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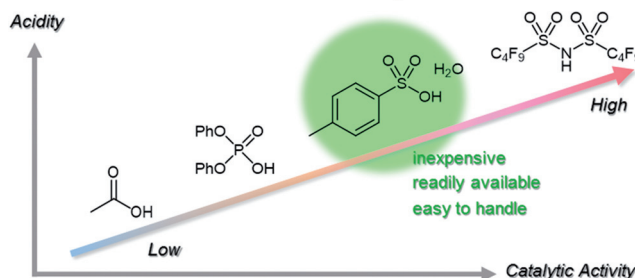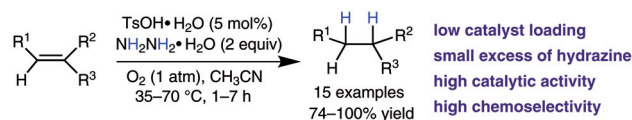
# Brønsted Acid Catalysed Aerobic Reduction of Olefins by Diimide Generated In Situ from Hydrazine

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**Abstract** Aerobic reduction of olefins with hydrazine was proven to be efficiently catalysed by readily available Brønsted acids, such as *p*-toluenesulfonic acid monohydrate, providing hydrogenated products in very good yields and chemoselectivity under mild conditions.

**Key words** Brønsted acid, diimide, reduction, olefins, hydrazine

Generation of diimide from hydrazine and its use as a hydrogen transfer agent in situ, first discovered in 1905[1] and studied in depth in the 1960s,[2] have been recently revisited by chemists to develop advanced olefin reduction technologies that utilise no transition metals or hydrogen to produce hydrogenated products in a chemoselective and stereospecific manner with nontoxic by-products (Scheme 1). The groups of Dong[3] and Balci[4] independently reported that the aerobic reduction of olefins with hydrazine proceeded smoothly under an atmosphere of O$_2$ in ethanol without any additives or catalysts, although large excesses of hydrazine (4–8 equivalents) along with prolonged reaction times (mostly ≥24 h) and/or high reaction temperatures were required to be efficient due to the rapid disproportionation of diimide into hydrazine and N$_2$. Prabhu et al. reported the catalytic activity of guanidine nitrate, which allowed the amounts of hydrazine to be lowered to two equivalents at ambient temperature but this process still required long reaction times (12–24 h) even in the presence of 10 mol% of the catalyst.[5] Leow et al. demonstrated that UVA light irradiation could accelerate the reduction performed at ambient temperature in acetonitrile under air by inducing the *trans* to *cis* isomerization of diimide, in which

reaction times of 18–24 h (even under 1 atm of O$_2$) were often required with 2–3 equivalents of hydrazine.[6] Guin et al. reported that the addition of a stoichiometric amount of arylboronate ester could accelerate reduction such that the reaction was complete within 1.5–8 h at 32 °C in acetonitrile with four equivalents of hydrazine; although stoichiometric amounts of phenol and boric acid were formed.[7] We introduced synthetic flavins as efficient catalysts for the generation of diimide from hydrazine, which provided a convenient and safe process for the aerobic reduction of olefins, requiring as little as one equivalent of hydrazine.[8] However, despite their versatility, expanded by ourselves[8] and others,[9] the *N*5-alkylated flavin derivatives with highest activities are not commercially available and so this methodology has not been generally adopted in the laboratory or in industry. Kappe et al. utilised a gas–liquid continuous-flow system for diimide olefin reduction, which dramatically shortened reaction times to 10–30 min at 100 °C under 20 bar with 4–5 equivalents of hydrazine.[10] Although such flow technologies are a useful and safe way of using highly labile diimide,[10,11] they require special instrumentation that is still not common in research laboratories. As a result, the development of an efficient and readily available methodology for the aerobic reduction of olefins with hydrazine remains desirable.
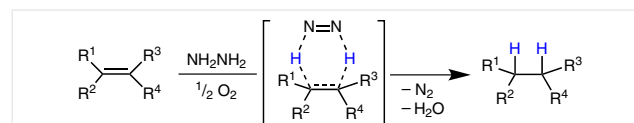


