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Neutral Flavins: Green and Robust Organocatalysts for Aerobic Hydrogenation of Olefins

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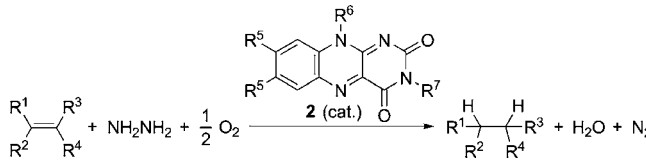
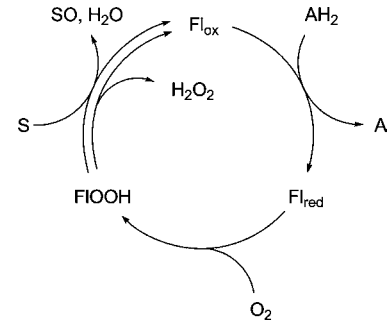
ABSTRACT



Various olefins can be hydrogenated quantitatively with neutral flavin 2 catalysts in the presence of 1−2 equiv of hydrazine under 1 atm of O_2. Vitamin B_2 derivative 2g acts as a highly efficient and robust catalyst for the present environmentally benign process producing water and nitrogen gas as the only waste products.

Flavins, simple model compounds of various flavin-containing oxidases[1] and monooxygenases,[2] attract much attention as a very rare class of organocatalysts that can perform aerobic oxidative transformations of organic compounds under mild conditions.[3−5] Most aerobic oxidative transformations with flavoenzymes and synthetic flavin catalysts proceed via substantially similar catalytic cycles, which include the following: (i) hydrogen transfer from reductants (AH_2) to oxidized flavin (Fl_{ox}); (ii) O_2 incorporation into the resulting reduced flavin (Fl_{red}) to afford 4a-hydroperoxyflavin (FlOOH); and (iii) oxygen transfer to substrates S followed by dehydration of FlOH or dissociation of H_2O_2 to regenerate

Scheme 1. Redox Process for Oxidative Transformations with Flavoenzymes and Synthetic Flavin Catalysts



Fl_{ox} (Scheme 1). Reductases and oxidases use the first dehydrogenation process as a crucial step for oxidative transformation.[1] Simulation of these enzymatic functions with flavins, isoalloxazines, provides catalytic dehydrogenative oxidations of alcohols,[6] primary and secondary amines,[7] and thiols[8] under O_2 atmosphere. Monooxygenases promote the third process, employing FlOOH as the active species for oxygen transfer to the substrates.[2] Various heteroatom

(1) Fitzpatrick, P. F. *Acc. Chem. Res.* **2001**, *34*, 299–307.
(2) (a) van Berkel, W. J. H.; Kamerbeek, N. M.; Fraaije, M. W. *J. Biotechnol.* **2006**, *124*, 670–689. (b) Ballou, D. P. In *Flavins and Flavoproteins*; Massey, V., Williams, C. H., Eds.; Elsevier: New York, 1982; pp 301−310.
(3) Reviews on flavin-catalyzed oxidations: (a) Gelalcha, F. G. *Chem. Rev.* **2007**, *107*, 3338–3361. (b) Imada, Y.; Naota, T. *Chem. Rec.* **2007**, *7*, 354–361.
(4) Ishii, Y.; Sakaguchi, S. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 119−163.
(5) (a) Ohkubo, K.; Suga, K.; Morikawa, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 12850–12859. (b) Ohkubo, K.; Nanjo, T.; Fukuzumi, S. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1489–1500. (c) Ohkubo, K.; Suga, K.; Fukuzumi, S. *Chem. Commun.* **2006**, 2018–2020.

