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Graphical Abstract

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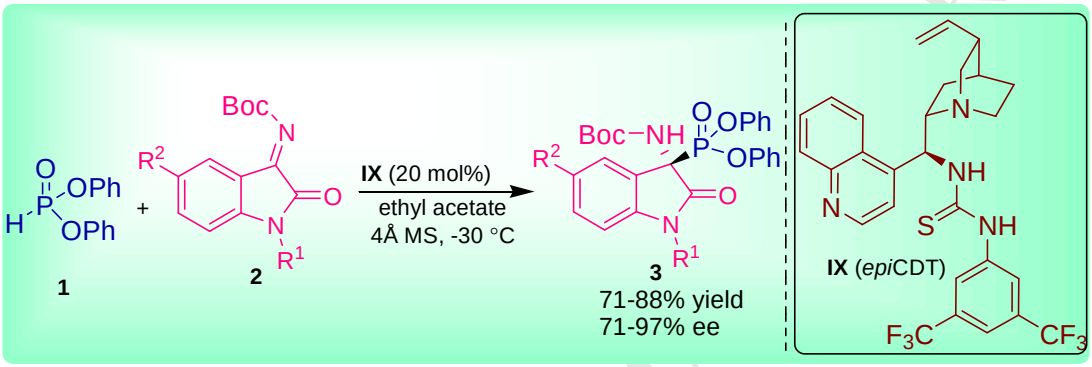

Cinchona-derived Thiourea Catalyzed Hydrophosphonylation of Ketimines - An Enantioselective Synthesis of α-Amino Phosphonates

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ABSTRACT: A highly enantioselective addition of diphenyl phosphite to ketimines derived from isatins has been developed employing bifunctional thiourea-tertiary amine organocatalysts. A variety of isatins derived ketimines react well with diphenyl phosphite in the presence of *Cinchona*-derived thiourea (***epi*CDT**) to provide biologically important chiral 3-substituted 3-amino-2-oxindoles (**3a-3l**) in good yield (up to 88%) and good enantioselectivity (up to 97% *ee*). The three-component version of the reaction through a domino *aza*-Wittig/phospha-Mannich sequence has successfully been explored.

KEYWORDS: Organocatalysis, 3-Substituted 3-amino-2-oxindoles, α-Amino phosphonates, *Cinchona*-thioureas, Ketimines

1. Introduction

The addition of compounds containing phosphorous-hydrogen bonds to C-C/C-X double bonds provides an atom economic method for the synthesis of organophosphorus derivatives.[1] Among them, the α-aminophosphonic acid derivatives, mimicking α-amino acids,[2] are important pharmacophores and play key role in various biological activities such as anti-bacterial,[3] anti-HIV[4] and protease inhibition.[5] The biological activity related to the α-aminophosphonic acid units depends on their absolute configuration. Therefore, the access to optically active α-amino phosphonic acids by stereoselective synthesis has been the object of great efforts in organic chemistry.[6] The enantioselective addition of phosphite to imines is certainly one of the most straightforward routes toward this end. In this context, large number of methodologies has been developed for the enantioselective addition of phosphites to aldimines[7], but asymmetric addition of phosphite to ketimines[8] is still a challenging task because of their low reactivity and difficulty in enantiofacial discrimination.

On the other hand, oxindole skeleton with a stereogenic quaternary carbon centre at C3 position is a privileged heterocyclic framework, that is present in the large family of bioactive natural products and a series of pharmaceutically active compounds.[9] Owing to the significance of this structural motif, a great progress has been made in the asymmetric synthesis of all-carbon quaternary oxindoles and tetrasubstituted 3-hydroxy/amino- 2-oxindoles.[10] However, asymmetric synthesis of oxindoles with two heteroatoms at the C3 position is still undeveloped[11], despite the wide occurrence of such structural motifs in the pharmaceutically active compounds.

Recently, isatin derived electrophiles have emerged as valuable electrophile for the synthesis of 3-substituted 3-amino-2-oxindoles *via* nucleophlic addition at C3 position of

oxindole and have successfully been used in variety of organocatalytic reactions.[12] As a part of our current investigations on *Cinchona* alkaloids catalyzed asymmetric transformations and synthesis of 3,3'-disubstituted oxindoles,[13] herein, we report our evaluation of the catalytic potential of *Cinchona*-derived thioureas for enantioselective addition of diphenyl phosphite with *N*-Boc ketimines to construct oxindole motifs bearing both a phosphorus and a nitrogen at the C3 position (**Figure 1**). During the preparation of this manuscript, a quinine-squaramide catalyzed reaction of phosphite with ketimines was reported by Reddy and co-workers.[14]

