Aldehyde Oxidation

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Biomimetic Carbene-Catalyzed Oxidations of Aldehydes Using TEMPO**

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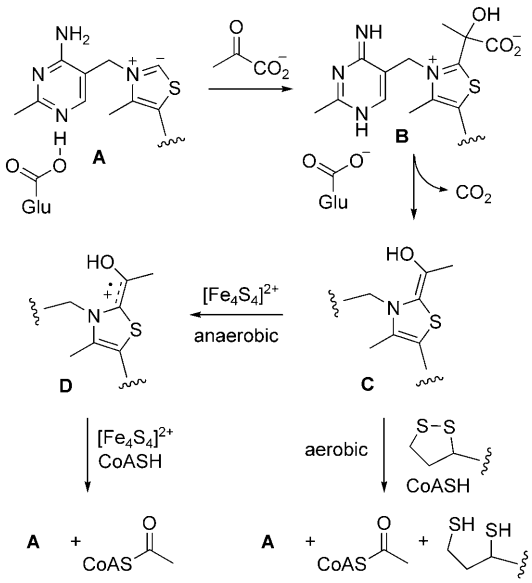
Pyruvate ferredoxin oxidoreductase (PFOR), which catalyzes the oxidative decarboxylation of pyruvate to form acetyl-CoA and CO_2, belongs to the family of 2-keto acid oxidoreductases.[1] This CoA-dependent enzyme uses thiamine pyrophosphate (TPP) as an additional cofactor. The anaerobic decarboxylation is a reversible process, and the two electrons obtained during one turnover are transferred to ferredoxine via $[Fe_4S_4]$ clusters.[1]

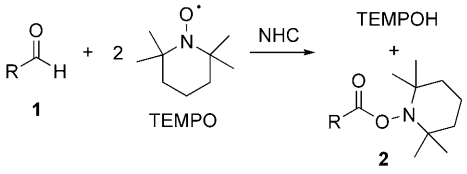
The initial steps of the oxidative decarboxylation resemble those of the aerobic TPP-dependent 2-oxoacid dehydrogenases.[2] Pyruvate reacts with **A** to form **B** after proton transfer, and **B** subsequently undergoes CO_2 elimination to generate **C** (Scheme 1). Electron transfer to a $[Fe_4S_4]$ cluster leads to radical cation **D**. Although intensive studies (X-ray and EPR) have been conducted on **D**, the structure of the radical cation is still under debate.[3] Renewed electron transfer in the presence of CoASH eventually leads to CoASAc.



Scheme 1. TPP-mediated enzymatic transformation of pyruvate to CoASAc.

In aerobic organisms lacking the $[Fe_4S_4]$ clusters, **C** reacts with the dithiolane ring of a lipoyl group in a formal two-electron transfer to an acetyl lipoamide thioester intermediate, which is further transformed in the presence of CoASH using another enzyme to CoASAc. The liberated dithiol is eventually reoxidized to the cyclic disulfide by a FAD-dependent dihydrolipoyl dehydrogenase.[2]

It is known in synthesis that reaction of aldehydes with thiazolium carbenes leads to intermediates of type **C** which react as "umpoled"[4] nucleophiles with aromatic aldehydes (benzoin condensation)[5] or with electron-poor olefins (Stetter reaction).[6] Recently, N-heterocyclic carbene (NHC) catalyzed transformations have gained increasing attention.[7] However, these investigations have focused on ionic processes.[8] Guided by PFOR we planned to oxidize enamines of type **C** by organic single-electron transfer (SET) oxidants.[9] The process would represent a biomimetic transition-metal-free organocatalytic oxidation of an aldehyde. As the oxidant we used 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO), which has been used successfully by our group in transition-metal-mediated reactions and in various radical processes.[10] Hence, the oxidizing $[Fe_4S_4]$ clusters in PFOR can be replaced by two oxidizing TEMPO units [Eq. (1)].[11,12]



(1)