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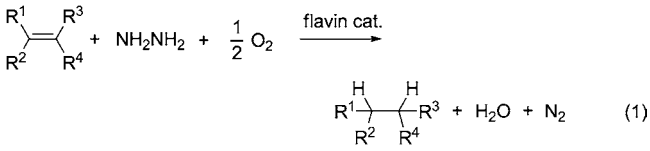
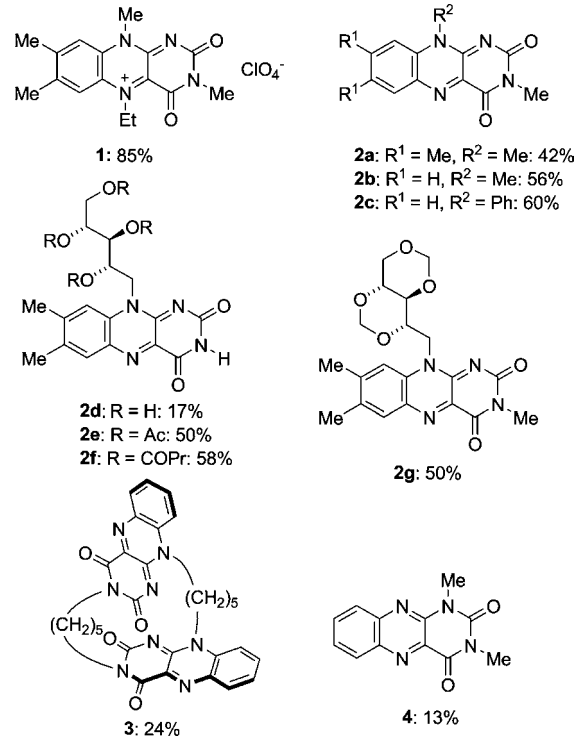
compounds such as tertiary amines,[9] sulfides,[9] and ketones[10] undergo aerobic oxidations with 5-ethylflavinium perchlorate catalysts in the presence of reductants.[3]

Recently, we found that diimide (HN═NH), a powerful reducing agent for a variety of unsaturated bonds,[11] can be generated by aerobic oxidation of hydrazine with flavin catalyst **1** through both dehydrogenation and oxygenation processes of the above redox system. This method can be applied to a new type of "aerobic hydrogenation" of olefins, performing efficiently under 1 atm of molecular oxygen or air (eq 1).[12] The method provides an alternative, convenient method for the catalytic hydrogenation of olefins, which proceeds without transition metals and dangerous oxidants, producing water and nitrogen gas as waste products. This is rare for organocatalytic hydrogenation reactions.[13]



In this paper we describe 5-unsubstituted isoalloxazines **2**, which act as highly efficient and robust catalysts for this new type of reduction. 5-Unsubstituted isoalloxazines **2** are inexpensive, safe, and common materials, and are widely used as medicines, cosmetics, and health supplements.[14] Compared to cationic flavin species $FlEt^{+}\cdot ClO_4^{-}$ **1**[3,9,10] and its reduced form FlEtH,[15,16] this class of compounds is considerably safer and easier to prepare, handle, and store, thus the development of general methods for oxidative transformations with **2** catalysts is highly desired from synthetic, industrial, and environmental viewpoints. However, the catalytic use of **2** for molecular transformations has been limited to just a few reactions,[6,8,17] mainly due to the lower stability of FlOOH. The present finding adds further synthetic utility to this new environmentally benign process. A recent paper on a similar type of reaction with a much more unstable reduced flavin catalyst[16] prompted us to report our new results.

Scheme 2. Catalytic Activities for Aerobic Hydrogenation of Styrene to Ethylbenzene with Various Flavin Compounds[a]



[a] The experimental conditions are described in the text.

The catalytic activity of various flavin compounds (1 mol %) (Scheme 2) was examined for the hydrogenation of styrene (0.1 mmol) with $NH_2NH_2\cdot H_2O$ (0.12 mmol) in CH_3CN (0.4 mL) at 30 °C under O_2 (1 atm). Yields of ethylbenzene were evaluated by GLC analysis after stirring for 8 h. While flavinium perchlorate **1** showed the highest catalytic activity among the catalysts examined,[12] a series of 5-unsubstituted neutral flavins **2a**−**c** showed comparably high activities. This is in contrast to the fact that compounds **2** gave unsatisfactory results for catalytic oxidations of amines and sulfides with O_2[9,10] and H_2O_2.[18] Vitamin B_2 derivatives **2e**−**g** also showed high activities, while unprotected vitamin B_2 (**2d**) gave unsatisfactory results due to its low solubility in organic solvents. Bisflavin **3**[19] had decreased activity owing to intramolecular electron transfer. The flavin analogue, 1,3-dimethylalloxazine (**4**), exhibited much lower catalytic activity in this case, while its 5-ethyl-1,5-dihydro