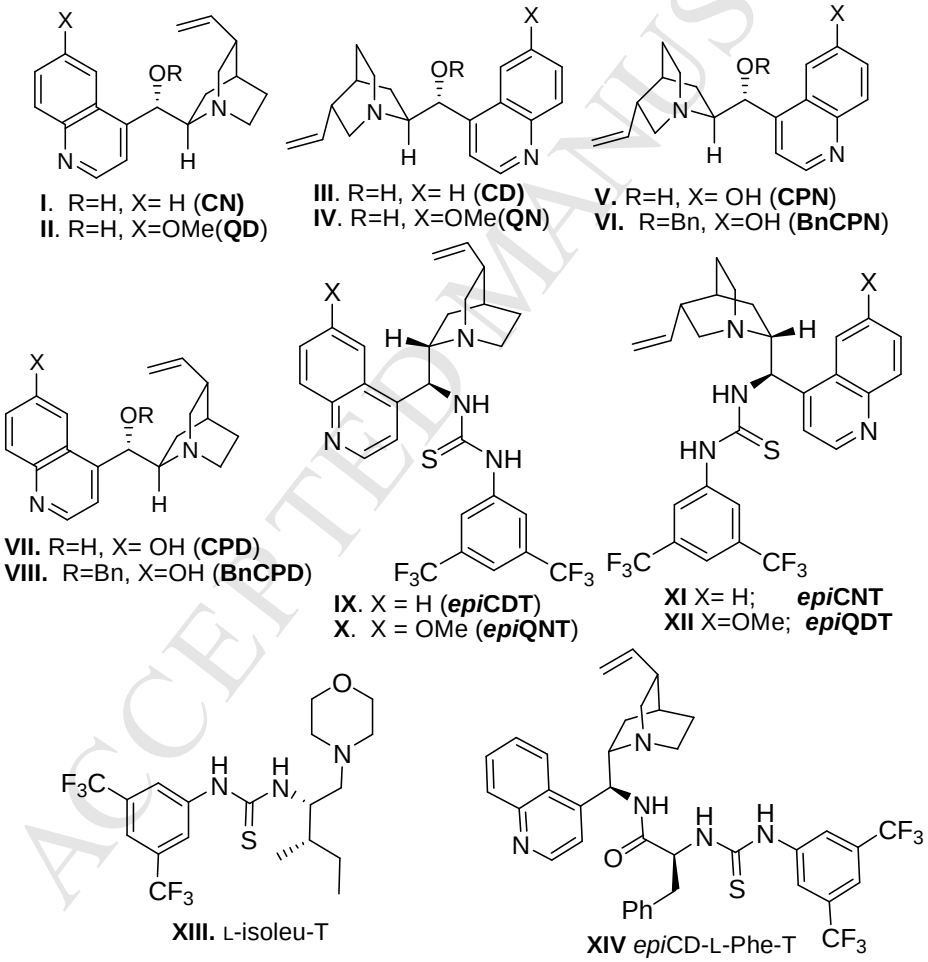


Figure 1. *Cinchona*-derived organocatalysts catalyzed hydrophosphonylation reaction

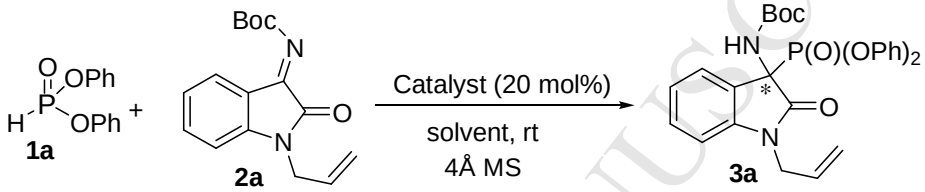
2. Results and Discussion

Initially, the catalytic ability of *Cinchona* alkaloids **CD**, **CN**, **QN** and **QD** were studied for the addition of diphenyl phosphite to the ketimines by using 20 mol% of the catalyst in THF in the presence of 4 Å molecular sieves (**Table 1**). The product **3a** was isolated in high yield and moderate to low enantioselectivity (**Table 1**, **entry 1-4**). The same reaction with modified *Cinchona* catalyst **CPN** (**V**) provided the product **3a** in 82% yield and 12% *ee* (**Table 1, entry 5**), while its *pseudo* enantiomer **CPD** (**VII**) gave the opposite enantiomer **3a** in 88% yield and 30% *ee* (**Table 1, entry 7**). The 6'-OH *Cinchona* alkaloids **BnCPN** (**VI**) and **BnCPD** (**VIII**) also provided adduct **3a** with low enantioselectivity (**Table 1, entry 6** and **8**). Next, we examined the catalytic ability of 9-thiourea derivatives of *Cinchona* alkaloids on the model reaction. Interestingly, the thiourea derivatives (**IX**, **X, XI** and **XII**) provided the **3a** in good yield and with enhanced enantioselectivity (**Table 1, entry 9-12**). The *epi*CDT (**IX**) emerged as a best catalyst providing the adduct **3a** in 79% yield and 73% *ee* (**Table 1, entry 9**). L-Isoleucine derived bifunctional thiourea (**XIII**) afforded product **3a** in good yield, but with low enantioselectivity (**Table 1, entry 13**). The organocatalyst (**XIV**) having thiourea group at distance of six bonds from tertiary amine functionality, yielded the adduct **3a** in 73% yield with 38% *ee* (**Table 1, entry 14**).

Further optimization of reaction conditions was performed by screening of different solvents (**Table 1, entry 15-22**). Among different solvents, the polar aprotic solvent ethyl acetate emerged as the best because it provided adduct **3a** in good yield (76%) and good enantioselectivity (75% *ee*) (**Table 1, entry 22**). Next, the effect of benzoic acid as an additive on the reaction was examined, which afforded **3a** in 75% yield and with 73% *ee* (**Table 1, entry**

23). Lowering of temperature to –30 °C resulted in the enhanced enantioselectivity (**Table 1, entry 24**). Thus, the best conditions for the reaction of diphenyl phosphite with isatin imines consists of 20 mol% of **IX**, 4Å molecular sieves and ethyl acetate as a solvent at –30 °C providing adduct **3a** in 75% yield and 94% *ee*; the optimized condition was used to study the substrate scope of this reaction.

