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# Catalytic Enantioselective Reactions from Research to Application. Diarylmethanol-Containing Auxiliaries as a Study Case<sup>a)</sup>

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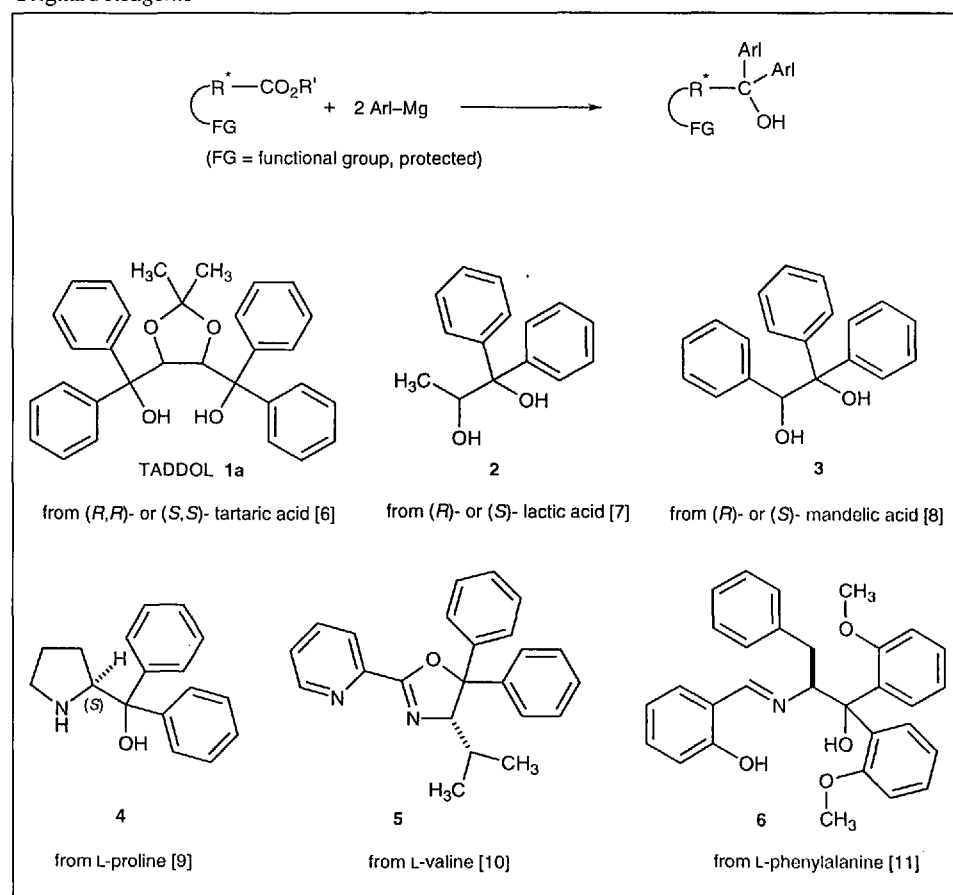
**Abstract.** Chiral auxiliaries – in the broadest possible definition of the term – can be obtained by *Grignard* reactions of Aryl–MgX with chiral esters R\*CO<sub>2</sub>R. The products formed all contain a diarylmethanol structural moiety. They can be used in stoichiometric and catalytic enantioselective reactions, preferably as ligands on metal centers. They have also found applications for enantioselective inclusions, for solid-phase reactions, and for liquid-crystal preparations.

The reaction of phenyl *Grignard* reagent with esters to give tertiary alcohols containing a diarylmethanol group is the first step of a carboxylic-acid degradation method used for structure elucidations at the beginning of this century (*Barbier-Wieland* [1]). In 1982, we used the same reaction for preparing a chiral ligand to be used for enantioselective synthesis, a major task of organic chemistry towards the end of this century [2]. Since our first experiment [3][4], numerous readily available chiral carboxylic acids have been converted to auxiliaries containing the *magic* [5] diarylmethanol moiety (see *Scheme 1* for a general equation and the formulae 1–6 for some compounds thus prepared from hydroxy and amino acids [6][7–11]).

