DOI: 10.1002/ejoc.201000985

Facile and Efficient Synthesis of Benzoxazoles and Benzimidazoles: The Application of Hantzsch Ester 1,4-Dihydropyridines in Reductive Cyclization Reactions

Rui-Guang Xing,[a] Ya-Nan Li,[a] Qiang Liu,*[a] Qing-Yuan Meng,[a] Jing Li,[a] Xiao-Xia Shen,[a] Zhengang Liu,[a] Bo Zhou,[a] Xiaojun Yao,[a] and Zhong-Li Liu[a]

Dedicated to Professor You-Cheng Liu on the occasion of his 90th birthday

Keywords: Fused-ring systems / Heterocycles / Biomimetic synthesis / Reduction / Cyclization

Both benzoxazole and benzimidazole are common heterocyclic scaffolds in biologically active and medicinally significant compounds. Reductive cyclization of *ortho*-substituted nitrobenzene derivatives provides an attractive route to benzoxazole or benzimidazole ring formation. Unfortunately, only a few synthetic methods by reductive cyclization of *ortho*-nitro compounds have been reported and the yields are rather low. In continuation of the development of biomimetic reductants in synthetically useful organic transformations, Hantzsch ester 1,4-dihydropyridine (HEH), analogues of NAD(P)H, has attracted a considerable amount of attention. Hence, we wish to report that benzoxazoles and benzimidazoles can be efficiently synthesized by the reaction of *ortho*-substituted nitrobenzene derivatives with HEH catalyzed by Pd/C. A range of functionalized *ortho*-nitrophenyl esters or *ortho*-nitrophenyl amides were efficiently reduced by HEH and cyclized to the corresponding benzoxazoles or benzimidazoles. Especially, working in the presence of the same substituents, benzimidazoles could be obtained in higher yields with respect to the corresponding benzoxazoles. Moreover, in the present work, the recycling of Pd/C was studied and was shown to maintain its high catalytic activity over five runs. On the basis of our experimental results and DFT calculations, a plausible reaction mechanism was proposed.

Introduction

Benzo-fused azoles such as benzoxazoles[1] and benzimidazoles[2] are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Intrigued by the appealing pharmaceutical perspective, some methods have been developed for the synthesis of benzoxazoles and benzimidazoles. The most common approaches for 2-substituted benzoxazoles involve the coupling of 2-aminophenols with carboxylic acid derivatives[3,4] or the reaction of 2-aminophenols with an aldehyde by oxidative cyclization of imine intermediates.[5] Similarly, a traditional method for the synthesis of benzimidazoles is the condensation of 1,2-diaminoarene derivatives with carbonyl compounds.[6] The development of alternative routes to benzoxazole or benzimidazole ring formation is an important goal because it would allow the use of milder reaction conditions and it would overcome the requirement for using 2-aminophenols or 1,2-diaminoarenes as precursors. For example, considerable progress has been made in the area of metal-catalyzed direct arylation of five-membered heterocycles.[7] Comparing with those intermolecular or intramolecular coupling methodologies, reductive cyclization of *ortho*-substituted nitrobenzene derivatives also provides an attractive route to benzoxazole or benzimidazole ring formation. Unfortunately, only a few synthetic methods by reductive cyclization of *ortho*-nitro compounds have been reported.[8] For instance, metallic reducing agents such as Fe[8d] and $SnCl_2$[8b] have been employed in the synthesis of benzoxazole and benzimidazole but the yields are rather low. The reduction of *ortho*-substituted nitrobenzene by catalytic hydrogenation,[8c] followed by acid-catalyzed cyclization provides an efficient approach to synthesize phenanthro[2,3-*d*]-imidazoles. However, the reaction has been accomplished in one pot only in two cases and a pressurized hydrogen atmosphere was required. Thus, the development of an environmentally benign and efficient reducing agent should significantly increase the attraction of this synthetic approach.

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China
Fax: +86-931-8625657
E-mail: liuqiang@lzu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000985.

