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Communication

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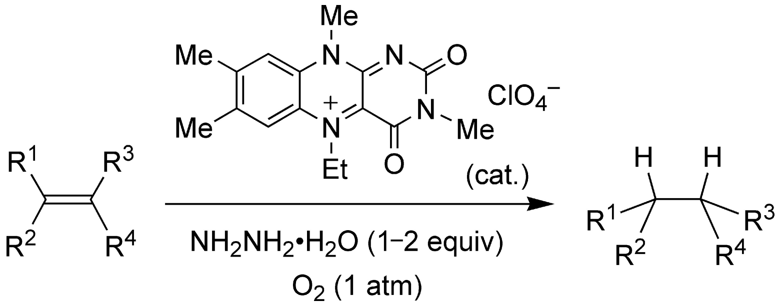

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COMMUNICATIONS

Flavin-Catalyzed Generation of Diimide: An Environmentally Friendly Method for the Aerobic Hydrogenation of Olefins

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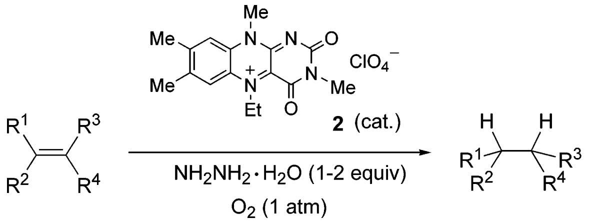
The development of new processes for catalytic hydrogenation has become an important area of research, with the potential to provide environmentally benign processes as alternatives to the established technologies based on hydrogen gas (eq 1).[1] Considerable effort has been devoted to the investigation of alternative hydrogenation methods which use organic hydrogen donors (DH_2) with transition metal[2] or organic catalysts[3] (eq 2). However, despite their safe and convenient procedures, these methods are always accompanied by the production of stoichiometric amounts of organic waste (D). It is this dilemma that has prompted us to develop new methodologies employing the fusion of flavin[4] and diimide[5] chemistries. In this communication, we describe the first green and practical method for "aerobic hydrogenation". The method is performed using an organocatalyst under O_2 atmosphere and produces environmentally benign water and molecular nitrogen as the only waste products (eq 3).

$$\mathrm{S} + \mathrm{H_2} \xrightarrow[\text{M cat.}]{} \mathrm{SH_2} \qquad (1)$$

$$\mathrm{S} + \mathrm{DH_2} \xrightarrow[\text{M cat. or org. cat.}]{} \mathrm{SH_2} + \mathrm{D} \qquad (2)$$

$$\mathrm{S} + 1/2\ \mathrm{O_2} + \mathrm{NH_2NH_2} \xrightarrow[\text{org. cat.}]{} \mathrm{SH_2} + \mathrm{H_2O} + \mathrm{N_2} \qquad (3)$$

Diimide, NH═NH, acts as a mild reducing agent for a variety of symmetrical unsaturated bonds.[5] This reduction process has the potential to be environmentally benign since nitrogen gas is the sole waste product. However, the strong reducing properties of the diimide reagent result in a rapid disproportionation reaction, which produces molecular nitrogen and hydrazine; therefore, the reagent must be generated in situ.[6] As a result of this, an excess of the diimide precursor is generally required to produce a complete reaction.[5] The catalytic aerobic oxidation of hydrazine, which would be the ideal method for generating diimide,[7] also remains problematic from the point of view of green chemistry since a great excess of hydrazine (10 to >400 equiv) is required to achieve this.[8] Our strategy for the generation of diimide involves the novel application of a flavin redox system, which has previously been used for the catalytic aerobic oxidation of organic substrates.[4] The diimide generated by this system is highly protected from the inevitable disproportionation reaction. The method thus provides an organocatalytic method for the hydrogenation of olefins that requires only 1 equiv of hydrazine and 1 atm of molecular oxygen (eq 4). This reaction provides an alternative, highly efficient, safe, facile, and economic strategy for the catalytic hydrogenation of olefins.



