Organocatalysis

DOI: 10.1002/ange.201301304

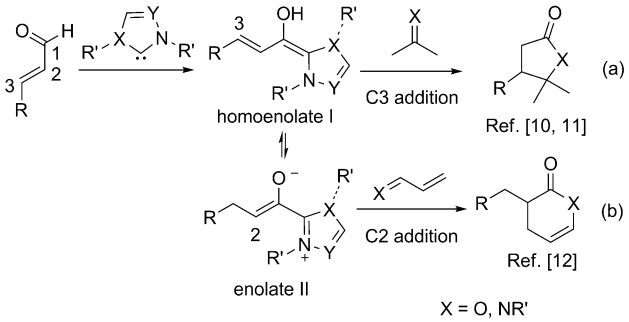
Enantioselective N-Heterocyclic Carbene Catalyzed Aza-Benzoin Reaction of Enals with Activated Ketimines**

*Li-Hui Sun, Zhi-Qin Liang, Wen-Qiang Jia, and Song Ye**

Dedicated to Professor Zhi-Tang Huang on the occasion of his 85th birthday

The carbon–carbon bond formation plays a central role in the synthesis of organic compounds. Most organic reactions for carbon–carbon bond formation are polar, involving formation of a covalent bond between an electrophile (acceptor a) with a nucleophile (donor d). The umpolung strategy, switching the polarity of functional groups, is an interesting approach for organic synthesis.[1] A typical example of an umpolung reaction is the N-heterocyclic carbene (NHC)-catalyzed transformation of an aldehyde to an acyl anion (a^1 to d^1; for the numbering see Scheme 1).[2,3] Thus NHC-catalyzed additions of aldehydes to carbonyl compounds (benzoin reaction)[4] and Michael acceptors (Stetter reaction)[5] have received wide attention. The NHC-catalyzed addition of aldehydes to imines (aza-benzoin reaction) has also been developed, resulting in highly useful α-amino ketones.[6] The first enantioselective aza-benzoin reaction of an aryl aldehyde was reported by Miller and co-workers in 2005,[7] and very recently the reaction of aliphatic aldehydes was report by Rovis and DiRocco.[8] Herein, we wish to report the enantioselective aza-benzoin reaction of enals with activated ketimines.

In the last decade, the NHC-catalyzed extended umpolung of functionalized aldehydes was extremely successful.[3d,9] In 2004, Bode and co-workers and Glorius and Burstein independently reported a pioneering NHC-catalyzed [3+2] cycloaddition of enals with aldehydes, in which the a^3 to d^3 umpolung was realized with homoenolate I as the key intermediate (Scheme 1 a).[10] Consequently, the NHC-catalyzed generation of a homoenolate from an enal has been widely applied for a variety of reactions.[11] Enolate II could also be generated by proton shifts and thus react in a C2 addition (Scheme 1 b).[12] Very recently, the oxidative γ-addition of enals was also reported by Chi and co-workers.[13] In these reports, the normal C1 addition is circumvented possibly owing to the hindrance of the C1-position by the bulky R′ group in the catalyst. Considering the wide application of the a^1 to d^1 umpolung, we envision that the normal C1 addition is also possible for enals when an NHC with less bulky substituent is employed. Recently, an elegant Stetter reaction of enals with nitroalkenes was reported by Rovis and DiRocco, using catechol as the critical additive.[14] Chi and co-workers reported a Stetter reaction of enals with modified chalcones.[15] Herein, we demonstrate that the aza-benzoin reaction of enals through C1 addition is also feasible when appropriate catalyst and reaction conditions are employed.



Scheme 1. Reported NHC-catalyzed reactions of enals.

