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Enantioselective hydrophosphonylation of *N*- benzyl imines, isatin derived ketimines and isatins catalyzed by in-situ generated Ti(IV) macrocyclic salen complexes

Mohd Nazish[a,b], Ajay Jakhar[a,b], Noor-ul H. Khan[a,b,*], Shailesh Verma[a,b], Rukhsana I. Kureshy[a,b], Sayed H.R. Abdi[a,b], Hari C. Bajaj[a,b]

[a] *Discipline of Inorganic Materials and Catalysis*
[b] *Academy of Scientific and Innovative Research, CSIR—Central Salt and Marine Chemicals Research Institute (CSIR-CSMCRI), G.B. Marg, Bhavnagar 364 002, Gujarat, India*

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ABSTRACT

Ti-salen complexes were generated by using a series of chiral macrocyclic salen ligands and were used as catalysts for enantioselective hydrophosphonylation (**EHP**) reaction of benzylimines, isatin derived ketimines and isatins. The corresponding phosphonylated products were obtained with excellent yield (up to 92%) and enantioselectivity (ee up to 99%) with low catalyst loading at room temperature using dimethyl phosphite as nucleophile **(IIa)** for isatins and benzylimines, whereas for ketimines diphenyl phosphite (**IIb**) gave best results with very good yield (up to 88%) and ee (up to 99%). The Ti(IV) complex was recoverable and recyclable with retention of its catalytic performance at gram scale level. To understand the reaction mechanism NMR studies have been carried out using benzylimine as a model substrate and dimethyl phosphite as a nucleophile.

1. Introduction

Chiral α-amino- [1] and α-hydroxy- [2] phosphonates are important class of synthetic intermediates used for pharmaceutical compounds. These potentially bioactive compounds are having anti-fungal [3], anti-bacterial [4], anti-HIV [5] and anti-protease [6] properties. Enantioselective hydrophosphonylation of aldimines/ketimines and ketones are straightforward methods for the synthesis of α-amino- and α- hydroxy-phosphonates respectively, however, for achieving high enantioselectivity and yield in the desired product under mild reaction conditions is still a challenge. Nevertheless, since last two decades there are several reports on metal catalysts and organo-catalysts mediated enantioselective addition of phosphite to aldehydes [7,8] and aldimines,[9,10,7k] but the substrates like ketones [11,12] and ketimines [13] are less explored. Furthermore, reports on hydrophosphonylation of less reactive ketones like isatins (**4a**) [11(c,d)] and isatin derived ketimines (**6a**) [13(b,c)] are fewer in number. Notwithstanding the above, there is no report for hydrophosphonylation reaction that can effectively handle these less-reactive substrates as well as benzylimine (**Ia**). Hence, development of an efficient catalytic protocol is desirable from commercials and practical point of view. With our ongoing interest in developing chiral catalysts for various asymmetric organic transformations [14], herein, we report the use of macrocyclic Ti(IV)-salen complexes as catalysts for EHP of benzylimine, isatin derived ketimines and isatins. We have found that macrocylic ligand **1d** (having pentagol linker) in combination with $Ti(O^iPr)_4$ is the best catalyst among others (**1a**–**1d**, **2d** and **3d**) for all the three types of substrates stated above using dimethyl phosphite (DMP)/diphenyl phosphite (DPP) as nucleophile under mild reaction condition to get enantioenriched phosphonylated products in good to excellent yield. To the best of our knowledge, this is the most efficient Ti complex based catalytic system for the enantioselective hydrophosphonylation reaction with an advantage of handling varied substrates.

2. Results and discussion

Chiral macrocyclic ligands **1a–d**, **2d** and **3d** were synthesised and characterized according to the reported procedure (Scheme 1)

* Corresponding author. Fax: +91 2782566970.
E-mail address: khan251293@yahoo.in (N.-u.H. Khan).

