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Reduction of Carbon−Carbon Double Bonds Using Organocatalytically Generated Diimide

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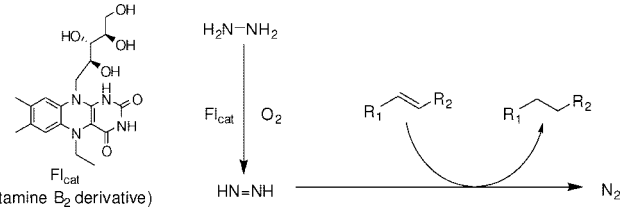
Received August 8, 2008



An efficient method has been developed for the reduction of carbon−carbon double bonds with diimide, catalytically generated in situ from hydrazine hydrate. The employed catalyst is prepared in one step from riboflavin (vitamin B_2). Reactions are carried out in air and are a valuable alternative when metal-catalyzed hydrogenations are problematic.

The reduction of carbon−carbon double bonds is a central reaction in organic synthesis, although in principle it lowers the complexity of the molecule.[1] Nevertheless, carbon−carbon double bonds are often used in the synthesis of natural products and pharmaceutical compounds either to introduce chirality via asymmetric hydrogenation or as a consequence of the strategy applied to connect molecular fragments. Established methods to form carbon−carbon double bonds are the Wittig and related reactions, the Julia−Kocienski, Ramberg−Bäcklund, aldol, and Knoevenagel reactions, and more recently olefin metathesis and allylic substitution reactions.

Reduction of nonpolarized carbon−carbon double bonds is normally accomplished by using hydrogen and heterogeneous transition metal catalysts, e.g. Rh/C, Pd/C, Raney Nickel, or Adams catalyst (PtO_2). Alternatively, homogeneous transition metal complexes such as Wilkinson's catalyst are applied, whereas enantioselective hydrogenation is mostly based on homogeneous catalysis as well.[2]

Although these hydrogenations with transition metal catalysts often proceed efficiently, there are important limitations. When using heterogeneous catalysts, hydrogenolysis[3] of benzylic, allylic, and propargylic alcohols and amines is often inevitable, and an important drawback when the corresponding benzyl, Cbz, and Alloc protecting groups are present.[4] In addition, several functional groups such as nitro groups, benzylic ketones, and aryl halides are rapidly reduced as well.

A less recognized feature of transition metals is their tendency to isomerize double bonds.[5] This holds for all commonly used transition metals both in heterogeneous and in homogeneous catalysis. Although often overlooked in cases in which the isomerized product is subsequently reduced without consequence, this process can lead to epimerization, ring opening of cyclopropanes, and, most difficult to detect, racemization. Several studies in natural product synthesis have explicitely reported epimerization or racemization in the course of the synthetic route.[6] Mori et al. observed partial racemization in the synthesis of 6-acetoxy-19-methylnonacosane.[7] Curran et al. observed, upon careful analysis during the synthesis of the pinesaw fly sex pheromones, epimerization due to hydrogenation with Pd/C and Ra Ni.[8] Very recent examples include the synthesis of the mating hormone of *Phythophthera infestans*, which was hampered by the same problem,[9] whereas in the course of an absolute configuration determination, Hayashi et al. observed a small amount of racemization upon the hydrogenation of a terminal alkyn.[10]

One of the few alternatives to transition metal catalyzed hydrogenation for the reduction of carbon−carbon double bonds is the use of diimide (diazene, HN═NH), generated from hydrazine hydrate or its derivatives. With diimide, nonpolarized double bonds are reduced via a cycloaddition mechanism and therefore hydrogenolysis, reduction of polarized bonds, or isomerization do not take place.[11]

Diimide itself is unstable and a large number of methods for its in situ generation have been reported. The most well-known among these methods are the generation of diimide from a large excess of hydrazine hydrate with oxygen, generally in the presence of Cu(II) and/or a carboxylic acid, the oxidation of

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(2) *Handbook of Homogeneous Hydrogenation*; de Vries J. G., Elsevier, C. J., Eds.; Wiley-VCH: New York, 2007.

