

SYNLETT Spotlight 290

Lombardo's Reagent

Compiled by Hemender R. Chand



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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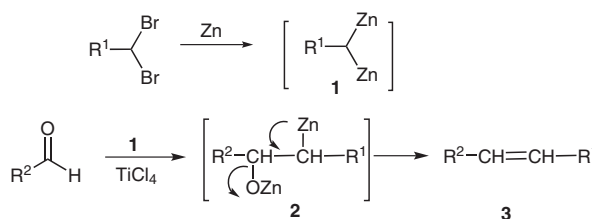
Introduction

The reagent combination $\text{Zn}/\text{CH}_2\text{Br}_2/\text{TiCl}_4$ gives rise to an organometallic reagent which is known as Lombardo's reagent. It converts ketones into methylene groups.¹ The active reagent is presumed to be a dimetalated species (**1**) which adds to the ketone under the influence of the Lewis acidity of titanium to give a β -oxymetal-substituted organometallic compound (**2**). Following β -elimination generates the methylene group (**3**)² (Scheme 1).

Ketones are not enolized by the reagent and as an important consequence adjacent enolizable chiral centers are not epimerized. The reagent is compatible with a wide variety of functional groups, e.g., THP and *tert*-butyldimethylsilyl ethers, acetals, esters, carboxylic acids, alcohols, and lactones.³ Such selectivity makes it a valuable procedure in organic synthesis and appreciably augments Wittig methodology.

Preparation

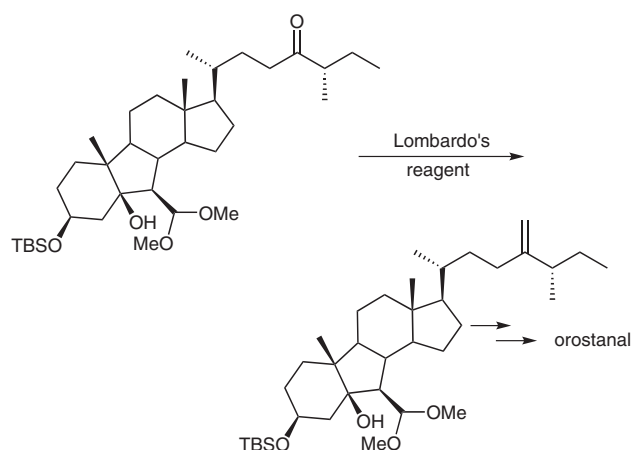
For the preparation of Lombardo's reagent, TiCl_4 is added dropwise to a stirred suspension of zinc dust in dibromomethane and tetrahydrofuran at -40°C over ten minutes. The mixture is allowed to warm to 5°C and stirred for three days to furnish thick grey slurry of an active species. The active species reacts instantaneously with aldehydes and ketones to afford the methylenated products. The reagent can be stored under refrigerated conditions.^{1b}



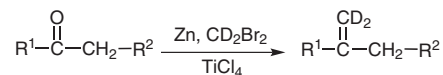
Scheme 1 Mechanism of methylenation using Lombardo's reagent

Abstracts

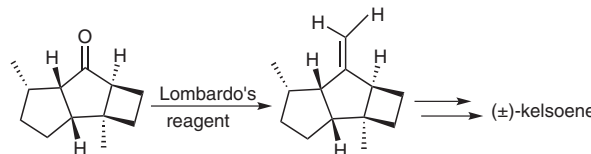
(A) *Stereoselective Synthesis of Orostanal*: Orostanal is isolated from the marine sponge *Stelletta hiwasaensis*. It shows bioactivity against HL-60 cells at $10\text{ }\mu\text{g/mL}$. One of the twelve synthetic key steps is the methylenation of a ketone using Lombardo's reagent.⁴



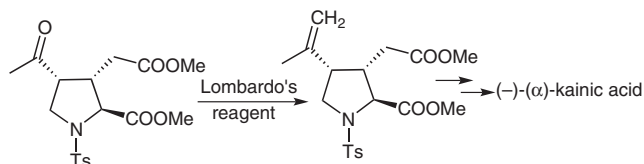
(B) *Deuterium Labeling*: One of the much studied problems is the methylenation of a carbonyl compound to obtain position specific deuterium incorporation. Various methods are limited by their cumbersome nature, loss of label, scrambling, or the presence of other functionalities in the molecule. Specific labeling of deuterium can be achieved by using Lombardo's reagent.^{1b}



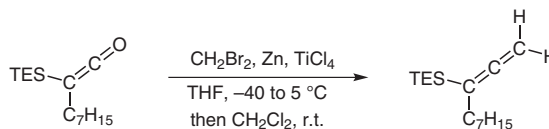
(C) *Methylenation of Highly Hindered Ketones*: Sterically hindered carbonyl groups can be successfully methylenated using Lombardo's reagent, e.g. in the total synthesis of (±)-kelsoene.⁵



(D) *Chemoselective Methylenation of Ketones*: Carbonyl groups of ketones can be easily methylenated in the presence of ester carbonyl functionalities without epimerization of adjacent chiral centers. One example is the total synthesis of (–)-(α)-kainic acid.⁶



(E) *Methylenation of Silyl Ketenes*: Modest yields of allenyl silanes were obtained by methylenation of silyl ketenes using Lombardo's approach, whereas the Wittig reagent products were obtained in low yields.⁷



References

- (1) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 19, 2417. (b) Lombardo, L. *Tetrahedron Lett.* **1982**, 23, 4293.
- (2) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, 109, 951.
- (3) (a) Lombardo, L. *Org. Syn.* **1993**, Coll Vol. 8, 386. (b) Lombardo, L. *Org. Syn.* **1987**, Coll Vol. 65, 81.
- (4) Liu, B.; Zhou, W.-S. *Tetrahedron* **2003**, 59, 3379.
- (5) Piers, E.; Orellana, A. *Synthesis* **2001**, 2138.
- (6) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, 7, 3045.
- (7) Marsden, P. S.; Ducept, P. C. *Beilstein J. Org. Chem.* **2005**, 1, 5.