

SYNLETT Spotlight 216

(-)-Diisopinocampheyl Chloroborane [(-)-DIP-ChlorideTM]: A Versatile Reagent in Asymmetric Synthesis

Compiled by Peng Zhang



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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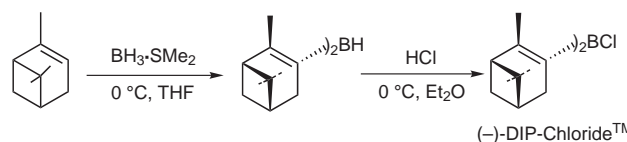
Introduction

Since its introduction in 1985,¹ (-)-diisopinocampheyl chloroborane [(-)-DIP-ChlorideTM] has become one of the most effective reagents in asymmetric synthesis for the reduction of prochiral ketones.² It exhibits the phenomenon of asymmetric amplification in this reduction reaction.³ The types of ketones delivering high enantioselectivity upon DIP-ChlorideTM are aralkyl,⁴ hindered alkynyl,⁵ trifluoromethyl,⁶ α -acetylenic α' -fluoroalkyl,⁷ α -fluoromethyl,⁸ benzofuryl halomethyl,⁹ olefinic, and cyclic ketones.¹⁰ 2-Amino acetophenones,¹¹ *ortho*-substituted benzophenones,¹² 1,2- and 1,3-hydroxy ketones,¹³ aliphatic acylsilanes,¹⁴ 2-acetylbenzofuran,¹⁵ and α -oxocarboxylic acids¹⁶ have also been asymmetrically reduced with high enantiomeric excess using this reagent. This reagent has also been applied in key steps in the preparation of several important pharmaceutical compounds such as antidepressant fluoxetine hydrochloride,¹⁷ a selective D1 agonist,¹⁸ PAF-antagonists L-659,989¹⁹ and MK-287,²⁰

Dolastatin 10,²¹ a potential antipsychotic and bronchodilator,²² (-)-Lobeline,²³ and an LTD₄ antagonist.²⁴ It is found to be a useful reagent in the synthesis of chiral ligands²⁵ and is also capable of effecting asymmetric aldol reactions.²⁶

Preparation

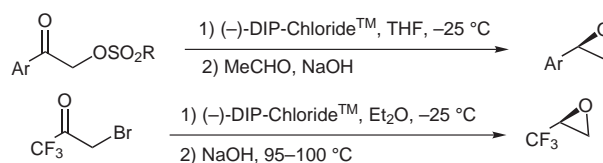
(+)- and (-)-DIP-ChlorideTM are commercially available now. (-)-DIP-ChlorideTM can be readily prepared from commercially available (+)- α -pinene by hydroboration, followed by treatment with dry hydrogen chloride in diethyl ether. Removal of ether and cooling to 0 °C provided solid (-)-DIP-ChlorideTM, which could be recrystallized from pentane, mp 54–56 °C.¹



Abstracts

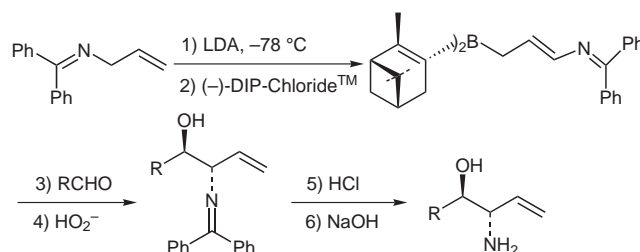
(A) One-Pot Synthesis of Chiral Epoxide:

Cho et al.^{27a} reported an efficient synthesis of optical active epoxides with high enantiomeric excess by asymmetric reduction of 2-sulfonyloxyacetophenone derivatives using (-)-DIP-ChlorideTM. Chiral (trifluoromethyl)oxirane can be obtained via the asymmetric reduction of 1-bromo-3,3,3-trifluoro-2-propanone with this reagent, followed by ring closure in high enantioselectivity.^{27b}



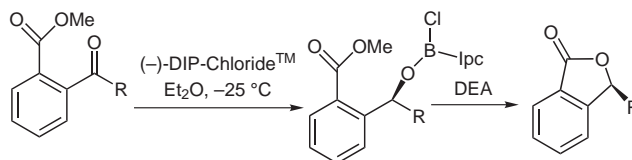
(B) Asymmetric Synthesis of anti- β -Amino Alcohols:

(-)-DIP-ChlorideTM has been employed in the preparation of *anti*- β -amino alcohols in three steps via deprotonation of 1,1-diphenyl-2-aza-1,4-pentadiene in the presence of LDA, followed by meta-*thetical* exchange with (-)-DIP-ChlorideTM, reaction with aldehyde and subsequent deprotection of the imine.²⁸

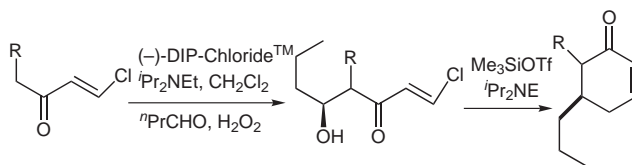


(C) *Asymmetric Synthesis of 3-Substituted 1(3H)-Isobenzofuranones*:

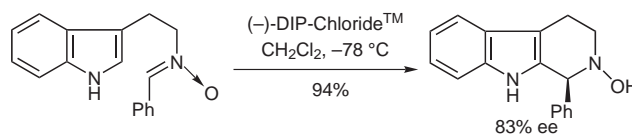
Ramachandran et al. reported a convenient and general synthesis of chiral 3-substituted 1(3H)-isobenzofuranones in very high enantiomeric excess via asymmetric reduction using this reagent. The treatment of methyl 2-acetylbenzoate with (–)-DIP-Chloride™ in diethyl ether at –25 °C, followed by the usual diethanolamine (DEA) workup provides an 87% yield and 97% ee of 3-methylphthalide.²⁹

(D) *Asymmetric Aldo Reaction*:

A novel and convenient two-step diastereoselective synthesis of dihydropyrones from readily available β -chlorovinyl ketones and aldehydes via (–)-DIP-Chloride™ mediated aldo reaction has been developed.³⁰

(E) *Enantioselective Pictet–Spengler Reaction*:

(–)-DIP-Chloride™ behaved as a chiral Lewis acid catalyst in Pictet–Spengler reaction to promote enantioselective cyclization of nitrones to give optically active N_b-hydroxytetrahydro- β -carboline.³¹



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