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Carbene-catalyzed and Pnictogen Bond-assisted Access to P^{III}-Stereogenic Compounds

Jianjian Liu,[a] Rui Deng,[a] Xuyang Liang,[a] Mali Zhou,[a] Pengcheng Zheng,*[a] and Yonggui Robin Chi*[a,b]

Abstract: Intermolecular pnictogen bonding (PnB) catalysis has received increased interest in non-covalent organocatalysis. It has been demonstrated that organic electron-deficient pnictogen atoms can act as prospective Lewis acids. Here, we present a catalytic approach for the asymmetric synthesis of chiral P^{III} compounds by combining intramolecular PnB interactions and carbene catalysis. Our design features a pre-chiral phosphorus molecules bearing two electron-withdrawing benzoyl groups, resulting in the formation of a σ-hole at the P atom. X-ray and non-covalent interaction (NCI) analysis indicate that these phosphorus substrates exhibit intrinsic PnB interactions between the oxygen atom of the formyl group and the phosphorus atom. This induces a conformational locking effect, leading to the crystallization of the phosphorus substrates in a preferred conformation ($P2_12_12_1$ chiral group). Under the catalysis of *N*–heterocyclic carbene, the aldehyde moiety activated by the pnictogen bond selectively reacts with an alcohol to yield the corresponding chiral monoester/phosphorus products with excellent enantioselectivity. This Lewis acidic phosphorus center, aroused by the non-polarized intramolecular pnictogen bond interaction, assists in conformational and selective regulations, providing unique opportunities for catalysis and beyond.

Phosphorus is one of the most abundant non-metallic elements in earth's crust and plays a crucial role in living organisms and physiological reactions[1]. Concurrently, phosphorus is prevalent in numerous drugs[2], pesticides[3] and bio-materials[4], such as Remdesivir, a leading treatment for COVID-19[5]. Salithion, a broad-spectrum insecticide, finds extensive use in pest prevention for vegetables and fruits[6]. More attentively, chiral ligands with P-stereogenic center have received remarkable applications in asymmetric synthesis conducted by transition metals[7]. The phosphorus ligands developed by Tang[8] and Zhang[9] respectively, have significant application in asymmetric hydrogenation and have been commercialized. Additionally, electron-rich P^{III} compounds serve as indispensable catalysts in catalytic asymmetric MBH and Lu reactions[10] (Figure 1a). Over the past decades, chemists have primarily focused on four methodologies for constructing optically pure phosphorus compounds. Firstly, the use of natural chiral auxiliaries like menthol[11] and D-glucose[12] necessitates pre-splicing of the auxiliaries. Recent advancements include transition metal-catalyzed intramolecular C-H functionalization of diphenyl phosphide oxides, offering representative desymmetrization protocols for accessing enantioenriched phosphorus products, albeit requiring the introduction of directing groups[13]. Now days, asymmetric coupling reactions between phosphine hydrides and aryl halides catalyzed by metals (such as Cu, Ni, Pd) have developed as the prospective strategies[14]. However, despite these metals participated tactics have realized outstanding yields and stereo-selectivities, some low-cost and environmentally benign methods still have significant research value. Obviously, Ingenious design of substrates for KR[11b, 15] and DKR[14c-g, 16] processes to synthesize chiral phosphide is also a common strategy. In light of these challenges, the development of a highly efficient organocatalysis system for synthesizing valuable P-