The family of compounds of which we prepared the first representative (**1a**, from the acetonide of tartrate ester) is now referred to as TADDOLs [6], and more than 70 analogs with various substituents in the 2-position of the dioxolane ring and a great variety of aryl groups in the diarylmethanol moieties have been prepared [12]. Furthermore, the OH groups of the TAD-

DOLs can be derivatized or substituted by other functional groups, so that ligands for different types of metals are available (**1b–1o** in *Fig. 1*) [13][14].

Scheme 1. Preparation of Some Chiral Ligands 1–6 Derived from Carboxylic Acids and Aryl Grignard Reagents



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<sup>a)</sup> Abstract of the lecture given by D.S. at the spring meeting of the New Swiss Chemical Society (NSCS) in Visp, Switzerland, on April 10, 1997.

In *Scheme 2* there are seven equations demonstrating the many substoichiometric applications of TADDOL derivatives: the addition of organometallic compounds to aldehydes [15], and to an enone [16], the enantioselective ring opening of a cyclic anhydride [17], silane reduction of ketones [18], [2+2] and [4+2] cycloadditions [19][20], and an iodolactonization reaction [21].

In *Scheme 3* we show applications of an amino-diarylmethanol ligand in enantioselective catalysis: the borane reduction of ketones catalyzed by chiral oxazaborolidines (*Corey-Itsuno* method [9]) has become a very important process [22], both in the research laboratory and in industry [23].

When a styryl TADDOL is copolymerized (to give a crosslinked polystyrene), and then treated with Ti(OCHMe<sub>2</sub>)<sub>4</sub>, a heterogeneous catalyst results which has a surprisingly high activity in most of the reactions which had previously been studied under homogeneous conditions. As shown in *Scheme 4*, the enantioselectivity of homoallyl addition to benzaldehyde is almost identical under the two sets of conditions, and multiple use of the catalyst beads is possible [25][26].