**Scheme 1** Aerobic reduction of olefins with hydrazine

In the course of our research on the aerobic reduction of olefins with hydrazine,[8] we examined an article published by Koch in 1968, in which the catalytic effect of acetic acid
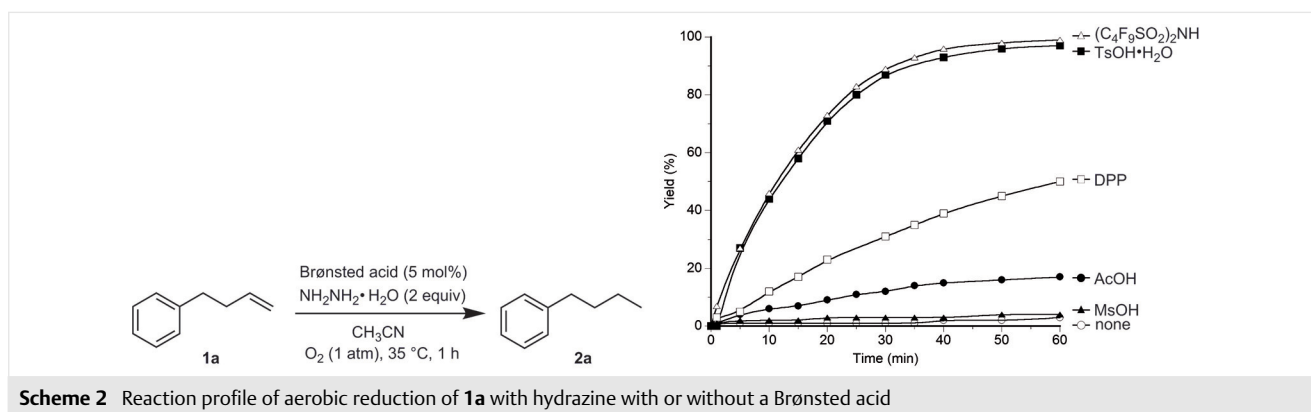
(AcOH) for the aerobic reduction of methyl oleate with hydrazine in aprotic solvents such as acetonitrile and the kinetics of the process were presented.[12] Although the role of AcOH was not fully rationalised in the original report, it was commented later by Pasto and Taylor in a review[2a] that AcOH could catalyse slow equilibration of unreactive *trans*-diimide and reactive *cis*-diimide. Nevertheless, we were quite surprised that no other Brønsted acids have so far been explored as catalysts for the aerobic reduction of olefins with hydrazine.

Within this manuscript, the catalytic activities of a variety of Brønsted acids for the aerobic reduction of olefins with hydrazine are disclosed. We demonstrate that *p*-toluenesulfonic acid monohydrate (TsOH·H$_2$O), one of the most common, inexpensive, and readily available organic acids, is particularly useful as a catalyst in terms of both reaction efficiency and availability, which allows a range of olefins to be reduced with high chemoselectivity under mild conditions.

Initially, several commercially available organic acids having different acidities, AcOH [p$K_a$ = 23.51 (CH$_3$CN),[13a] 4.76 (H$_2$O)[13b]], diphenylphosphate [DPP, p$K_a$ = 1.9 (H$_2$O)[13c]], methanesulfonic acid [MsOH, p$K_a$ = 10.0 (CH$_3$CN)[13d]], toluenesulfonic acid monohydrate [TsOH·H$_2$O, p$K_a$ = 8.6 (CH$_3$CN)[13a], and bis(1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl)imide [(C$_4$F$_9$SO$_2$)$_2$NH, p$K_a$ = 0.0 (CH$_3$CN)[13e]], were explored for the aerobic reduction of 4-phenyl-1-butene (**1a**) to butylbenzene (**2a**). The reactions were carried out with 0.25 mmol of **1a** and 2 equivalents of hydrazine monohydrate (NH$_2$NH$_2$·H$_2$O) under 1 atm of O$_2$ at 35 °C in the presence of 5 mol% of each acid in acetonitrile and the reaction was closely monitored by GC analysis for 60 minutes (Scheme 2). A control experiment showed that the reaction in the absence of any acids could proceed only very slowly to give **2a** in 5% yield after 60 minutes. The catalytic behaviour of AcOH, reported by Koch,[12] was reproduced, resulting in **2a** being obtained in 17% yield after the same reaction time. We anticipated that much stronger acids