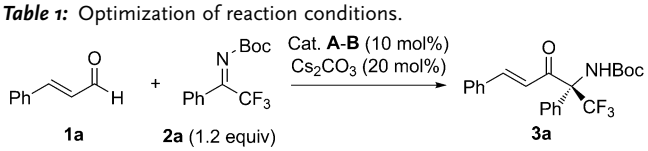
Initially, the reaction of cinnamic aldehyde **1a** with trifluoromethyl ketimine **2a** was investigated under the catalysis of various NHCs derived from L-pyroglutamic acid (Table 1).[4b,16] It was found that NHC **A1** with a bulky *tert*-butyldimethylsilyl (TBS) group afforded only a trace of the aza-benzoin product **3a**, and the corresponding extended umpolung product via the intermediate of a homoenolate or enolate was not observed (Table 1, entry 1). Gratifyingly, the desired product **3a** could be obtained in 41 % yield with 81 % *ee* when NHC **A2** with a free hydroxy group was employed (Table 1, entry 2).[17] The removal of the silyl group could reduce the hindrance to C1 in the Breslow intermediate, and more importantly, the possible H-bonding between the hydroxy group and the ketimine could enhance the reactivity and enantioselectivity. To further take advantage of H-bonding, NHC **B1** with an α,α-bis[3,5-di(trifluoromethyl)-phenyl]hydroxy substituent was tested, which afforded the desired product **3a** in 71 % yield with 93 % *ee* (Table 1, entry 3). In contrast, NHC **B2** with the bulky *N*-2-isopropyl-phenyl substituent showed no catalytic activity (Table 1, entry 4). NHCs with an *N*-benzyl group feature more flexibility and have been demonstrated to be superior over NHCs with an *N*-aryl group for the Stetter reaction of aldehydes by Enders and co-workers.[18] NHC **B3** was thus

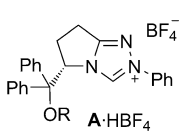
[*] L.-H. Sun, Z.-Q. Liang, W.-Q. Jia, Prof. Dr. S. Ye
Beijing National Laboratory for Molecular Sciences
CAS Key Laboratory of Molecular Recognition and Function
Institute of Chemistry, Chinese Academy of Sciences
Beijing 100190 (China)
E-mail: songye@iccas.ac.cn

[**] Financial support from the Ministry of Science and Technology of China (2011CB808600), National Natural Science Foundation of China (No. 20932008, 21072195), and the Chinese Academy of Sciences is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301304.

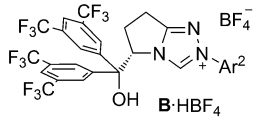
Table 1: Optimization of reaction conditions.





A·HBF$_4$

A1, R = TBS
A2, R = H



B·HBF$_4$

B1, Ar^2 = Ph
B2, Ar^2 = 2-*i*PrC$_6$H$_4$
B3, Ar^2 = Bn

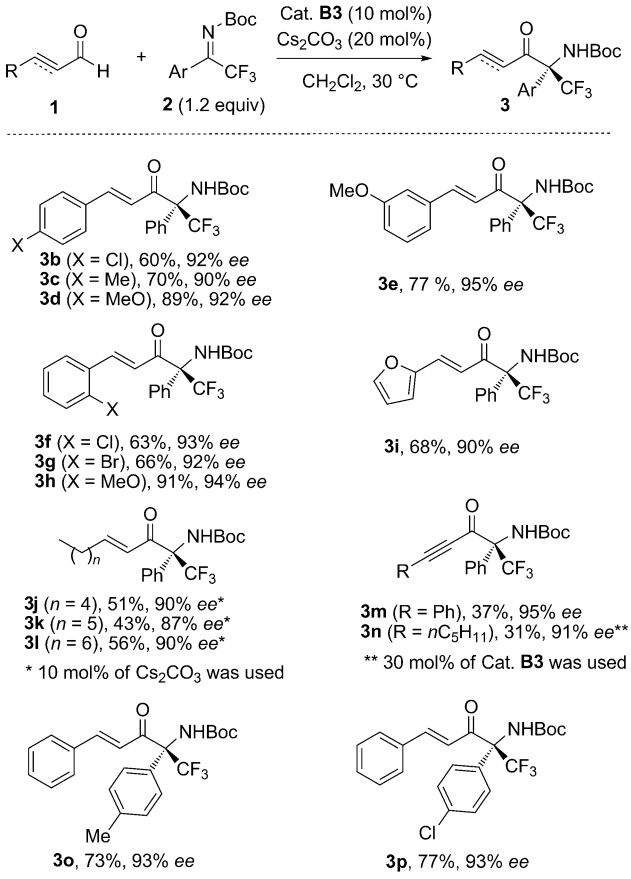
Entry	Catalyst[a]	Solvent	Yield [%][b]	*ee* [%][c]
1	**A1**	CH_2Cl_2	trace	/
2	**A2**	CH_2Cl_2	41	81
3	**B1**	CH_2Cl_2	71	93
4	**B2**	CH_2Cl_2	trace	/
5	**B3**	CH_2Cl_2	70	94
6	**B3**	THF	26	64
7	**B3**	dioxane	22	84
8	**B3**	Et_2O	62	94
9	**B3**	toluene	31	93
10[d]	**B3**	CH_2Cl_2	77	96
11[e]	**B3**	CH_2Cl_2	71	93