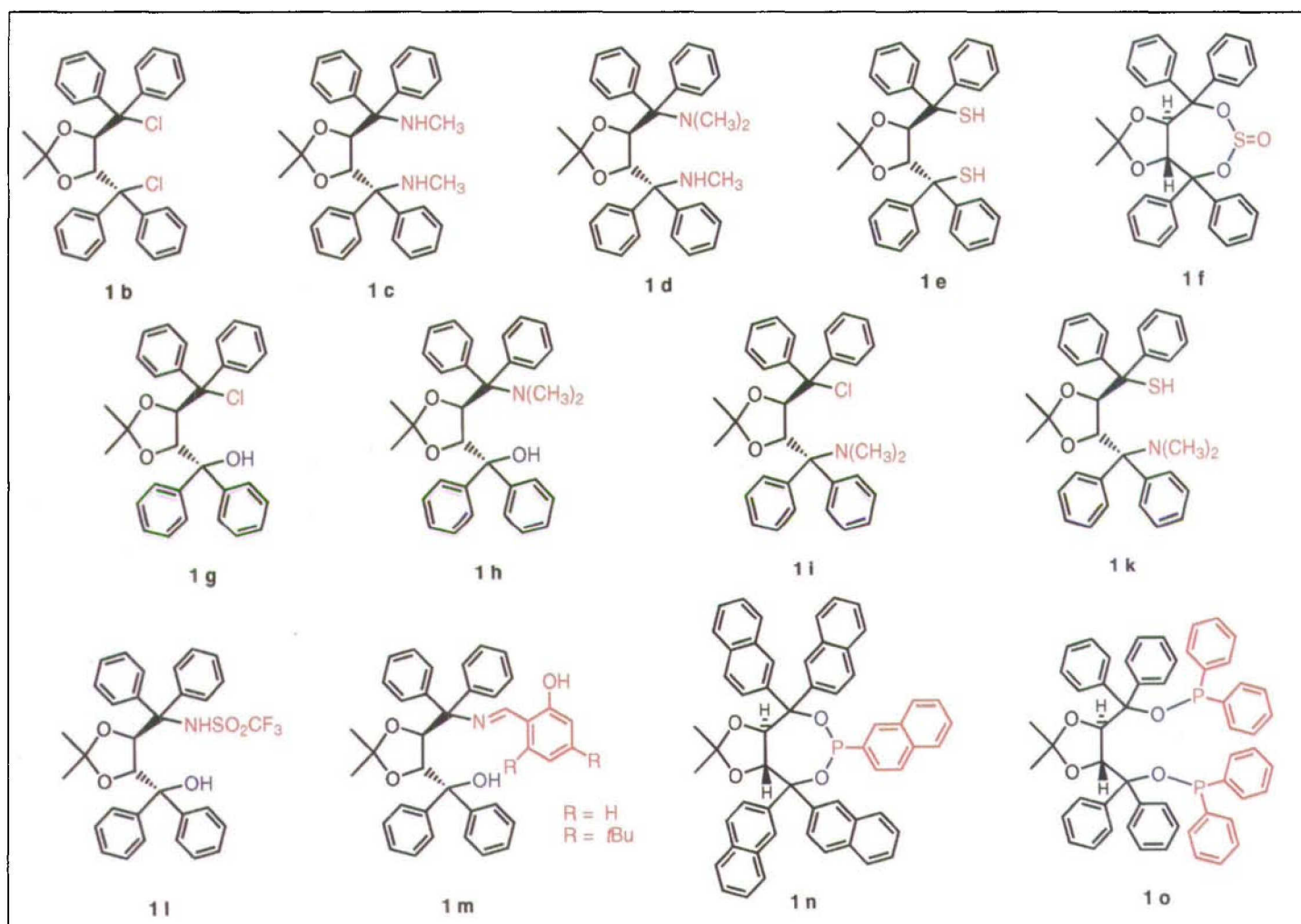


Fig. 1. Selected examples of TADDOL derivatives 1b–1o obtained by esterification or substitution of diarylmethanol OH groups.