Initial studies were performed in THF at room temperature with the three carbene precursors **3**–**5**.[13] Carbenes were generated upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). As a test substrate we chose *trans*-cinnamaldehyde (**1a**, R = PhCH=CH) to give acyl-TEMPO derivative **2a** (R = PhCH=CH, Table 1).[14] Pleasingly, the carbene generated from **3** (10 mol%) was able to catalyze the TEMPO-mediated oxidation of cinnamaldehyde, and **2a** was isolated in 87% yield (entry 1, Table 1). Similar results were achieved with carbenes derived from **4** and **5**, showing that the carbene structure does not influence oxidation to a large extent (entries 2 and 3, Table 1). We performed the following studies with readily available **5**. Reducing catalyst loading to 5 and 2 mol% led to improved yields, and even

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TEMPO = 2,2,6,6,-tetramethylpiperidine-*N*-oxyl radical.

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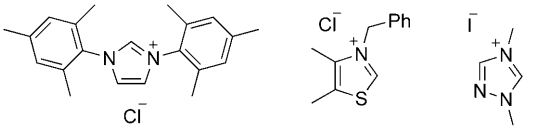
Table 1: NHC-catalyzed oxidation of various aldehydes with TEMPO (2 equiv) and DBU in THF at room temperature for 6–12 h.

Entry	Catalyst (mol%)	Product	R	Yield [%]
1[a]	**3** (10)	**2a**	$C_6H_5CH{=}CH$	87
2[a]	**4** (10)	**2a**	$C_6H_5CH{=}CH$	86
3[a]	**5** (10)	**2a**	$C_6H_5CH{=}CH$	85
4[a]	**5** (5)	**2a**	$C_6H_5CH{=}CH$	91
5[a]	**5** (2)	**2a**	$C_6H_5CH{=}CH$	94
6[a]	**5** (1)	**2a**	$C_6H_5CH{=}CH$	92
7[b]	**5** (2)	**2a**	$C_6H_5CH{=}CH$	94
8[b]	**5** (2)	**2b**	C_6H_5	95
9[b]	**5** (2)	**2c**	4-$NO_2C_6H_4$	92
10[b]	**5** (2)	**2d**	4-$CH_3OC_6H_4$	91
11[b]	**5** (2)	**2e**	4-BrC_6H_4	93
12[b]	**5** (2)	**2f**	4-$CH_3OC(O)C_6H_4$	96
13[b]	**5** (2)	**2g**	2-FC_6H_4	91
14[b]	**5** (2)	**2h**	2-$CF_3C_6H_4$	89
15[b]	**5** (2)	**2i**	3-ClC_6H_4	98
16[b]	**5** (0.5)	**2i**	3-ClC_6H_4	97
17[b]	**5** (2)	**2j**	β-naphthyl	94
18[b]	**5** (2)	**2k**	2-thienyl	98
19[b]	**5** (2)	**2l**	2-pyridyl	94
20[b]	**5** (2)	**2m**	$C_6H_5C(O)CO$	54
21[b]	**5** (2)	**2n**	$CH_3CH{=}CH$	83
22[b]	**5** (2)	**2o**	4-$(CH_2{=}CH)C_6H_4$	95
23[b]	**5** (2)	**2p**	4-$(CH_3OCH{=}CH)C_6H_4$	87
24[b]	**5** (2)	**2q**	4-([1,3]dithiolan-2-yl)C_6H_4	92
25[b]	**5** (2)	**2r**	4-$([EtO]_2CH)C_6H_4$	89
26[c]	**5** (10)	**2s**	$PhCH_2CH_2$	44
27[c]	**5** (14)	**2s**	$PhCH_2CH_2$	51

[a] Conducted with 1–1.1 equiv DBU. [b] Conducted with 3 mol% DBU. [c] Conducted with 10 mol% DBU.