Hantzsch ester 1,4-dihydropyridine (HEH), an analogue of NAD(P)H, has been widely used as a biomimetic reductant in synthetically useful organic transformations.[9] Recently, tremendous progress has been made in the area of biomimetic enantioselective transfer hydrogenation by employing the combination of an organocatalyst and a Hantzsch ester 1,4-dihydropyridine.[10] Following our interest in the exploration of organic molecules as reducing agents, we have found that the behavior of HEH in Pd/C-catalyzed reactions contrasts the general trend observed in organocatalyzed reactions.[11] For instance, nitro compounds could be reduced to amine by HEH in the presence of Pd/C,[11c] whereas they are tolerated in organocatalytic asymmetric nitroolefin reduction.[10c] In the present work, we wish to report that benzoxazoles and benzimidazoles can be efficiently synthesized by the reaction of *ortho*-substituted nitrobenzene derivatives with HEH catalyzed by Pd/C.

Results and Discussion

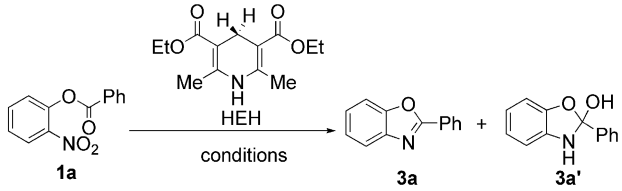
Our initial studies focused on 2-nitrophenyl benzoate (**1a**), a substrate that is known to undergo reductive cyclization by Fe and $SnCl_2$. We began our investigation by using the conditions previously developed for the reductive cyclization of 1,2-epoxy-3-(2-nitroaryloxy)propanes.[11d] Under these conditions, only **3a′** was isolated in 80% yield (Table 1, Entry 1). A similar result was obtained by heating a mixture of the substrate, HEH, and Pd/C in toluene at reflux (Table 1, Entry 2). However, compound **3a′** easily afforded **3a** under careful dehydration in acidic medium. Thus, performing the reaction in refluxing acetic acid, **3a** was obtained in 84% yield (Table 1, Entry 3). The reductive cyclization proceeded efficiently also when the amount of the catalyst was decreased to 2 wt.-% of HEH (Table 1, Entry 4). Importantly, no conversion was observed when the reaction was carried out in the absence of Pd/C (Table 1, Entry 5) or at room temperature (Table 1, Entry 6).

The optimized procedure was as follows: an acetic acid solution (20 mL) of 2-nitrophenyl benzoate (**1a**, 1.0 mmol), HEH (3.6 mmol), 10% Pd/C (2 wt.-% of HEH) was stirred at reflux under a N_2 atmosphere for 15 h. Upon completion of the reaction, as monitored by TLC, the mixture was filtered through Celite, and the filtrate was evaporated in vacuo. 2-Phenylbenzo[*d*]oxazole (**3a**) was isolated in 83% yield after column chromatography (silica gel). The product was identified by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry (EI).

By using this procedure, a range of functionalized *ortho*-nitrophenyl esters were efficiently reduced by HEH and cyclized to the corresponding benzoxazoles (Table 2). The reaction works well with electron-rich substituents, methyl, *tert*-butyl, or methoxy groups, on the nitrobenzene ring (Table 2, Entries 2–4). However, when the R^2 substituent was ethoxycarbonyl (Table 2, Entry 5) or trifluoromethyl (Table 2, Entry 6), the yields were moderate, giving **3e** and **3f** in 70 and 56% yield, respectively. In particular, the product naphthoxazole (**3g**) was obtained in 90% yield (Table 2, Entry 7) by using 1-nitronaphthalen-2-yl benzoate (**1g**) as the starting material. Interestingly, the substituent located on the benzoyl ring of the 2-nitrophenyl benzoates had no appreciable effect on the reaction outcome. For instance, when the R^1 substituent is an electron-rich (Table 2, Entry 8) or an electron-deficient (Table 2, Entry 9) aryl compound, the corresponding product **3h** or **3i** was obtained in 86 and 80% yield, respectively. Similarly, 2-nitrophenyl 1-naphthoate (Table 2, Entry 10) can be also cyclized in good yields (85%). Furthermore, this reductive cyclization procedure is also applicable to 2-nitrophenyl alkanoates. For example, several 2-alkylbenzoxazoles were successfully synthesized with good yields (Table 2, Entries 11–15).