Table 1. Optimization study.[a]



Entry	Catalyst	Solvent	Time (h)	Yield [%][b]	*ee* [%][c]
1	**I**	THF	12	85	46 (+)
2	**II**	THF	12	80	44 (+)
3	**III**	THF	12	82	40 (-)
4	**IV**	THF	12	81	28 (-)
5	**V**	THF	12	82	12 (-)
6	**VI**	THF	12	69	15 (+)
7	**VII**	THF	12	88	30 (+)
8	**VIII**	THF	12	75	19 (-)
9	**IX**	THF	12	79	73 (-)
10	**X**	THF	12	81	60 (-)
11	**XI**	THF	12	81	50 (+)
12	**XII**	THF	12	75	52 (+)

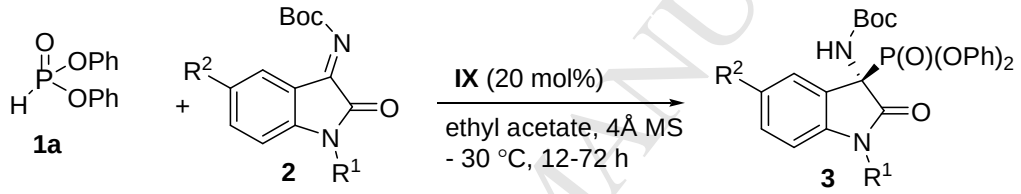
13	**XIII**	THF	24	77	24 (-)
14	**XIV**	THF	24	73	38 (-)
15	**IX**	DCM	12	81	73 (-)
16	**IX**	$CHCl_3$	12	75	64 (-)
17	**IX**	Toluene	12	77	64 (-)
18	**IX**	Xylene	12	87	72 (-)
19	**IX**	MTBE	12	80	62 (-)
20	**IX**	Dioxane	12	77	65 (-)
21	**IX**	Methanol	12	48	72 (-)
22	**IX**	Ethyl acetate	12	76	75 (-)
23[d]	**IX**	Ethyl acetate	12	75	73 (-)
24[e]	**IX**	Ethyl acetate	15	75	94 (-)

[a] Reaction conditions : 0.1 mmol ketimine **2a**, 0.15 mmol of diphenyl phosphite **1a**, 4Å molecular sieves (50 mg) and catalyst in dry solvent. [b] Yield refers to isolated yield after column chromatography. [c] Enantiomeric excess (*ee*) determined by chiral HPLC. [d] Reaction was performed in presence of benzoic acid. [e] Reaction was performed at -30 °C. THF = tetrahydrofuran, DCM = dichloromethane, $CHCl_3$ = Chloroform and MTBE = methyl *tert*-butyl ether.

Once armed with the optimized conditions, the substrate scope was investigated by studying different derivatives of *N*-Boc ketimines and diphenyl phosphite (**Table 2**). The reaction of diphenyl phosphite with *N*-allylated isatin imines provided adducts (**3a-3d**) in good yield (71-82%) and good enantioselectivity (71-94% *ee*) (**Table 2, entry 1-4**). The addition of diphenyl phosphite to 5-chloro-*N*-substituted isatin imines **2e** and **2f** yielded adducts **3e** and **3f** in good yield (75% and 79%) and good enantioselectivity (80% *ee* and 92% *ee*) (**Table 2, entries 5-6**). 5-Halogen-*N*-benzylisatin imines (**2h-2j**) reacts well with diphenyl phosphite, yielding

α-aminophosphonates (**3h-3j)** in good yield (72-79%) and good to high enantioselectivity (78-93% *ee*) (**Table 2, entries 8-10**). Ketimines **2k** substituted with electron donating group gave the product **3k** in good yield (88%) and excellent enantioselectivity (97% *ee*) (**Table 2, entry 11**).The nucleophilic addition of diphenyl phosphite to ketimines (**2l**) derived from *N*-unprotected isatin was also studied. The adduct **3l** was isolated in 73% yield with 78% *ee* (**Table 2, entry 12**). The *R* absolute configuration of adducts was assigned by comparing their HPLC chromatograms with that reported in the literature.[14]

Table 2 Substrate scope.[a]