(6) (a) Fukuzumi, S.; Kuroda, S.; Tanaka, T. *J. Am. Chem. Soc.* **1985**, *107*, 3020–3027. (b) Shinkai, S.; Kameoka, K.; Ueda, K.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 923–924. (c) Svoboda, J.; Schmaderer, H.; König, B. *Chem.*−*Eur. J.* **2008**, *14*, 1854–1865.

(7) (a) Hoegy, S. E.; Mariano, P. S. *Tetrahedron* **1997**, *53*, 5027–5046. (b) Li, W.-S.; Zhang, N.; Sayre, L. M. *Tetrahedron* **2001**, *57*, 4507–4522.

(8) Yano, Y.; Ohshima, M.; Yatsu, I.; Sutoh, S.; Vasquez, R. E.; Kitani, A.; Sasaki, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 753–758.

(9) (a) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2003**, *125*, 2868–2869. (b) Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S.-I. *Chem. Asian J.* **2006**, *1*, 136–147.

(10) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704–1706.

(11) For reviews, see: (a) Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271–280. (b) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91–155.

(12) Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544–14545.

(13) Organocatalytic transfer hydrogenations :(a) Yoneda, F.; Kuroda, K.; Tanaka, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1194–1195. (b) Yang, J. W.; Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660–6662. (c) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.

(14) Powers, H. J. *Am. J. Clin. Nutr.* **2003**, *77*, 1352–1360.

(15) (a) Bergstad, K.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6650–6655. (b) Lindén, A. A.; Krüger, L.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 5890–5896.

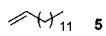
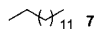
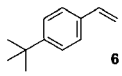
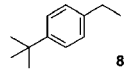
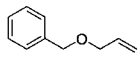
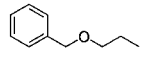
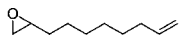
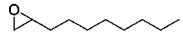
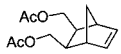
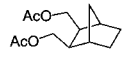
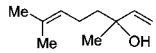
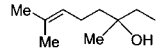
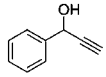
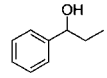
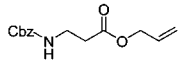
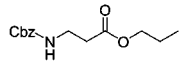
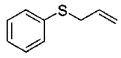
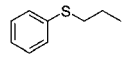
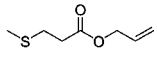
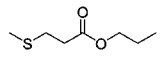
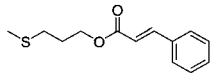
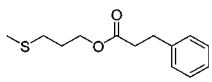
(16) Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482–9485.

(17) (a) Tamao, K.; Hayashi, T.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 795–797. (b) Akiyama, T.; Simeno, F.; Murakami, M.; Yoneda, F. *J. Am. Chem. Soc.* **1992**, *114*, 6613–6620.

(18) (a) Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002–5003. (b) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8–9. (c) Murahashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366–2368. (d) Imada, Y.; Ohno, T.; Naota, T. *Tetrahedron Lett.* **2007**, *48*, 937–939.

(19) Imada, Y.; Ohno, T.; Naota, T. *Tetrahedron Lett.* **2008**, *49*, 2523–2526.

Table 1. Aerobic Hydrogenation with Neutral Flavin Catalyst[a]

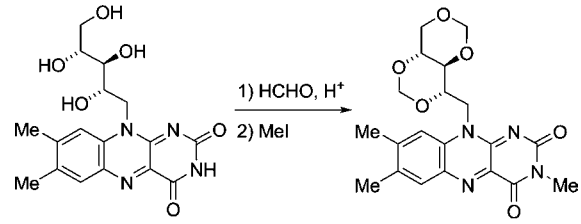
entry	alkene	alkane	yield (%)[b]
1	 **5**	 **7**	89
2			96[c]
3	 **6**	 **8**	94
4			93[d]
5			93
6			91[e]
7			85
8			90[e]
9			99
10			92[f]
11			92[g]
12			86
13			90
14			91[d]
15			89
16			94[h]