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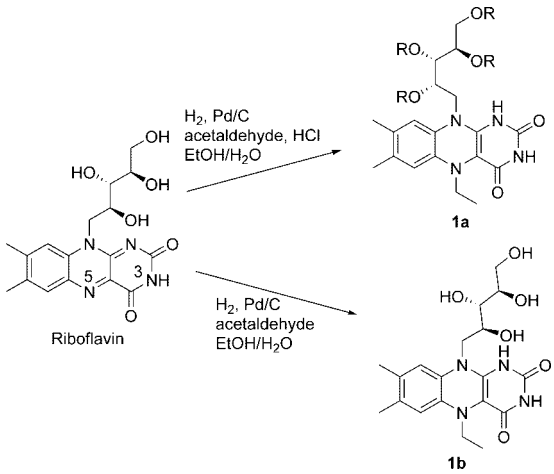
10.1021/jo801588d CCC: $40.75
Published on Web 11/01/2008

SCHEME 1. Synthesis of 5-Ethylriboflavin

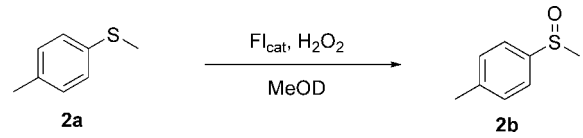


hydrazine hydrate with periodate, and the protolytic decarboxylation of azodicarboxylate. More modern approaches use the base-induced elimination of substituted hydrazines[12] and the copper-catalyzed oxidation of anhydrous hydrazine.[13] For all these approaches it holds that in general a (large) excess of the reagent is needed and although excellent yields are occasionally reported, disappointing yields are commonly observed together with the recovery of starting material.

Recently, Imada et al. reported the generation of diimide from hydrazine hydrate and oxygen using flavin-type compounds as catalysts.[14] Remarkably, a large excess of hydrazine hydrate was not needed. Because the synthesis of the reported catalyst required several steps and the reactions were carried out under an oxygen atmosphere instead of air, we aimed in our studies to develop a readily prepared flavine catalyst that would efficiently generate diimide from hydrazine hydrate and air. This catalyst system should efficiently reduce carbon−carbon double bonds in high yields and also be applicable in solid phase organic synthesis, an area in which double bond reduction is particularly difficult.

Flavine-based catalysts are invariably inspired by naturally occurring riboflavine (vitamine B_2, Scheme 1) and Flavine Adenine Dinucleotide (FAD). To enhance the catalytic cycle of flavines, N^5 is alkylated to facilitate the elimination of water.[15] Bruice et al.[16] reported reductive alkylation with $NaCNBH_3$ and aldehydes under aerobic conditions as a general method for the synthesis of N^5-alkylflavins. As flavins are more stable in their reduced state, this approach has been replaced by the use of H_2 and Pd/C for the reductive alkylation under acidic conditions. A review detailing different flavin catalysts and the reactions they catalyze appeared recently.[17] In the catalysts derived from riboflavin by Imada et al., the ribose chain was first protected, followed by methylation of N^3 and subsequent reductive alkylation.[18]

SCHEME 2. Oxidation of Methyl *p*-Tolylsulfide with Flavin Catalyst 1a[a]



[a] Conditions: 600 μL of methanod_4, 1.58 mg of **1a**, 30 μL of methyl-*p*-tolylsulfide, 40 μL of H_2O_2 (30% in H_2O), full conversion within 1 h.

To the best of our knowledge, direct reductive alkylation of riboflavine has not been reported. Herein we report the one-pot synthesis of an active oxidation catalyst from commercially available riboflavin (Scheme 1). Application of this low-cost catalyst for the efficient reduction of carbon−carbon double bonds with hydrazine hydrate and air is described.

Riboflavin was treated with excess acetaldehyde and H_2, Pd/C in acidic aqueous ethanol. It was noticed that progress of the reaction could be followed by UV analysis (see the Experimental Section). After filtration of the reaction mixture over celite and evaporation of the volatiles, catalyst **1a** was obtained in excellent yield. Although ^{1}H NMR gave no indicative spectra,[19] analysis on LC-MS showed the expected mass of monoethylated riboflavin. The mass spectra, however, also indicated the presence of compounds with higher masses correlating with acetal formation in the ribose chain, together with dimer and trimer formation. Ethylation on N^3 could be excluded by comparing the UV spectra of independently prepared N^3-methylated riboflavin with the product. The UV spectrum also correlated well with that of similar ethylated flavins described by Bruice et al.[16]