(4)

A typical procedure for aerobic hydrogenation is exemplified by the reduction of 1-decene (**1**). A mixture of **1** (140 mg, 1.0 mmol), 5-ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate (**2**, $FlEt^+{\cdot}ClO_4^-$, 4.0 mg, 0.01 mmol), and $NH_2NH_2{\cdot}H_2O$ (60.1 mg, 1.2 mmol) in CH_3CN (4.0 mL) was stirred at 25 °C for 4 h under oxygen atmosphere (1 atm, O_2 balloon). After extraction with pentane (10 mL × 3), the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to afford decane (142 mg, 99%) as a colorless oil. The catalytic activities of a series of functionalized isoalloxazinium perchlorates were examined for the aerobic hydrogenation of decenes. $FlEt^+{\cdot}ClO_4^-$ ($E^{\circ\prime} = 306, -389$ mV) showed the best catalytic activity among those examined. Moderate yields of products were obtained with the 5-ethyl-7,8,10-trimethyl ($E^{\circ\prime} = 316, -323$ mV) and 5-ethyl-3-methyl-10-phenyl ($E^{\circ\prime} = 427, -274$ mV) derivatives; however, electropositive flavins bearing 7-cyano-5-ethyl-3,10-dimethyl functionalities ($E^{\circ\prime} = 512, -177$ mV) and bulky flavins, such as $DMRFlEt^+{\cdot}ClO_4^-$ ($E^{\circ\prime} = 322, -364$ mV),[4b] gave unsatisfactory results. CH_3CN was found to be the best solvent; however, other polar solvents, such as DMSO and DMF, can also be used for the reaction. The specific ability of flavin catalysts to limit the deactivation of hydrazine was demonstrated by the reaction of 9-decen-1-ol with 1.0 equiv of hydrazine under standard conditions (1 mol % of catalyst). After completion of the reduction, only 13 mol % of hydrazine was converted to molecular nitrogen using catalyst **2**, whereas when using $CuSO_4$ as catalyst (1 mol %), almost half the hydrazine (46 mol %) was deactivated.

Table 1 shows representative results for the $FlEt^+{\cdot}ClO_4^-$-catalyzed aerobic hydrogenation of olefins. A variety of linear and cyclic olefins (entries 1−6) can be converted to the corresponding hydrogenated products quantitatively, at room temperature and under O_2 atmosphere (1 atm). In contrast to the conventional method,[8] the use of 1−2 equiv of hydrazine is sufficient to complete the reactions. It is noteworthy that the selective *cis*-1,2-deuteration of olefins[7b] can be achieved to complete conversion with little over 1 equiv of deuterium source (entry 3). Reactive substituents, such as tertiary amino, sulfoxy, and hydroxy groups, are tolerated by the reaction (entries 2, 4, 5, 6, and 7). Exomethylenes are selectively reduced in the presence of other substituted olefins (entry 6). α,*β*-Unsaturated esters and amides also undergo smooth hydrogenation under similar conditions (entries 7 and 8). Because the substrates are completely consumed and the only chemical wastes are nitrogen gas and water, all of the products can be readily isolated by simple extraction.

A plausible mechanism for the catalytic aerobic hydrogenation is shown in Scheme 1, with reduction, O_2 incorporation, and oxygen transfer to the flavin catalyst acting as crucial steps in the reaction.[4] To explain the hydrazine efficiency, a mechanism proceeding via the direct reduction of the olefin with the flavin/diimide complex is proposed. Thus, a flavinium cation $FlEt^+$ **2** is reduced with hydrazine to afford the reduced flavin/diimide complex **3**; this

