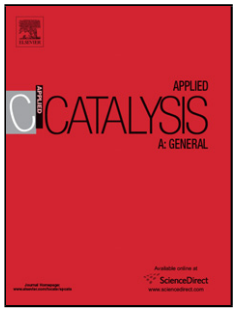

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Enantioselective hydrophosphonylation of *N*-benzyl imines, isatin derived ketimines and isatins catalyzed by in-situ generated Ti(IV) macrocyclic salen complexes

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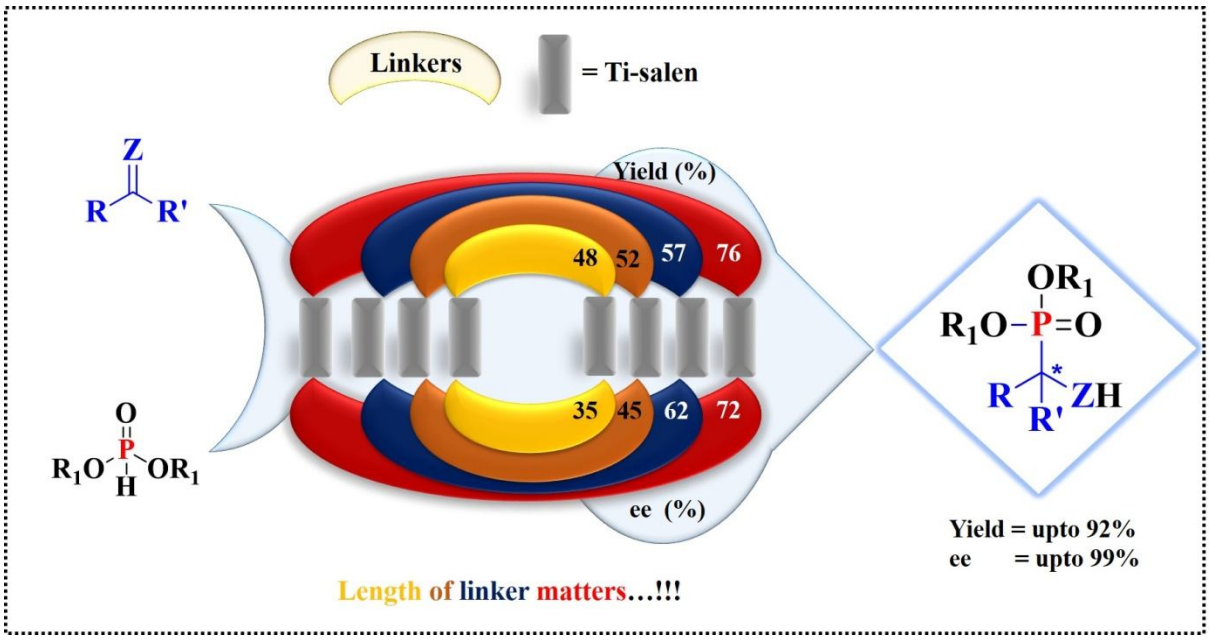

Highlights

- macrocyclic salen-titanium complex
- catalyst recyclable five times
- Asymmetric hydrophosphonylation reaction with 21 examples
- Simple, ideal and efficient catlytic protocol
- Proposed a mechanism based on NMR spectroscopic study

Abstract:

Ti-salen complexes were generated *in situ* by using a series of chiral macrocyclic salen ligands and were used as catalysts hytfor 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.

Keywords: Hydrophosphonylation, isatin imine, ketone, titanium, phosphite

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-1d**, **2d** and **3d** were synthesised and characterized according to the reported procedure (Scheme 1).[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 Figure 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 (**Figure 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 flexible linker is beneficial to provide favourable environment for the enantioselective catalytic process (**Figure 1**). For further improve the catalytic protocol, we have screened the effect of different titanium sources (**Figure 2**) using the ligand **1d** to generate active catalyst *in situ* and found that $Ti(O^iPr)_4$ (yield 76%, ee 72%) is the best metal source as compared to other titanium sources like $Ti(O^tBu)_4$ (yield 45%, ee 42%), $TiCl_4$ (yield 18%, ee 20%) and $TiBr_4$ (yield 16%, ee 15%). The high reactivity of $Ti(O^iPr)_4$ is probably due to the presence of isopropoxide ion, which is relatively better for activating the nucleophile via abstracting the proton.[15] Having identified the suitable metal source, we froze $Ti(O^iPr)_4$ as the right choice of metal source (5 mol%) in combination with 5 mol% of **1d** to optimize other reaction parameters.