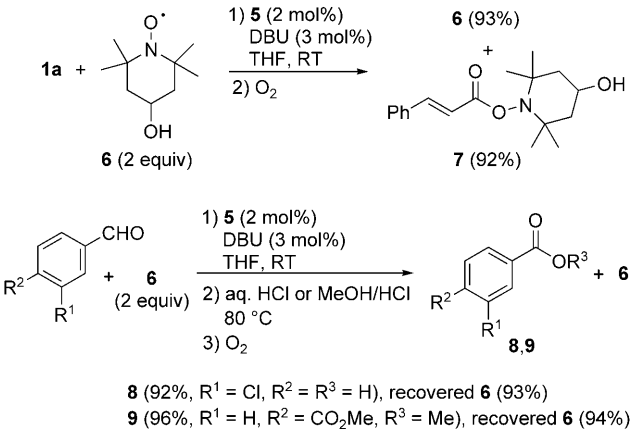


3 **4** **5**

1 mol% of **5** provided an excellent yield (entries 4–6, Table 1). Oxidation did not proceed without **5**. As the reaction can be conducted with 3 mol% DBU, the base serves only for carbene generation (entry 7, Table 1).[15]

To study the scope we tested other aldehydes. Benzaldehyde (→**2b**, 95%; entry 8, Table 1) and electron-rich and electron-poor *para*-substituted benzaldehyde derivatives were oxidized to the corresponding esters **2c–f** in excellent yields (91–96%, entries 9–12, Table 1). *ortho*-Substituted aromatic aldehydes also underwent clean oxidation (entries 13 and 14, Table 1). Excellent yields were obtained for the oxidation of *m*-chlorobenzaldehyde (98%, entry 15, Table 1). With this reactive aldehyde, catalyst loading could be reduced to 0.5 mol% without affecting the yield (entry 16, Table 1). β-Naphthaldehyde and heteroarenes such as 2-thiophenecarboxaldehyde and 2-pyridinecarboxaldehyde also underwent clean oxidation to give the corresponding TEMPO esters in excellent yields (entries 17–19, Table 1). Oxidation of phenylglyoxal monohydrate and crotonal afforded the esters **2m** and **2n** in moderate to good yields (entries 20 and 21, Table 1). Double bonds were not oxidized under the applied conditions. Thus, 4-vinylbenzaldehyde and 4-$(CH_3OCH{=}CH)C_6H_5CHO$ bearing the electron-rich vinyl ether were chemoselectively oxidized (entries 22 and 23, Table 1). Moreover, S oxidation was not a problem, as the transformation of a dithiolanyl-substituted aldehyde to ester **2q** demonstrates (92% yield, entry 24, Table 1). Importantly, oxidation occurs under neutral conditions. Hence, acid-labile enol ethers (see entry 23, Table 1) and acetals were tolerated (entry 25, Table 1). Aliphatic aldehydes such as 3-phenylpropanal reacted more slowly. Carbene catalyst loading had to be increased to 10 mol%, and ester **2s** was isolated in 44% yield (entry 26, Table 1). When 14 mol% of **5** was employed in the presence of 10 mol% DBU, the yield was improved to 51% (entry 27, Table 1).

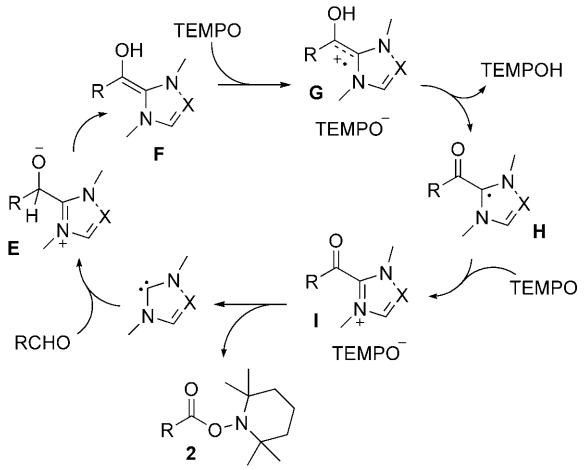
It is important to note that TEMPOH [see Eq. (1)], which can be quantitatively oxidized to TEMPO by O_2 or air, was formed in these reactions as a stoichiometric byproduct.[16] However, owing to the volatility of TEMPO its recovery was difficult. Therefore, oxidation of **1a** was repeated with less volatile HO-TEMPO (**6**). After completion of the oxidation the reaction mixture was purged with O_2 to recover **6**. Ester **7** was isolated in 92% yield along with **6** (93% yield, Scheme 2). To further improve the economy of the process



