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COMMUNICATION

Guanidine catalyzed aerobic reduction: a selective aerobic hydrogenation of olefins using aqueous hydrazine†

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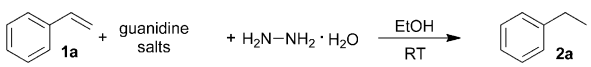
An efficient aerobic reduction of olefins, internal as well as terminal, is developed using guanidine as an organocatalyst. A remarkable chemoselectivity in reduction has been demonstrated in the presence of a variety of functional groups and protective groups and a selective reduction of a terminal olefin in the presence of an internal olefin is revealed.

Reduction of olefins is one of the fundamental transformations in organic chemistry, usually accomplished using transition metal catalysts such as Pd, Pt, Rh, Ni, *etc.*[1] Although transition metal catalyzed reductions are facile and efficient, there are concerns regarding the selective reduction of double bonds in the presence of sensitive functional groups and protecting groups.[2,3] Hence, there has been a continued effort to find alternate reduction methods, particularly metal-free reactions, which are important in manufacturing pharmaceutically active compounds and their intermediates.[4] Efforts in this direction have resulted in reexamining the utility of simple molecules such as diimide, which is a useful mild reducing agent for C–C multiple bonds.[5] Generally, diimide is obtained by reacting a large excess of hydrazine (10–400 equiv.) with metal catalysts such as copper(II) salts.[6,7] Attempts to use organocatalysts to generate diimide have resulted in the use of flavin derived catalysts under aerobic conditions, as reported by Imada *et al.*,[8a] which has been quickly adopted by several groups using several engineered flavins for the reduction reaction.[8] Flavins are organic redox systems and are based on a simple model of enzymes such as oxidases and monooxygenases,[9] both of which have been well exploited in organic synthesis as organocatalysts for aerobic oxidations as well as catalytic reductions.[9] Although neutral flavins serve as good catalysts for reduction, they are either expensive or long reaction sequences are required to synthesize them.[8d,h] Even though vitamin B_2 (riboflavin) is inexpensive, it is not effective as a catalyst for the reduction and exhibits lower activity which was attributed to its poor solubility in organic solvents.[8d] Therefore, it is important to find an easily available and inexpensive alternative catalyst for flavin derivatives to perform reduction using hydrazine. In this search we realized that guanidine could be a suitable molecule.[10,11] The guanidine moiety is found in several biologically active natural products and is a familiar organic reagent as a super base as well as an organocatalyst.[10] In continuation of our quest to investigate the effective utility of aq. hydrazine[12] herein we present our recent studies on the reduction of a variety of olefins using aq. hydrazine (2 equiv.) in the presence of a catalytic amount of guanidine.

The screening studies for this reduction were carried out using styrene as a model substrate with guanidine salts, such as guanidine carbonate, guanidine hydrochloride and guanidine nitrate. As seen from Table 1, the reduction of styrene (**1a**) with 4 equiv. of aq. hydrazine required 24 h to furnish ethyl benzene (**2a**) in 75% yield. Decreasing the amount of hydrazine to 2 equiv. and performing the reaction either in air or oxygen resulted in the formation of reduced product **2a** in 25% and 52% yield respectively (entries 2 and 3). However, a similar reaction of styrene in the presence of oxygen and 4 equiv. of aq. hydrazine resulted in the formation of ethyl benzene in

Table 1 Optimization studies[a]



Entry	Catalyst (mol%)	Aq. hydrazine (equiv.)	Oxygen/ air/argon	Time (h)	Conversion % (GCMS)
1	None	4	Air	24	75
2	None	2	Air	24	25
3	None	2	O_2	24	52
4	None	4	O_2	24	70
Guanidine carbonate					
5	10	4	O_2	24	99
6	10	2	O_2	24	67
Guanidine hydrochloride					
7	2	2	O_2	21	50
8	5	2	O_2	21	55
9	10	2	O_2	13	94
10	10	3	O_2	15	100
11	10	4	O_2	8	100
12	10	4	Air	20	100
Guanidine nitrate					
13	5	2	O_2	14	40
14	10	1	O_2	14	12
15	10	1.5	O_2	14	35
16	10	2	O_2	14	99
17	10	2	Argon	24	5

[a] Reaction conditions: olefin (1 mmol), aq. hydrazine (2 mmol), catalyst, O_2 (1 atm), EtOH (2 mL), RT.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra for all products. See DOI: 10.1039/c2cc32611f

Table 2 Reduction of multiple bonds[a]