In an attempt to broaden this approach to the synthesis of benzo-fused azoles by the reductive cyclization of *ortho*-substituted nitrobenzene derivatives, we firstly employed **2a** as a model compound in the reaction with HEH (3.6 mmol), 10% Pd/C (2 wt.-% of HEH) at 120 °C in acetic acid for 15 h under an atmosphere of N_2. At the end of the reaction the mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel, and desired cyclic

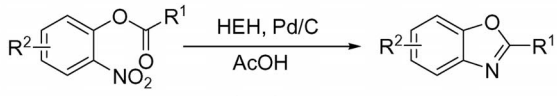
Table 1. Screening reaction conditions.



Entry	Conditions[a]	Product (% yield)
1	10% Pd/C (5 wt.-% of HEH), ethanol, reflux, 15 h	**3a** (0), **3a′** (80)
2	10% Pd/C (5 wt.-% of HEH), toluene, reflux, 15 h	**3a** (0), **3a′** (92)
3	10% Pd/C (5 wt.-% of HEH), acetic acid, reflux, 15 h	**3a** (84), **3a′** (0)
4	10% Pd/C (2 wt.-% of HEH), acetic acid, reflux, 15 h	**3a** (83), **3a'** (0)
5	no catalyst, acetic acid, reflux, 15 h	**3a** (0), **3a′** (0)
6	10% Pd/C (2 wt.-% of HEH), 20 mL acetic acid, r.t., 15 h	**3a** (0), **3a'** (0)

[a] Reactions were performed by using **1a** (1.0 mmol), HEH (3.6 mmol), and the solvent (0.05 M/[substrate]).

Table 2. The synthesis of benzoxazoles.[a]



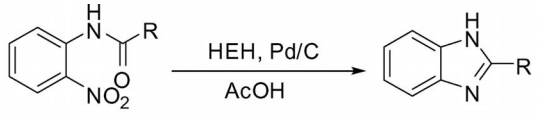
Entry	Substrate	Product	% Yield
1	1a	3a	83
2	1b	3b	81
3	1c	3c	80
4	1d	3d	85
5	1e	3e	70[b]
6	1f	3f	56
7	1g	3g	90
8	1h	3h	86
9	1i	3i	80
10	1j	3j	85
11	1k	3k	88
12	1l	3l	75
13	1m	3m	78
14	1n	3n	84
15	1o	3o	75

[a] Substrate (1.0 mmol), HEH (3.6 mmol), 10% Pd/C (2 wt.-% of HEH), AcOH (20 mL), 120 °C, 15 h. Yields are isolated yields. All products are known compounds and were characterized by MS (EI) and ^{1}H and ^{13}C NMR spectroscopy. [b] Product is an unknown compound.

product **4a** was obtained in 95% yield. Therefore, the scope of this reduction was further extended to a variety of *ortho*-substituted nitrobenzene derivatives. As shown in Table 3, the reduction worked well and the yield exceeded 90% in all cases (Table 3, Entries 1–8).

Again, good functional group tolerance was observed for the reductive cyclization reaction on the benzimidazole units. Both electron-rich and electron-poor substituents behaved well in this reaction, and most yields were higher than 95%. Especially, working in the presence of the same substituents, benzimidazoles could be obtained in higher yields with respect to the corresponding benzoxazoles (Table 2, Entry 1; Table 3, Entry 1; Table 2, Entry 8; Table 3, Entry 4). Gratifyingly, not only benzoyl-substituted (Table 3, Entries 1–5) but also 1-naphthoyl (Table 3, Entry 6) and alkanoyl (Table 3, Entries 7 and 8) *ortho*-nitroanilines furnished the desired benzimidazoles in excellent yields.

Table 3. The synthesis of benzimidazole.[a]

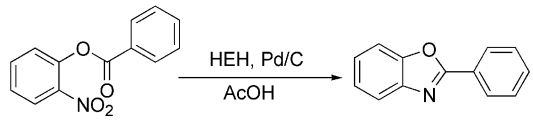


Entry	Substrate	Product	% Yield
1	**2a**	**4a**	95
2	**2b**	**4b**	94
3	**2c**	**4c**	91
4	**2d**	**4d**	99
5	**2e**	**4e**	99
6	**2f**	**4f**	98
7	**2g**	**4g**	97
8	**2h**	**4h**	99

[a] Substrate (1.0 mmol), HEH (3.6 mmol), 10% Pd/C (2 wt.-% of HEH), AcOH (20 mL), 120 °C, 15 h. Yields are isolated yields. All products are known compounds and were characterized by MS (EI) and ^{1}H and ^{13}C NMR spectroscopy.