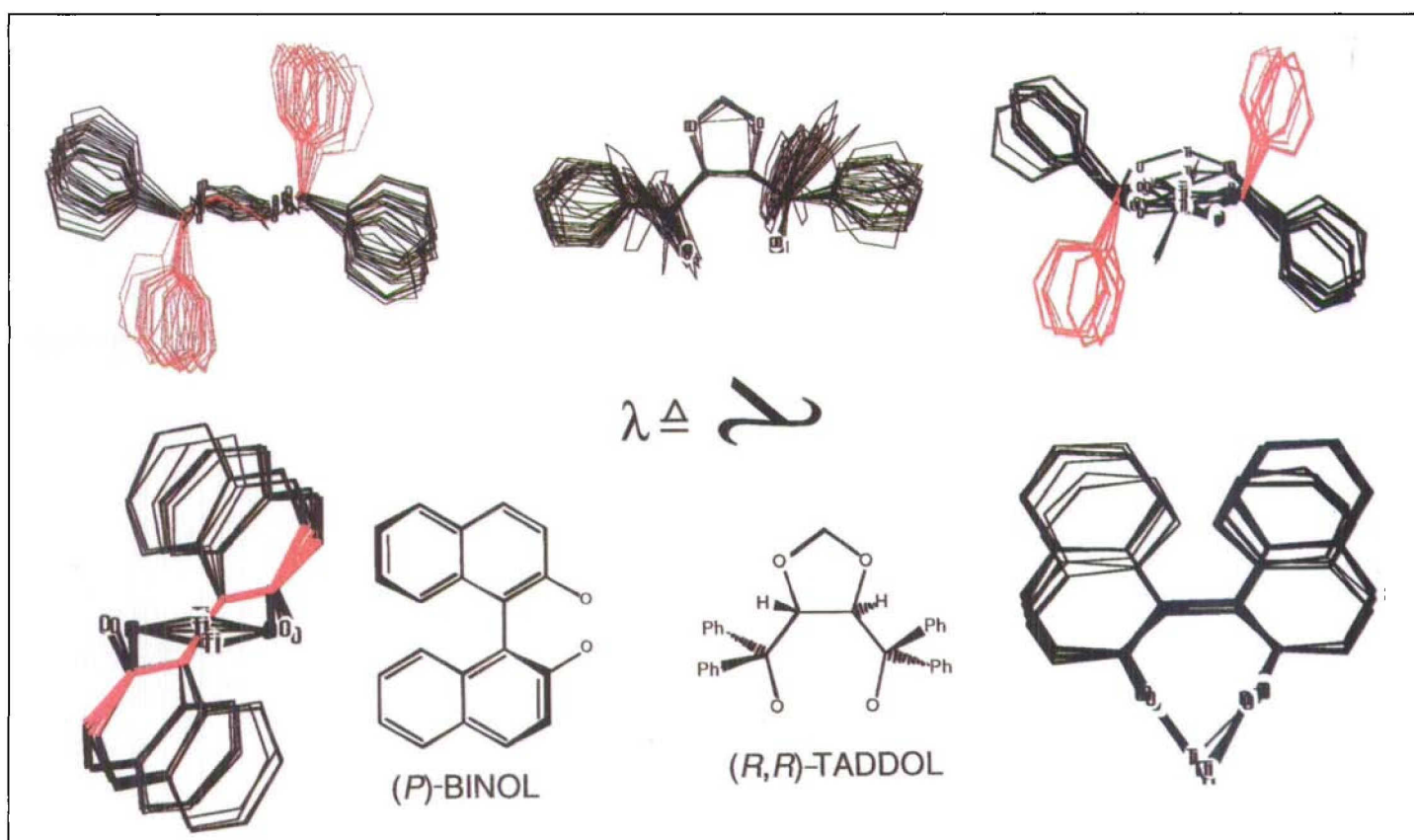


Fig. 2. Superpositions of 29 TADDOL, of 8 Ti-TADDOLate, and of 9 Ti-BINOLate structures. In metal complexes, (P)-BINOL and (R,R)-TADDOLs provide similar ligand spheres with  $\lambda$ -shape of axially disposed aromatic groups [20][28].

The many applications published and extensive mechanistic investigations, supported by numerous crystal structures, have led to rules for predicting and to models for rationalizing the enantioselective courses of many TADDOL-mediated reactions, and it has been shown that there are common features with reactions involving BINOLs (see Fig. 2) [20][25][27].

Besides the substoichiometric uses of TADDOL derivatives, many stoichiometric applications have been reported, for instance the addition of *Grignard* reagents to