Tetrahedron 71 (2015) 2487–2524

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 1076

Enantioselective titanium-promoted 1,2-additions of carbon nucleophiles to carbonyl compounds

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ARTICLE INFO

Article history:
Received 4 December 2014
Received in revised form 23 February 2015
Accepted 2 March 2015
Available online 6 March 2015

Keywords:
Asymmetric catalysis
Chirality
Titanium
1,2-Additions
Carbon nucleophiles
Carbonyl compounds

Contents

List of abbreviations: Ad, adamantyl; Ar, aryl; BDMAEE, 2,2′-oxy-bis(*N*,*N*-dimethylethanamine); BINOL, 1,1′-bi-2-naphthol; Bn, benzyl; BTME, 1,2-bis(trimethoxysilyl) ethane; Cy, cyclohexyl; DAIB, dimethylamino isoborneol; DIBAL, diisobutylaluminium hydride; DIMPEG, dimethoxy polyethylene glycol; DIPEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DME, dimethoxyethane; DPP, 3,5-diphenylphenyl; Dppp, 1,3-bis(diphenylphosphine)propane; ee, enantiomeric excess; FG, functionalised group; HMPA, hexamethylphosphoramide; L, ligand; MCF, mesocellular foam; Mes, mesyl; MOM, methoxymethyl; MTBE, methyl-*tert*-butylether; Naph, naphthyl; NOBIN, 2-amino-2-hydroxy-1,1′-binaphthalene; PMB, *para*-methoxybenzyl; rt, room temperature; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, *p*-tolyl; Tr, triphenylmethyl (trityl); Ts, 4-toluenesulfonyl (tosyl).

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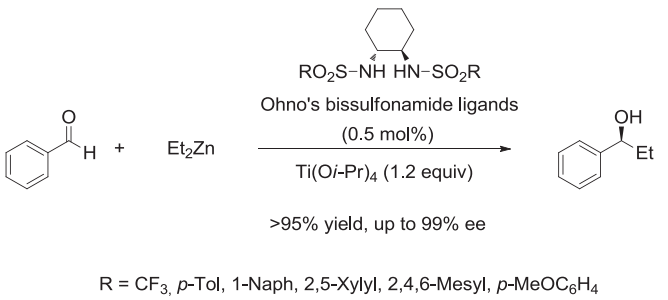
http://dx.doi.org/10.1016/j.tet.2015.03.001

1. Introduction

The catalysis of organic reactions by metal complexes constitutes one of the most useful and powerful tools in organic chemistry.[1] Although asymmetric synthesis is sometimes viewed as a subdiscipline of organic chemistry, actually this topical field transcends any narrow classification and pervades essentially all chemistry. Of the methods available for preparing chiral compounds, catalytic asymmetric synthesis has attracted most attention. In particular, asymmetric transition-metal catalysis has emerged as a powerful tool to perform reactions in a highly enantioselective fashion over the past few decades. Efforts to develop new asymmetric transformations focused preponderantly on the use of few metals, such as titanium, nickel, copper, ruthenium, rhodium, palladium, iridium and more recently gold. However, by the very fact of the lower costs of titanium catalysts in comparison with other transition metals, and their nontoxicity, which has permitted their use for medical purposes (prostheses), enantioselective titanium-mediated transformations have received a continuous ever-growing attention during the last decades that leads to exiting and fruitful researches.[1j,2] This interest might also be related to the fact that titanium complexes are of high abundance, exhibit a remarkably diverse chemical reactivity, and constitute ones of the most useful Lewis acids in asymmetric catalysis. This usefulness is particularly highlighted in the area of enantioselective 1,2-alkylation, 1,2-arylation, 1,2-alkynylation, 1,2-allylation and 1,2-vinylation reactions of carbonyl compounds. These methodologies have a strategically synthetic advantage to form a new C–C bond, a new functionality (alcohol) with concomitant creation of a stereogenic centre in a single transformation. Since the first enantioselective titanium-promoted addition of diethylzinc to benzaldehyde reported in 1989 by Ohno and Yoshioka, which used chiral *trans*-1,2-bis(trifluoromethanesulfonylamino)cyclohexane as ligand (Scheme 1),[3] enantioselective titanium-promoted additions of organometallic reagents to prochiral aldehydes and ketones have been studied extensively.