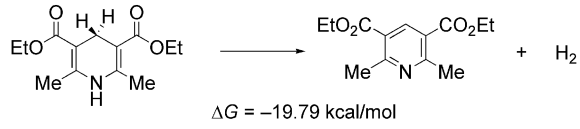
The role of Pd/C is crucial for the HEH-based reductive cyclizations. Preliminary experiments well established that Pd/C is the more advantageous catalyst for HEH-based reductive reactions.[11] Moreover, in this work, the recycling of Pd/C was studied with 2-nitrophenyl benzoate (**1a**) as a model substrate. As reported in Table 4, Pd/C maintains its high catalytic activity over five runs.

Table 4. Reuse of Pd/C in the reaction.

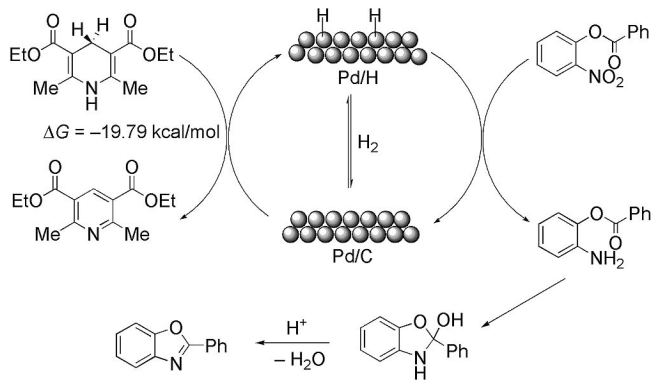


Run	% Yield of **3a**
1	83
2	82
3	78
4	73
5	74

We also observed the evolution of hydrogen gas in a refluxing alcoholic solution containing HEH and catalytic Pd/C.[11e] DFT calculations on the ambient-temperature transformation of HEH to pyridine and hydrogen (Scheme 1) predict a strongly exergonic reaction in the gas phase at 298 K, ΔG = –19.79 kcal/mol.[12] Actually, a significant amount of hydrogen gas was detected and HEH was converted into pyridine in quantitative yield when HEH was heated at reflux with 10% Pd/C (2 wt.-% of HEH) in acetic acid for 3 h.[13] On the other hand, a refluxing solution containing 2-nitrophenyl benzoate (**1a**), HEH, and catalytic Pd/C produced only a trace amount of hydrogen gas, which indicates that most of the hydrogen is consumed before evolution. On the basis of our experimental results and the report of Gigante,[14] we believe that the present reductive cyclization is very efficient and that **1a** is reduced by the hydrogen gas generated in situ from HEH in the presence of Pd/C. A plausible reaction mechanism is shown in Scheme 2. The aromatization of HEH catalyzed



Scheme 1.



Scheme 2. Plausible mechanism.

by Pd/C causes the formation of palladium hydride, which can generate hydrogen if it is not captured by **1a**. The reduction of **1a** could lead to the formation of 2-aminophenyl benzoate. The amine can undergo intramolecular cyclization to give dihydrobenzoxazol-2-ol, which loses a water molecule in the presence of acetic acid to produce desired product **2a**.

Conclusions

In summary, a mild and efficient method for the synthesis of benzo-fused azoles has been developed by using Hantzsch ester 1,4-dihydropyridine (HEH) as a biomimetic reducing agent. To the best of our knowledge, the reported procedure represents the first application of the model compound of coenzyme NAD(P)H in the synthesis of benzo-fused azoles. Extension of this method to other potential substrates is in progress in our laboratory.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Varian instrument (300 and 75 MHz, respectively) or a Bruker instrument (400 and 100 MHz, respectively) and internally referenced to the tetramethylsilane signal or residual protio solvent signals. Mass spectra were recorded by EI methods, and IR spectra were recorded with a Nicolet NEXUS 670 FTIR spectrometer. HRMS data were determined with a Bruker Daltonics APEXII 47e FTICR spectrometer. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Silica gel (200–300 mesh) was used for column chromatography. The employed solvents were dried by the standard procedures. Commercially obtained reagents were used without further purification.