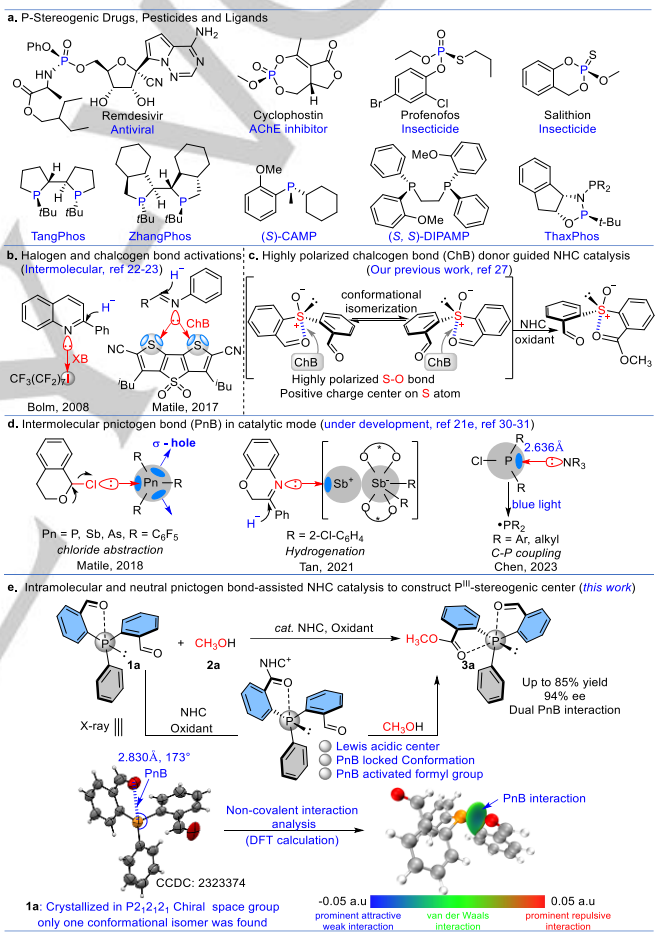

Figure 1. a. P-stereogenic drugs and ligands. **b**. Halogen and chalcogen bonds in catalytic system. **c**. Highly polarized chalcogen bond donor guided NHC catalysis. **d**. Intermolecular pnictogen bond in catalytic system. **e**. Intramolecular and neutral pnictogen bond-assisted NHC catalysis to synthesize chiral P compounds.

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stereogenic functional molecules would be particularly meaningful and complementary to the existing methods[17].

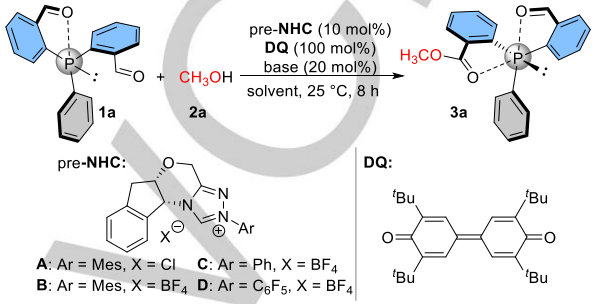
σ-hole[18] type catalysis, including halogen bond (XB)[19], chalcogen bond (ChB)[20] and pnictogen bond (PnB)[21], has attracted an increasing interest as Lewis acids for the activation of various organic reactions. When the electron pair of Lewis base fill into the σ-hole, an intermolecular non–covalent interaction is formed, and its strength depends on the depth of the σ-hole. In the recent years, intermolecular XB and ChB interaction between catalysts and substrates have developed by Bolm[22], Matile[23], Huber[24] et al and well applicated in organocatalysis (Figure 1b). Inspired by the work of Birman[25] and Smith[26], transient intramolecular ChB interactions could stabilize the conformation of intermediate. So, in our previous work[27], we disclosed a carbene and ChB cooperative catalytic strategy for the synthesis of chiral sulfoxides. We employed intramolecular ChB interactions to guide the conformational isomerization and improve the regioselectivity. However, in these sulfoxide containing molecules, the electronegativity difference between sulfur and oxygen atoms render the S-O bonds are highly polarized and S atoms can be worked as a σ-hole donor, although the whole molecule is neutral (Figure 1c).