Since there are two salen units in the macrocyclic ligand (**1d**), it was prudent to vary metal to ligand ratio. Accordingly, experiments were carried out with different amounts of $Ti(O^iPr)_4$ with respect to **1d** (ratios ranged over 1:0.5 to 1:1.5) using 5 mol% of $Ti(O^iPr)_4$ in all the cases. On decreasing the amount of ligand from metal:ligand ratio 1:1 (Table 1, entry 1) to 1:0.5 there was a significant improvement in the product yield (92%) and enantioselectivity (77%, Table 1, entry 2). While on increasing the ligand amount (M:L ratio 1:1.5, entry 3) there was no substantial change in the reaction outcome. On the other hand lowering of the catalyst loading using M:L ratio 1:0.5 from 5 mol% (as per entry 2) to 2.5 mol%, resulted in slight increase in ee (82% ee, entry 4) of the product but the yield was decreased. However, on increasing the catalyst loading to 10 mol% and 15 mol% (entries 5 and 6) product yield (96% and 97% respectively) was increased, but the ee (72% and 60%) decreased significantly. So based on the above observations we concluded that a metal to ligand ratio of 1:0.5 with 2.5 mol% catalyst loading is optimum to get product in high yield and ee (entry 4). Next, the solvent screening study showed that toluene is the best solvent as compare to other solvents such as CH_2Cl_2, $CHCl_3$ and THF which gave lower product yield and

enantioselectivity (Figure 3). Variation in reaction temperature is known to affect both yield and enantioselectivity of the product significantly; therefore we investigated the outcomes of EHP reaction at lower temperatures like 0°C and -10°C. Unfortunately, we observed a drastic drop in the yield and minor decrease in enantioselectivity at lower temperatures (**Figure 3**). Besides DMP, we have also tried other commercially available phosphonylating reagents in order to explore the possibility of getting better product yield and enantioselectivity. Accordingly, we took 1.5 equivalents of diphenyl phosphite (DPP), diethyl phosphite (DEP) and dibenzyl phosphite (DBP) to study the influence of these nucleophiles under the above optimized reaction condition (**Figure 3**). Among all the phosphite sources used here, DMP was found to be the best (yield 89% and ee 82%) for this reaction (Table 2, entry 1). Ideally substrate and phosphite should be taken in equimolar quantities, often variation in nucleophile concentration leads to variation in reaction outcome. Accordingly, the reaction was carried out with 0.8 to 2.0 equivalent of phosphite (DMP) with respect to substrate and found that only a slight excess i.e., 1.1 equivalent of DMP is sufficient enough to achieve highest enantioselectivity (92%) with good yield (84%) (Table 2, entry 7). To get a deeper insight into the matter, we have tested the nonlinear effect (NLE) of the present bimetallic titanium system (**Figure 4**) and observed a positive NLE of this catalytic system. At this point of time, the specific reason for this effect on reactivity and enantioselectivity is unknown but based on **Figure 4** a possible cooperative effect in bimetallic complex cannot be ruled out. Further, with the optimized reaction condition (as per Table 2, entry 7), this protocol was extended to various substituted imines **Ia**-**Ih** bearing electron donating as well as withdrawing groups at various positions of aromatic ring (of aromatic aldehyde origin) and got the products in high yield (82-92%) and excellent enantioselectivity (92-98%, Table 3). As such we have not got any trend in the results on varying substituents, but in general higher ee in the products were achieved with substituted imines as substrates, except for 4-trifluromethyl substituted imine **Ih** (Table 3, entry 8) where the results were at par with unsubstituted imine **Ia** (Table 3, entry 1).

3. Asymmetric hydrophosphonylation reaction of isatins derived ketimines (IVa)

The catalytic protocol that was used above for imines **Ia**-**Ih**, was explored for its effectiveness in the EHP of isatin derived ketimine **IVa** where we got the corresponding product **Va** in high yield (85%) but with lower ee (40%) (Table 4, entry 1). In order to improve the results we first varied several reaction conditions e.g., temperature, solvent and catalyst loading but with little or no success (data not included). However, when we used phosphonylating agents namely, DEP, DBP and DPP there was significant improvement in the enantioselectivities (Table 4, entries 2-4). Highest enantioinduction was obtained in the case of phosphonylating agent DPP (ee, 88%; Table 4, entry 4). To take these results forward we explored the role of additives in EHP of **IVa** using DPP as phosphonylating agent under the above optimized conditions. Accordingly methanol, water, 4Å molecular sieve (MS), benzoic acid and lutidine were

used as additives for this reaction (Table 4, entries 5-9). Clearly, the use of 4Å-MS significantly improved the enantioselectivity of the desired product **Va** (Table 4, entry 7) with marginal improvement in the product yield.

The above optimized conditions were further extended to other related substrates **IVa-IVf** to get the products **Va-Vf** in very good yields (up to 84-88%, Table 5, entries 1-6). However, excellent enantioselectivities were obtained with substrates **IVa** and **IVb** (ee's >99 and 98%) having no substituent or with electron donating methyl group respectively. Presence of an electron-withdrawing groups (Cl and F) adversely effected enantioselectivty (Table 5; entries 3 and 4; ee's 68 and 63% respectively) whereas yields remained same. A substrate with *N*-methyl isatin derived ketimine **IVe** gave results (Table 5, entry 5; yield, 86%; ee, >99%) at par with *N*-benzyl isatin derived ketimine **IVa**. On the other hand substrate isatin having no substituent at *N*- (**IVf**) provided the product with significantly lower ee (46%; entry, 6) but with good yield (88%).

4. Asymmetric Hydrophosphonylation reaction of isatins (VIa)

In order to further expand the scope of the above-developed hydrophosphonylation protocol, we used isatins (**VIa-VIg**) as substrates to get biologically important target compounds (**VIIa-VIIg**). The catalytic system that was explored for the substrates **Ia-Ig**, was also used for EHP of isatin derivatives (**VIa-VIg**) to get the corresponding products **VIIa-g** (Table 6) in high yield (up to 88%) as well as high enantioselectivity (up to 99%) except for the *N*-protected isatins **VId** and **VIg**, which gave racemic products **VIId** and **VIIg**. These results are in contrast to those obtained for the EHP reaction of isatin imines (Table 5) where *N*-protected isatins gave products with better ee's.

