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# $TiCl_4$-Mediated Reduction of 1,3-Diketones with $BH_3$–Pyridine Complex: A Highly Diastereoselective Method for the Synthesis of *syn*-1,3-Diols

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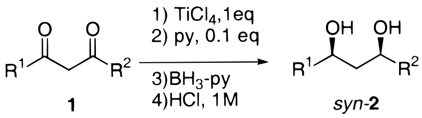
## ABSTRACT

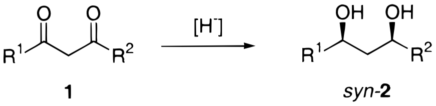


**1,3-Diketones can be reduced in high yields and with excellent diastereoselectivity to the corresponding *syn*-1,3-diols by carrying out the reaction with $BH_3$–pyridine complex in $CH_2Cl_2$ at –78 °C in the presence of an equivalent of $TiCl_4$ and 0.1 equiv of pyridine. This protocol shows a general character: excellent results are obtained when the groups bound to the carbonylic functions are linear or branched carbon chains and aromatic or benzylic frameworks as well.**

The development of new protocols for the diastereoselective synthesis of 1,3-diols continues to be of great interest in organic chemistry since this unit is present either in a *syn* or *anti* relationship in a large variety of natural products.[1] Toward this goal, stereocontrolled reductions of $\beta$-hydroxy ketones[2,3] and the Tishchenko reaction[4] are the most investigated approaches to date.

The reduction of 1,3-diketones should represent an alternative protocol. However, while a large variety of methodologies for catalytic hydrogenation[5] and enzymatic methods[6] are available, at the present time the stereoselective reduction by metallic hydrides[7] remains an unresolved problem (see Scheme 1).

**Scheme 1.** Reduction of 1,3-Diketones with Hydrides [H−]



In fact, from the few reports present in the literature, it can be argued that low yields and low selectivities are observed, even when sophisticated reducing agents, such as

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(1) (a) Evans, D. A.; Sheppard, G. S. *J. Org. Chem*. **1990**, *55*, 5192. (b) Sletzinger, M.; Verhoven, T. R.; Volante, R. P.; McNamora, J. M.; Liu, T. M. H. *Tetrahedron Lett.* **1985**, *26*, 2951

(2) For *syn*-reduction, see: (a) Hoveyda, A. H.; Evans, D. A. *J. Org. Chem*. **1990**, *55*, 5190. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233. (c) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. S.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.

(3) For *anti*-reduction, see: (a) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1997**, *62*, 3409. (b) Hoveyda, A. H.; Evans, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (c) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761.

(4) (a) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674. (b) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 3409. (c) Marwald, R.; Cortisella, B. *Synthesis* **1996**, 1087. (d) Evans, D. A.; Hoveyda, H. A. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

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**Table 1.** Reduction of Benzoylacetone **1a** with Various Reducing Agents under Different Reaction Conditions

| entry | Lewis acid | reducing agent | solvent | amine (equiv) | yields (%)[a,b] | *syn*/*anti* |
|---|---|---|---|---|---|---|
| 1 | | $BH_3$−py | $CH_2Cl_2$ | | no reaction | |
| 2 | | $BH_3$-py | $CH_2Cl_2$ | py (0.1) | no reaction | |
| 3 | $TiCl_4$ | Na−Selectride | toluene−THF | | 20 | 70/30 |
| 4 | $TiCl_4$ | $BH_3$-py | toluene | py (0.1) | 50 | 80/20 |
| 5 | $TiCl_4$ | $BH_3$-py | $CH_2Cl_2$ | | 78 | 85/15 |
| 6 | $TiCl_4$ | $BH_3$-py | $CH_2Cl_2$ | py (0.1) | 87 | 97/3 |
| 7 | $TiCl_4$ | $BH_3$-lutidine | toluene | | 65 | 70/30 |
| 8 | $TiCl_4$ | $BH_3$-lutidine | $CH_2Cl_2$ | lutidine (0.1) | 85 | 90/10 |
| 9 | $TiCl_4$ | $BH_3$-lutidine | $CH_2Cl_2$ | lutidine (1) | 50 | 60/40 |
| 10 | $TiCl_4$ | $BH_3$-DMAP | $CH_2Cl_2$ | DMAP (0.1) | 70 | 95/5 |
| 11 | $TiCl_4$ | $BH_3$-$PhNEt_2$ | $CH_2Cl_2$ | $PhNEt_2$ (0.1) | 65 | 75/25 |

[a] Yields refer to pure isolated products. [b] The decomposition of cyclic boronates was carried out with method A.

