Facile Protocol for Water-Tolerant “Frustrated Lewis Pair”-Catalyzed Hydrogenation

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Supporting Information

ABSTRACT: Despite rapid advances in the field of metal-free, “frustrated Lewis pair” (FLP)-catalyzed hydrogenation, the need for strictly anhydrous reaction conditions has hampered wide-scale uptake of this methodology. Herein, we report that, despite the generally perceived moisture sensitivity of FLPs, 1,4-dioxane solutions of B(C6F5)3actually show appreciable moisture tolerance and can catalyze hydrogenation of a range of weakly basic substrates without the need for rigorously inert conditions. In particular, reactions can be performed directly in commercially available nonanhydrous solvents without subsequent drying or use of internal desiccants.

KEYWORDS: “frustrated Lewis pairs”, catalytic hydrogenation, water tolerance, solvent effects, metal-free
the adduct \([1-\text{OH}_2]\) is also prone to decomposition via \(\text{B}--\text{C}\) bond protonolysis (Scheme 1).

**Scheme 1. Pathways for Deactivation of 1 by \(\text{H}_2\text{O}\)**

Recently, we\(^{6a}\) and Stephan et al.\(^{6b}\) have independently reported the hydrogenation of ketones and aldehydes to alcohols, catalyzed by 1 in ethereal solvents (Scheme 2). These reactions are clearly tolerant of hydroxyl functionalities, which is attributed to the weak Bronsted basicity of the ethers employed, which inhibits irreversible deprotonation of the highly acidic \([1-\text{ROH}]\) adducts.

Following on from these results, we reasoned that these systems might also be capable of tolerating the presence of \(\text{H}_2\text{O}\), for similar reasons, which would represent an important advance for the field of FLP chemistry. Initial investigations focused on the hydrogenation of acetone (the simplest system). Gratifyingly, when 1 was replaced with the preformed adduct \([1-\text{OH}]\) under identical conditions, selective hydrogenation to 2-propanol was observed to proceed cleanly and with good rate enhancement (Table 1, entry 2). Although the rate of reaction is reduced (c.f. Table 1, entry 1), confirming that \(\text{H}_2\text{O}\) acts as a significant catalyst poison, inhibition by \(\text{H}_2\text{O}\) is nonetheless clearly reversible. At the time, this represented the first example of an FLP-catalyzed hydrogenation that is tolerant of stoichiometric (relative to catalyst) \(\text{H}_2\text{O}\).

Increasing the \(\text{H}_2\) pressure led to a significant rate enhancement, even at lower catalyst loadings (Table 1, entry 3) and without any detectable catalyst decomposition (ascertained by \(^{19}\)F and \(^{11}\)B NMR spectroscopy). Under these conditions, several more equivalents of \(\text{H}_2\text{O}\) could be tolerated, with an attendant decrease in rate yet otherwise no major difference in reaction outcome (Table 1, entries 4 and 5).

On the basis of the ability of this system to tolerate multiple equivalents of water, we reasoned that the use of "undried" solvents ought to be achievable; impressively, the reaction could be performed very effectively in nonanhydrous commercial solvents\(^5\) even without any need for subsequent drying, degassing, or other purification. Furthermore, doubling the substrate and catalyst concentrations allowed for a significant decrease in reaction time (Table 1, entry 6).

The mechanism by which the hydrogenation is believed to occur is identical to that proposed for the anhydrous reaction, with \([1-\text{OH}_2]\) acting as an off-cycle resting state (Scheme 3).\(^{18}\) As with previously observed alcohol tolerance, \(\text{H}_2\text{O}\) tolerance is attributed to the lack of any strong base, meaning irreversible deprotonation of \([1-\text{OH}_2]\) does not occur (c.f. Scheme 1). Even so, it seems possible that reversible deprotonation does occur, which could be consistent with the acidity of this adduct (vide supra).\(^{19}\) Evidence for deprotonation comes from \(^{11}\)B NMR spectroscopy: although \([1-\text{OH}_2]\) alone shows an \(^{11}\)B NMR resonance at 4.6 ppm in the noncoordinating yet highly polar solvent 1,2-difluorobenzene (DFB), addition of 1,4-dioxane leads to a clear upfield shift, to −0.6 ppm with 1 equiv of ethereal base, and −2.1 ppm with 10 equiv (Figure 1).\(^{20}\) Typical nonanhydrous reaction mixtures, which contain \([1-\text{OH}_2]\) in neat 1,4-dioxane, produce resonances farther upfield still, at −3.0 ppm. For comparison, the \(^{11}\)B NMR shift of \([\text{NMe}_2][1-\text{OH}_2]\), which contains the "free" conjugate base of \([1-\text{OH}_2]\), has been reported as −2.1 ppm in CD$_2$Cl$_2$, with similar shifts for related salts.\(^{21}\) \(^{1}H\) NMR analysis also suggests an interaction between \([1-\text{OH}_2]\) and 1,4-dioxane, with the 1,4-dioxane resonance shifted slightly downfield, from 3.56 ppm in the absence of \([1-\text{OH}_2]\), to 3.59 ppm in the presence of 1 equiv, indicating overall deshielding. Although displacement of \(\text{H}_2\text{O}\) for 1,4-dioxane could also potentially explain these shifts in the NMR spectra, this possibility can be discounted: addition of 1 and 10 equiv of 1,4-dioxane to dry 1 in DFB leads to \(^{11}\)B NMR resonances at 9.8 and 5.7 ppm, respectively, and 1,4-dioxane \(^{1}H\) resonances at 3.96 and 3.59 ppm, respectively; in all cases significantly farther downfield than when \(\text{H}_2\text{O}\) is also present.