The catalyst obtained was studied in the oxidation reaction of methyl *p*-tolyl sulfide, showing activity comparable to that of alkylated flavins prepared by Bäckvall et al.[20] (Scheme 2) The fact that **1a** shows excellent activity in sulfoxidation reactions with hydrogen peroxide clearly indicates alkylation at N^5, since only alkylation at this position will produce active catalysts.[21]

To obtain a single product in the reductive alkylation reaction and suppress acetal formation, the reductive alkylation was carried out without acid present in the reaction mixture. The reaction proceeded considerably slower, but the desired product was again obtained in decent yield and this time without acetal formation as shown by LC-MS and NMR. UV confirmed the N^5-alkylated product. As the activity of both **1a** and **1b** was similar, catalyst **1a**, which was prepared more rapidly, was used in the subsequent studies. It is worth mentioning that multigram amounts of **1a** could be stored as a dry powder under nitrogen atmosphere at −18 °C for several months without losing catalytic activity.

The activity of **1a** as a catalyst in the conversion of hydrazine hydrate to diimide with O_2 (air) was investigated by following the reduction of cyclooctene. Initially, a solvent investigation was carried out (Table 1).

Cyclooctene is reduced most efficiently in polar solvents. The low reactivity in apolar solvents is probably due to low solubility

(12) *o*-Nitrophenylsulfonylhydrazide (2-nitrobenzenesulfonhydrazide, NBSH) has been introduced as an easy to handle diimide precursor, see: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771–1774.

(13) Anhydrous hydrazine is not easily prepared, however, and in general not commercially available.

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(15) In the case of flavin as a cofactor, the enzyme normally facilitates this step.

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

(19) The signal of the N^5 ethyl group appears in the same region as the signal from the ribose chain. Peak broadening as a result of radical species present, however, blurs these NMR data. See: Bruice, T. C.; Yano, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5263–5271.

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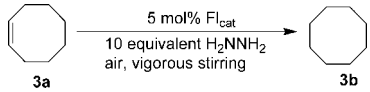
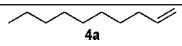
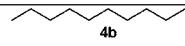
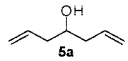
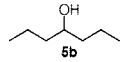
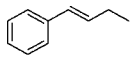
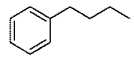
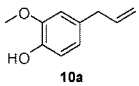
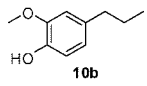
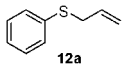
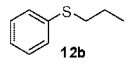
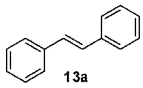
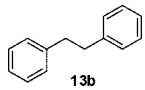
TABLE 1. Solvent Dependency on Cyclooctene Reduction Using 1a and Hydrazine Hydrate in Air[a]



solvent	conversion
DMSO	100
THF	24
2-propanol	95
2,2,2-trifluoroethanol	100
n-heptane	4
methanol	49
ethanol	100
toluene	12
hydrazine hydrate	100

[a] Reaction conditions: 0.5 mmol of substrate, 3.5 mL of solvent, 0.5 mL of hydrazine hydrate, 10 mg (5 mol%) of catalyst, vigorous stirring in air for 4 h.

TABLE 2. Reduction of Terminal and Internal Carbon−carbon Double Bonds[a]

entry	substrate	product	conversion (isolated yield)
1	 4a	 4b	*quant.*
2	 5a	 5b	*quant.*
3	 6a	 6b	*quant.*
4	 3a	 3b	*quant.*
5	 7a	 7b	*quant.*
6	 8a	 8b	*quant.*
7	 9a	 9b	*quant (99)*[b]
8	 10a	 10b	*quant.(78)*[b]
9	 11a	 11b	*quant.(73)*[b]
10	 12a	 12b	*quant.(99)*[b]
11	 13a	 13b	*no conversion*

