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Frustrated Lewis pairs-assisted reduction of carbonyl compounds

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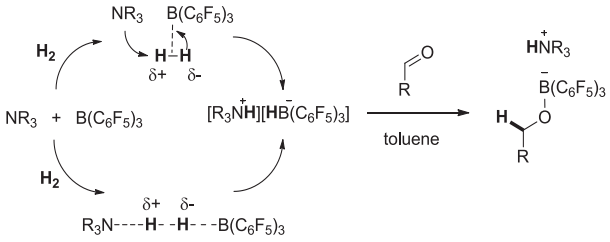
ABSTRACT

An alternative and robust method for the reduction of carbonyl groups by frustrated Lewis pairs (FLPs) is reported in this paper. With its very mild reaction conditions, good to excellent yields, absolute regioselectivity and the non-metallic character of the reagent, it provides an excellent tool for ^{1}H, ^{2}H as well as ^{3}H chemistry. It is a new strategy for the one-pot synthesis of aromatic alcohols selectively labeled with heavy isotopes of hydrogen.

1. Introduction

Reductive processes are among the principal transformations in organic synthesis. Hydrogenation, using the cleanest reducing agent—H_2 gas, is arguably the most important catalytic method in synthetic organic chemistry both on the laboratory and the production scale.[1] The essential activation of dihydrogen molecule is almost exclusively achieved by a transition-metal center. Since a complete absence of transition metals is required in pharmaceutical products because of toxicity concerns, alternative reagents have been intensively sought. Recently, the class of nonmetallic compounds called 'frustrated Lewis pairs' (FLPs) has received a great amount of interest due to its ability to activate dihydrogen.[2,3] Therefore, FLPs have become an attractive alternative to conventional hydrogenation catalysts currently applied in the pharmaceutical industry.[4] In addition, FLPs make even asymmetric hydrogenation achievable.[5] FLPs, consisting of a sterically encumbered Lewis base (frequently an amine or phosphine) and a Lewis acid containing electron-withdrawing substituents, e.g., tris(pentafluorophenyl)borane, are the most frequently used to cooperatively induce the heterolytic splitting of a hydrogen molecule under mild conditions.[2] The resulting H^+/H^- pairs (stabilized in the form of phosphonium or ammonium cation/hydridoborate anion salt) serve as noble metal-free catalysts for the hydrogenation of bulky imines,[6,7] enamines,[6b,6c] and enol ethers.[6c,7a,7e] Carbonyl compounds, used as substrates for the reduction carried out by FLPs, provide a stable intermediate ammonium cation/alcohol-borate anion (Scheme 1).[6a,6c,8] Efforts to design a FLP catalyst with fine-tuned Lewis acidity at the boron center to preclude the formation of an intermediate have been described in the literature as 'in progress' so far.[6a,8b]



Scheme 1. The generally accepted mechanism of the heterolytic splitting of hydrogen molecule by FLPs and the reagent thus formed with carbonyl compounds.

Isolation of the alcohol product from the reaction mixture has not been reported yet. The mild conditions, non-metallic character and commercial availability of the reagents make this methodology suitable for exploitation in the synthesis of compounds labeled by a radioactive isotope of hydrogen—tritium [the low pressure of tritium gas during the reaction (<1000 mbar) is an obligatory condition because of security considerations]. To the best of our knowledge, there is no mention in the literature of the use of FLPs for labeling organic compounds with heavy isotopes of hydrogen. Even though tritium is the most versatile radionuclide in chemical and biochemical research, the tools for the synthesis of tritium-

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labeled organic compounds with a high specific activity (i.e., higher than 5 Ci/mmol ~ 0.2 atom of tritium per molecule) are rather limited. The most accessible source of tritium is always carrier-free gaseous tritium. It is possible to prepare lithium tritide from gaseous tritium and from it the whole range of borotritides and aluminum tritides.[9] These reagents in the carrier-free form are not stable, cannot be stored and must be used without delay. Commercially available tritides usually have less than 25% of the maximum theoretical specific activity. Therefore, new and sophisticated tritium labeling methodologies are constantly required.

Our research was devoted to the $B(C_6F_5)_3$-Lewis base-assisted reduction of carbonyl compounds using deuterium (later tritium) gas. Bearing in mind that the investigated ^2H-labeling methodology is supposed to pave the way toward a 'hot' experiment (handling carrier-free tritium gas), the general procedure was designed as a 'one-pot' reaction sequence without the isolation of intermediates (the generation of FLPs, the reduction of a carbonyl compound and the decomposition of an intermediate).