5. Mechanism

To understand the reaction mechanism during hydrophosphonylation reaction we carried out a series of NMR experiments using *N*-benzylimine as representative substrate. The formation of Ti(IV) complex was evident from the ^{1}H NMR spectra of ligand **1d** alone (**Figure 5a**) and **1d** + Ti(O^{i}pr)$_4$ (**Figure 5b**) where phenolic proton of **1d** disappears on complexation with a significant upfield shift (0.25 ppm) in the imine proton. To the complex thus formed, the imine **Ia** was added. We observed a downfield (0.05 ppm, **Figure 5d**) shift in the imine proton suggesting a weak interaction between imine nitrogen of **Ia** with titanium (bearing Lewis acidity) (Scheme-2, intermediate-**A**). Consequently the substrate was activated and makes it available for the attack by P of phosphonylating agent **IIa**. We also carried out ^{31}PNMR experiments to see the involvement of **IIa** (**Figure 6a**) in the catalytic cycle and found a 0.10 ppm downfield shift in its peak when added to the reaction mixture containing titanium complex and substrate **Ia** (**Figure 6b**)

(**Scheme 2**, intermediate-**B**). Based on the above observation we have proposed a probable mechanism as given in **Scheme 2.**

6. Recycling of catalyst

In an oven dried sample vial, ligand **1d** (2.5 mol%) and titanium tetra isopropoxide (5 mol%) were taken in dry toluene (1 mL). The mixture thus obtained was stirred at room temperature under N_2 for 2 h. Subsequently, Substrate **Ib** (10 mmol) was added to the above stirring yellow solution followed by the addition of DMP. After the completion of the reaction (20-30 h) the solvent and the volatile compounds were evaporated under reduced pressure. The residue was extracted and washed with hexane to remove excess DMP, unreacted substrate and product were dried under reduced pressure for 1–2 h and was used as catalyst **Ti-1d** for the next cycle of asymmetric hydrophosphonylation reaction. This process was repeated over five consecutive cycles with retention of catalyst activity and enantioselectivity (**Figure 7**).

7. Conclusions

In conclusion, we have developed a chiral Ti(IV)-salen complex as an efficient catalyst for enantioselective hydrophosphonylation reaction of *N*-benzylimines, isatin derived ketimines and isatins. In most of the cases, the corresponding phosphonylated products were obtained in very good yield and excellent ee at RT. The catalyst was recycled five times with retention of its catalytic activity and enantioselectivity. A probable mechanism for this reaction was proposed based on a series of NMR experiments by using *N*-benzylimine as a representative substrate.

8. Experimental

8.1 Materials and methods;

All the solvents were dried using standard procedures, distilled and stored under nitrogen. NMR spectra were obtained by using Bruker Avance DPX_{200} and Bruker Avance II 500 spectrometers and were referenced internally to trimethylsilane (TMS). Enantiomeric excess (ee) values were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD-H, IC, IA and OJ chiral columns with 2-propanol/hexanes as eluent. For the product purification, flash chromatography was performed using 230−400 mesh silica gel.

8.2 Typical experimental procedure for the enantioselective hydrophosphonyation reaction Uusing catalyst 1d.

In an oven dried reaction vial, ligand **1d** (2.5 mol %) was dissolved in dry toluene (1 mL), and to the resulting solution $Ti(O^iPr)_4$ (5 mol%) was added and the resulting solution was stirred for 2 h under N_2 at RT. To the above stirred solution **(Ia)**/isatin (0.17 mmol) was added and the stirring was further continued for another 30 min. After that, DMP (0.19 mmol) was added drop-wise to the above solution over 30 min. While in the case of isatin derived ketimines, initially ligand **1d** (2.5 mol%) was dissolved in dry toluene (1 mL), and $Ti(O^iPr)_4$ (5 mol%) was added to it and the resulting solution was stirred for 2 h at RT. Then 4Å MS (20 mg) and isatin derived ketimines **(IVa)** were added under stirring condition. After 30 min, DPP (**IIb**) was added over a period of 30 min. The reaction was monitored by TLC using hexane/ethyl acetate (70/30) as eluent. After the completion of the reaction, the solvent was removed on a rotary evaporator, and the product was purified by flash column chromatography on a silica gel column (eluted with hexane/ethyl acetate=70/30). The purified products were characterized by LCMS and NMR.

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Supplementary data

For additional characterization data of hydrophosphonylated products (see the supporting information).