Scheme 2. Regeneration of the nitroxide.

we treated the reaction mixture after completed oxidation with aqueous HCl to transform the TEMPO ester into the corresponding acid. This was shown for *meta*-chlorobenzaldehyde. After oxidation and hydrolysis, acid **8** and HO-TEMPOH formed were readily separated by simple liquid/liquid extraction. The organic layer obtained by basic workup was purged with O_2 to regenerate **6**. Thus, O_2 formally acts as a terminal oxidant and the nitroxide was readily recovered in high yield rendering this protocol attractive for industrial-scale synthesis. It was also possible to transfer TEMPO esters with methanolic HCl to the corresponding methyl esters (→**9**, 96%, recovered **6**: 94%).

The suggested mechanism is depicted in Scheme 3. Reaction of the carbene with RCHO provides enamine **F** via **E**.[7] SET to TEMPO would lead to radical cation **G** and $TEMPO^-$.[17] Deprotonation of **G** by $TEMPO^-$ should generate radical **H** and TEMPOH.[18] Direct hydrogen trans-



Scheme 3. Suggested mechanism (X = N, CH).

fer from **F** to TEMPO to give **H** and TEMPOH cannot be ruled out. Renewed SET from **H** to TEMPO might provide activated ester **I**, which can react further with $TEMPO^-$ to give **2** and the corresponding carbene.

The structure of the intermediate radical cation **D** in the enzymatic reaction has been debated in the literature.[1,3] It has been suggested that its structure is better described as a σ radical complexed with an acyl cation (a tautomeric form of **D**) rather than a π-type radical.[3] We therefore studied the intermediate radical cation by using computational methods. DFT calculations were performed on the two tautomeric radical cations **G** and **G′** (for X = CH and N, R = Ph).[19] We found that for the phenyl-substituted system in the gas phase without environmental effects the OH tautomer **G** (X = CH) is about 11 kcal mol^{-1} lower in energy than **G′** (X = CH). The spin-density distributions are in agreement with the given Lewis structures: **G** corresponds to a mainly carbon-centered radical with a partial double bond (1.43 Å) between the carbonyl and carbene C atoms. In **G′** the spin density is delocalized mostly in the carbene fragment, which forms a weakened σ bond (1.58 Å) with an acyl-type cation (Figure 1). Similar results (but with an even increased energy gap of 20.4 kcal mol^{-1} at the PBEh/TZVP level between OH and C=O forms) were obtained for the two tautomers with X = N, which indicates that the electronic structure of this system is not very sensitive with respect to substituents or structural changes of the carbene. This is in agreement with the experimental results (Table 1).

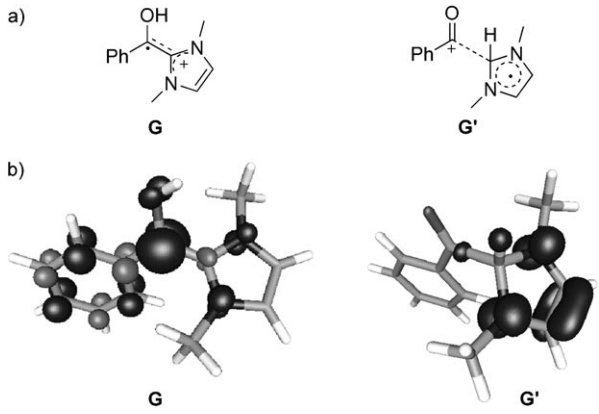


Figure 1. Lewis formulas and calculated structures (PBEh/TZVP) including a plot of the spin-density distribution (isosurface value of 0.01 a.u., positive values in black, negative values in gray) of the two tautomeric forms of the radical cation (**G** and **G′**).

