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New Chiral *o*-Hydroxyphenyl Diazaphospholidine Oxide. Catalytic Application in Asymmetric Addition of Diethylzinc to Aromatic Aldehydes.

Jean-Michel Brunel, Thierry Constantieux, Olivier Legrand and Gérard Buono*

Ecole Nationale Supérieure de Synthèse, de Procédés et d'Ingénierie Chimiques d'Aix Marseille, UMR CNRS 6516, Faculté de St Jérôme, Av. Escadrille Normandie Niemen, 13397 Marseille, Cedex 20, France.

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Abstract : Synthesis of diastereomerically pure *o*-hydroxyphenyl diazaphospholidine oxide **2** was achieved from a chiral diamine derived from (*S*)-proline. This new compound has been tested as catalyst in the asymmetric addition of diethylzinc to aromatic aldehydes. Corresponding *sec*-alcohols were obtained in high yields (up to 90%) with enantiomeric excesses varying from 15 to >99%. The influence of the solvent and also the important relation existing between the nature of the aldehydes and the enantioselectivity have been investigated.

In recent years, there was a great interest in the development of transition metal catalyzed asymmetric reactions[1] and more precisely in the synthesis of highly enantioselective ligands[2]. In this area, the most commonly applied are chiral phosphines[3], and more recently, phosphorus/nitrogen mixed donnor bidentate compounds[4]. Tertiary chalcogenides were known to be efficient ligands[5a], but few catalytic applications principally limited to the use of triphenyl phosphine oxide have been reported[5b]. Nevertheless, asymmetric synthesis using chiral phosphoramides[6] as auxiliaries is well known. Recently, these compounds[7] as well as phosphinamides[8] or oxazaphospholidine oxides[9] have been shown to be efficient catalysts in various enantioselective reactions. Moreover, pentavalent phosphorus systems such as phosphoramidates and thiophosphinamides provided catalysts which give dramatically improved enantiomeric excesses (ee)[10]. The presence of a proximal hydroxyl group on these compounds revealed the importance of the secondary ligand-substrate interaction on the enantioselective process[11].

In this context, our interest in asymmetric catalysis prompted us to design a new chiral *o*-hydroxyphenyl diazaphospholidine oxide **2** possessing bothly a basic site (P=O) and an acid site (OH)[12]. In this paper, we report the synthesis of optically active compound **2** and its use as highly efficient catalyst for the enantioselective diethylzinc aldehyde addition.

Diastereomerically pure *o*-hydroxyphenyl diazaphospholidine **1** was easily prepared by exchange reaction from the key intermediate bis(dimethylamino)-*o*-anisyl phosphine[13] and a chiral diamine derived from (*S*)-proline[14] (Scheme 1).[1]

[1] Fax : 04-91-02-77-76 E-mail : buono@spi.u-3mrs.fr

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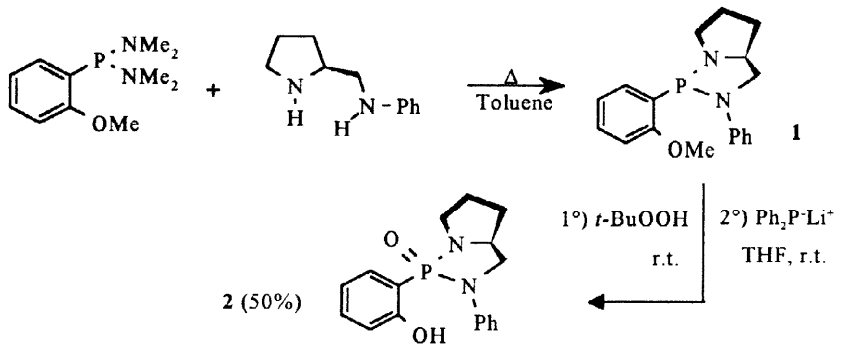
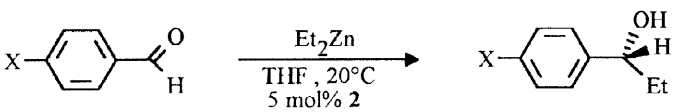


Scheme 1

The latter gave rise only one diastereomer **1** with the *R* configuration at the phosphorus atom[15]. Oxidation by *tert*-butyl hydroperoxide and deprotection of the methoxy group by lithium diphenylphosphine lead to the formation of **2**[16]. After flash chromatography on silicagel, compound **2** was isolated as a white solid stable to air and moisture.

Addition of dialkylzinc to aldehydes is one of the most reliable method to synthesize optically active *sec*-alcohols[17]. Compound **2** has been tested as catalyst in this reaction and we firstly studied the influence of the solvent in presence of 5 mol% of **2** with respect to the substrate on the enantioselectivity. The reactions were conduced at 20°C under argon atmosphere during 48 hours with 2 equiv. of Et_2Zn (Table)[18].

Table . Enantioselective addition of Diethylzinc to Aromatic Aldehydes in Presence of 5 mol% of **2**.



Entry	X	Solvent	Yield (%)[b]	ee (%)[c]	Config[d]
1	H	Hexane	96	15	*R*
2	H	Toluene	95	21	*R*
3	H	CH_2Cl_2	96	46	*R*
4	H	DMF	92	68	*R*
5	H	THF	98	73	*R*
6	H	THF[a]	44	60	*R*
7	NMe_2	THF	98	71	*R*[e]
8	Cl	THF	84	86	*R*
9	**CN**	**THF**	**91**	**> 99**	***R***[e]

[a] Experiment performed at 0°C. [b] Isolated yield. Experiment performed at 1 mmol scale. [c] Ee determined by HPLC analysis on a Daicel Chiralcel OD-H column at λ = 254 nm. [d] Absolute configurations determined by comparison of reported optical rotations[19]. [e] Absolute configurations determined by analogy of previously reported results.

In all cases, 1-phenyl propanol was obtained in high chemical yields varying from 92 to 98%. Nevertheless, DMF and THF appeared to be the best solvents in term of enantioselectivity (entries 4 and 5, respectively 68% and 73% ee) whilst apolar solvents such as hexane or toluene led to poor ee (entries 1 and 2, respectively 15% and 21% ee). This study has been extended to a serie of aromatic aldehydes bearing various substituents in the *para* position (entries 7-9). It appears that the enantioselectivity remarkably increases with more reactive substrates. The aromatic aldehydes bearing electron withdrawing groups on the para-position afforded important ee than those with electron donating groups[20].

In this paper, we have developped the synthesis of a new chiral *o*-(hydroxyphenyl)diazaphospholidine oxide and its use in asymmetric addition of diethylzinc to aromatic aldehydes with moderate to high enantioselectivity. Moreover, we have clearly shown the influence of the solvent on the ee and established the important relation existing between the nature of the aldehydes and the enantioselectivity.

We are currently extending the synthesis of such catalysts using diols and aminoalcohols as chiral auxiliaries. Further investigations of their catalytic ability are still in progress.

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