Scheme 1. First Ti-promoted enantioselective addition of diethylzinc to benzaldehyde reported by Ohno and Yoshioka in 1989.

For example, important progress has been made recently in the design and development of chiral titanium Lewis acids for asymmetric catalysis of additions of organozinc reagents to carbonyl compounds to reach various chiral functionalised alcohols under relatively mild conditions on the basis of the extraordinary ability of chiral titanium catalysts to control stereochemistry, which can be attributed to their rich coordination chemistry and facile modification of titanium Lewis acid centre by structurally modular ligands.[2a,d,4] In this context, good results have been recently reported dealing with enantioselective titanium-promoted dialkylzinc additions to more challenging aliphatic aldehydes than commonly used aromatic ones. In addition, a range of challenging functionalised alkylzinc reagents could be highly enantioselectively added to aldehydes. Concerning the alkylation and arylation of carbonyl compounds by organometallic reagents other than organozinc reagents, impressive advances have been made in the last few years by using chiral titanium catalysts. For example, the first highly efficient enantioselective titanium-promoted alkylations of aldehydes with organolithium reagents have been recently developed. Moreover, the direct additions of highly reactive alkyl and aryl Grignard reagents to all types of aldehydes at room temperature were recently demonstrated to give general excellent enantioselectivities when induced by chiral titanium catalysts. Importantly, the first direct titanium-promoted asymmetric additions of alkyl- and aryltitanium reagents to various aldehydes including aliphatic ones performed at room temperature were successfully developed. Another important advance was the first titanium-promoted enantioselective direct addition of alkylboranes including functionalised ones to aldehydes including aliphatic ones. Furthermore, in the context of enantioselective titanium-promoted additions to ketones, the first highly efficient enantioselective additions of (2-furyl)- and (2-thienyl) aluminium reagents to ketones have been described. For all these types of nucleophilic reagents, remarkable enantioselectivities were reached for alkylation/arylation reactions. In another context, the enantioselective addition of organometallic alkynyl derivatives to carbonyl compounds is today the most expedient route toward chiral propargylic alcohols, which constitute strategic building blocks for the enantioselective synthesis of a range of complex important molecules. In the last few years, impressive advances have been made in this area particularly in the variety of alkynes used to be added to aldehydes. Besides excellent results afforded with phenylacetylene, remarkable enantioselectivities were observed for a range of other terminal (functionalised) alkynes, such as *para*-tolylacetylene, trimethylsilylacetylene, ethynylcyclohexene, 4-phenyl-1-butyne, 5-chloro-1-pentyne, 1-hexyne, 1-heptyne, 1-octyne, various alkynoates, as well as 1,3-diynes and 1,3-enynes. In the context of enantioselective alkynylations of ketones, the first successful use of aryltrifluoromethyl ketones was described. Importantly, several supported chiral ligands have been recently successfully applied to the catalysis of almost all types of 1,2-additions, such as enantioselective dialkylzinc additions to ketones, enantioselective alkynylations of aldehydes and enantioselective allylations of ketones. Although most of the novel methods collected in this review require superstoichiometric amounts of titanium sources (along with catalytic amounts of chiral ligands), they remain highly useful regarding the advantages of titanium elements, such as low cost, abundance and low toxicity. The goal of this review is to provide a comprehensive overview of the major developments in enantioselective titanium-promoted 1,2-alkylation, 1,2-arylation, 1,2-alkynylation, 1,2-allylation and 1,2-vinylation reactions of carbonyl compounds reported since the beginning of 2008, since this general