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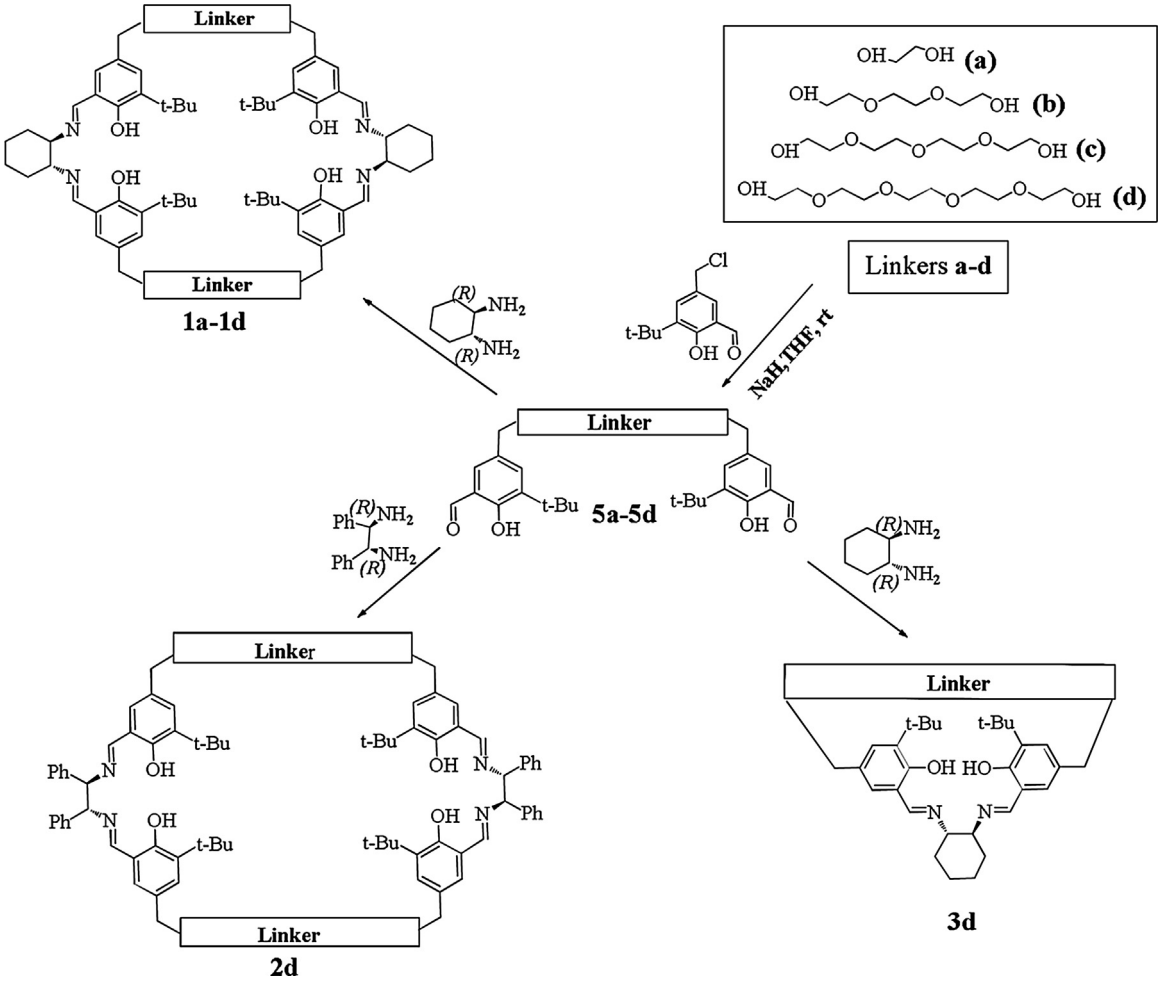

Scheme 1. Synthesis of chiral ligands with different type of chiral sources (**1a–1d**) (R,R)-cyclohexane-1,2-diamine, Dry THF, RT. (**2d**) (R,R)-1,2-diphenylethane-1,2-diamine, Dry THF, RT. (**3d**) (R,R)-cyclohexane-1,2-diamine, MeOH, RT.

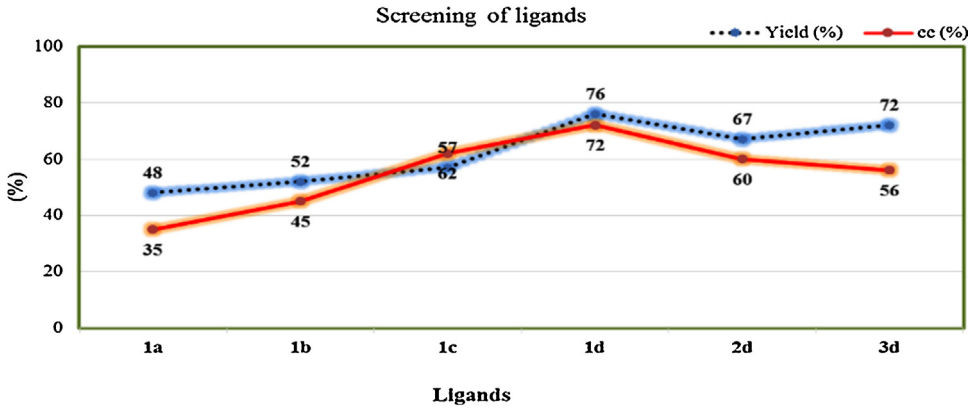

Fig. 1. Screening of ligands for asymmetric HP reaction. Isolated yield after flash chromatography. ee's were determined by chiral HPLC using chiralpak IA column.

[14a]. To evaluate their efficacy in EHP reaction, these ligands were allowed to react with Ti(O^iPr)$_4$ in 1:1 L:M molar ratio in order to in situ generate the corresponding complex. To begin with, benzylimine **Ia** was used as a model substrate for the EHP using in situ generated Ti(IV) macrocyclic salen complexes as catalyst (5 mol%) and 1.5 equivalent of **IIa** (with respect to substrate) as nucleophile at room temperature (RT) under N_2 atmosphere using toluene as a solvent for 30 h and the data are shown in Fig. 1. In all the cases the desired product (**IIIa**) was obtained in moderate to good yield (48–76%) with low to moderate enantioselectivity (35–72%). It is evident from the results that the nature of the linker played a significant role in yield and enantioselectivity of the desired product **IIIa**. Lower yield and enantioselectivity (Fig. 1) was achieved with ligand 1a which had a short and rigid linker as compared to the ligand **1b** and **1c**. Among them (**1a–1d**, **2d** and **3d**), the ligand 1d having (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and pentagol as a linker in combination of Ti (O^iPr)$_4$ turned out to be a better catalyst to give phosphonylated products in better yield. This shows that a more