In conclusion, we have developed NHC-catalyzed oxidations of aldehydes by using TEMPO as an oxidant. Inspired by nature, we report that NHCs can be applied in synthesis to activate aldehydes to react as organic electron-transfer reagents.[17] This type of NHC catalysis is not well explored. Importantly, the oxidant identified does not destroy the NHC catalyst. We believe that this type of aldehyde activation will open new avenues in the field of organocatalysis by NHCs.[20] The TEMPO esters can be hydrolyzed and the nitroxide be regenerated by O_2 which formally acts as terminal oxidant rendering these processes economic.[21]

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[1] S. W. Ragsdale, *Chem. Rev.* **2003**, *103*, 2333.
[2] T. D. H. Bugg, *Introduction to Enzyme and Coeenzyme Chemistry*, Blackwell, Oxford, **2004**.
[3] a) E. Chabière, X. Vernède, B. Guigliarelli, M. H. Charon, E. C. Hatchikian, J. C. Fontecilla-Camps, *Science* **2001**, *294*, 2559; b) S. O. Mansoorabadi, J. Seravalli, C. Furdui, V. Krymov, G. J. Gerfen, T. P. Begley, J. Melnick, S. W. Ragsdale, G. H. Reed, *Biochemistry* **2006**, *45*, 7122.
[4] D. Seebach, *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
[5] a) F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249; b) A. Lapworth, *J. Chem. Soc.* **1903**, *83*, 995; c) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.
[6] H. Stetter, H. Kuhlmann, *Chem. Ber.* **1976**, *109*, 2890.
[7] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606.
[8] NHC-catalyzed reactions of aldehydes leading to acid derivatives: 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; c) N. T. Reynolds, J. R. deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; d) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406; e) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126; f) A. Chan, K. Scheidt, *Org. Lett.* **2005**, *7*, 905; g) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873; h) K. Zeitler, *Org. Lett.* **2006**, *8*, 637; i) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; j) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088; k) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; l) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; m) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798.
[9] MnO_2-mediated oxidation of the adduct formed by reaction of an NHC with an enal: a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371. Fe^{III} salt as oxidant: b) L. Jimenez, F. Diederich, *Tetrahedron Lett.* **1989**, *30*, 2759. Organic oxidants: c) H. Inoue, K. Higashiura, *J. Chem. Soc. Chem. Commun.* **1980**, 549; d) S. Shinkai, T. Yamashita, Y. Kusano, O.

Manabe, *J. Org. Chem.* **1980**, *45*, 4947; e) J. Castells, F. Pujol, H. Llitjós, M. Moreno-Mañas, *Tetrahedron* **1982**, *38*, 337; f) S. W. Tam, L. Jimenez, F. Diederich, *J. Am. Chem. Soc.* **1992**, *114*, 1503; g) A. Miyashita, Y. Suzuki, I. Nagasaki, C. Ishiguro, K. I. Iwamoto, T. Higashino, *Chem. Pharm. Bull.* **1997**, *45*, 1254.

[10] Review on the use of TEMPO in synthesis: a) T. Vogler, A. Studer, *Synthesis* **2008**, 1979. See also: b) T. Vogler, A. Studer, *Org. Lett.* **2008**, *10*, 129; c) A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27; d) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267.

[11] It has recently been suggested that the lipoyl group might act as an electron acceptor to oxidize enamines of type **C**: R. A. W. Frank, C. W. M. Kay, J. Hirst, B. F. Luisi, *J. Am. Chem. Soc.* **2008**, *130*, 1662. We tested diphenyldisulfide as an oxidant; however, no conversion was observed.

[12] Review on biomimetic oxidations: J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506.

[13] Review on NHCs: F. E. Hahn, M. C. Jahnke, *Angew. Chem.* **2008**, *120*, 3166; *Angew. Chem. Int. Ed.* **2008**, *47*, 3122.

[14] Acyl-TEMPO derivatives: a) S. Marque, H. Fischer, E. Baier, A. Studer, *J. Org. Chem.* **2001**, *66*, 1146; b) A. D. Allen, M. F. Fenwick, H. Henry-Riyad, T. T. Tidwell, *J. Org. Chem.* **2001**, *66*, 5759; c) R. Braslau, M. O. Anderson, F. Rivera, A. Jimenez, T. Haddad, J. R. Axon, *Tetrahedron* **2002**, *58*, 5513.