Albeit these superb evolutions, PnB as a new subclass of weak non–covalent interactions are much less explored in organic synthesis especially in asymmetrical catalysis. As disclosed by Matile[21e, 28] and Gabbaï[29] more recently, a new Lewis acidic PnB catalytic models are founded to activate the carbon-halogen bond. Later on, Tan's group design a series of chiral ion-pairing antimony PnB donor catalyst, and perform a new catalytic asymmetric hydrogenation reaction to access chiral benzomorpholines[30]. Additionally, the coordination of PnB and blue light has introduced an elegant C-P coupling methodology[31] (Figure 1d). Although these impressive advancements, the development of PnB in asymmetric synthesis is still slow, posing challenges in designing the weak intermolecular chelation interactions between catalysts and substrates.

In this study, we present a non-polarized and neutral intramolecular PnB-assisted NHC (*N*-heterocyclic carbene)[32] catalysis to construct the P^{III}-stereogenic compounds. Motivated by the unique properties of PnB, we proposed the P atoms bearing the σ-holes could act as the Lewis acidic center, simultaneously activate the bonded formyl group and stabilize the conformation of Breslow intermediates, it may help to achieve high stereo and regio-selectivities. Following the oxidation of the Breslow intermediate, nucleophile facilitates recycling of NHC to generate enantioenriched trivalent phosphorus compounds (Figure 1e). The newly formed intramolecular PnB also contributes to conformational regulation. We sincerely hope that reasonable synergistic application of such non-covalent interactions and NHC will provide novel sight for organic synthesis.

Primarily, we aimed to ascertain whether the model substrate **1a** bearing an intramolecular PnB interaction. Fortunately, X-ray analysis revealed that the distance between oxygen of formyl group and phosphorus atom is 2.83Å[33], which is less than the sum of their van der Waals radii (3.30Å), and the angle is 173°. In addition, non-covalent interaction (NCI) analysis[34] demonstrates an attractive P-O interaction (as indicated by green surface in Figure. 1e), these results suggested that the presence of an intramolecular PnB interaction in the solid–state of **1a**. More interestingly, substrate **1a** crystallized in a $P2_12_12_1$ chiral group, only one conformational isomer was found in the unite cell (Figure 1e, see SI for details), this outcome may attribute to the intramolecular PnB interaction, which locks the conformation and break the C_2 symmetry of the whole molecule, only the preferred conformation of **1a** facilitates crystal formation.

Table 1. Initial Studies and Reaction Optimization[a]



Entry	Pre-NHC	Base	Solvent	Yield (%)[b]	Er[c]
1	**A**	K_2CO_3	THF	32	96:4
2	**B**	K_2CO_3	THF	13	93:7
3	**C**	K_2CO_3	THF	21	95:5
4	**D**	K_2CO_3	THF	trace	--
5	**A**	KOAc	THF	70	97:3
6	**A**	Cs_2CO_3	THF	trace	--
7	**A**	K_3PO_4	THF	trace	--
8	**A**	DBU	THF	42	80:20
9	**A**	Et_3N	THF	11	98:2
10	**A**	KOAc	DME	43	98:2
11	**A**	KOAc	EtOAc	65	98:2
12	**A**	KOAc	toluene	68	93:7
13	**A**	KOAc	CH_2Cl_2	33	94:6
14	**A**	KOAc	PhOMe	86	94:6
15[d]	**A**	KOAc	THF	78	97:3
16[e]	**A**	KOAc	THF	85	97:3

[a]Unless otherwise specified, the reactions were carried under N_2 atmosphere using **1a** (0.10 mmol), **DQ** (0.10 mmol), CH_3OH (0.12 mmol), pre–**NHC** (0.01 mmol), base (0.02 mmol), solvent (2.0 mL), 25℃, 8 h. [b]Isolated yield of **3a**. [c]The er values of **3a** were determined *via* HPLC on the chiral stationary phase. [d]The reaction time is 4h. [e]The reaction time is 2h.