General Procedure for the Synthesis of Benzo-Fused Azoles: To a stirred solution of **1a**–**o** or **2a**–**h** (1.0 mmol) in acetic acid (20 mL) was added HEH (3.6 mmol) and 10% Pd/C (2 wt.-% of HEH), and the reaction mixture was heated at reflux for 15 h under an atmosphere of N_2. Then the mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding product.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

We thank the National Natural Science Foundation of China (Grant No. 20702023) and the Special Fund for Doctoral Program from the Ministry of Education of China (Grant No. 20070730040) for financial support.

[1] a) M. O. Chaney, P. V. Demarco, N. D. Jones, J. L. Occolowitz, *J. Am. Chem. Soc.* **1974**, *96*, 1932–1933; b) T. Kusumi, T. Ooi, M. R. Walchli, H. Kakisawa, *J. Am. Chem. Soc.* **1988**, *110*, 2954–2958; c) A. D. Rodriguez, C. Ramirez, I. I. Rodriguez, E. Gonzalez, *Org. Lett.* **1999**, *1*, 527–530; d) R. N. Brown, R. Cameron, D. K. Chalmers, S. Hamilton, A. Luttick, G. Y. Krippner, D. B. McConnell, R. Nearn, P. C. Stanislawski, S. P. Tucker, K. G. Watson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2051–2055; e) M. S. Malamas, E. S. Manas, R. E. McDevitt, I. Gunawan, Z. B. Xu, M. D. Collini, C. P. Miller, T. Dinh, R. A. Henderson, J. C. Keith Jr., H. A. Harris, *J. Med. Chem.* **2004**, *47*, 5021–5040; f) H. Razavi, S. K. Palaninathan, E. T. Powers, R. L. Wiseman, H. E. Purkey, N. N. Mohamedmohaideen, S. Deechongkit, K. P. Chiang, M. T. A. Dendle, J. C. Sacchettini, J. W. Kelly, *Angew. Chem. Int. Ed.* **2003**, *42*, 2758–2761.

[2] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235–2246; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930 and references cited therein.

[3] a) M. Terashima, M. Ishii, Y. Kanaoka, *Synthesis* **1982**, 484–485; b) D. W. Hein, R. J. Alheim, J. J. Leavitt, *J. Am. Chem. Soc.* **1957**, *79*, 427–429.

[4] a) K. Bourgrin, A. Loupy, M. Soufiaoui, *Tetrahedron* **1998**, *54*, 8055–8064; b) R. S. Pottorf, N. K. Chadha, M. Katkevics, V. Ozola, E. Suna, H. Ghane, T. Regberg, M. R. Player, *Tetrahedron Lett.* **2003**, *44*, 175–178.

[5] Various oxidants, such as DDQ, $Mn(OAc)_3$, $PhI(OAc)_2$, thianthrene cation radical perchlorate, $BaMnO_4$, NiO_2, $Pb(OAc)_4$, and O_2 with activated carbon, as well as MnO_2/silica (under microwave conditions, see ref.[4a]), have been used. For examples, see: a) J. Chang, K. Zha, J. Chang, K. Zhao, S. Pan, *Tetrahedron Lett.* **2002**, *43*, 951–954; b) R. S. Varma, D. Kumar, *J. Heterocycl. Chem.* **1998**, *35*, 1539–1540; c) R. S. Varma, R. K. Saini, O. Prakash, *Tetrahedron Lett.* **1997**, *38*, 2621–2622; d) K. H. Park, K. Jun, S. R. Shin, S. W. Oh, *Tetrahedron Lett.* **1996**, *37*, 8869–8870; e) R. G. Srivastava, P. S. Venkataramani, *Synth. Commun.* **1988**, *18*, 1537–1544; f) K. Nakagawa, H. Onoue, J. Sugita, *Chem. Pharm. Bull.* **1964**, *12*, 1135–1138; g) F. F. Stephens, J. D. Bower, *J. Chem. Soc.* **1949**, 2971–2972; h) Y. Kawashita, N. Nakamichi, H. Kawabata, M. Hayashi, *Org. Lett.* **2003**, *5*, 3713–3715.