should promote the reaction more by rendering the equilibration of *trans*- and *cis*-diimide faster. As expected, DPP showed considerably higher catalytic activity compared with AcOH, giving a yield of 50% in 1 hour. Remarkably, nearly quantitative yields were observed when TsOH·H$_2$O or (C$_4$F$_9$SO$_2$)$_2$NH (even stronger acids than DPP) was used under the same conditions; while MsOH was unexpectedly sluggish. In this case, the reaction mixture became heterogeneous, with formation of a white precipitate that could be a hydrazonium salt of MsOH, rendering the catalyst ineffective. To evaluate the catalytic activity of each Brønsted acid more precisely, the ratios ($k_{obs}/k_0$) of the initial rate of the reaction with acid ($k_{obs}$) and that without acid ($k_0$) were determined to be 20 for AcOH, 70 for DPP, 185 for TsOH·H$_2$O, 4 for MsOH, and 215 for (C$_4$F$_9$SO$_2$)$_2$NH. Although the highest value of $k_{obs}/k_0$ was obtained with (C$_4$F$_9$SO$_2$)$_2$NH, it was not as high as expected from the difference in p$K_a$ values of (C$_4$F$_9$SO$_2$)$_2$NH and TsOH·H$_2$O (see above). In addition, TsOH·H$_2$O is much less expensive than (C$_4$F$_9$SO$_2$)$_2$NH and it is readily available. Thus, we decided to optimise the reaction conditions for the present aerobic reduction catalysed by TsOH·H$_2$O.

A significant decrease in reactivity was observed when 1.1 equivalents of NH$_2$NH$_2$·H$_2$O were employed (Table S1, entries 1–3). Reducing the amount of TsOH·H$_2$O to 2 mol% led to lower efficiency, while increasing it to 10 mol% did not improve the reactivity appreciably (Table S1, entries 4–6). When the reaction was carried out under air, a white precipitate – presumably a hydrazonium salt of TsOH – was observed to form gradually, which could explain why a prolonged reaction time even with 3.5 equivalents of NH$_2$NH$_2$·H$_2$O was required to give **2a** in a reasonable yield under such conditions (Table S1, entry 7). It should be noted that no reaction occurred under a nitrogen atmosphere (Table S1, entry 8). Further optimization of the reaction parameters showed acetonitrile to be the best solvent and 35 °C to be the most suitable reaction temperature for efficient catalysis (Table S1, entries 9–17).



**Scheme 2**  Reaction profile of aerobic reduction of **1a** with hydrazine with or without a Brønsted acid

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**Table 1** Aerobic Reduction of Olefins Catalysed by TsOH·H$_2$O[a]

| Entry | Substrate | Product | Time (h)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | **1a** | **2a** | 2 | 92 |
| 2 | **1b** | **2b** | 2.5 | 74 |
| 3 | **1c** | **2c** | 1 | 100[d] |
| 4 | **1d** | **2d** | 1.5 | 93 |
| 5 | **1e** | **2e** | 2.5 | 87 |
| 6 | **1f** | **2f** | 1.5 | 96 |
| 7 | **1g** | **2g** | 1.5 | 99[e] |
| 8 | **1h** | **2h** | 3 | 89 |
| 9 | **1i** | **2i** | 2.5 | 90 |
| 10 | **1j** | **2j** | 2 | 95[e] |
| 11 | **1k** | **2k** | 1.5 | 96 |
| 12 | **1l** | **2l** | 1.5 | 100[d] |
| 13[f] | **1m** | **2m** | 7 | 83 |
| 14[f] | **1n** | **2n** | 7 | 89[e] |
| 15[f] | **1o** | **2o** | 7 | 100[d] |

[a] Reactions were performed using 1 mmol of olefin, 2 mmol of hydrazine monohydrate in 4 mL of acetonitrile in the presence of 5 mol% TsOH·H$_2$O under 1 atm of O$_2$ at 35 °C and monitored by GC analysis.
[b] Time for full conversion.
[c] Isolated yield, unless otherwise noted.
[d] Conversion determined by GC analysis.
[e] Determined by $^1$H NMR measurement.
[f] Conducted at 70 °C.

With the optimal reaction conditions in hand, we demonstrated the utility of the TsOH-catalysed aerobic olefin reduction with hydrazine by applying the procedure to a range of substrates (Table 1).[14] The reactions were performed on a 1 mmol substrate scale and evaluated by GC analysis and/or isolated yields of hydrogenated products after full conversion of the substrates. Monosubstituted olefins **1a–k** as well as disubstituted olefins **1l–o** could be efficiently reduced with excellent functional group tolerance. For instance, benzyl, epoxy, nitro, and azide groups, which are typically labile under metal-catalysed hydrogenation conditions, were unaffected by the reaction conditions (entries 5–8 and 14). There was also no adverse effect in the reduction of an olefin containing a sulfide functional group (entry 9), which often inhibits the catalytic activity of transition-metal complexes. The reduction of linalool (**1j**), bearing two carbon–carbon double bonds, afforded the mono-hydrogenated product **2j** and the fully hydrogenated product in a ratio of 95:5, indicating the compatibility of the trisubstituted olefin as well as acid-labile tertiary alcohol group to the reaction conditions (entry 10). In addition, the present method can complement the aerobic hydrazine reduction catalysed by neutral flavins, because phenolic olefins such as *o*-allylphenol (**1k**, entry 11) are less reactive under flavin-related catalysis due to their acidic property reducing the reactivity of the basic hydrazine.[8] Reduction of sterically more demanding α,β- as well as α,α-disubstituted olefins was also feasible without using extra hydrazine, although higher temperatures and prolonged reaction times were required for acyclic substrates **1m**, **1n**, and **1o** (entries 13–15).

