-**6a**, (*S*)-**6b** and (*R*)-**6c** as precatalyst, the reaction of benzaldehyde afforded only moderate or trace amounts of benzoin in the presence of 1.0 equiv. of *t*-BuOK as base (en-

Table 1. Enantioselective benzoin condensation of benzaldehyde in the presence of precatalysts **5–6**.[a]



Entry	Catalyst (mol%)	*t*-BuOK (mol%)	Yield [%][b]	*ee* [%][c]
1	(*S*)-**5a-1** (1)	0.5	trace	–
2	(*S*)-**5a-1** (1)	1	58	98
3	(*S*)-**5a-1** (1)	2	95	95
4	(*S*)-**5a-1** (1)	3	96	83
5	(*S*)-**5a-1** (0.5)	1	53	98
6	(*S*)-**5a-1** (2)	4	98	83
7	(*S*)-**5a-2** (1)	2	81	86
8	(*S*)-**5b-1** (1)	2	trace	–
9	(*S*)-**5b-2** (1)	2	trace	–
10	(*R*)-**5c-1** (1)	2	56	−74[d]
11	(*R*)-**5c-2** (1)	2	40	−69[d]
12	(*S*)-**6a** (1)	1	27	88
13	(*S*)-**6b** (1)	1	trace	–
14	(*R*)-**6c** (1)	1	trace	–

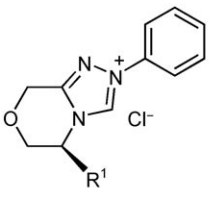
[a] Reactions were performed on a 1.0 mmol scale with **5** or **6** and *t*-BuOK in 1.0 mL of THF under N_2 atmosphere at room temperature for 20 h.

[b] Yield of isolated product based on benzaldehyde.

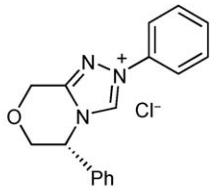
[c] Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H). The absolute configurations were assigned by comparison with the optical rotation values in the literature.[6,21,22]

[d] The absolute configuration of this adduct is *R*.

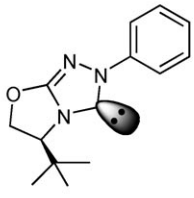
tries 12–14). It should be pointed out that Leeper's catalytic system afforded only 45% yield for the benzoin condensation of benzaldehyde even using 30 mol% of (*S*)-**6a**.[5]



(*S*)-**6a** $R^1 = CH_2Ph$
(*S*)-**6b** R^1 = *i*-Pr



(*R*)-**6c**



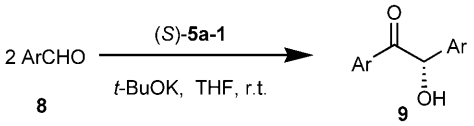
(*S*)-**7**

With optimized conditions now in hand, the scope of the catalytic enantioselective benzoin condensation was demonstrated with aromatic aldehydes. We were delighted to find that our catalytic system was capable of tolerating a relatively wide range of aromatic aldehydes when the reactions were conducted in the presence of 1 mol% of (*S*)-**5a-1** and 2 mol% of *t*-BuOK in THF at room temperature for 20 h. As is evident in Table 2, in most cases the condensation of aromatic aldehydes **8** led to the corresponding hydoxy ketones **9** with reasonable product yields and excellent enantioselectivities of up to 95% *ee* including electron-rich, electron-poor, and sterically hindered examples. It is important to stress that limitations on the structures of aromatic aldehydes were encountered when (*S*)-**6a** or (*S*)-**7** catalyst systems were employed.[4–6] For example, electron-rich aromatic aldehydes generally showed better asymmetric induction than electron-deficient ones. However, these +I/+M substituents in the *para* position resulted in distinct drop in the turnover numbers of triazolium salts. In the presence of 10 mol% of (*S*)-**7**, the coupling reactions of *p*-methylbenzaldehyde **8b** and *p*-methoxybenzaldehyde **8d** afforded the acyloin products **9b** and **9d** in 16% and 8% yields, respectively.[6] In sharp contrast, using only 1 mol% of (*S*)-**5a-1** as precatalyst, the acyloins **9b** and **9d** could be obtained in good yields and with high enantiomeric excesses of up to 95% *ee* (entries 2 and 5). When the catalyst loading was increased to 2 mol%, the yields of **9b** and **9d** were improved dramatically from 62% and 41% to 83% and 65%, respectively (entries 2, 3, 5, 6). Most remarkably, 2-naphthylaldehyde **8h** also underwent the coupling reaction in excellent yield of 80% with an enantiomeric excess of 92% (entry 10), demonstrating the best result reported so far. The reaction of the recalcitrant-hindered and deactivated *o*-methoxybenzaldehyde **8f** could even be conducted smoothly to afford the corresponding acyloin **9f** in 50% yield with 85% *ee* (entry 8).