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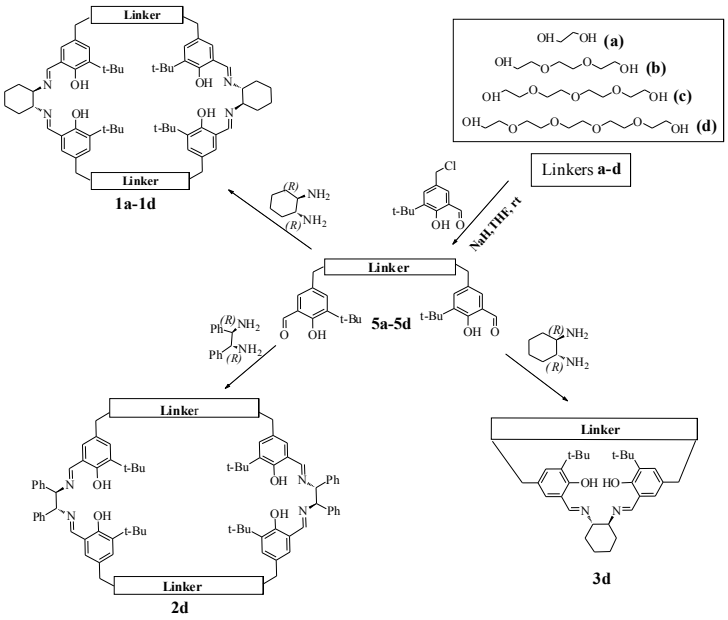
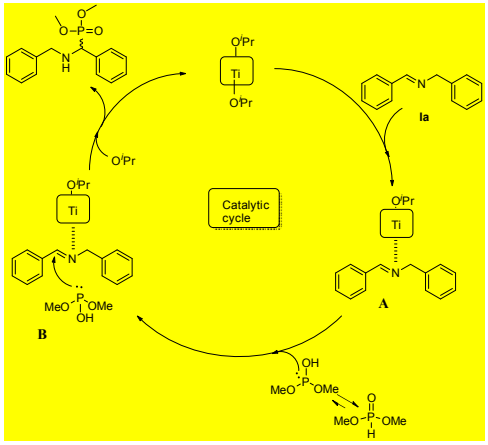


Scheme 1: Synthesis of chiral ligands with different type of chiral sources (**1a-1d**) (R,R)-cyclohexane-1,2-diamine, Dry THF, RT. (**2d**) (R,R)-1,2-diphenylethane-1,2-diamine, Dry THF, RT. (**3d**) (R,R)-cyclohexane-1,2-diamine, MeOH, RT.



Scheme 2. Proposed Reaction Mechanism with *N*-benzylimine substrate.

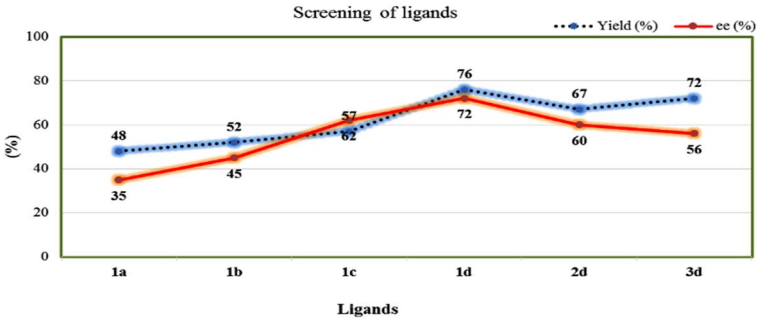


Figure 1. Screening of ligands for asymmetric HP reaction. Isolated yield after flash chromatography. ee's were determined by chiral HPLC using chiralpak IA column.

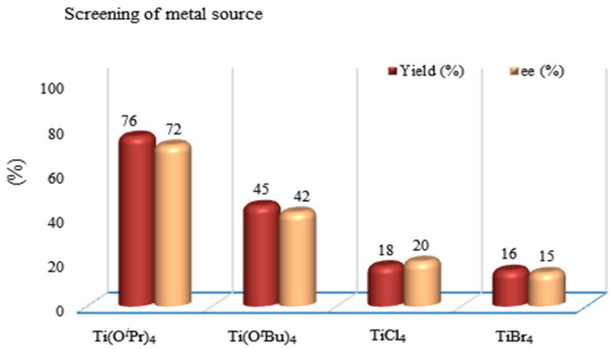


Figure 2. Reaction condition: ligand **1d** (5 mol%), Ti(O^{i}pr)$_4$ (5 mol%), *N*-benzylimine (1 mmol), DMP (1.5 mmol) at RT Isolated yield after flash chromatography. ee's were Determined by chiral HPLC using an chiralpak IA column.

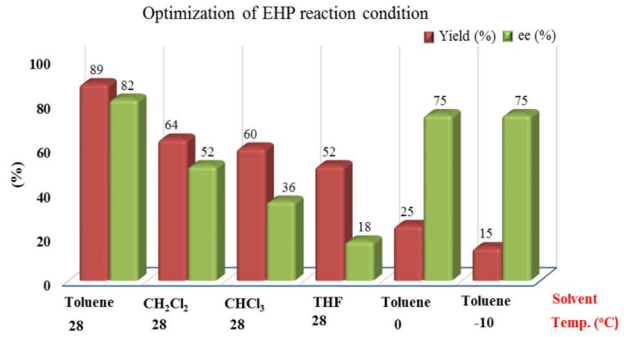


Figure 3. Reaction condition: ligand **1d** (2.5 mol %), Ti(O^{i}Pr)$_4$ (5 mol%), *N*-benzylimine (1 mmol), DMP (1.5 mmol) at RT. Isolated yield after flash chromatography. ee's were Determined by chiral HPLC using an chiralpak IA column.