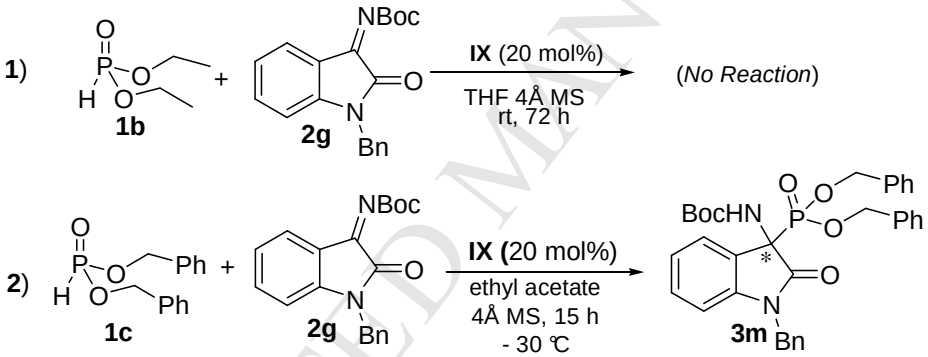


Entry	**2** (R_1, R_2)	**3**	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a** (R_1= CH_2CHCH_2, R_2=H)	**3a**	15	73	94
2	**2b** (R_1= CH_2CHCH_2, R_2=Cl)	**3b**	15	82	71
3	**2c** (R_1= CH_2CHCH_2, R_2=Br)	**3c**	15	71	72
4	**2d** (R_1= CH_2CHCH_2, R_2=I)	**3d**	15	77	78
5	**2e** (R_1=-$CH_2C(CH_3)CH_2$, R_2=Cl)	**3e**	15	75	80
6	**2f** (R_1= $CH_2CHCHCH_3$, R_2=Cl)	**3f**	15	79	92
7	**2g** (R_1= $CH_2C_6H_5$, R_2=H)	**3g**	15	75	89
8	**2h** (R_1= $CH_2C_6H_5$, R_2=Cl)	**3h**	15	72	92
9	**2i** (R_1= $CH_2C_6H_5$, R_2=Br)	**3i**	16	79	93

10	**2j** (R_1= $CH_2C_6H_5$, R_2=I)	**3j**	16	76	78
11	**2k** (R_1= $CH_2C_6H_5$, R_2=OMe)	**3k**	72	88	97
12	**2l** (R_1=H, R_2=Cl)	**3l**	24	73	78

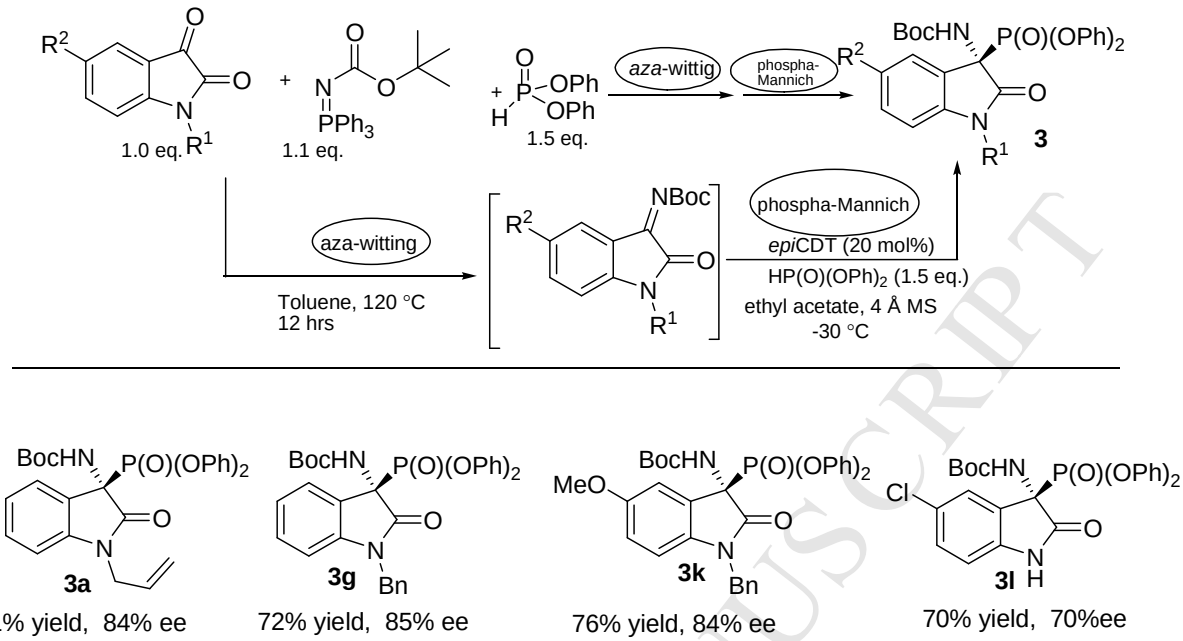
[a] Reaction conditions: 0.1 mmol of isatin imines **2**, 0.15 mmol diphenyl phosphite **1a**, 4Å molecular sieves (50 mg) and catalysts **IX** (20 mol%) in ethyl acetate. [b] Yield refers to isolated yield after column chromatography. [c] Enantiomeric excess (*ee*) determined by chiral HPLC.

Further, we carried out the reaction of ketimine **2g** with dibenzyl- and diethyl- phosphite (**Scheme 1**). The reaction of dibenzyl phosphite **1c** with **2g** provided **3m** in good yield (79%) but with low enantioselectivity (12% *ee*) **(eq. 2**, **Scheme 1**). The diethyl phosphite **1b** did not react with **2g** even after 72 hrs, which might be due to their low reactivity[15] (**eq. 1, Scheme 1**).



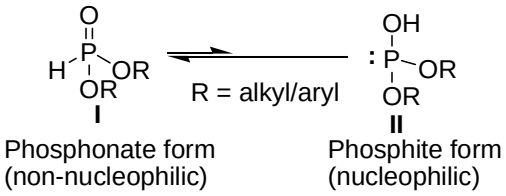
Scheme 1: Reaction with other dialkyl phosphites (**1b** and **1c**) with **2g**.

To improve the synthetic efficiency, we further tried the combination of *aza*-Wittig and phospha-Mannich reactions in a one pot sequential protocol (**Scheme 2**). By this novel sequence, α-aminophosphonates (**3a, 3g, 3k** and **3l)** was isolated in good yield and good enantioselectivity.