To explore suitable conditions for the above design, we commenced our esterification reaction under oxidative condition (**DQ**[35] as an oxidant) by employing 2,2'-(phenylphosphanediyl)dibenzaldehyde **1a** as the model phosphorus substrate and methanol **2a** as a nucleophile, the key results summarized in Table 1. Encouragingly, an er value of 96:4 was achieved when aminoindanol–derived triazolium salt **A** was utilized as the pre-NHC catalyst, the desired chiral phosphorus product **3a** was obtained in 32% yield with K_2CO_3 as a base in

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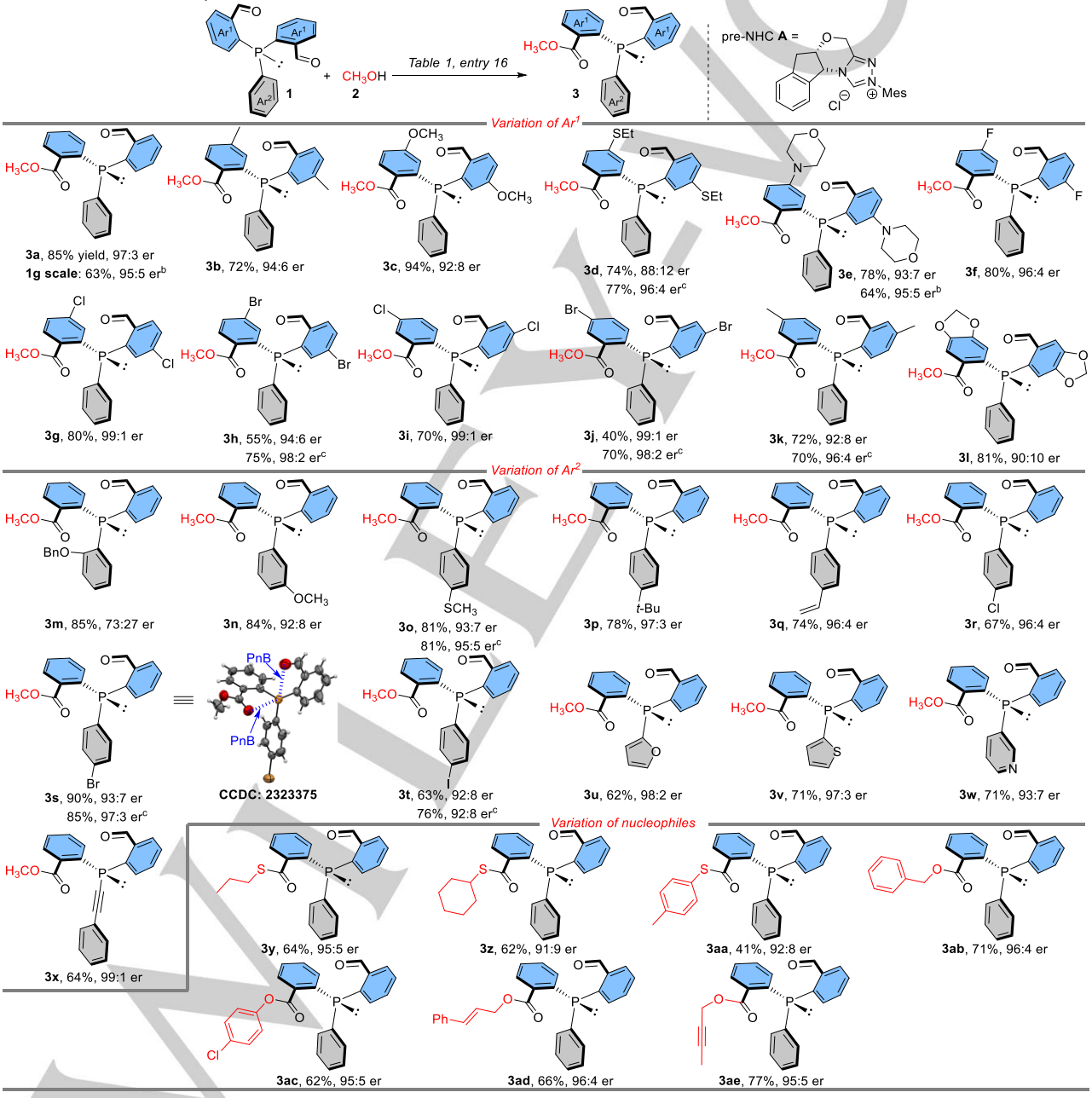
THF (entry 1). However, switching the counter anion (Cl^-) in **A** to a BF_4 anion (pre–NHC catalyst **B**) dramatically reduced the yield and enantiomeric ratio (93:7, entry 2). The electron-deficient aryl group in catalysts appeared ineffective for this reaction, converting the electron donating Mes group to a neutral and strong electron withdrawing C_6F_5 substituent resulted in low yield and even trace monoester product (entry 3-4). After entrenched the optimal catalyst, various organic and inorganic bases with different strength were also examined, as listed in entry 5-9, the use of inorganic weak base (KOAc) in THF proved beneficial for both yield and enantioselectivity, it accomplished a receivable 70% yield with excellent 97:3 er value. For the sake of improving the yield, solvent optimizations were conducted using catalyst **A** and KOAc as the base, it was found that the er value rose to 98:2 albeit mild drop of yield when EtOAc as the solvent (entry 11). Other ether solvents were also explored, the yield can be significantly improved when PhOMe is used as a solvent although the stereoselectivity reduced to 94:6. It is noteworthy that as the reaction time increased, the oxidation products of phosphorus also increased, to our delight, we found that the reaction time of 2 hours under the conditions of entry 5 yielded the desired product in 85% yield with an excellent er value of 97:3, representing an optimal condition (entry 16).