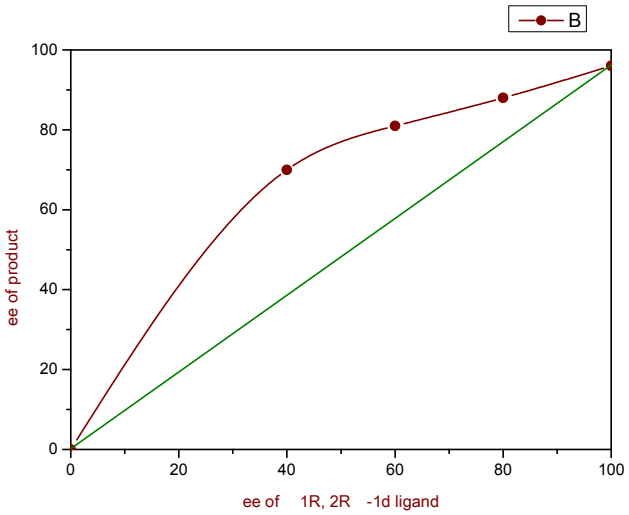


Figure 4. Positive NLE in the HP of N-benzylimine with *in situ* generated bimetallic Ti-complex from dimeric ligand **1d**.

Figure 4. Positive NLE in the HP of N-benzylimine with *in situ* generated bimetallic Ti-complex from dimeric ligand **1d**.

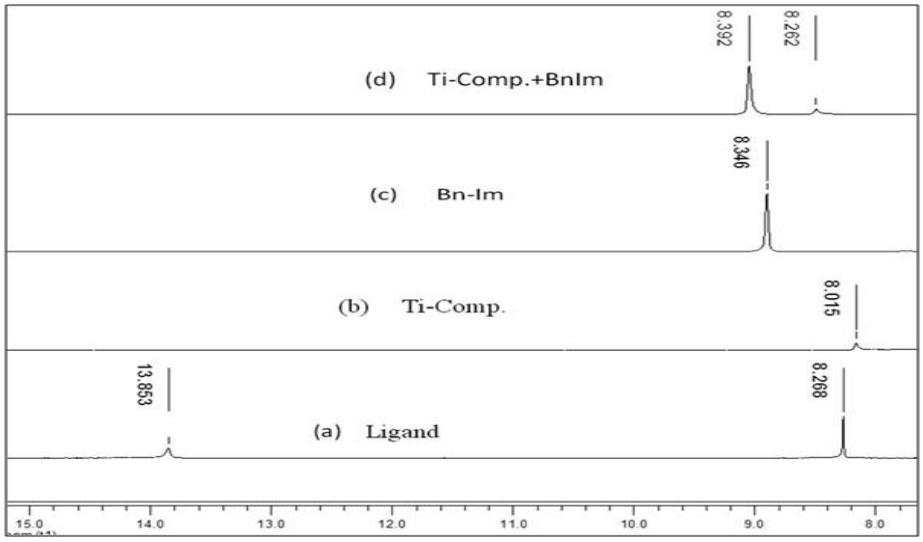


Figure 5. (a)^{1}H NMR of Ligand in $CDCl_3$, (b)Ti-Complex, (c)Substrate *N*-benzylimine, (d)Ti-Complex + Substrate *N*-benzylimine.

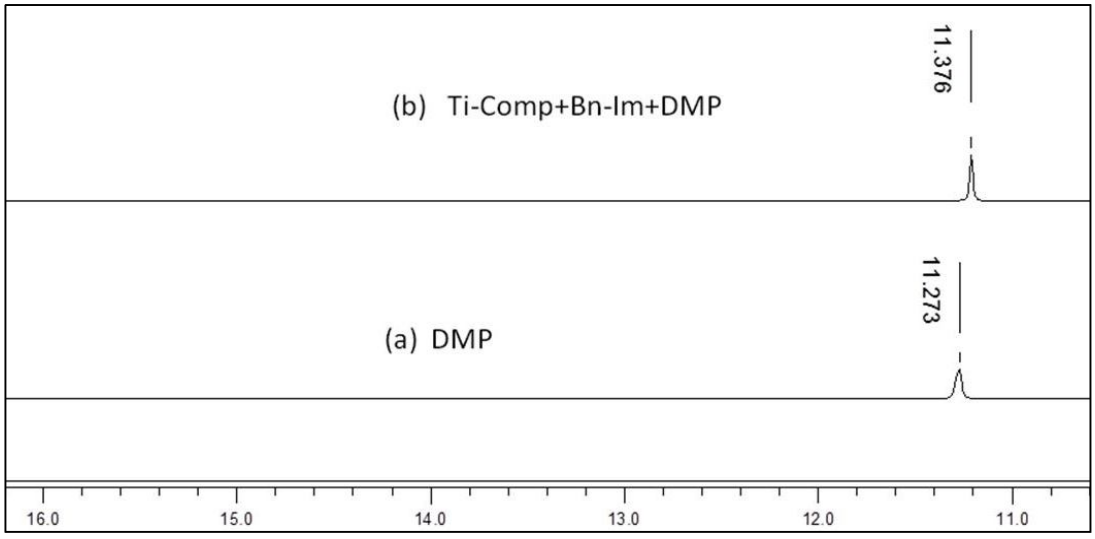


Figure 6. ^{31}P NMR in $CDCl_3$ (a) DMP (b) Ti-Complex + Substrate *N*-benzylimine + DMP.