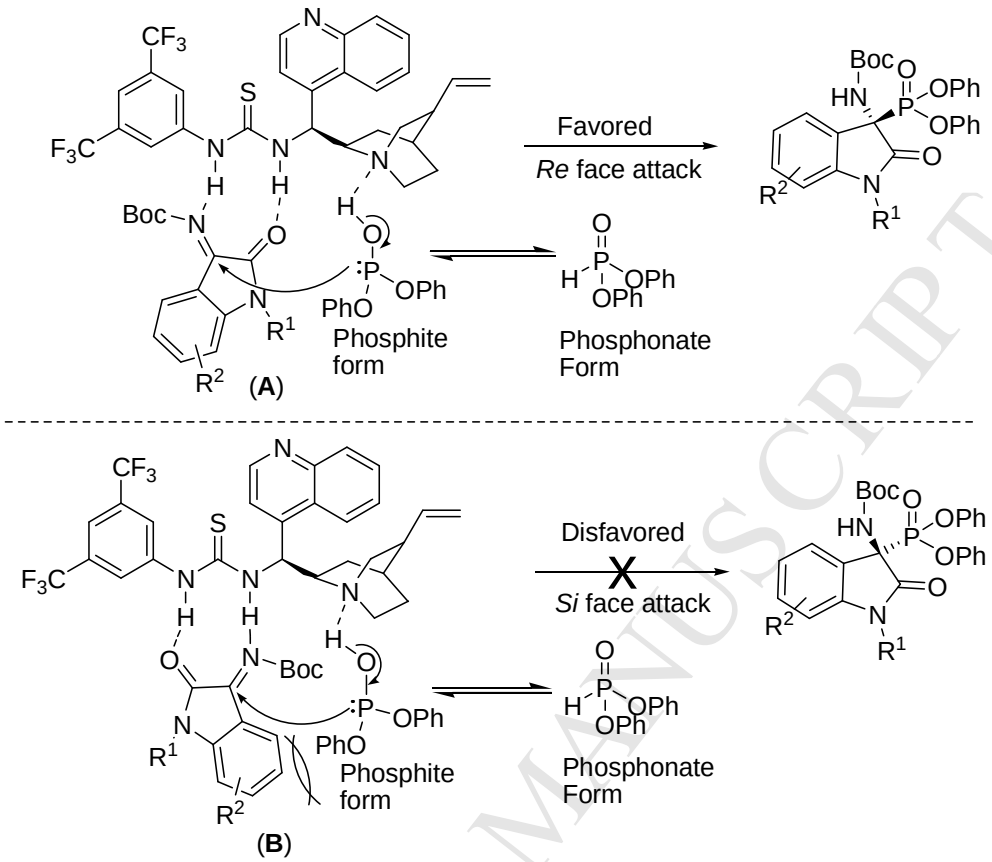
Scheme 2: One pot tandem *aza*-Wittig/Phospha-Mannich reaction.

It is generally believed that the dialkyl phosphite exist as a phosphite–phosphonate tautomer under neutral conditions, with the phosphonate tautomer (**I**) as the almost exclusively favored (**Scheme 3**).[16] However, the equilibrium would be shifted towards more nucleophilic phosphite form (**II**) in the presence of Lewis base/Brønsted base.[17] Hence, it is proposed that the quinuclidinic nitrogen atom of the catalyst **IX** is involved in corresponding phosphite–phosphonate equilibrium and shifts it towards reactive phosphite form (**Scheme 4**).



Scheme 3: Equilibrium between phosphonate-phosphite tautomerization.

Over the past decade, the bifunctional mode of catalysis of cinchona-thioureas has been extensively studied and well accepted by the scientific community.[18] Therefore, it is proposed that the thiourea moiety of the catalyst activates and orients the ketimines for face selective attack, through double hydrogen bonding.[12g] Simultaneously, the tertiary amine of the catalyst activates the phosphite that undergoes addition to activated ketimines in an enantioselective fashion. Based upon the absolute configuration of the product, it is postulated that the ketimines will organize in such a fashion so as to avoid the unfavorable interaction between ketimine benzene ring and aryl group of phosphite, which results in the attack of phosphite from the *Re* face of the ketimines favorable to afford *R* enantiomer as the major product (**A**, **Scheme 4**). The reaction of ketimine with diphenylphosphite favorably proceeds through the transition state A leading to high enantiomeric excess of **3g** whereas in case of dibenzylphosphite it leads to low enantiomeric excess of **3m**. In the latter case the presence of benzyl group does not lead to a rigid transition state and allows probable contribution from the transition state B (**Scheme 4**).



Scheme 4: Plausible mechanistic mode of catalysis.

3. Conclusions

We have developed a highly efficient organocatalytic approach for the enantioselective addition of diphenyl phosphite to ketimines derived from isatins using 20 mol% of ***epi*CDT** as the catalyst. This simple protocol which leads to α-aminophosphonates in good yields (up to 88%) and good enantioselectivity (up to 97% *ee*) makes this asymmetric transformation practically important and extends the generality of catalytic enantioselective hydrophosphonylations.

4. Experimental

4.1 General Note

All reactions were performed in oven-dried glassware. All solvents and commercially available chemicals were used without further purification. The molecular sieves were activated at 200 ˚C for 2 hours in an oven. The column chromatography was carried out on a column packed with silica gel 60-120. ^{1}H NMR spectra were recorded in $CDCl_3$ on a JNM-ECS400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on JNM- ECS400 (100 MHz). Chemical shifts (δ) are expressed in ppm downfield from internal TMS. Optical rotation was determined with AUTOPOL IV polarimeter at 25 °C using sodium D light. MS were recorded on micrOTOF-Q II 10356 Mass Spectrometer. IR spectra were recorded on Varian 660-IR spectrometer. HPLC analyses were performed on a Shimadzu LC-20AD using Daicel Chiralpak IA, IB, IC and AD-H columns.