Conclusions

In summary, we have described a solution to the long-standing challenge of developing a highly effective method for the enantioselective intermolecular benzoin condensation of aromatic aldehydes. Particularly noteworthy are the generally better product yields and enantioselectivities as well as the relatively broader reaction scope facilitated by our catalytic systems even in the presence of 1 mol% of (*S*)-**5a-1** in comparison with the mono-triazolium salts reported previously. The chiral bis-bicyclic triazolium salt (*S*)-**5a-1** is currently the most efficient precatalyst for the asymmetric variant of the benzoin condensation. Detailed mechanistic studies to elucidate the origin of excellent catalytic performance and further investiga-

Table 2. Enantioselective synthesis of (*S*)-acyloins **9** catalyzed by (*S*)-**5a-1**.[a]



Entry	Loading (mol%)	Ar	Product	Yield [%][b]	*ee* [%][c]
1	1	Ph (**8a**)	**9a**	95	95
2	1	4-MeC_6H_4 (**8b**)	**9b**	62	95
3	2	4-MeC_6H_4 (**8b**)	**9b**	83	90
4	1	3-MeC_6H_4 (**8c**)	**9c**	82	91
5	1	4-$MeOC_6H_4$ (**8d**)	**9d**	41	95
6	2	4-$MeOC_6H_4$ (**8d**)	**9d**	65	91
7	1	3-$MeOC_6H_4$ (**8e**)	**9e**	70	93
8	1	2-$MeOC_6H_4$ (**8f**)	**9f**	50	85
9	1	4-FC_6H_4 (**8g**)	**9g**	91	84
10	1	2-naphthyl (**8h**)	**9h**	80	92

[a] *Reactions conditions:* see Table 1; a 1:2 (*S*)-**5a-1**/*t*-BuOK ratio was used.
[b] Yield of isolated product based on aldehyde.
[c] Enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, or OJ). The (*S*)-configurations were assigned by comparison with optical rotation values in the literature.[6,21,22]

tions into other versions of asymmetric organic catalysis are currently underway and will be reported in due course. In particular, it is reasonable to suggest that this new class of chiral triazolium salts could also be widely applicable in asymmetric organometallic catalysis.

Experimental Section

General Procedure for the Preparation of Chiral Triazolium Salts 5a-c

1,3-Bis{(*S*)-5-benzyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*]-[1,2,4]triazol-2-ium-2-yl}benzene dichloride [(*S*)-5a-1]: To a flame-dried Schlenk flask charged with a suspension of triethyloxonium tetrafluoroborate (5.7 g, 30 mmol) and dichloromethane (40 mL) was added a solution of the morpholin-3-one **3a** (3.8 g, 20 mmol) in dichloromethane (20 mL). After being stirred for 15 h at room temperature, the mixture was then diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate (3×50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel with elution with ethyl acetate/petroleum ether (1:20) to give the imino ether **4a** as viscous oil; yield: 71%.

A flame-dried Schlenk flask was charged with the imino ether **4a** (3.5 g, 16 mmol), *m*-phenylenedihydrazine dihydrochloride (1.7 g, 8 mmol) and methanol (16 mL). The reaction mixture was heated at 50 °C for 1 h to afford the *m*-phenylenedihydrazone dihydrochloride, which was used in the next reaction without further purification after being cooled to room temperature. To the reaction mixture was added triethyl orthoformate (11.8 g, 80 mmol). The mixture was transferred under argon into a pyrex tube, and the sealed tube was then heated in an oven at 80 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The resulting residue was recrystallized from methanol to afford the pure triazolium salt (*S*)-**5a-1** as a white solid; yield: 64% over three steps.

1,3-Bis{(*S*)-5-benzyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*]-[1,2,4]triazol-2-ium-2-yl}benzene dihexafluorophosphate [(*S*)-5a-2]: A tube with a magnetic stirring bar was charged with the triazolium salt (*S*)-**5a-1** (577.5 mg, 1 mmol) and water (25 mL) at room temperature, followed by addition of aqueous solution of NH_4PF_6 (1.0 M, 2 mL, 2 mmol). After the mixture was stirred for 10 min, the solid was separated and washed with distilled water and then dried under vacuum for 24 h. Compound (*S*)-**5a-2** was obtained as a colorless crystalline after purification by crystallization from acetone; yield: quantitative.