As initially envisaged, it is plausible that Brønsted acids accelerate the interconversion between *trans*- and *cis*-diimide and thereby facilitate the aerobic olefin reduction system. Although it could be expected that they would irreversibly form hydrazonium salts ($^+$NH$_3$NH$_2$) and be deactivated, such an undesirable situation is apparently negligible as far as they are used under an atmosphere of O$_2$ in acetonitrile, except in the case of MsOH. For the representative catalysis with TsOH·H$_2$O, hydrazine can undergo reversible protonation to form $^+$NH$_3$NH$_2$ as well as irreversible oxidation to form diimide (Scheme 3). Whereas the former is disfavoured in acetonitrile due to the low cation-solvation ability of this solvent, the latter is favoured because of the high oxygen-dissolving ability of acetonitrile.[12] The present TsOH-catalysed aerobic olefin reduction was not accelerated under 365 nm UV light irradiation (entries 18 and 19, Table S1 in the Supporting Information), indicating that the equilibrium of the isomeric diimides induced by TsOH is much faster than that induced by UV light irradiation as previously reported.[6]
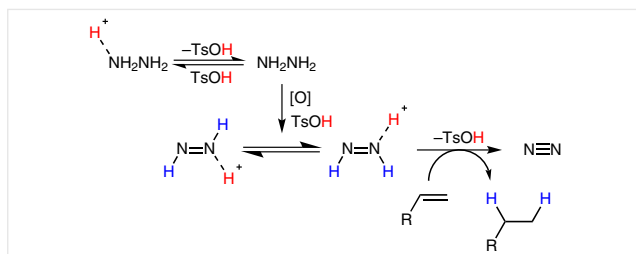
**Scheme 3** Plausible reaction mechanism

In conclusion, we have introduced a new protocol for the aerobic reduction of olefins with hydrazine by using readily available Brønsted acids as catalysts. In particular, the use of 5 mol% TsOH·H$_2$O and two equivalents of hydrazine monohydrate allowed a range of olefins to be reduced with excellent chemoselectivities under mild aerobic conditions. The present method is straightforward and should find wide application in organic synthesis. An asymmetric version of the protocol with chiral Brønsted acids[15] is being explored in our laboratory.

## Acknowledgment

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588790.

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(14) A mixture of a solution of the olefin (1.0 mmol) in acetonitrile (2 mL) and a 0.05 M stock solution of TsOH·H$_2$O in acetonitrile (1 mL, 5 mol%) was stirred under an atmosphere of oxygen at 35 °C (for **1a–l**) or 70 °C (for **1m–o**) for 5 min. To the resulting mixture was then added a solution of NH$_2$NH$_2$·H$_2$O (60 mg, 1.2 mmol) in acetonitrile (1 mL) and the mixture was further stirred at the corresponding temperature and monitored by GC analysis. After complete consumption of the olefin, the reaction was quenched with saturated aqueous NaHCO$_3$ (3 mL), and Et$_2$O (15 mL) and H$_2$O (7 mL) were added. The aqueous layer was removed and the residual organic layer was washed with H$_2$O (2 × 10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give the corresponding hydrogenated product **2a–o**. Data for butylbenzene (**2a**) [CAS Reg. No. 104-51-8]: yield: 127 mg (92%). $^1$H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, CH$_3$), 1.30–1.42 (m, 2 H, CH$_2$), 1.55–1.65 (m, 2 H, CH$_2$), 2.61 (t, *J* = 7.8 Hz, 2 H, ArCH$_2$), 7.12–7.31 (m, 5 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.9, 22.4, 33.7, 35.7, 125.5, 128.2, 128.4, 142.9. MS (EI): *m/z* (%) = 134 (26) [M$^+$], 105 (8) [C$_6$H$_5$CH$_2$CH$_2$], 91 (100) [C$_6$H$_5$CH$_2$], 77 (6) [C$_6$H$_5$], 65 (16) [C$_5$H$_5$], 51 (11) [C$_4$H$_3$], 39 (18) [C$_3$H$_3$]
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