[6] a) B. Yadagiri, J. W. Lown, *Synth. Commun.* **1990**, *20*, 955–963; b) Q. Sun, B. Yan, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 361–364; c) P. N. Preston in *The Chemistry of Heterocyclic Compounds* (Eds.: A. Weissberger, E. C. Taylor) Wiley, New York, **1981**, vol. 40, part 1, pp. 6–60; d) M. R. Grimmett in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, vol. pp. 457–487; e) T. Benincori, F. Sannicolò, *J. Heterocycl. Chem.* **1988**, *25*, 1029–1033; f) J. G. Smith, I. Ho, *Tetrahedron Lett.* **1971**, *12*, 3541–3542; g) R. Weidenhagen, *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 2263–2272; h) see ref.[5g]; i) S. Kumar, K. K. Kapoor, *Synlett* **2007**, 2809–2814.

[7] a) H. Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405; b) G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem. Int. Ed.* **2007**, *46*, 7996–8000; c) B. Sezen, D. Sames, *Org. Lett.* **2003**, *5*, 3607–3610.

[8] a) D. G. Saunders, *J. Chem. Soc. C* **1969**, *12*, 680–680; b) Y. A. M. Marghlani, S. A. M. Metwally, A. M. Mahmoud, A. M. Osman, *Pak. J. Sci. Ind. Res.* **1980**, *23*, 166–168; c) T. Fonseca, B. Gigante, T. L. Gilchrist, *Tetrahedron* **2001**, *57*, 1793–1799; d) A. Alberti, P. Carloni, L. Greci, P. Stipa, R. Andruzzi, G. Marrosu, A. Trazza, *J. Chem. Soc. Perkin Trans. 2* **1991**, *7*, 1019–1023; e) H. C. Waterman, D. L. Vivian, *J. Org. Chem.* **1949**, *14*, 289–297.

[9] a) X.-Q. Zhu, H.-Y. Wang, J.-S. Wang, Y.-C. Liu, *J. Org. Chem.* **2001**, *66*, 344–347; b) J. Zhang, M.-Z. Jin, W. Zhang, L. Yang, Z.-L. Liu, *Tetrahedron Lett.* **2002**, *43*, 9687–9689; c) S. J. Garden, C. R. W. Guimaraes, M. B. Correa, C. A. F. de Oliveira, A. D. Pinto, R. B. de Alencastro, *J. Org. Chem.* **2003**, *68*, 8815–8822; d) Z. G. Zhang, P. R. Schreiner, *Synthesis* **2007**, 2559–2564 and references cited therein.

[10] a) G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18–19; b) S. G. Ouellet, A. M. Walji, D. W. C. Macmillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; c) N. J. A. Martin, X. Cheng,

B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863; d) R. J. He, P. H. Toy, Y. L. Lam, *Adv. Synth. Catal.* **2008**, *350*, 54–60 and references cited therein.

[11] a) X. X. Shen, Q. Liu, R. G. Xing, B. Zhou, *Catal. Lett.* **2008**, *126*, 361–366; b) Q. Liu, J. Li, X. X. Shen, R. G. Xing, J. Yang, Z. G. Liu, B. Zhou, *Tetrahedron Lett.* **2009**, *50*, 1026–1028; c) X. Q. Niu, Z. G. Liu, W. Yu, L. M. Wu, *Chin. J. Org. Chem.* **2009**, *29*, 229–233; d) Q. Y. Meng, Q. Liu, J. Li, R. G. Xing, X. X. Shen, B. Zhou, *Synlett* **2009**, 3283–3286; e) Y. Zhao, Q. Liu, J. Li, Z. Liu, B. Zhou, *Synlett* **2010**, 1870–1872.

[12] Thermochemical values were computed in the gas phase by using the B3LYP density functional method with the 6-31G* basis set.

[13] The generated hydrogen was collected and identified by GC analysis by using a 5-Å molecular sieves column, thermal conductivity detector, and nitrogen carrier gas.

[14] The reaction was carried out under 150 psi hydrogen pressure, see ref.[8c]

Received: July 13, 2010
Published Online: October 13, 2010