Reversible deprotonation of \([1-\text{OH}_2]\) and the related \([1-\text{ROH}]\) adducts may partially explain the large effect that pressure has been observed to have on both the anhydrous and nonanhydrous reactions. Increasing \(\text{H}_2\) pressure will increase the solution concentration of \(\text{H}_2\) and, in turn, the degree of \(\text{H}_2\) activation. The resulting increase in Bronsted acid concentration should perturb the equilibrium between \([1-\text{OH}_2]/[1-\text{IPrOH}]\) and \([1-\text{OH}^-]/[1-\text{OIrP}^-]\) in favor of the more weakly bound neutral adducts, hence facilitating catalytic turnover via ROH/H$_2$O dissociation from 1.

**Scheme 2. Previously-Reported Hydrogenation of Aldehydes and Ketones Catalyzed by 1.**\(^{6a,6b}\)

\(\text{R} = \text{aryl, alkyl; R}’ = \text{alkyl, H.}\)

**Table 1. Metal-free catalytic hydrogenation of acetone in the presence of various amounts of \(\text{H}_2\text{O}\)**

| Entry | \([\text{Me}_2\text{CO}]_\text{M}\) | \([\text{Ir}]\) | \([\text{H}_2\text{O}]\)/([1]) | \(P_\text{bar}\) | \(t, h\) | Conv. | TON |
|-------|----------------|-----------|----------------|--------|-----|------|-----|
| 1\(^{bc}\) | 0.50 | 5 | 0 | 13 | 6 | 99 | 20 |
| 2\(^{c}\) | 0.39 | 5 | 1\(^{d}\) | 13 | 70 | 94 | 19 |
| 3\(^{c}\) | 0.27 | 2.5 | 1 | 50 | 39 | 92 | 37 |
| 4\(^{c}\) | 0.27 | 2.5 | 2 | 50 | 84 | 98 | 39 |
| 5\(^{c}\) | 0.27 | 2.5 | 5 | 50 | 108 | 92 | 37 |
| 6\(^{c}\) | 0.53 | 2.5 | >1\(^{e}\) | 50 | 15 | 94 | 38 |

All conversions measured by \(^1\)H NMR integration. \(^{b}\)Result taken from Ashley et al.\(^{\text{a}}\) 0.2 mmol acetone. \(^{c}\)Added as \([1-\text{OH}_2]\), 4.0 mmol acetone. \(^{d}\)8 mmol acetone, ACS reagent grade commercial solvent (Sigma-Aldrich). \(^{e}\)Confirmed by control experiments (see the SI).
Given that the rationale for H₂O tolerance in this system depends primarily on the absence of a strong base, it seemed reasonable that catalytic hydrogenation without the need for rigorously dry conditions might also be achievable for other weakly basic substrates. To this end, a variety of additional substrates (both carbonyls and noncarbonyls) were treated under similar conditions. For most, clean, efficient catalytic reduction was observed without the need for extensive further optimization (Table 2, entries 1−7), clearly indicating the generality of this water-tolerant methodology. As well as using undried solvent, reactions could be performed under open bench conditions without the need for inert atmosphere containment systems (although long-term storage of 1 is best carried out in a glovebox). By contrast, the attempted reduction of cyclohexanone under the same conditions was unsuccessful (Table 2, entry 8), which is qualitatively consistent with previous observations made under dry conditions, for which higher pressures were required for hydrogenation than for the other carbonyl substrates. Collectively, these results suggest a similar substrate scope for the anhydrous and nonanhydrous reaction protocols.