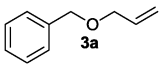
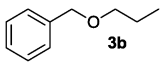
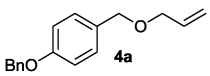
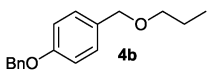
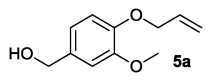
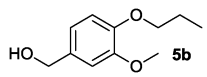
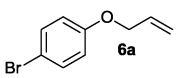
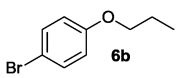
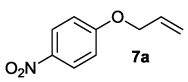
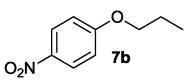
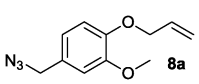
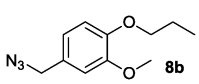
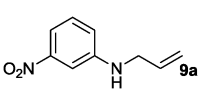
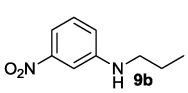
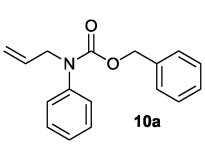
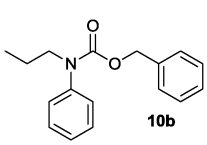
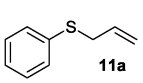
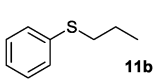
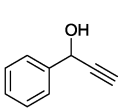
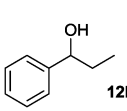
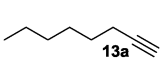
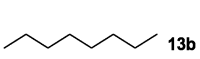
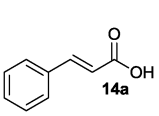
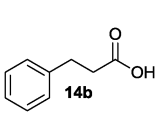
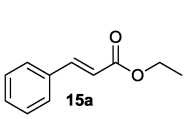
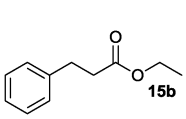
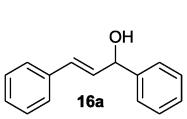
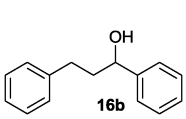
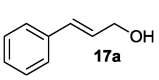
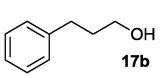
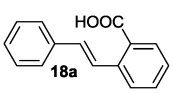
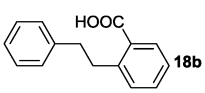
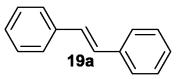
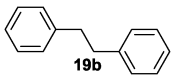
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **2a**	 **2b**	17	99[c]
2	 **3a**	 **3b**	24	90
3	 **4a**	 **4b**	24	92
4	 **5a**	 **5b**	24	85
5	 **6a**	 **6b**	24	91
6	 **7a**	 **7b**	30	90[d]
7	 **8a**	 **8b**	24	85
8	 **9a**	 **9b**	12	92[d]
9	 **10a**	 **10b**	24	99[d]
10	 **11a**	 **11b**	24	94
11	 **12a**	 **12b**	24	80[e]
12	 **13a**	 **13b**	24	99[c,e]
13	 **14a**	 **14b**	24	97
14	 **15a**	 **15b**	24	55
15	 **16a**	 **16b**	24	90[d]
16	 **17a**	 **17b**	24	90[d]
17	 **18a**	 **18b**	16	95[d]

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[b] (%)
18	 **19a**	 **19b**	24	98[f]

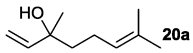
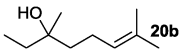
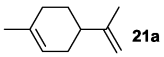
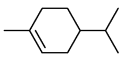
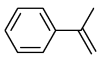
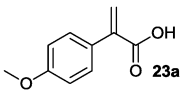
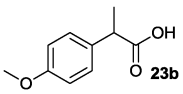
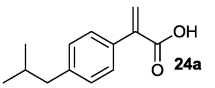
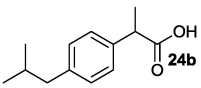
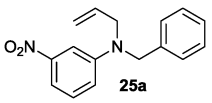
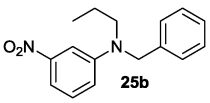
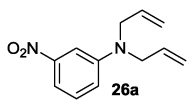
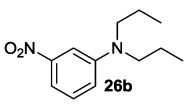
[a] Reaction conditions: olefin (1 mmol), aq. hydrazine (2 mmol), guanidine nitrate (0.1 mmol), O_2 (1 atm), EtOH (2 mL), RT. [b] Isolated yield. [c] GCMS conversion. [d] 2 equiv. of aq. hydrazine at 80 °C. [e] 4 equiv. of aq. hydrazine at RT. [f] 4 equiv. of aq. hydrazine at 80 °C.

70% yield (entry 4, Table 1). On the other hand, the same reaction in oxygen (1 atm), with 4 equiv. of aq. hydrazine in the presence of 10 mol% of guanidine carbonate resulted in the formation of reduced product **2a** in almost quantitative yield (24 h, entry 5). Whereas the same reaction with 2 equiv. of aq. hydrazine gave ethyl benzene in 67% yield (24 h, entry 6). Further studies indicated that with aq. hydrazine (2–4 equiv.), guanidine hydrochloride (10 mol%) in oxygen is a better catalyst than guanidine carbonate (entries 7–12, Table 1). As seen in Table 1, guanidine nitrate turned out to be a good choice of catalyst for the reduction of styrene (entries 13–16). Hence, the reduction of styrene at room temperature can be efficiently performed by using 10 mol% of guanidine nitrate, 2 equiv. of aqueous hydrazine in an oxygen atmosphere (14 h, 99%, entry 16). It was also noted that in the absence of air or oxygen the reaction was not successful (entry 17, Table 1).