4.2 General Procedure

To a solution of isatin derived ketimine (0.1 mmol), diphenyl phosphite (0.15 mmol), 4Å MS (50 mg) in 0.3 mL of ethyl acetate, the catalyst *epi*CDT (**IX**, 20 mol%) was added at -30 °C. The reaction mixture was stirred for 12-72 hours and the progress of the reaction was monitored at regular intervals by thin layer chromatography (tlc). After the completion of reaction, the crude reaction mixture was purified by column chromatography on silica gel (mesh 60–120) using hexane–ethyl acetate (1:1) as eluent. The enantiomeric excess of the purified **3a-3m** were

determined using Diacel Chiralpak columns. The racemic standards were prepared using triethylamine (20 mol%) as a catalyst.

4.2.1. (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-allyl-2-oxoindolin-3-ylcarbamate[14] (3a)

White solid; m.p. = 123-126 °C; yield = 73%; R_f (30% EtOAc/hexane) 0.47; $[\alpha]_{20}^{D}$= -2.79 (c 0.25, $CHCl_3$); enantiomeric excess: 94% determined by HPLC [Chiralpak IB, hexane/*i*-PrOH, 90:10, 1 mL/min, 254 nm, t_R = 7.6 min (major) and t_R = 10.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 4.0 Hz, 1H), 7.19-7.33 (m, 9H), 6.74-6.83 (m, 4H), 5.78-5.86 (m, 3H), 5.38 (d, J = 4.0 Hz, 1H), 4.58 (d, J = 20.0 Hz), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.37, 42.87, 43.31, 81.87, 110.9, 118.1, 120.2, 120.3, 120.8, 120.9, 125.9, 126.1, 127.8, 128.9, 129.9, 130.0, 130.5, 132.9, 155.3, 170.5; IR (KBr, cm^{-1}) υ 3260, 2960, 2854, 1740, 1705, 1610, 1489; HRMS calcd. for $C_{28}H_{29}N_2O_6P$ $[M + Na]^+$ 543.1660; found 543.1670.

4.2.2. (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-allyl-5-chloro-2-oxoindolin-3-ylcarbamate (3b)

White semi-solid; yield = 82%; R_f (30% EtOAc/hexane) 0.61; $[\alpha]_{20}^{D}$= -1.42 (c 0.25, $CHCl_3$); enantiomeric excess: 71% ee determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 6.3 min (minor) and t_R = 8.3 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.31 (m, 10H), 6.80 (d, J = 12.0 Hz, 2H), 6.48 (d, J = 8.4 Hz, 1H), 5.78-5.87 (m, 2H), 5.39 (d, J = 0.8 Hz, 1H), 5.20 (d, J = 0.8 Hz, 1H), 4.58 (d, J = 16.0 Hz, 1H), 4.22-4.32 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 42.8, 43.3, 81.8, 110.2, 110.5, 120.2, 120.3, 120.8, 120.9, 125.9, 126.1, 129.9, 130.0, 142.3, 142.4, 150.0, 150.1, 153.5, 153.7, 170.5; IR (KBr, cm^{-}

^{1}) υ 3267, 2972, 2929, 1740, 1713, 1589, 1487; HRMS calcd. for $C_{28}H_{28}ClN_2O_6P$ $[M + Na]^+$ 577.1271; found 577.1259.

4.2.3. (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-allyl-5-bromo-2-oxoindolin-3-ylcarbamate (3c)

Semi-solid; yield = 71%; R_f (30% EtOAc/hexane) 0.47; $[\alpha]_{20}^{D}$= -4.32 (c 0.25, $CHCl_3$); enantiomeric excess: 72% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 6.4 min (minor) and t_R = 8.5 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 4.0 Hz, 1H), 7.20-7.26 (m, 9H), 6.75-6.83 (m, 3H), 5.91 (d, J = 12.0 Hz, 1H), 5.79 (d, J = 4.0 Hz, 1H), 5.39 (d, J = 4.0 Hz, 1H), 5.18 (d, J = 8.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 42.8, 43.3, 81.8, 110.8, 110.9, 120.2, 120.3, 120.8, 120.9, 125.9, 126.1, 129.8, 130.0, 130.5, 142.7, 142.8, 150.0, 150.1, 153.5, 153.7, 170.4; IR (KBr, cm^{-1}) υ 3267, 2980, 2869, 1742, 1711, 1607, 1486; HRMS calcd. for $C_{28}H_{28}BrN_2O_6P$ $[M + Na]^+$ 621.0766; found 621.0771.

4.2.4 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-allyl-5-iodo-2-oxoindolin-3-ylcarbamate (3d)

Semi-solid; yield = 77%; R_f (30% EtOAc/hexane) 0.53; $[\alpha]_{20}^{D}$= -5.63 (c 0.25, $CHCl_3$); enantiomeric excess: 78% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 6.9 min (minor) and t_R = 9.4 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 4.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.20-7.26 (m, 8H), 6.82 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 8.0 Hz, 1H), 5.77-5.89 (m, 2H), 5.36 (d, J = 16.0 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.23 (d, J = 20.0 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 43.2, 63.7, 81.8, 85.2, 111.5, 118.0, 120.3, 120.7, 120.8, 125.9, 126.1, 129.8, 130.0, 130.5, 138.9, 143.4, 143.5, 150.0, 150.1, 153.5, 153.7, 170.2; IR (KBr, cm^{-1}) υ 3266, 2981,

2928, 1742, 1712, 1600, 1481; HRMS calcd. for $C_{28}H_{28}IN_2O_6P$ $[M + Na]^+$ 669.0622; found 669.0617.