[a] The reaction was carried out in CH_3CN in the presence of **2f** (2.0 mol %), and $NH_2NH_2{\cdot}H_2O$ (2.0 equiv) at 30 °C for 24 h under O_2 (1 atm). [b] Isolated yield. [c] **2a** was used instead of **2f**. [d] **2g** was used instead of **2f**. [e] **2e** was used instead of **2f**. [f] $NH_2NH_2{\cdot}H_2O$ (1.5 equiv) was used at 25 °C. [g] $NH_2NH_2{\cdot}H_2O$ (4.0 equiv) was used. After 24 h, additional $NH_2NH_2{\cdot}H_2O$ (1.0 equiv) was added, and the mixture was stirred another 6 h. [h] $NH_2NH_2{\cdot}H_2O$ (2.4 equiv) was used at 50 °C.

analogue can be used as an efficient catalyst for oxidations of amines and sulfides with H_2O_2.[15]

Table 1 shows representative results for the neutral flavin-catalyzed aerobic hydrogenation of olefins. A variety of linear and cyclic olefins were converted to the corresponding hydrogenated products when the reaction was performed in CH_3CN with neutral flavin catalyst **2** and 2 equiv of hydrazine at ambient temperature under O_2 (1 atm). In addition to **2a**, vitamin B_2 derivatives **2e**−**g** can be used as efficient catalysts for quantitative hydrogenation. Conveniently, there is no significant difference in product yields between cationic flavin **1** and neutral **2** under the present conditions, although control experiments with 1 equiv of hydrazine showed that the catalytic activity of **1** is higher than those with **2**. Monosubstituted olefins are hydrogenated chemoselectively in the presence of trisubstituted ones (entry 10). Alkynes can be converted to the corresponding alkanes with 5 equiv of hydrazine (entry 11). Various heteroatom-containing substituents such as alkoxy, epoxy, acyloxy, hydroxy, and amido groups are tolerated by the reaction (entries 5−12). Noteworthy is that benzyloxy and carbobenzyloxy groups, highly labile protecting groups under reducing

Scheme 3. Synthesis of **2g**



Vitamin B_2 (**2d**) DMRFl (**2g**)

Sigma-Aldrich (601 USD/kg, 2009)

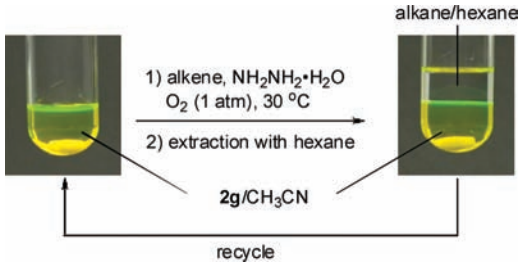
conditions,[20] remain intact under the present reaction conditions (entries 5, 6, and 12). Another synthetic utility of the present method is illustrated by the highly efficient reduction of sulfur-containing olefins (entries 13−16), which are negligibly reduced by conventional hydrogenation with transition metal catalysts.

One important advantage of the present reaction is the availability of the catalysts. A series of neutral flavin **2** catalysts can be prepared much more easily than cationic[9,12,18] or reduced forms.[16] Neutral flavin **2a** can be prepared readily by a conventional process including reduction of *o*-nitroaniline, condensation with alloxane, and subsequent *N*-methylation, while cationic flavin **1** requires subsequent reductive amination and oxidation, both of which are synthetically difficult.[9b] Vitamin B_2 **2d** is an inexpensive mass-produced material, and its derivatives **2e** and **2f** are also commercially available. 3-Methyl-2′,4′:3′,5′-di-*O*-methylenedioxyriboflavin (DMRFl) **2g** can be readily derived from **2d** by a conventional process (Scheme 3). Also, neutral flavins **2** can be purified readily, and preserved for a long time under ambient atmosphere. This is in contrast to less stable, cationic flavins which cannot be purified by ordinary experimental procedures such as extraction, chromatographic separation, and recrystallization. Preparation and treatment of reduced flavins require much more sophisticated techniques to prevent spontaneous incorporation of O_2.