unsymmetrical ketones to give tertiary alcohols with an *er* > 99:1 [29], or the ring opening of *meso-N*-(methylsulfonyl)imides by  $(\text{Me}_2\text{CHO})_2\text{Ti}$ -TADDOLate [30].

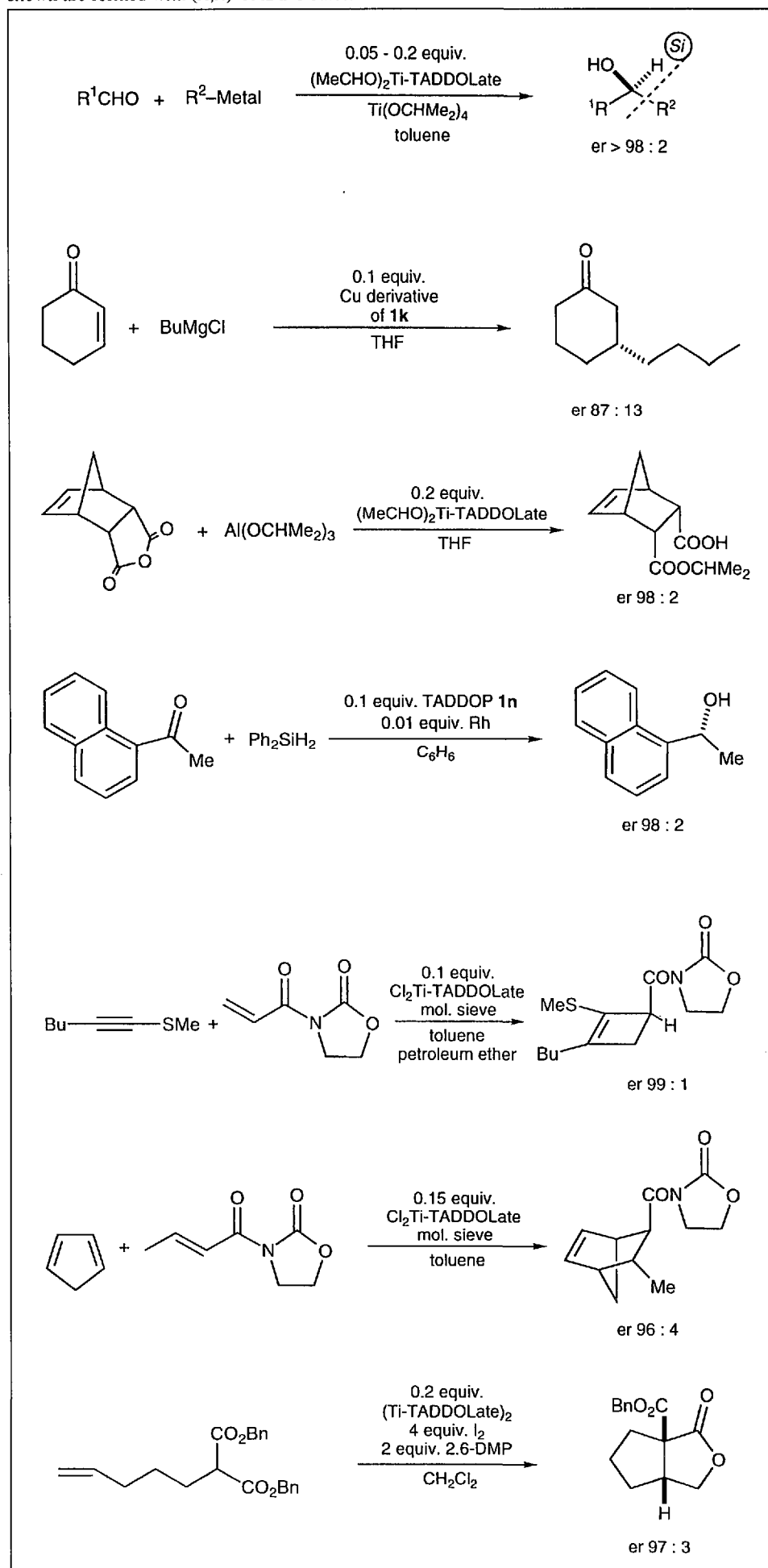
Furthermore, TADDOLs have also been applied in other areas of chemistry. Thus, they are probably the most often used enantioselective inclusion or guest-host compounds in *Toda's* and *Weber's* work [31], they have been tested for enantioselective solid-phase reactions [32], and they can be exploited as chiral additives for determination of enantiomeric ratios by NMR spectroscopy [33]. Finally, some TADDOLs cause liquid crystals consisting of achiral compounds to become cholesteric, with a so-called helical twisting power unrivalled by any other additive known today [34].