$LiInH_4$,[8] are employed since the reaction suffers from the occurrence of extensive side processes such as enolization, reductive elimination, and reduction to monoalcohol. Only when two methyl groups are present at position 2 are high yields of 1,3-diols obtained.

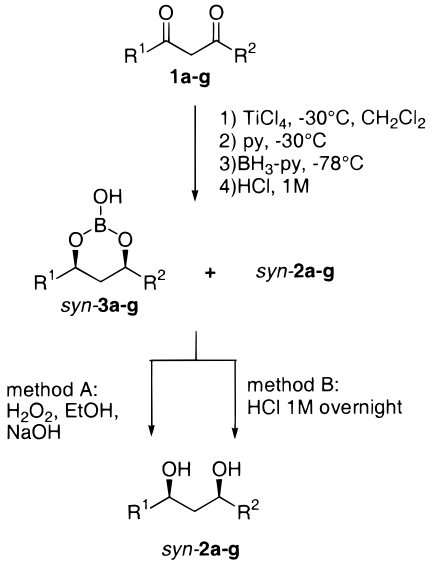
In the present Letter we report a general and simple method for the reduction of 1,3-diketones to the corresponding *syn*-1,3-diols based on the use of borane complexes as reducing agents in the presence of $TiCl_4$.

A series of preliminary experiments was performed on benzoyl acetone **1a** in order to determine the best reaction conditions (see Table 1).

From the obtained data the following indications emerged: (a) The presence of $TiCl_4$ is essential for the reaction; in fact the reaction carried out in absence of the Lewis acid does not work (Table 1, entries 1 and 2). (b) The use of a borane−amine complex in nonpolar solvent is necessary to achieve high yields and high selectivity; in fact the reduction carried out with N-Selectride in a toluene−THF solvent mixture (Table 1, entry 3) gives moderate selectivity (*syn*/*anti* = 70/30) and very low yields (20%). (c) Among nonpolar solvents, $CH_2Cl_2$ gives better results than toluene. (d) We tested a variety of $BH_3$−amine complexes as reducing agents, and the best results were obtained with the simple $BH_3$−pyridine system. (e) Yields and diastereoselectivity increase if, after mixing the substrate with $TiCl_4$, 0.1 equiv of the appropriate amine is added prior to treatment with the borane−amine complex (see Table 1, entries 5 and 6). Stoichiometric amounts of amine give worse results (Table 1, entry 9).

As a consequence, the best reaction conditions follow: 1 equiv of 1,3-diketone **1**, dissolved in $CH_2Cl_2$, is treated with 1.1 equiv of $TiCl_4$ (solution 1 M in $CH_2Cl_2$) and 0.1 equiv of pyridine at −30 °C. After 30 min an excess of $BH_3$−py (3−4 equiv) is added at −78 °C. After 2 h the reaction is quenched with aqueous HCl (1 M). The usual workup gives a mixture of *syn*-**2** and the boron cyclic derivative *syn*-**3**.[9,10] To convert *syn*-**3** to *syn*-**2** this mixture is submitted to treatment with $H_2O_2$ in a basic medium (method A). Alternatively, pure *syn*-**2** can be obtained by quenching the reaction with aqueous HCl (1 M) and stirring the mixture overnight (method B) (Scheme 2).

**Scheme 2**



This methodology was applied to a series of 1,3-diketones. While the reactions reported in Table 1 were carried out by adopting exclusively decomposition method A, r the reactions reported in Table 2 employed both methods A and B.

The obtained results (Table 2, entries 1, 4, and 5) showed that both decomposition methods are practically equivalent, giving very similar results.

The reaction proceeds with excellent diastereoselectivities in all examined examples, showing that this procedure works

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(5) For example, see: (a) Chan, A. S. C.; et al. *Tetrahedron: Asymmetry* **1997**, *8*, 4041. (b) Brunner, H.; Terfort, A. *Tetrahedron: Asymmetry* **1995**, *6*, 919.