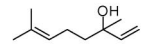
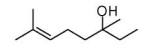
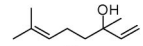
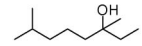
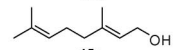
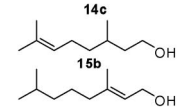
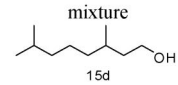
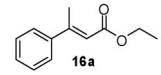
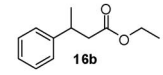
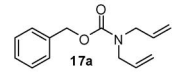
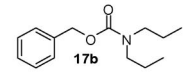
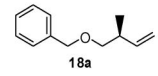
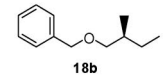
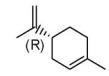
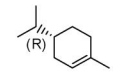
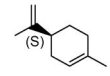
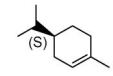
[a] Reaction conditions: 0.5 mmol of substrate, 3.5 mL of EtOH, 0.5 mL of hydrazine hydrate, 10 mg (5 mol %) of catalyst, vigorous stirring in air for 4 h. [b] Reactions performed with 5 mmol of substrate, 20 mL of EtOH, 5 mL of hydrazine hydrate, 100 mg of catalyst.

of the catalyst whereas the lower conversion in methanol remained unexplained. Ethanol was chosen as the optimal and most practical solvent. Vigorous stirring was necessary, probably to facilitate the uptake of O_2 in the solvent.

The reduction of a variety of substrates was investigated by using the flavin/hydrazine hydrate system in ethanol (Table 2).

As expected, the reduction of terminal and strained alkenes is fast with full conversion reached within 4 h. With additional

TABLE 3. Reduction of Carbon−carbon Bonds in Selected Substrates[a]

entry	substrate	product	conversion (isolated yield) 4h	20h
1	 14a	 14b	90	-
	 14a	 14c	5	30
2	 15a	 15b 15c mixture	11	42
		 15d	0	11
3	 16a	 16b	5	n.d.-
4	 17a	 17b	quant. (99)[b]	
5	 18a	 18b	quant. (99)	
6	 19a	 19b	quant. (72)[b]	
7	 20a	 20b	quant. (89)[b]	
8[c]	21a	21b	quant. (90)	

[a] Conditions: 0.5 mmol of substrate, 3.5 mL of EtOH, 0.5 mL of hydrazine hydrate, 10 mg (5 mol %) of catalyst, vigorous stirring for 4 h. [b] Reactions performed with 5 mmol of substrate, 20 mL of EtOH, 5 mL of hydrazine hydrate, 100 mg of catalyst. [c] Reaction performed under an oxygen atmosphere for 24 h.

substituents on the double bond, the reduction proceeded slower. Entry 5 showed fast reduction of the alkyn to the exocyclic alkane. The intermediate alkene was not observed whereas the internal trisubstituted double bond is not reduced. In entries 8, 9, and 10, a number of functional groups are present which did not affect the reduction. In the presence of a ketone or imine, however, as expected, hydrazone formation took place. Stilbene turned out to be unreactive. Next, a number of more challenging alkenes were studied (Table 3).

Entries 1, 2, and 3 clearly show that the reduction of terminal double bonds proceeds considerably faster than the reduction of internal triple-substituted double bonds. Tetra-substituted double bonds were not reduced at all.

To illustrate the versatility of the present catalyst system in cases where transition metal-catalyzed reduction is problematic, we selected a number of challenging substrates in this respect. Entries 4 and 5 show compounds with hydrogenolysis sensitive CBz and benzyl groups, respectively. With use of **1a** and hydrazine hydrate, quantitative conversion into the desired products took place without hydrogenolysis. In entries 5−7, the

double bond is situated next to a chiral center. **1a**/hydrazine reduction afforded the desired products in quantitative conversions and, as expected, without racemization as determined by chiral GC.

In solid-phase organic synthesis, reduction of double bonds is especially challenging as heterogeneous catalysts are ineffective due to transfer limitations whereas homogeneous catalysts appear to be slow and are quickly deactivated. Building on earlier work,[21] it has been shown recently by Buszec and Brown that the reduction of carbon−carbon double bonds in solid phase synthesis can be performed by using diimide generated from *o*-nitrophenylsulfonylhydrazide.[12,22] Entry 8 illustrates that diimide reduction with **1a** takes place readily, although slower compared to solution phase reduction, and does not cleave the resin-coupled substrate. Apparently, even in ethanol as the solvent in which the polystyrene resin swells badly, the reaction still takes place due to the ease with which diimide penetrates the resin and reaches the double bond. This phenomenon has also been observed in the hydrogenation of polybutadiene-based rubbers in latex form with diimide by Wideman.[23]

In conclusion, 5-ethylriboflavine **1a** is an efficient catalyst for the diimide reduction of carbon−carbon double bonds. The catalyst is prepared in one step on multigram scale from readily available riboflavin (Vitamin B_2) in excellent yield. Reductions are carried out in air and at room temperature. As this catalyst system affords high yields for terminal and disubstituted alkenes and does not give double bond isomerization, it is a valuable alternative when metal-catalyzed hydrogenations are problematic.