1,3-Bis{(*S*)-5-isopropyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*][1,2,4]triazol-2-ium-2-yl}benzene dichloride [(*S*)-5b-1]: This compound was prepared by the same procedure as described above (*S*)-**5a-1** but starting material from **3b**. Compound **4b** was obtained as a viscous oil after purification by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:20); yield: 80%. The crude product (*S*)-**5b-1** was purified by column chromatography on silica gel eluting with methanol, followed by recrystallization from methanol to afford the pure form as a pale yellow solid; yield: 54% over three steps.

1,3-Bis{(*S*)-5-isopropyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*][1,2,4]triazol-2-ium-2-yl}benzene dihexafluorophosphate [(*S*)-5b-2]: This compound was prepared by the same procedure as described above for (*S*)-**5a-2**. Starting material was (*S*)-**5b-1**. Compound (*S*)-**5b-2** was obtained as a pale yellow solid; yield: quantitative.

1,3-Bis{(*R*)-5-phenyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*]-[1,2,4]triazol-2-ium-2-yl}benzene dichloride [(*R*)-5c-1]: This compound was prepared by the same procedure as described above for (*S*)-**5a-1**. Starting material was **3c**. Com-

pound **4c** was obtained as a viscous oil after purification by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:20); yield: 64%. The crude product (*R*)-**5c-1** was purified by column chromatography on silica gel eluting with methanol, followed by recrystallization from methanol to afford the pure form as a pale yellow solid; yield: 51% over three steps.

1,3-Bis{(*R*)-5-phenyl-6,8-dihydro-5*H*-[1,4]oxazino[2,1-*c*]-[1,2,4]triazol-2-ium-2-yl}benzene dihexafluorophosphate [(*R*)-5c-2]: This compound was prepared by the same procedure as described above for (*S*)-**5a-2**. Starting material was (*R*)-**5c-1**. Compound (*R*)-**5c-2** was obtained as a pale yellow solid.; yield: quantitative.

General Procedure for the Asymmetric Benzoin Condensation

A flame-dried Schlenk tube with a magnetic stirring bar was charged with the triazolium salt (*S*)-**5a-1** (0.01 mmol) and dry THF (1.0 mL) at room temperature, followed by addition of a THF solution of *t*-BuOK (0.2 M, 100 μL, 0.02 mmol). After the mixture was stirred for 10 min, the aromatic aldehyde (1.0 mmol) was added. The reaction mixture was then stirred at the same temperature for 20 h, poured into water, and extracted twice with dichloromethane. The combined organic layers were evaporated and the resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether to provide the aromatic acyloin.

The reported yields of asymmetric benzoin reactions are isolated yields and are the averages of at least three runs. The benzoin reaction products are known and their ^{1}H and ^{13}C NMR spectra agreed with those in the literature cited. Enantiomeric excesses were determined by HPLC (LabTech 600 series) with Chiracel OD-H or OJ columns. The (*S*)-configurations were assigned by comparison with optical rotation values in the literature.[6,21–22]

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (Nos. 20572074 and 20772086), the Program for New Century Excellent Talents in University (NCET-04–0881), and the Outstanding Young Scientist Award of Sichuan Province. We also thank the Centre of Testing and Analysis, Sichuan University for NMR and X-ray measurements.

References

[1] a) D. Gala, D. J. DiBenedetto, J. E. Clark, B. L. Murphy, D. P. Schumacher, M. Steinman, *Tetrahedron Lett.* **1996**, *37*, 611–614; b) V. M. Girijavallabhan, A. K. Ganguly, P. A. Pinto, O. Z. Sarre, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 349–352; c) T. Konishi, T. Miyaoka, Y. Tajima, S. Oida, *Chem. Pharm. Bull.* **1991**, *39*, 2241–2246; d) A. S. Demir, Ö. Şeşenoglu, P. Dünkelmann, M. Müller *Org. Lett.* **2003**, *5*, 2047–2050; e) L. Xin, C. C. Bausch, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 1833–1840; f) C. C. Bausch, J. S. Johnson, *J. Org. Chem.* **2004**, *69*, 4283–4285.

[2] J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667.

[3] a) J. C. Sheehan, T. Hara, *J. Org. Chem.* ***1974***, *39*, 1196–1199; b) C. A. Dvorak, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 2925–2928; c) W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478–480; d) R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611–3614.

[4] D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217–1221.

[5] R. L. Knight, F. J. Leeper, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891–1893.

[6] D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822–1824; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743–1745.