Another feature of the present method is the high reusability of the catalysts arising from their thermal and chemical stabilities. DMRFl **2g** has proven to be the most robust catalyst among those examined. Table 2 shows typical recycling use of catalyst **2g** in the hydrogenation of 1-tetradecene (**5**) and 4-*tert*-butylstyrene (**6**). The product alkanes **7** and **8** can be obtained quantitatively upon simple extraction with hexane. After the reaction, the resulting CH_3CN phase including **2g** can be stored for a long time, and reused repeatedly for subsequent runs without loss of efficiency. Vitamin B_2 derivative **2f** also exhibited comparably higher reusability for the present aerobic hydrogenations, although the yield in the second run decreased (**8**: 64%) due to deactivation by slow hydrolysis of the catalyst. Cationic flavins are not robust toward such a tough recycling use.

(20) Wuts, P. G.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New York, 2006.

Table 2. Aerobic Hydrogenation of **5** and **6** with **2g** Catalyst



	isolated yield (%)	
run	tetradecane (**7**)	4-*tert*-butylethylbenzene (**8**)
1[a]	98	93
2[b]	97	94
3[b]	96	94

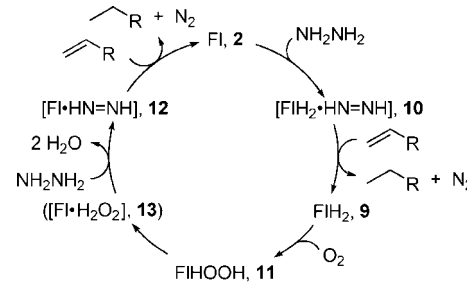
[a] The reaction of 1-tetradecene (**5**) or 4-*tert*-butylstyrene (**6**) was carried out in CH_3CN in the presence of **2g** (2.0 mol %), and NH_2NH_2•H_2O (2.0 equiv) at 30 °C for 24 h under O_2 (1 atm). [b] The acetonitrile solution from the previous run was reused instead of a recharged catalyst.

The yield of **8** did not exceed 40% after the second run with recycled **1** catalyst.

The present catalytic reaction can be rationalized by the consecutive anaerobic and aerobic processes as shown in Scheme 4.[12] Although neutral flavin **2** is less reactive than cationic **1**, it undergoes smooth nucleophilic attack of hydrazine due to the high nucleophilic properties of hydrazine arising from the α-nitrogen effect.[21] Subsequent 1,3-hydrogen shift generates reduced flavin FlH_2 (**9**) and diimide.[7] FlH_2 **9** and diimide then form the H-bonded FlH_2•HN═NH complex **10**, which prevents the problematic self-disproportionation reaction of the diimide, which produces hydrazine and molecular nitrogen.[11] The diimide in

(21) (a) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16–24. (b) Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545–3547.

Scheme 4. Proposed Catalytic Cycle for Aerobic Hydrogenation of Olefins with Neutral Flavin Catalyst **2**



complex **10** reacts with olefins to afford the hydrogenated products and molecular nitrogen. Incorporation of O_2 to the liberated FlH_2 **9** gives 4a-hydrodioxyflavin FlHOOH **11**. The second hydrazine undergoes fast oxygen transfer directly from **11** to afford the Fl•HN═NH complex **12**. An alternative pathway for the formation of **12** is elimination of H_2O_2 from **11** and subsequent oxidation of hydrazine with the resulting Fl•H_2O_2 complex **13**. Similar hydrogenation of a second olefin with **12** generates **2** to complete the catalytic cycle. The stoichiometry of reduction of 2 equiv of olefins with 1 equiv of O_2, depicted in eq 1, was confirmed experimentally, with 0.027 mmol of O_2 being consumed in the hydrogenation of 0.058 mmol of 9-decen-1-ol under standard conditions with neutral flavin catalyst **2g**. Efforts are currently underway to investigate the full scope of the reaction.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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