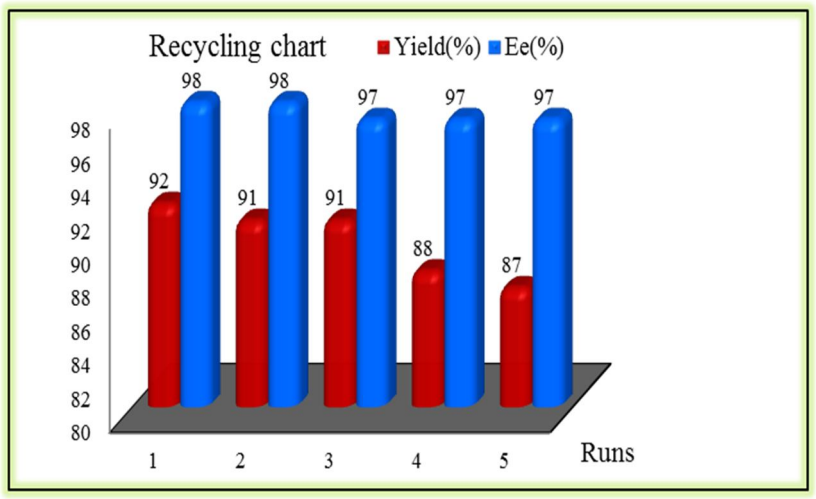
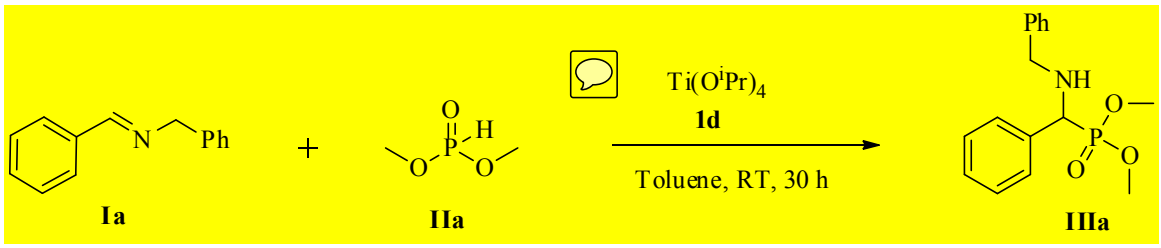


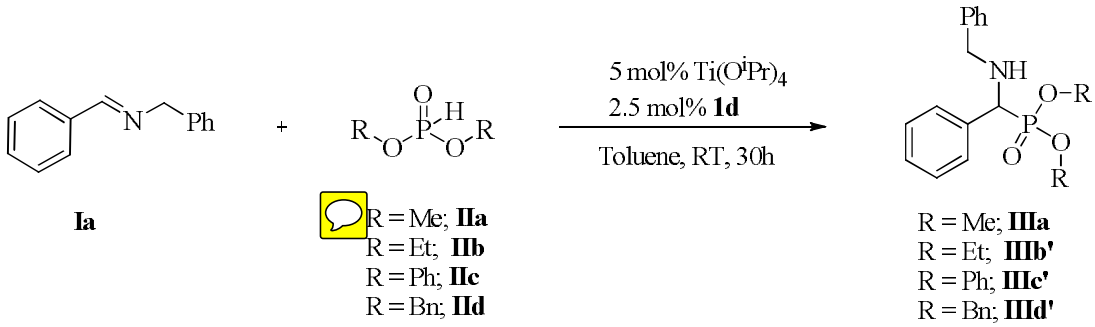
Table 1 Optimization catalyst loading and metal/ligand ratio[a]



Entry	Cat. loading (mol%)	$Ti(O^iPr)_4$/**1d**	Yield[b] (%)	ee[c] (%)
1	5	1:1	76	72
2	5	1:0.5	92	77
3	5	1:1.5	74	75
4	2.5	1:0.5	89	82
5	10	1:0.5	96	72
6	15	1:0.5	97	60

[a]Reaction condition: ligand **1d**, $Ti(O^iPr)_4$, *N*-benzylimine (1 mmol), DMP (1.5 mmol) at RT [b]Isolated yield after flash chromatography. [c]ee's were determined by chiral HPLC using chiralpak IA column.

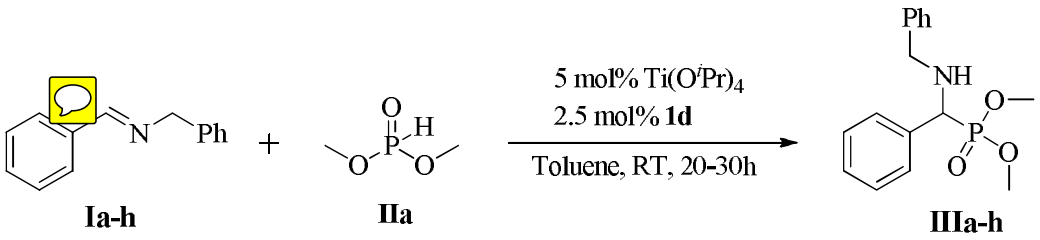
Table 2 Screening of phosphorous sources for asymmetric HP of *N*-benzylimine[a]