2. Results and discussion

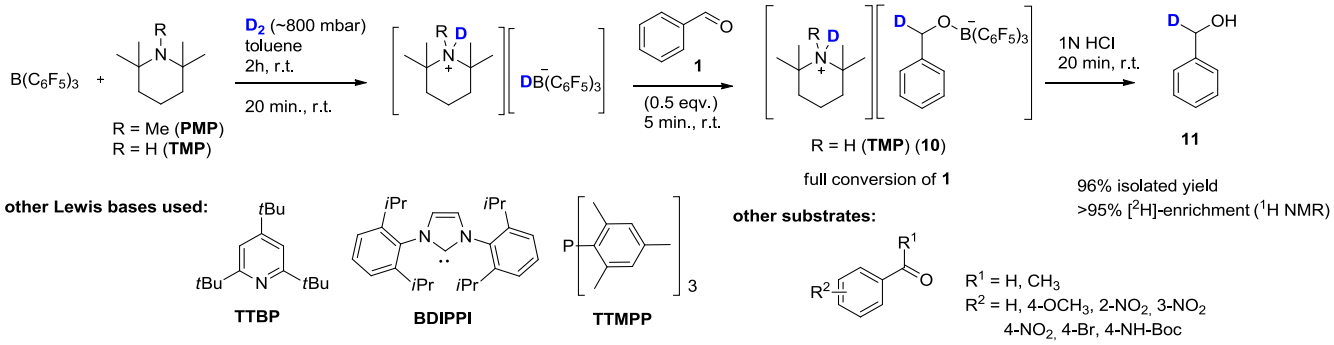
FLPs reduce the carbonyl compound as a stoichiometric reagent (not as a catalyst) due to the formation of a stable zwitterionic intermediate [Lewis base cation][alcoholborate anion] of the generated alcohol with the borane aggregate (Scheme 1). We synthesized the intermediate $[TMP^2H][C_6H_5CH^2HOB(C_6F_5)_3]$ (**10**) following the procedure reported by Sumerin et al. (Scheme 2).[8b] Hydrolysis of this complex was carried out very mildly by the addition of water (20 eqv.) into the benzene suspension of intermediate **10**. The complete hydrolysis of **10** was achieved after 16 h of vigorous stirring of the heterogenous mixture at ambient temperature, providing $C_6H_5CH^2HOH$ (**11**) in an almost quantitative yield (96%). However, in order to design the reaction conditions for the experiment with radioactive tritium, we sought faster hydrolysis conditions for **10**. Thus the 1N water solution of strong Brønsted acid HCl dramatically accelerated the hydrolysis, providing full conversion of **10** into alcohol **11** in a sufficiently short reaction time; in 20 min at ambient temperature (Scheme 2).

bases [2,4,6-tri-*tert*-butylpyridine (TTBP), 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (BDIPPI), tris(2,4,6-trimethylphenyl)phosphine (TTMPP)] used for the formation of FLPs and the subsequent reduction of **1** provided moderate to good conversion (31–64%), but unidentified side-products made the isolation of the pure product complicated (Table 1, entries 5–10).

With the optimized combination of the Lewis base/Lewis acid pair in hand (TMP or PMP/$B(C_6F_5)_3$), we proceeded to the reduction of other types of substrates. We followed this protocol using 4-methoxybenzaldehyde and 4-nitrobenzaldehyde, which likewise led to the desired compounds **12**–**13** in excellent yields (94–97%). In addition, the position of the nitro substituent (**3**–**5**) does not have a large effect on the reduction process (Table 1, entries 12–15). Both *para*- and *meta*-nitro substituted benzaldehydes smoothly underwent the reduction; full conversion was achieved in five minutes and afforded nearly quantitative yields (94–96%). On the other hand, an *ortho*-nitro derivative (**5**) needed a substantially longer reaction time (up to four hours) to achieve full conversion (the reaction course was followed by TLC and HPLC), providing an isolated yield of 82%. A similar procedure, applying *p*-(*N*-Boc)-substituted benzaldehyde (**7**), afforded full conversion to alcohol **17** in one hour in an isolated yield of 60–69%. We did not observe any remarkable differences in the yields depending on the Lewis base employed for the formation of FLPs (Table 1, entry 19 and 21).

Encouraged by such a smooth reaction course, we investigated the reactivity of appropriate FLPs toward less reactive ketone analogues. As expected, no product of the reduction of phenylmethylketone (**8**) was detected even after two hours and four equivalents of $[TMP^2H][^2HB(C_6F_5)_3]$. In contrast, the electron deficient 4-nitroacetophenone (**9**) provided a promising 42% yield of **18** after four hours with two equivalents of FLP used for the reduction. The reaction was significantly accelerated by using three equivalents of FLP and provided a quantitative yield of **18** in five minutes.

The successful isolation of the series of [^{2}H]-labeled alcohols was encouraging for the use of this procedure analogically to the tritium experiment. In general, a transfer of the conditions developed in the deuterium-modeling experiment to the [3*H*]-labeling experiment is sometimes problematic (mostly because of ionizing radiation), and both the yield and isotope enrichment can drop sharply.[9d] Therefore, only the experiment with carrier-free tritium gas would be the ultimate proof of the suitability of FLP-catalyzed reductions for [^{3}H]-labeling. The optimized procedure (Table 1—entry 26, 505 mbar of $^3H_2$, toluene, room temperature) was used to synthesize the $[TMP^3H][^3HB(C_6F_5)_3]$ reagent. To achieve full conversion of the precursor **7** in a short time (two hours), an excess of FLP (2 equiv) was needed. The reduction of precursor **7** and the subsequent hydrolysis of the intermediate (not isolated) (Scheme 3) gave the desired [^{3}H]-labeled benzyl alcohol [60% conversion of **7** according to HPLC (245 nm)].



Scheme 2. A synthesis of the representative [^{2}H]-labeled benzyl alcohol. The reduction of **1** and the hydrolysis of the intermediate **10**.