[7] a) S. Orlandi, M. Caporale, M. Benaglia, R. Annunziata, *Tetrahedron: Asymmetry* **2003**, *14*, 3827–3830; b) J. Pesch, K. Harms, T. Bach, *Eur. J. Org. Chem.* **2004**, 2025–2035; c) Y. Tachibana, N. Kihara, T. Takata, *J. Am. Chem. Soc.* **2004**, *126*, 3438–3439.

[8] Highly selective thiamine-dependent enzymatic benzoin/acyloin reactions, see: a) T. Dünnwald, A. S. Demir, P. Siegert, M. Pohl, M. Müller, *Eur. J. Org. Chem.* **2000**, 2161–2170; b) H. Iding, T. Dünnwald, L. Greiner, A. Liese, M. Müller, P. Siegert, J. Grötzinger, A. S. Demir, M. Pohl, *Chem. Eur. J.* **2000**, *6*, 1483–1495; c) A. S. Demir, M. Pohl, E. Janzen, M. Müller, *J. Chem. Soc. Perkin Trans. 1* **2001**, 633–635; d) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085.

[9] Metallophosphites as umpolung catalysts for the enantioselective cross silyl benzoin reaction, see: L. Xin, J. R. Potnick, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 3070–3071.

[10] a) Y. Hachisu, J. W. Bode, K. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433; b) D. Enders, O. Niemeier, *Synlett* **2004**, 2111–2114; c) Y. Hachisu, J. W. Bode, K. Suzuki. *Adv. Synth. Catal.* **2004**, *346*, 1097–1100; d) D. Enders, O. Niemeier, G. Raabe, *Synlett* **2006**, 2431–2434; e) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491–1495; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463–1467; f) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572–3574; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492–3494; g) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713–2716.

[11] For preparation of chiral triazolium salts: a) M. S. Kerr, J. Read deAlaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725–5728; b) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277–280.

[12] Selected recent reviews: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541; b) J. S. Johnson, *Angew. Chem.* **2004**, *116*, 1348–1350; *Angew. Chem. Int. Ed.* **2004**, *43*, 1326–1328; c) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674–7678; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506–7510; d) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046–3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000; e) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.

[13] a) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726; b) H. Stetter, H. Kuhlmann, *Angew. Chem.* **1974**, *86*, 589; *Angew. Chem. Int. Ed.* **1974**, *13*, 539; c) T. Dudding, K. N. Houk, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5770–5775.

[14] a) R. W. Alder, M. E. Blake, L. Chaker, J. N. Harvey, F. Paolini, J. Schütz, *Angew. Chem.* **2004**, *116*, 6020–6036; *Angew. Chem. Int. Ed.* **2004**, *43*, 5896–5911; b) G. Occhipinti, H.-R. Bjørsvik, V. R. Jensen, *J. Am. Chem. Soc.* **2006**, *128*, 6952–6964; c) O. Kühl, *Chem. Soc. Rev.* **2007**, *36*, 592–607; d) S. T. Liddle, I. S. Edworthy, P. L. Arnold, *Chem. Soc. Rev.* **2007**, *36*, 1732–1744.

[15] For a review on asymmetric Stetter reactions, see: M. Christmann, *Angew. Chem.* **2005**, *117*, 2688–2690; *Angew. Chem. Int. Ed.* **2005**, *44*, 2632–2634.

[16] Selected examples for the Stetter reactions, see: a) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899–1902; b) M. S. Kerr, J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299; c) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; d) A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315; e) J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289; f) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553.

[17] Selected examples for chiral triazolium salts as asymmetric organocatalysts, see: a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420; b) S. S. Sohn, J. W. Bode, *Angew. Chem.* **2006**, *118*, 6167–6170; *Angew. Chem. Int. Ed.* **2006**, *45*, 6021–6024; c) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407; d) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; e) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521; f) M. He, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 418–419.

[18] G. Parr, W. Yang, *Density functional theory of atoms and molecules*, Oxford University Press, New York, **1989**.

[19] The C_2-symmetrical bis-thiazolium and bis-benzimidazolium salts, in which two identical azolium units are connected by a flexible linker, were developed as catalysts in the asymmetric dimerization of benzaldehyde to give benzoin in moderate yields (up to 40%) with very low enantioselectivities (15–27% *ee*): J. Martí, J. Castells, F. López-Calahorra, *Tetrahedron Lett.* **1993**, *34*, 521–524; see also ref.[7a]

[20] CCDC-682524 contains 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.

[21] A. S. Demir, P. Ayhan, A. C. Igdir, A. N. Duygu, *Tetrahedron* **2004**, *60*, 6509- 6512.

[22] A. S. Demir, T. Dünnwald, H. Iding, M. Pohl, M. Müller, *Tetrahedron: Asymmetry* **1999**, *10*, 4769–4774.