[a] NHCs **A**–**B** were freshly generated from the corresponding azolium salts in the presence of Cs_2CO_3 at room temperature for 30 min and used immediately. Boc = *tert*-butoxycarbonyl. [b] Yields of isolated products. [c] Determined by HPLC on a chiral column. [d] The reaction was carried out at 30 °C for 12 h. [e] The reaction was carried out at 0 °C for 24 h.

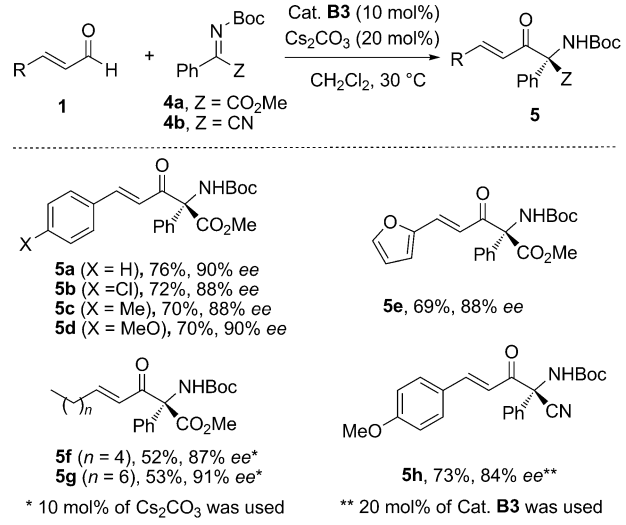
prepared and further improved the enantioselectivity (Table 1, entry 5). Solvent screening revealed that reactions worked in several other solvents but with varying yields (Table 1, entry 6–9). The reaction at 30 °C afforded a better yield and enantioselectivity compared to that at 40 °C (Table 1, entry 10),[19] while the reaction at 0 °C showed no improvement and required a longer reaction time (Table 1, entry 11).

With the optimized reaction conditions in hand, the scope of the enals has been briefly investigated (Scheme 2). Cinnamic aldehydes with electron-withdrawing (4-ClC$_6$H$_4$) and electron-donating substituents (4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$) all gave the aza-benzoin product **3b**–**3d** in good yields with high enantioselectivities. *meta*- (3-MeOC$_6$H$_4$) and *ortho*-substituents (2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, or 2-MeOC$_6$H$_4$) were also tolerated in the reaction without apparent change of yield and enantioselectivity (**3e**–**h**). The reaction of (*E*)-3-(furan-2-yl)acrylaldehyde gave the desired product **3i** in 68 % yield with 90 % *ee*. Notably, β-alkylenals also worked well in the reaction albeit in somewhat decreased yield (**3j**–**l**), and the amount of base has to be reduced to decrease the possible side reaction. Furthermore, the use of both β-aryl and β-alkyl ynals resulted in decreased yields, but high enantioselectivities were kept under the current reaction conditions (**3m** and **3n**).[20] Substituted aryltrifluoromethyl ketimines (Ar = 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$) reacted as well as the parent one (**3o**,**p**).