Scheme 1. Substrates scope of the reaction[a]



[a]Reaction conditions as stated in Table 1, entry 16. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase. [b]EtOAc as solvent. [c]The temperature is 0°C.

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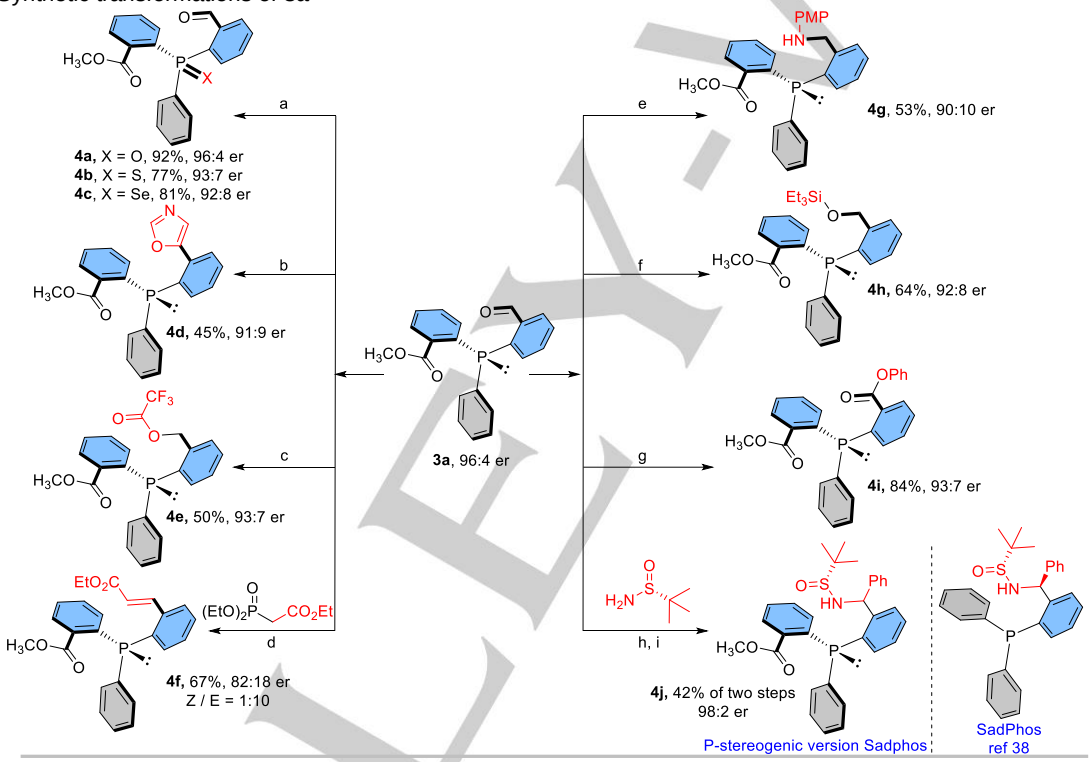
Having an acceptable condition after screening the reactive factor, the generality of the reaction was then examined. As illustrated in Scheme 1, we initially investigated various electron-donating substituents installed on the para–carbon of the aldehyde moiety on the Ar^1 ring, most of the corresponding mono–ester products maintained good er values (**3a**-**3e**) except for **3d** bearing a SEt group, which exhibited a diminished er value of 88:12, these electron-donating groups may weaken the strength of PnB bonding interaction which leaded poor regio-selectivity of NHC. Pleasingly, regardless of the halogen pattern placing to the para or meta carbons of the formyl group, giving the target products in good yields with excellent enantioselectivities (up to 99:1 er, **3f**-**3j**), but the growth of diester byproducts were responded for the decreased yield of **3h** and **3j** which bearing the Br atoms in the phenyl ring. Introducing two electron-donating groups, such as **3l**, led to a decrease in ee values due to lessened pnictogen bonding interaction. Additionally, the universality of the Ar^2 ring attached to the phosphorus atom was also evaluated, whatever the electron donating or withdrawing groups installed on the para- and meta- position of the phosphorus atom, all the results exhibited good yields