In addition to the advantages already discussed, moisture-tolerance should also allow FLPs to catalyze reactions that produce H₂O. To this end, acetophenone was exposed to our anhydrous reaction conditions. Clean, catalytic reductive deoxygenation to ethylbenzene was observed, despite the concomitant formation of H₂O (5 equiv relative to catalyst) that necessarily occurs (Scheme 4).

In conclusion, we have demonstrated a number of examples of FLP-catalyzed hydrogenation reactions demonstrating appreciable water tolerance. As a result, a variety of weakly basic substrates can be hydrogenated cleanly and in high yield, in the absence of a transition metal catalyst, in commercial-grade “bench” (undried) solvents. By removing the need for both extensive, laborious drying of reaction solvents and inert atmosphere reaction techniques, this development significantly improves the efficiency and ecological friendliness of such reactions.

**Scheme 3. Proposed Mechanism for Moisture-Tolerant Hydrogenation of Acetone**

"Possible hydrogen bonding of solvent with [1·ROH] and [1·OH₂] omitted for clarity.

**Figure 1.** Variation in ¹¹B NMR chemical shift of [1·OH₂] upon addition of 1,4-dioxane in DFB.
increases the practicality of the FLP hydrogenation methodology. These findings extend the current reach of FLP hydrogenation catalysis from rigorously anhydrous research laboratory conditions into industrially relevant, commercially available solvent grades and reaction conditions.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01417.

Full experimental details (PDF)

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**Table 2. Metal-Free Hydrogenation of Weakly-Basic Substrates in Non-Anhydrous Solvent**

| Entry<sup>a</sup> | Substrate | Product | [1] / mol% | t / h | Conv. / %<sup>b</sup> | TON |
|-------------------|-----------|---------|------------|------|-----------------|-----|
| 1                 |           |         | 5          | 20   | 50              | 10  |
| 2<sup>c</sup>     |           |         | 10         | 17   | >99<sup>c</sup> | 10  |
| 3<sup>d</sup>     |           |         | 5          | 20   | 77              | 15  |
| 4                 |           |         | 10         | 17   | >99<sup>c</sup> | 10  |
| 5                 |           |         | 5          | 17   | >99<sup>c</sup> | 20  |
| 6<sup>d</sup>     |           |         | 2.5        | 21   | 48              | 19  |
| 7<sup>c</sup>     |           |         | 10         | 44   | >99<sup>c</sup> | 10  |
| 8<sup>c</sup>     |           |         | 5          | 18   | 0               | 0   |

<sup>a</sup>Standard conditions: 4.0 mmol substrate, 0.53 M. <sup>b</sup>All conversions measured by <sup>1</sup>H NMR integration. <sup>c</sup>2.0 mmol substrate. <sup>d</sup>8.0 mmol substrate.

<sup>e</sup>Unquantified mixture of isomers.

**Notes**

The authors declare no competing financial interest.

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aldehydes and ketones using novel boranes specifically designed for moisture-tolerant hydrogenation of aldehydes and ketones using novel boranes specifically designed for that purpose. Their approach (targeted design of new catalysts, rather than adaptation of existing FLP hydrogenation protocols) complements the work reported herein. Gyömöre, Á.; Bakos, M.; Földes, T.; Pápai, I.; Domján, A.; Soós, T. ACS Catal. 2015, DOI: 10.1021/acscatal.5b01299.

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(17) ACS reagent grade 1,4-dioxane purchased from Sigma Aldrich was used. Karl Fischer titration indicated 220 ppm/0.022% H₂O (w/w) (advertised as up to 0.05%).

(18) We propose that 1,4-dioxane acts as the main base for hydrogen activation due to the vast excess (12 M) in which it is present; however, in principle, this role could also be played by water or 2-propanol.

(19) The pKₐ of protonated 1,4-dioxane has been measured as ~2.92 in aqueous solution. Although the aqueous pKₐ of [1-OH₂] has not been measured, our results indicate that it may be comparable. See: Arnett, E.; Wu, C. Y. J. Am. Chem. Soc. 1960, 82, 4999–5000.

(20) It should be noted that these observations could also be consistent with strong hydrogen bonding to the solvent rather than full formal deprotonation; in practice, the true situation might be expected to lie somewhere between these two extremes.

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(22) For all experiments [H₂O] > [1], as indicated by control experiments: see SI.

(23) ¹H NMR analysis of an aliquot taken at partial conversion showed formation of styrene (in addition to ethylbenzene and the expected alcohol intermediate), which is consistent with previous observations made at lower pressure. At completion, only ethylbenzene was observed, however, indicating that the alkene undergoes further reduction (either directly, or via rehydration to the alcohol).