(6) (a) Ikeda, H.; Sato, E.; Sugai, T.; Ohta, H. *Tetrahedron* **1996**, *52*, 8113. (b) Takeshita, M.; Miura, M.; Unuma, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2901. (c) Chenevert, R.; Thiboutot, S. *Can. J. Chem*. **1986**, *64*, 1599.

(7) For example, see: (a) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron.* **1992**, *48*, 9801. (b) Barluenga, J.; Resa, J.; Olano, B. *J. Org. Chem*. **1987**, *52*, 1425.

(8) Araki, S.; et al. *Tetrahedron* **1997**, *53*, 15685.

**Table 2.** Reduction of 1,3-Diketones **1a**−**g** with $BH_3$−py in the Presence of $TiCl_4$ (1 equiv) and py (0.1 equiv)

| entry | starting material | R[1] | R[2] | product | yields (%)[a] | *syn*/*anti* |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | Me | **2a** | 87[b](86)[c] | 97/3[b](96/4)[c] |
| 2 | **1b** | i-Bu | Me | **2b** | 83[b] | 96/4[b] |
| 3 | **1c** | PhCH$_2$CH$_2$ | Me | **2c** | 86[b] | 95/5[b] |
| 4 | **1d** | PhCH$_2$ | i-Pr | **2d** | 75[b](77)[c] | 95/5[b](95/5)[c] |
| 5 | **1e** | t-Bu | t-Bu | **2e** | 80[b](79)[c] | 98/2[b](97/3)[c] |
| 6 | **1f** | o-Cl-Ph | Pr | **2f** | 81[b] | 97/3[b] |
| 7 | **1g** | Ph | Ph | **2g** | 45[b,d] | >99/1[b] |

[a] Yields refer to pure isolated products. [b] Data refer to decomposition of cyclic boronates carried out with method A. [c] Data refer to decomposition of cyclic boronates carried out with method B. [d] Together with 37% of recovered starting material.

well both when R[1] and R[2] are linear carbon chains and when they are α- or β-branched ones. Analogous results were found when R[1] and R[2] were benzylic and aromatic groups (see Table 2, entries 4, 6, and 7).

Yields are generally high, except in the case of dibenzoylmethane **1g**. In this case, in fact, we were able to isolate, after 6 h at −78 °C, 45% of *syn*-**2g** together with 37% of starting material. Prolonged reaction times gave rise to the formation of undesired byproducts.[11] Increasing reaction temperatures led to a decrease in diastereoselectivity without any improvement in the yield.

Reactions products, when known, were characterized by comparison of spectroscopic data with those available from the literature. Structure and stereochemical assignment of unknown compounds were made on the basis of $^1$H and $^{13}$C NMR data (Hoffman rules).[12] The *syn/anti* ratio was determined by integration of some $^{13}$C NMR peaks using appropriate long delay times.

In conclusion, we were able to set up the first general protocol for the diastereoselective reduction of 1,3-diketones to *syn*-1,3-diols with metallic hydrides. This method utilizes the reducing system recently optimized for the diastereoselective reduction of various classes of functionalized ketones.[13]

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**Supporting Information Available:** Experimental procedures and spectroscopic data. This material is available free of charge via Internet at http://pubs.acs.org.

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(9) We were not able to isolate pure *syn*-**3** compounds; however it was possible to determine their formation through $^1$H NMR of the crude of the reduction of **1a**.

(10) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Tetrahedron Lett.* **1999**, *40*, 2845.

(11) Considerable amounts of 1,3-diphenyl-1-propanol and 1,3-diphenyl-2-propen-1-ol were observed.

(12) Hoffman, R. W.; Weidmann, U. *Chem. Ber*. **1985**, *118*, 3980.

(13) (a) Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E.; Dalpozzo, R. *Chem. Eur. J.* **1997**, *3*, 1941. (b) Bartoli, G.; Bosco, M.; Cingolani, S.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1998**, 63, 3624. (c) Bartoli, G.; Bellucci, M. C.; Alessandrini, S.; Malavolta, M.; Marcantoni, E.; Sambri, L.; Dalpozzo, R. *J. Org. Chem.* **1999**, *64*, 1986.