[15] Oxidation of 3-Cl-C_6H_4CHO with DBU (3 mol%) and **5** (2 mol%) gave **2i** in 98% yield (entry 15, Table 1); with DBU (2 mol%) and **5** (2 mol%) **2i** was isolated in 98% yield, and with DBU (2 mol%) and **5** (3 mol%) ester **2i** was formed in 97% yield, clearly proving that DBU is only acting as base to liberate the carbene catalyst.

[16] During chromatography TEMPOH was partially oxidized by air as indicated by the red color of the solution. In situ oxidation of TEMPOH by dioxygen during the reaction did not work. Dioxygen itself is a better oxidant than TEMPO and is able to oxidize intermediates of type **C** to the corresponding radical cations. However, dioxygen is known to oxidize carbenes.

[17] SET by organic electron donors: a) J. A. Murphy, T. A. Khan, S.-Z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem.* **2005**, *117*, 1380; *Angew. Chem. Int. Ed.* **2005**, *44*, 1356; b) F. Schoenebeck, J. A. Murphy, S. Z. Zhou, Y. Uenoyama, Y. Miclo, T. Tuttle, *J. Am. Chem. Soc.* **2007**, *129*, 13368.

[18] Trapping of **H** with TEMPO is unlikely since in the case of cinnamaldehyde, TEMPO trapping of the delocalized radical cation **G** (R = PhCH=CH) should occur at least in part at the benzylic position. Products derived from such a TEMPO trapping reaction were not identified. Moreover, when oxidation of **1a** was conducted in MeOH, methyl cinnamate was formed as a side product along with **2a**. This experiment clearly shows that reaction occurred via **I**.

[19] The DFT calculations were performed unrestricted using triple-zeta Gaussian AO basis sets (TZVP and TZVPP, see Ref. [19a]) with the TURBOMOLE program, see Ref. [19b]. For the structure optimizations we employed the non-empirical PBEh (see Ref. [19c]) density functional and the TZVP basis set. Because the so-called self-interaction error (see Ref. [19d]) is a problem in DFT calculations of radical cations, we also used the new B2PLYP functional (see Ref. [19f]) that includes a much larger fraction of exact Hartree–Fock exchange (i.e., 53% and further a nonlocal perturbation term for correlation). For the energy differences between **G** and **G′** (R = Ph, X = CH) we obtained 12.8 (PBEh/TZVP), 9.6 (B2PLYP/TZVP), and 11.4 kcal mol^{-1} (B2PLYP/TZVPP). These values are all in a rather narrow energy range and prove an energetic preference for the OH tautomer under gas-phase conditions; a) A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829. The basis sets are available from the TURBOMOLE homepage via the FTP Server Button (in the subdirectories basen, jbasen, and cbasen). See http://www.turbomole.com; b) TURBOMOLE, version 5.9: R. Ahlrichs et al., Universität Karlsruhe 2006. See http://www.turbomole.com; c) C. Adamo, V. Barone, *J. Chem. Phys.* **1999**, *110*, 6158; d) Y. Zhang, W. Yang, *J. Chem. Phys.* **1998**, *109*, 2604; e) O. Gritsenko, B. Ensing, P. R. T. Schipper, E. J. Baerends, *J. Phys. Chem. A* **2000**, *104*, 8558; f) S. Grimme, *J. Chem. Phys.* **2006**, *124*, 034108.

[20] Radical chemistry in organocatalysis: a) M. Dressel, T. Aechtner, T. Bach, *Synthesis* **2006**, 2206; b) A. Bauer, F. Westkaemper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139; c) T. Aechtner, M. Dressel, T. Bach, *Angew. Chem.* **2004**, *116*, 5974; *Angew. Chem. Int. Ed.* **2004**, *43*, 5849; d) D. H. Cho, D. O. Jang, *Chem. Commun.* **2006**, 5045; e) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124; f) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004; g) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; h) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398.

[21] Preliminary studies showed that NHC-catalyzed aerobic oxidation of aldehydes in MeOH affords the corresponding methyl esters in up to 50% yield.