From this *very* brief overview it may perhaps become evident that we, like others [35], are dreaming of having a universally applicable class of chiral auxiliaries (the TADDOLs and their diarylmethanol-substituted congeners), which are readily available with great structural variety and which are easily recoverable.

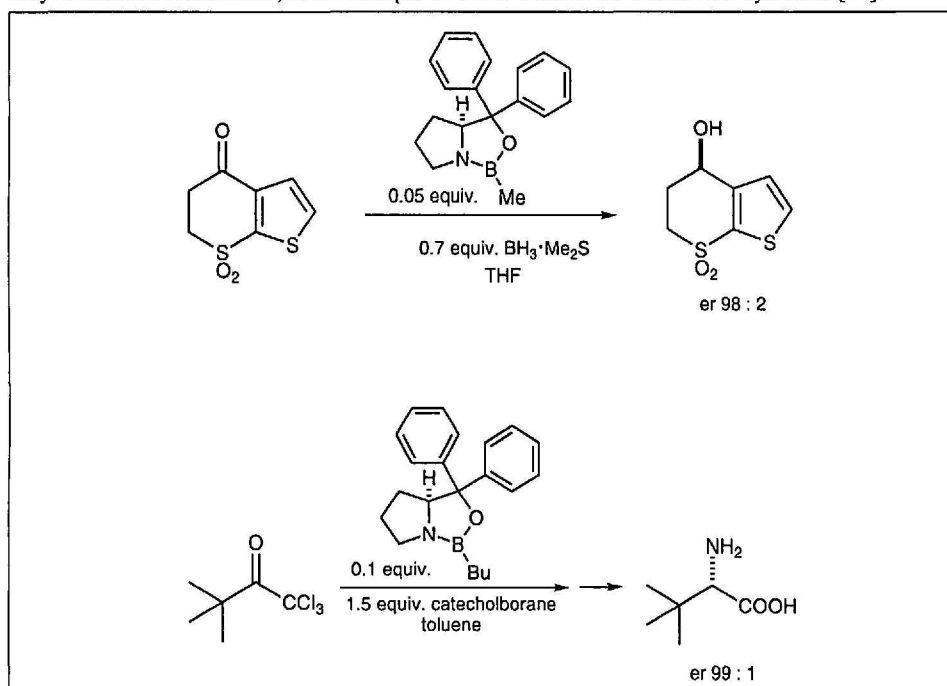
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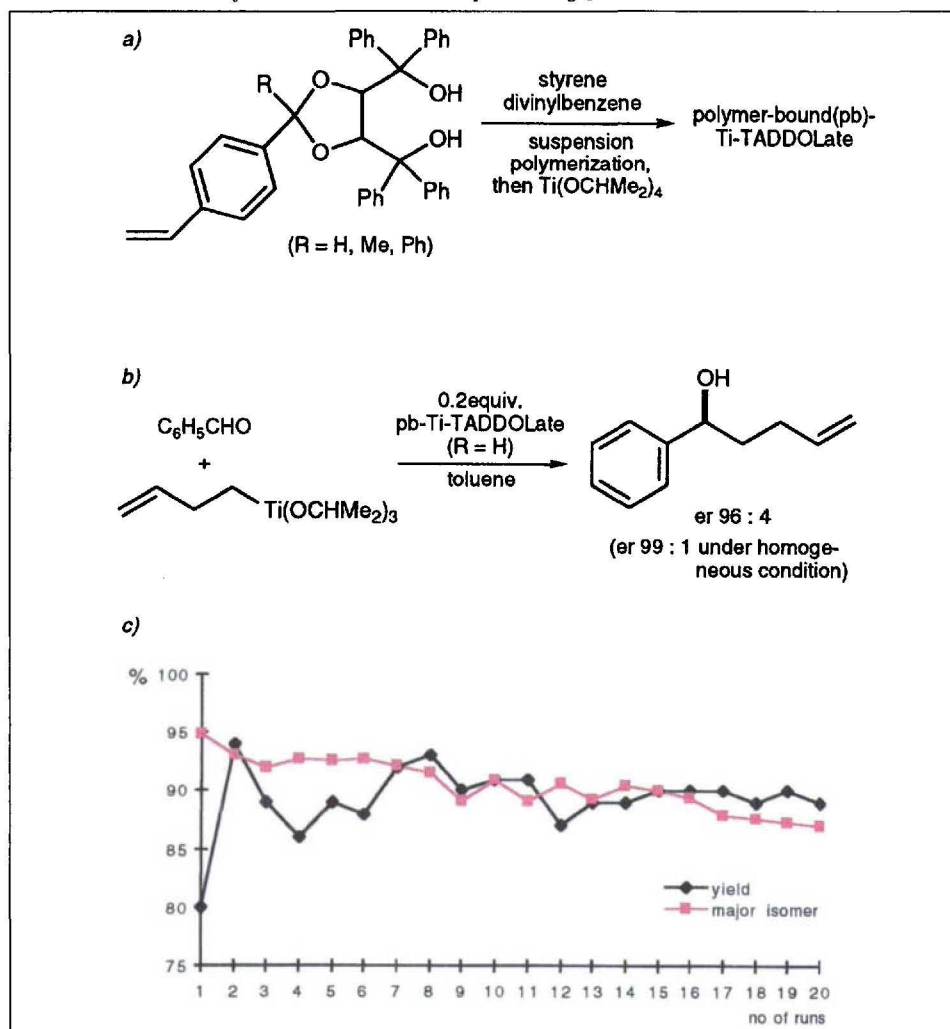
Scheme 2. Some Applications of TADDOL Derivatives in Enantioselective Catalysis. The products shown are formed with (*R,R*)-TADDOLates.



Scheme 3. *Borane Reductions of Two Ketones Catalyzed by a Proline Derivative*. The sulfur compound is an intermediate for the preparation of MK-0417 (carbonic anhydrase inhibitor reducing intraocular pressure) [23]. The enantioselective reduction of trichloromethyl ketones (such as the *tert*-butyl derivative shown here) is an example of a new method for amino-acid synthesis [24].



Scheme 4. a) *Preparation of Polymer-Bound Ti-TADDOLate* and b) *Nucleophilic Additions to Benzaldehyde* [25]. c) *Diagram of the result from 20 consecutive Et<sub>2</sub>Zn additions to PhCHO* (under conditions not optimized for enantioselectivity) in a specially designed reactor which allows for addition and removal of reaction solutions, and for rinsing [26].