Experimental Section

Caution: Hydrazine is a cancer suspect agent.

5-Ethylriboflavin (1a). To a round-bottomed flask charged with 100 mL of degassed ethanol/water (5:4) was added 1.12 g of riboflavin (3.0 mmol) and 200 mg of 10% Pd/C. Subsequently, hydrogen atmosphere was applied, and after 5 min, 5.6 mL of acetaldehyde (100 mmol) and 5 mL of concentrated hydrochloric acid were added and the resulting suspension was stirred for 48 h. To follow the progress of the reaction, 50-μL samples were taken from the reaction mixture and directly subjected to UV analysis in 1 mL of H_2O followed by UV analysis after addition of 50 μL of 6 N HCl. Completion of the reaction was indicated by the complete disappearance of the signal (shoulder) in the UV spectrum at 441 nm and full dissolution of the starting material in the reaction mixture. The reaction mixture was filtered over celite in a double Schlenk flask and the residue was washed with degassed ethanol. All volatiles were removed in vacuo to leave 1.29 g of the product **1a** as a pale yellow air sensitive powder. The product was kept in a reduced state by storage under a nitrogen atmosphere at −18 °C or alternatively by adding a small amount of Na_2SO_3. Upon air oxidation, **1a** turned red, but was still active as a catalyst. Using the same conditions, this reaction was performed on 10 g scale with comparable results. (HR)MS data indicate acetal bridged dimers ESI (*m*/*z*) [M^+] calcd for $C_{19}H_{25}O_6N_4$ 405.17796, found 405.17802; ESI (*m*/*z*) [M^+] calcd for $C_{21}H_{27}O_6N_4$ 431.19361, found 431.19361; and ESI (*m*/*z*) [M − H] calcd for $C_{40}H_{52}O_{12}N_8^-$ 837.3738, found 837.38037. UV spectra of **1a** are similar to those of **1b**.

5-Ethylriboflavin (1b). The same procedure was followed omitting the HCl and after a week the reaction was interrupted, the remaining starting material was removed by filtration, and the product was isolated in 60% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97 (br d, 3H,), 2.05 (br s, 6H), 2.48 (DMSO) 3.08 (br s, 1H), 3.31 (H_2O), 3.31−3.69 (br m, 8H), 4.10 (br s, 1H), 4.54 (br s, 1H), 4.93 (br s, 1H), 5.10 (br s, 1H), 6.26 (br s, 1H), 6.53 (br s, 1H), 6.73 (br s, 1H), 10.32 (br s, 1H), 10.59 (br s, 1H). Mass spectrum (flow injection analysis on LC-MS, ESI (−)) *m*/*z* 405. HRMS ESI (*m*/*z*) [M^+] calcd for $C_{19}H_{25}O_6N_4$ 405.17796, found 405.17802. UV 345 p, 378 sh, 508 p, 584 p. See the Supporting Information.

Procedure for Olefin Reduction. To 0.5 mmol of substrate dissolved in 3.0 mL of ethanol was added 10 mg of **1a** (24 μmol, 5 mol %) dissolved in 0.5 mL of ethanol. A 0.5 mL sample of hydrazine hydrate (10 mmol) was added and the reaction was stirred vigorously. Samples (50 μL) were taken, filtered over a small $MgSO_4$ plug with EtOH as the eluent, and subjected to GC and or GC-MS measurements. The product could be obtained by extracting four times with 5 mL of pentane, followed by washing of the combined organic fractions with brine. Evaporation of the solvent under reduced pressure yielded the product.

Acknowledgment. T. D. Tiemersma-Wegman is acknowledged for assistance with GC, HPLC, and LC-MS. A. W. van Zijl is acknowledged for the generous donation of substrates. We thank NRSC-Catalysis for financial support.

Supporting Information Available: Full experimental details, spectral data, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801588D

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