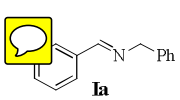
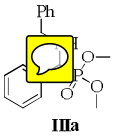
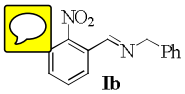
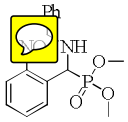
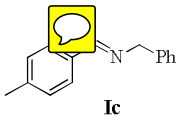
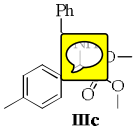
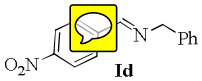
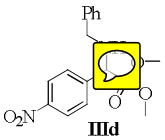
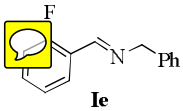
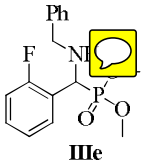
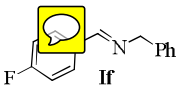
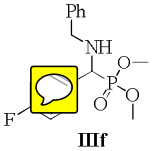
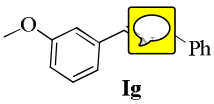
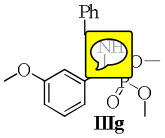
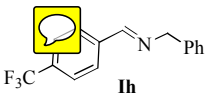
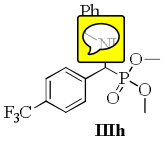
Entry	Phosphite sources	Loading (equivalent)	Yield[b] (%)	ee[c] (%)
1	DMP(**IIa**)	1.5	89	82
2	DEP(**IIb**)	1.5	44	63
3	DPP(**IIc**)	1.5	60	58
4	DBP(**IId**)	1.5	15	89
5	DMP	2	90	54
6	DMP	1.2	87	88
7	DMP	1.1	84	92
8	DMP	1	72	87
9	DMP	0.8	66	87

[a]Reaction condition: ligand **1d** (2.5 mol%), Ti(O^{i}Pr)$_4$ (5 mol%), *N*-benzylimine (1 mmol), **DMP** at RT [b]Isolated yield after flash chromatography. [c]ee's were determined by chiral HPLC using chiralpak IA column.

Table 3 Asymmetric HP reaction of various *N*-benzylimines (**Ia-Ih**) under optimized reaction condition[a]

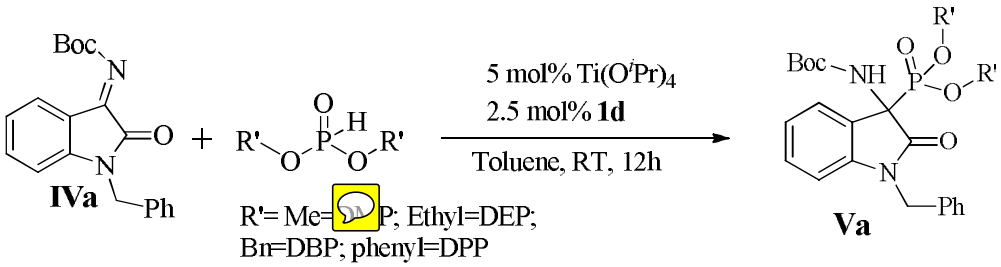


Entry	Substrates	Product	Yield[b] (%)	ee[c] (%)

1	 **Ia**	 **IIIa**	84	92
2	 **Ib**	 **IIIb**	90	98
3	 **Ic**	 **IIIc**	82	97
4	 **Id**	 **IIId**	92	98
5	 **Ie**	 **IIIe**	92	97
6	 **If**	 **IIIf**	90	97
7	 **Ig**	 **IIIg**	83	97
8	 **Ih**	 **IIIh**	84	92

[a]Reaction condition: ligand **1d** (2.5 mol%), Ti(O^{i}Pr)$_4$ (5 mol%), *N*-benzylimine (1 mmol), **DMP** (1.1 mmol) at RT [b]Isolated yield after flash chromatography. [c]ee's were Determined by chiral HPLC using an chiralpak AD-H column.

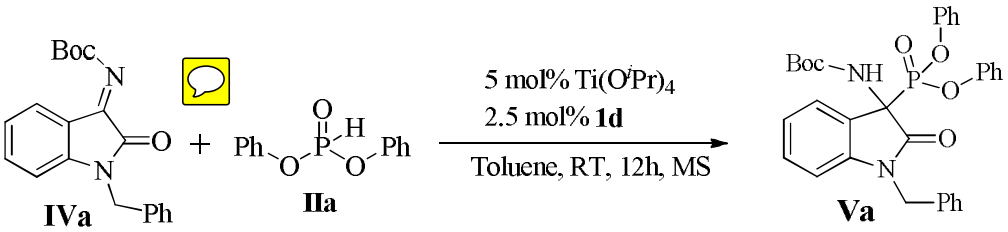
Table 4 Screening of phosphorous sources in asymmetric hydrophosphonylation reaction of isatin derived ketimine **IVa** [a]

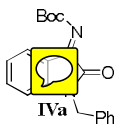
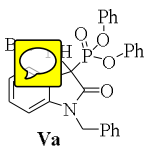
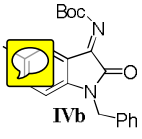
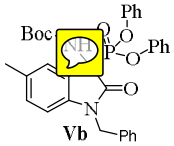