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# Enantioselective Catalysis for Agrochemicals: The Case History of the **DUAL MAGNUM<sup>®</sup>** Herbicide

Hans-Ulrich Blaser\* and Felix Spindler

**Abstract.** The use of enantioselective catalytic methods for the technical preparation of chiral agrochemicals is illustrated by the case history of the herbicide (*S*)-metolachlor (trade name **DUAL MAGNUM<sup>®</sup>**). The key step for the technical synthesis of the enantiomerically enriched compound is the asymmetric hydrogenation of an imine intermediate, made possible by a new iridium-ferrocenyldiphosphine catalyst system. Important aspects of the development of the catalyst system as well as minimal prerequisites for the use of enantioselective catalysts for the production of agrochemicals are discussed.

## 1. Introduction

Metolachlor is at the present time the most important herbicide of *Novartis*. It is produced since 1978 in volumes of > 20 000 t per year and is sold under the trade name **DUAL MAGNUM<sup>®</sup>**. Starting in 1997, an enantiomerically enriched form will replace the racemic mixture, leading to a reduction of the environmental load by ca. 40%. The case history that is presented here might not be prototypical for an agrochemical. Nevertheless, it is an impressive example demonstrating the importance of enantioselective catalysis to the fine chemicals industry. Second, it illustrates that the development of a new catalytic system can sometimes take many years (see the *Table*).

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Metolachlor was first described in 1972 [1]; it is an *N*-chloroacetylated, *N*-alkoxyalkylated *ortho*-disubstituted aniline (*Fig. 1*). The unusual functionalization pattern renders the amino function extremely sterically hindered. As a consequence, metolachlor has two stereogenic structure elements: a chiral axis (atropisomerism, due to hindered rotation around the C<sub>Ar</sub>-N axis) and a stereogenic center, leading to four stereoisomers. In 1982, it was found that the two (*1S*)-enantiomers provide most of the biological activity [2].

## 2. The Search for an Enantioselective Synthesis

When it became clear that the two (*1S*)-enantiomers of metolachlor were respon-

Table. Milestones in the History of (*S*)-Metolachlor

1970	Discovery of the biological activity of <i>rac</i> -metolachlor (patent for product and synthesis)
1978	Full-scale plant for the production of <i>rac</i> -metolachlor in operation (capacity > 10 000 t/y)
1982	Synthesis and biological tests of the four stereoisomers of metolachlor
1983	First unsuccessful attempts to synthesize ( <i>S</i> )-metolachlor <i>via</i> enantioselective catalysis
1985	Rhodium-cycphos catalyst gives 69% ee for the imine hydrogenation (UBC Vancouver)
1987	Discovery of new Ir-diphosphine catalysts that are more active and selective than Rh catalysts for the hydrogenation of MEA-imine
1993	Ir-ferrocenyldiphosphine catalysts and acid effect discovered
1993/4	Patents for <i>rac</i> -metolachlor expire
1995/6	Pilot results for ( <i>S</i> )-metolachlor: ee 79%, ton 1 000 000, tof > 200 000/h, first 300 t produced
1996	Full-scale plant for production of > 10 000 t/y ( <i>S</i> )-metolachlor starts operation

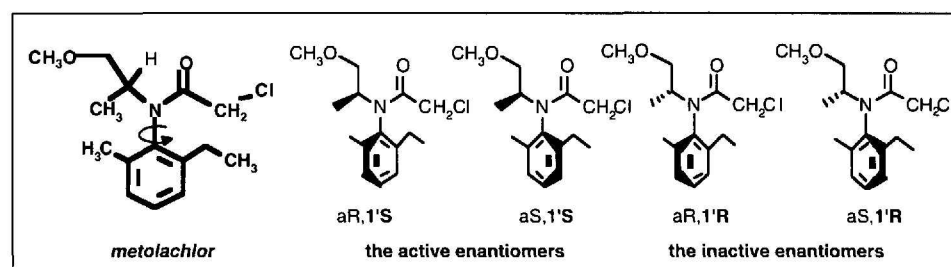


Fig. 1. Structure and stereoisomers of metolachlor