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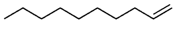
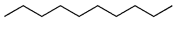
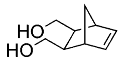
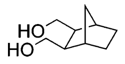
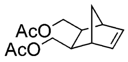
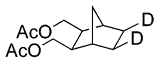
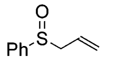
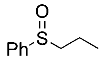
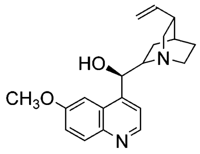
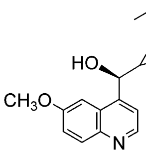
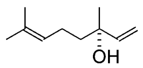
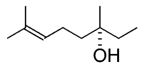
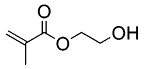
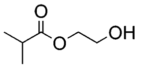
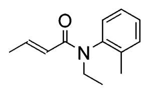
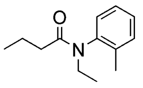
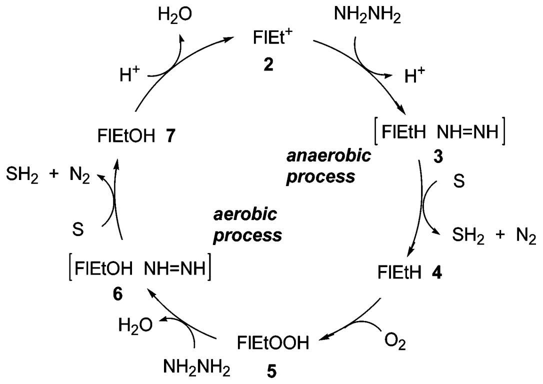
Table 1. Flavin-Catalyzed Aerobic Hydrogenation of Olefins[a]

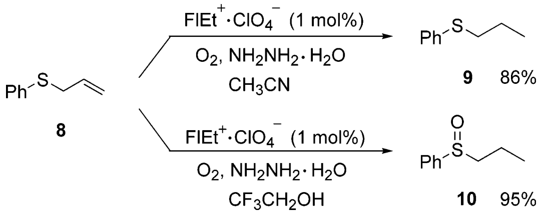
entry	substrate	product	hydrazine (eq)	time (h)	yield (%)
1			1.2	4	99
2			1.2	5	96
3			1.2[b]	8	93
4			2	6	92
5			2[c,d]	8	97
6			2	5	96
7			2[c]	5	90
8			2[c]	5	98

[a] The reaction was carried out as described in text. [b] $ND_2ND{\cdot}D_2O$ was used. [c] At 50 °C. [d] Using DMSO as a solvent.

complex then hydrogenates olefins faster than it liberates diimide. The presence of this anaerobic process has been confirmed by the reaction of 9-decen-1-ol with $FlEt^+{\cdot}ClO_4^-$ (0.2 equiv) under argon atmosphere, in which stoichiometric amounts of 1-decanol (19%) and FlEtH[9] were obtained after the reaction. Liberated FlEtH **4** incorporates O_2 to afford 4a-hydrodioxyflavin FlEtOOH **5**.[10] Oxygen transfer and subsequent dehydration provide FlEtOH/diimide complex **6**, which reduces a further olefin. Dehydration of FlEtOH **7** regenerates **2** to complete the catalytic cycle.[11] Thus, 2 molar equiv of product is formed by 1 mol of O_2 via the anaerobic and aerobic oxidation of hydrazine, as depicted in eq 3. This stoichiometry was confirmed experimentally, with 0.33 mmol of O_2 being consumed in the hydrogenation of 0.7 mmol of 9-decen-1-ol under standard conditions, a result that is consistent with the mechanism of Scheme 1.

Scheme 1. Proposed Catalytic Cycle





(5)

(6)

Another important feature of the flavin-catalyzed reaction is the unprecedented switching control possible in the oxygenation of heteroatoms. Typically, the treatment of phenyl allyl sulfide (**8**) under standard conditions in CH_3CN gives rise to the selective formation of phenyl *n*-propyl sulfide (**9**) with toleration of the thio functionality (eq 5). However, similar treatment in acidic CF_3CH_2OH affords phenyl *n*-propyl sulfoxide (**10**) as the sole product (eq 6). The selective formation of **9** in aprotic solvents can be ascribed to the faster electrophilic oxygenation of hydrazine with **5**, due to the α-effect of hydrazine.[12] The drastic change in product selectivity arises due to the deactivation of the nucleophilic hydrazine by the acidic media, which results in preferential S-oxygenation[4a] in the aerobic step of the catalytic cycle. This is a rare case of catalytic reductions proceeding simultaneously with oxygenation processes. Efforts are currently underway to investigate the full scope of the reaction.

Supporting Information Available: Experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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