To further explore the scope of the reaction, several other activated ketimines were tested (Scheme 3). The scope of the reaction with iminoester **4a** was found to be similar to that of



Scheme 2. Reaction with trifluoromethyl ketimines **2**.

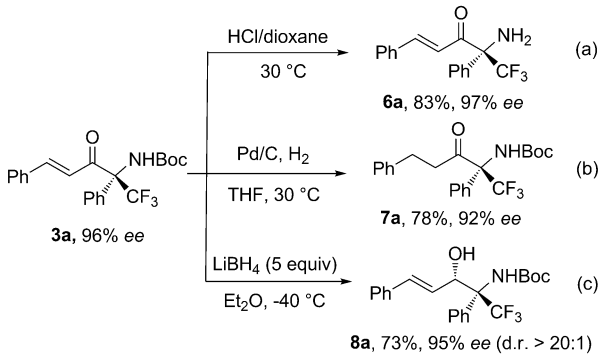


Scheme 3. Reaction with iminoester **4a** or iminonitrile **4b**.

the reaction with trifluoromethylketimine. All enals with β-aryl, β-heteroaryl, or β-alkyl groups gave the desired aza-benzoin products (**5a**–**g**) in good yields with high enantioselectivities. Furthermore, the reaction of iminonitrile **4b** afforded the desired product **5h** in 73 % yield with 84 % *ee*.

The structure of (−)-**3b** was unambiguously established by X-ray analysis of its crystal (Figure S1 in the Supporting Information).[21]

The aza-benzoin reaction products obtained from enals feature a highly functionalized structure and can be used in many chemical transformations (Scheme 4). The Boc protecting group could be easily removed by HCl in 1,4-dioxane to give the α-amino-α′,β′-unsaturated ketone **6a** in 83% yield with 97% *ee* (Scheme 4a). Pd/C catalyzed reduction with hydrogen gave the α-amino-α-trifluoromethyl ketone **7a** in 78% yield with 92% *ee* (Scheme 4b). Remarkably, the corresponding γ,δ-unsaturated-β-hydroxy amine **8a** could be obtained in 73% yield with 95% *ee* and exclusive diastereoselectivity (d.r. > 20:1) by reduction with $LiBH_4$ (Scheme 4c).[22]



Scheme 4. Transformations of product **3a**.

In summary, an enantioselective NHC-catalzyed aza-benzoin reaction of enals and activated ketimines was developed. The possible competing reaction through the corresponding homoenolate or enolate has not been observed by using NHC catalysts with a free hydroxy group and a sterically appropriate substituent. Further investigations on the mechanism and related reactions are underway.

Received: February 14, 2013
Revised: March 18, 2013
Published online: April 22, 2013

Keywords: aza-benzoin reaction · enals · N-heterocyclic carbenes · organocatalysis · synthetic methods

[1] D. Seebach, *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

[2] a) T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296; b) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.

[3] For reviews on NHC catalysis, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; c) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; d) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; e) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; f) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617; g) D. Enders, T. Balensiefer, O. Niemeier, M. Christmann, *Enantioselective Organocatalysis: Reactions and Experimental Procedures* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**, pp. 331–355; h) P.-C. Chiang, J. W. Bode, *N-Heterocyclic Carbenes*: *From Laboratory Curiosities to Efficient Synthetic Tools* (Ed.: S. Díez-González), Royal Society of Chemistry, Cambridge, **2010**, pp. 399–435; i) C. D. Campbell, K. B. Ling, A. D. Smith, *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, *Vol. 32* (Ed.: C. S. J. Cazin), Springer, Dordrecht, **2011**, pp. 263–297.

[4] a) D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; b) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463; c) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492; d) D. Enders, A. Henseler, *Adv. Synth. Catal.* **2009**, *351*, 1749; e) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun.* **2010**, *46*, 6282; f) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci.* **2012**, *3*, 735; g) 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; h) Y. Cheng, J.-H. Peng, Y.-J. Li, X.-Y. Shi, M.-S. Tang, T.-Y. Tan, *J. Org. Chem.* **2011**, *76*, 1844; i) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628.