4.2.5 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-5-chloro-1-(2-methylallyl)-2-oxoindolin-3ylcarbamate (3e)

Viscous oil; yield = 75%; R_f (30% EtOAc/hexane) 0.47; $[\alpha]_{20}^{D}$= -8.92 (c 0.25, $CHCl_3$); enantiomeric excess: 80% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.3 min (minor) and t_R = 8.2 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.19-7.31 (m, 9H), 6.78-6.80 (m, 3H), 5.88 (d, J = 12.0 Hz, 1H), 5.03 (s, 1H), 4.88-4.95 (m, 2H), 1.77 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 28.2, 44.7, 47.1, 81.8, 110.6, 113.3, 120.3, 120.4, 120.8, 120.9, 125.4, 125.9, 126.1, 129.9, 130.0, 138.8, 154.7, 170.9; IR (KBr, cm^{-1}) υ 3261, 2975, 2931, 1742, 1703, 1591, 1488; HRMS calcd. for $C_{29}H_{30}ClN_2O_6P$ $[M+Na]^+$ 591.1427; found 591.1427.

4.2.6 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-(but-2-enyl)-5-chloro-2-oxoindolin-3-ylcarbamate (3f)

White semi-solid; yield = 79%; R_f (30% EtOAc/hexane) 0.51; $[\alpha]_{20}^{D}$= -6.32 (c 0.25, $CHCl_3$); enantiomeric excess: 92% determined by HPLC [Chiralpak IA, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.8 min (major) and t_R = 11.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.31 (m, 12H), 6.79-6.81 (m, 1H), 5.88 (d, J = 12.0 Hz, 1H), 5.04 (s, 1H), 4.50-4.55 (m, 1H), 4.11 (s, 1H), 1.76 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 28.2, 46.4, 47.1, 81.8, 110.5, 110.6, 113.2, 113.3, 120.3, 120.8, 120.9, 126.1, 129.8, 130.0, 138.8, 152.5, 170.9; IR (KBr, cm^{-1}) υ 3252, 3021, 2977, 1731, 1713, 1528, 1484; HRMS calcd. for $C_{29}H_{30}ClN_2NaO_6P$ $[M + Na]^+$ 591.1427; found 591.1418.

4.2.7 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-benzyl-2-oxoindolin-3-ylcarbamate[14] (3g)

White solid; m.p. = 187-189 °C; yield = 75%; R_f (30% EtOAc/hexane) 0.58; $[\alpha]_{20}^{D}$= -10.4 (*c* 0.25, $CHCl_3$); enantiomeric excess: 89% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.8 min (minor) and t_R = 12.3 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.37 (m, 18H), 5.91 (d, J = 5.9 Hz, 1H), 5.28 (d, J = 16.0 Hz, 1H), 4.68-4.77 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 28.2, 44.7, 62.5, 81.5, 109.6, 120.3, 120.4, 121.0, 121.1, 127.4, 128.8, 129.9, 135.5, 143.6, 143.8, 149.9, 150.2, 153.6, 153.8, 171.2; IR (KBr, cm^{-1}) υ 3259, 2974, 2929, 1744, 1711, 1609, 1487; HRMS calcd. for $C_{32}H_{31}N_2O_6P$ $[M + Na]^+$ 593.1812; found 593.1796.

4.2.8 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-benzyl-5-chloro-2-oxoindolin-3-ylcarbamate[14] (3h)

White solid; m.p. = 198-201 °C; yield = 72%; R_f (30% EtOAc/hexane) 0.45; $[\alpha]_{20}^{D}$= +23.1 (c 0.25, $CHCl_3$); enantiomeric excess: 92% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.7 min (minor) and t_R = 10.4 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.20-7.26 (m, 16H), 6.73 (d, J = 11.2 Hz, 1H), 6.60 (s, 1H), 5.94 (d, J = 11.4 Hz, 1H), 5.24 (d, J = 6.8 Hz, 1H), 4.78 (d, J = 4.0 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 28.3, 44.7, 62.5, 81.9, 109.6, 110.0, 110.4, 110.6, 120.2, 127.3, 128.9, 129.8, 129.9, 130.0, 135.1, 135.5, 142.2, 142.3, 149.9, 150.0, 153.6, 153.8, 170.9; IR (KBr, cm^{-1}) υ 3259, 2974, 2931, 1743, 1609, 1486; HRMS calcd. for $C_{32}H_{30}ClN_2O_6P$ $[M + Na]^+$ 627.1427; found 627.1428.