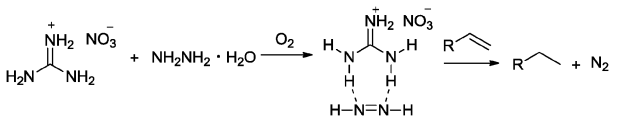
The scope and limitation of the reduction were studied and the results are compiled in Table 2. As can be seen, cyclooctene (**2a**) under the reaction conditions furnished cyclooctane (**2b**) in almost quantitative yield (entry 1, Table 2). Several *O*-allyl, *S*-allyl and *N*-allyl-substituted aromatic and aliphatic precursors (**3a–11a**) underwent smooth reduction to afford the reduced product in excellent yields (entries 2–10, Table 2). Reducible functional groups such as nitro, azido, bromo (**7a–9a**, entries 6–8) and protective groups like benzyloxy and Cbz groups (**4a** and **10a**, entries 3 and 9) were well tolerated under the reaction conditions. Terminal acetylene groups were reduced completely by employing 4 equiv. of aq. hydrazine (**12a** and **13a** entries 11 and 12). After successful reduction of terminal olefins, we turned our attention to reduction of internal olefins. Under the optimal reduction conditions, cinnamic acid (**14a**) furnished the corresponding acid **14b** in excellent yield (entry 13). Whereas, ethyl cinnamate (**15a**) afforded a moderate yield of the reduced product **15b** (entry 14). As expected the reduction of internal double bonds required heating conditions to afford the completely reduced product. Therefore, cinnamyl alcohol (**16a**), (*E*)-1,3-diphenylprop-2-en-1-ol (**17a**) and (*E*)-2-styrylbenzoic acid (**18a**) required 80 °C to afford the corresponding reduced products **16b**, **17b**, and **18b**, respectively, in excellent yields (entries 15–17). However, *trans*-stilbene (**19a**) required 4 equiv. of aq. hydrazine to undergo reduction to afford 1,2-diphenylethane (**19b**, entry 18, Table 2).

Our attempts to reduce terminal olefins selectively in the presence of internal olefins are illustrated in entries 1 and 2 of Table 3. As can be seen, linalool (**20a**) under the conditions reacted smoothly to afford 3,7-dimethyloct-1-en-3-ol (**20b**, 90%, entry 1), in which the terminal double bond was reduced in the

Table 3 Selective reduction of terminal double bonds[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **20a**	 **20b**	12	90
2	 **21a**	 **21b**	24	83[c,d]
3	 **22a**	 **22b**	24	99[g]
4	 **23a**	 **23b**	24	98[e]
5	 **24a**	 **24b**	24	80[e]
6	 **25a**	 **25b**	24	94[f]
7	 **26a**	 **26b**	14	98[g]

[a] Reaction conditions: olefin (1 mmol), aq. hydrazine (2 mmol), guanidine nitrate (0.1 mmol), O_2 (1 atm), EtOH (2 mL), RT. [b] Isolated yield. [c] GCMS conversion. [d] 4 equiv. of aq. hydrazine at 80 °C. [e] 2 equiv. of aq. hydrazine at 80 °C. [f] 4 equiv. of aq. hydrazine at RT. [g] 8 equiv. of aq. hydrazine at RT.



Scheme 1 A tentative mechanism.

presence of an internal double bond. A similar result was obtained in the reduction of limonene (**21a**), the terminal double bond was reduced, whereas the internal double bond was intact during the reaction (entry 2, Table 3). However, this reaction was carried out at 80 °C with 4 equiv. of aq. hydrazine. Similarly, the reduction of α-methyl styrene (**22a**) required heating of the reaction mixture at 80 °C with 4 equiv. of aq. hydrazine (99%, entry 3). The application of this strategy is demonstrated in reducing aryl acrylic acid to afford aryl propionic acids. As seen in examples in entries 4 and 5, 2-(4-methoxyphenyl)acrylic acid (**23a**) and 2-(4-isobutylphenyl)acrylic acid (**24a**) underwent a smooth reduction to furnish their saturated acids **23b** and **24b** in good to excellent yields (entries 4 and 5). To ensure the versatility of the reduction, *N*-allyl-*N*-benzyl-3-nitroaniline (**25a**) and *N*,*N*-diallyl-3-nitroaniline (**26a**) were subjected to the reduction and it was found that the reduction proceeded well but needed larger amounts of aq. hydrazine to afford the reduced products **25b** and **26b** respectively (entries 6 and 7, Table 3).

Regarding the reaction mechanism, we belive that the hydrogen bonding capability of guanidine[8e] is responsible for the catalytic reduction (Scheme 1).

In summary, we have shown for the first time that guanidine nitrate catalyzed diimide promoted reduction of olefins with a remarkable chemoselectivity.

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Caution! Hydrazine is a suspected carcinogen and should be handled with care in an efficient fume hood.

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