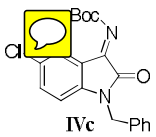
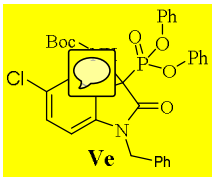
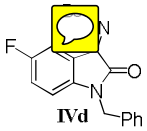
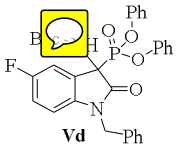
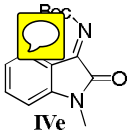
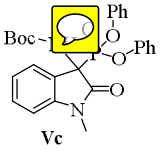
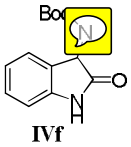
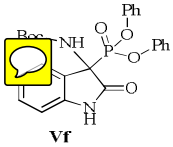
Entry	Phosphite source	Additives	Yield[b] (%)	ee[c] (%)
1	DMP	-	85	40
2	DEP	-	36	53
3	DPP	-	78	88
4	DBP	-	15	72
5	DPP	CH_3OH (1mol%)	90	88
6	DPP	H_2O (1mol%)	90	89
7	DPP	MS(4Å) (20mg)	84	>99
8	DPP	Benzoic acid (1mol%)	80	86
9	DPP	Lutidine (1mol%)	90	72

[a]Reaction condition: ligand **1d** (2.5 mol%), $Ti(O^iPr)_4$ (5 mol%), **IVa** (1 mmol), **IIa/IIb/IIc/IId** (1.1 mmol) at RT [b]Isolated yield after flash chromatography. [c]ee's were Determined by chiral HPLC using an chiralpak IC column.

Table 5. Substrates scope for the EHP reaction of isatin imines[a]

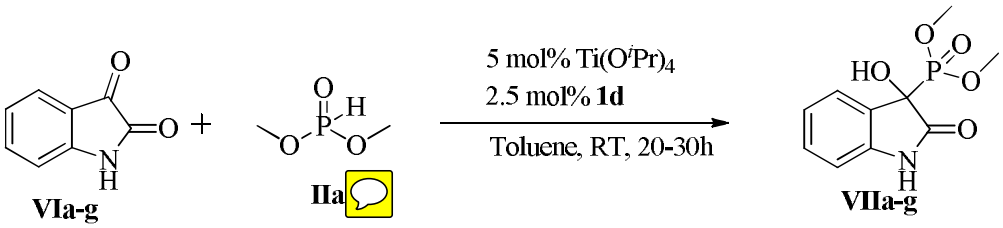


Entry	Substrates	Product	Yield[b] (%)	ee[c] (%)
1			84	>99
2			88	98

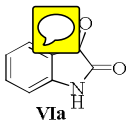
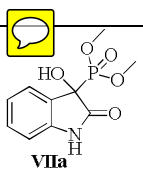
3	 IVc	 Ve	84	68
4	 IVd	 Vd	88	63
5	 IVe	 Vc	86	>99
6	 IVf	 Vf	88	46

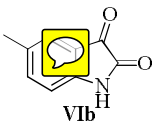
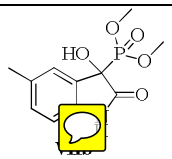
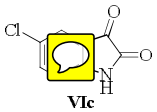
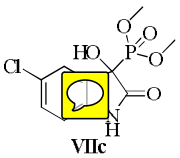
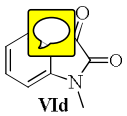
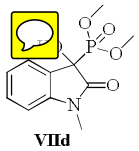
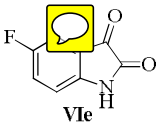
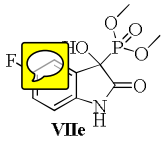
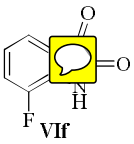
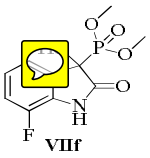
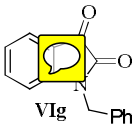
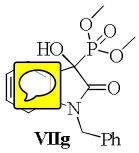
[a]Reaction condition: ligand **1d** (2.5 mol%), Ti(O^{i}Pr)$_4$ (5 mol%), **IV** (1 mmol), **DPP** (1.1 mmol), MS (20mg) at RT [b]Isolated yield after flash chromatography. [c]ee's were Determined by chiral HPLC using an chiralpak IC and ADH column.

Table 6. Asymmetric hydrophosphonylation reaction of various isatins[a]



VIa-g IIa VIIa-g

Entry	Substrates	Products	Yield[b] (%)	ee[c] (%)
1	 VIa	 VIIa	84	92

2	 VIb		80	>99
3	 VIc	 VIIc	88	91
4	 VId	 VIId	90	Racemic
5	 VIe	 VIIe	80	84
6	 VIf	 VIIf	74	92
7	 VIg	 VIIg	90	Racemic

[a]Reaction condition: ligand **1d** (2.5 mol%), $Ti(O^iPr)_4$ (5 mol%), **VI** (1 mmol), **DMP** (1.1 mmol) at RT [b]Isolated yield after flash chromatography. [c]ee's were determined by chiral HPLC using an chiralpak IC column.