[5] a) H. Stetter, M. Schreckenberg, *Angew. Chem.* **1973**, *85*, 89; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81; b) M. S. Kerr, J. R. deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298; c) R. J. de Alaniz, T. Rovis, *Synlett* **2009**, 1189; d) C. M. Filloux, S. P. Lathrop, T. Rovis, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20666.

[6] a) J. Castells, F. López-Calahorra, M. Basseda, P. Urrios, *Synthesis* **1988**, 314; b) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.* **2001**, *123*, 9696; c) G.-Q. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2007**, 852; d) D. Enders, A. Henseler, S. Lowins, *Synthesis* **2009**, 4125; e) K.-J. Wu, G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2011**, *47*, 493.

[7] S. M. Mennen, J. D. Gipson, Y. R. Kim, S. J. Miller, *J. Am. Chem. Soc.* **2005**, *127*, 1654.

[8] a) D. A. DiRocco, T. Rovis, *Angew. Chem.* **2012**, *124*, 6006; *Angew. Chem. Int. Ed.* **2012**, *51*, 5904; b) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094.

[9] a) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; b) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691.

[10] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.

[11] a) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem.* **2011**, *123*, 1716; *Angew. Chem. Int. Ed.* **2011**, *50*, 1678; b) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984; c) Y. Li, Z. A. Zhao, H. He, S.-L. You, *Adv. Synth. Catal.* **2008**, *350*, 1885; d) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; e) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; f) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334; g) M. He, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 418; h) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766; i) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; j) V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507; k) X. Fang, X. Chen, Y. R. Chi, *Org. Lett.* **2011**, *13*, 4708; l) C. B. Jacobsen, K. L. Jensen, J. Udmark, K. A. Jørgensen, *Org. Lett.* **2011**, *13*, 4790; m) V. Nair, R. R. Paul, D. V. M. Padmaja, N. Aiswarya, C. R. Sinu, A. Jose, *Tetrahedron* **2011**, *67*, 9885.

[12] a) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 3167; *Angew. Chem. Int. Ed.* **2007**, *46*, 3107; b) Y. Li, X.-Q. Wang, C. Zheng, S.-L. You, *Chem. Commun.* **2009**, 5823; c) Z. Fu, H. Sun, S. Chen, B. Tiwari, G. Li, Y. R. Chi,

Chem. Commun. **2013**, *49*, 261; d) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; e) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661; f) V. Nair, R. R. Paul, K. C. Seetha Lakshmi, R. S. Menon, A. Jose, C. R. Sinu, *Tetrahedron Lett.* **2011**, *52*, 5992.

[13] J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810.

[14] D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 10402.

[15] X. Fang, X. Chen, H. Lv, Y. R. Chi, *Angew. Chem.* **2011**, *123*, 11986; *Angew. Chem. Int. Ed.* **2011**, *50*, 11782.

[16] a) Y. R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277; b) D. Enders, J. Han, *Tetrahedron: Asymmetry* **2008**, *19*, 1367.

[17] a) L. He, Y.-R. Zhang, X.-L. Huang, S. Ye, *Synthesis* **2008**, 2825; b) X.-L. Huang, L. He, P.-L. Shao, S. Ye, *Angew. Chem.* **2009**, *121*, 198; *Angew. Chem. Int. Ed.* **2009**, *48*, 192; c) X.-L. Huang, S. Ye, *Chin. Sci. Bull.* **2010**, *55*, 1753; d) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214.

[18] D. Enders, J. Han, A. Henseler, *Chem. Commun.* **2008**, 3989.

[19] Reaction catalyzed by NHC **B1** at 30 °C gave **3a** in 58 % yield with 96 % *ee*.

[20] Along with the desired aza-benzoin product **3j**–**n**, around 20 % of **2j**–**n** was recovered plus the some unidentified byproducts.

[21] CCDC 923892 (**3b**) 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.

[22] The relative stereochemistry of compound **8a** was established by the NOE spectrum of its oxazolidinone, see the Supporting Information for details.