4.2.9 (*R*)-*tert*-Butyl-3-(phenoxyphosphono)-1-benzyl-5-bromo-2-oxoindolin-3-ylcarbamate[14] (3i)

White solid; m.p. = 210-215 °C; yield = 79%; R_f (30% EtOAc/hexane) 0.55; $[\alpha]_{20}^{D}$ = +27.9 (c 0.25, $CHCl_3$); enantiomeric excess: 93% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 10.9 min (minor) and t_R = 11.7 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 2.2 Hz, 1H), 7.20-7.26 (m, 16H), 6.74 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.3Hz, 1H), 5.93 (d, J = 11.6 Hz, 1H), 5.22 (d, J = 15.4 Hz, 1H), 4.79 (d, J = 13.6 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 44.3, 44.8, 81.9, 110.9, 111.1, 115.7, 120.8, 120.9, 125.9, 127.3, 127.8, 128.9, 129.8, 130.0, 142.6, 142.7, 149.9, 150.0, 153.6, 153.7, 170.8; IR (KBr, cm^{-1}) υ 3258, 2974, 2876, 1743, 1711, 1488; HRMS calcd. for $C_{32}H_{30}BrN_2NaO_6P$ $[M + Na]^+$ 671.0922; found 671.0918.

4.2.10 (*R*)- *tert*-Butyl 3-(phenoxyphosphono)-1-benzyl-5-iodo-2-oxoindolin-3-ylcarbamate (3j)

White solid; m.p. = 197-200 °C; yield = 76%; R_f (30% EtOAc/hexane) 0.55; $[\alpha]_{20}^{D}$= +36.2 (c 0.25, $CHCl_3$); enantiomeric excess: 78% determined by HPLC [Chiralpak IC, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.2 min (minor) and t_R = 15.4 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.34 (m, 15H), 6.74 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 12.0 Hz, 1H), 5.16-5.24 (m, 1H), 4.74-4.91 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 28.4, 44.7, 62.5, 81.9, 111.1, 115.7, 120.8, 120.9, 126.1, 127.3, 127.8, 128.9, 129.8, 130.1, 142.7, 142.8, 150.0, 150.1, 153.6, 153.7, 170.8; IR (KBr, cm^{-1}) υ 3254, 2974, 2869, 1742, 1601, 1488; HRMS calcd. for $C_{32}H_{30}IN_2O_6P$ $[M + Na]^+$ 719.0783; found 719.0805.

4.2.11 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-1-benzyl-5-methoxy-2-oxoindolin-3-ylcarbamate[14] (3k)

Brown solid; m.p. = 172-175 °C; yield = 88%; R_f (30% EtOAc/hexane) 0.40; $[\alpha]_{20}^{D}$= +18.3 (c 0.25, $CHCl_3$); enantiomeric excess: 97% determined by HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 16.3 min (minor) and t_R = 23.3 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.61 (m, 2H), 6.87-6.89 (m, 2H), 5.27-5.29 (m, 5H), 4.35-4.36 (m, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 44.7, 55.8, 64.3, 81.4, 110.0, 112.0, 115.1, 120.1, 120.2, 120.8, 120.9, 125.5, 125.8, 127.3, 127.5, 128.7, 129.6, 129.9, 135.5, 136.9, 137.0, 149.8, 149.9, 150.1, 150.2, 153.5, 153.7, 156.1, 156.2, 170.9; IR (KBr, cm^{-1}) υ 3277, 3030, 2924, 1730, 1703, 1493; HRMS calcd. for $C_{33}H_{33}N_2O_7P$ $[M + Na]^+$ 623.1923; found 623.1927.

4.2.12 (*R*)-*tert*-Butyl 3-(phenoxyphosphono)-5-chloro-2-oxoindolin-3-ylcarbamate (3l)

Semi-solid; yield = 73%; R_f (30% EtOAc/hexane) 0.57; $[\alpha]_{20}^{D}$= -4.34 (c 0.25, MeOH); enantiomeric excess: 78% determined by HPLC [Chiralpak AD-H, hexane/*i*-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 10.6 min (major) and t_R = 25.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.17-8.42 (m, 2H), 7.11-7.61 (m, 5H), 6.87-6.97 (m, 2H), 6.78-6.80 (m, 5H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 62.5, 79.8, 110.6, 111.1, 120.1, 120.2, 120.6, 120.7, 123.5, 124.6, 125.2, 125.6, 125.8, 125.9, 127.3, 129.3, 129.6, 141.0, 141.9, 142.0, 149.3, 149.5, 149.8, 171.9, 175.7; IR (KBr, cm^{-1}) υ 3400, 3291, 2983, 1758, 1695, 1488; HRMS calcd. for $C_{25}H_{24}ClN_2NaO_6P$ $[M + Na]^+$ 537.0958; found 537.0945.

4.2.13 (*R*)-*tert*-Butyl 3-((benzyloxy)phosphono)-1-benzyl-2-oxoindolin-3-ylcarbamate (3m)

Semi-solid; yield = 79%; R_f (30% EtOAc/hexane) 0.52; $[\alpha]_{20}^{D}$= -7.14 (c 0.25, $CHCl_3$); enantiomeric excess: 12% determined by HPLC [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 13.4 min (major) and t_R = 16.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.34-7.39 (m, 9H), 7.25-7.34 (m, 10H), 4.93-5.04 (m, 3H), 4.68-4.69 (m, 4H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 28.8, 44.6, 65.4, 70.7, 81.6, 110.9, 115.4, 115.5, 127.1, 127.8, 128.5, 128.6, 128.7, 128.9, 139.8, 140.9, 142.4, 142.5, 142.6, 152.8, 152.9, 170.4; IR (KBr, cm^{-1}) υ 3246, 2980, 2926, 1731, 1609, 1486; HRMS calcd. for $C_{34}H_{35}N_2O_6P$ $[M + Na]^+$ 621.2130; found 621.2127.

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