and prominent enantioselectivities (**3n**-**3t**). Remarkably, changing the Ar^2 to the heterocycle such as furan, thiophene and pyridine ring, allowed the reaction can proceed smoothly with brilliant yield and optical purities (**3u**-**3w**). To our surprise, switching the phenyl ring to an alkynyl revealed an excellent er value (99:1, **3x**). Meanwhile, many alcohols and thiols, including secondary thiols, allyl alcohol and propynol, could also serve as effective nucleophile to replace methanol (**3y**–**3ae**). As a backup condition shown in table 1 entry 11, the solvent EtOAc may benefit for the enantioselectivities of some substrates (**3a**, **3e**), and reducing the reaction temperature could improve the enantioselectivity ratio (**3d**, **3h**, **3k**, **3o**, **3s**).

Scheme 2. Synthetic transformations of **3a**[a-i]



[a]*m*-CPBA, CH_2Cl_2 for **4a**, S_8 powder for **4b**, Se powder for **4c**, THF, rt. [b]K_2CO_3, TosMIC, MeOH, rt. [c]Et_3SiH, TFA, DCM. [d]Cs_2CO_3, THF. [e]$PMPNH_2$, $MgSO_4$, CH_2Cl_2, then $NaBH_3CN$. [f]$B(C_6F_5)_3$, Et_3SiH. [g]achiral NHC, DQ, AcOK, PhOH, THF, rt. [h]$Ti(OEt)_4$, THF, 65℃. [i]PhMgBr, THF, -30℃.

In our synthetic endeavors, various functionalization of **3a** were carried out to display the synthetic utility of the present methodology. Firstly, our approach could be scaled up to 1.0 grams smoothly only with minimal impact on product yield after switch the solvent to EtOAc (63% yield, and 95:5 er; Scheme 1). The remaining aldehyde unit in our chiral P^{III} product could be easily transferred to a diverse array of functional groups (Scheme 2). For instance, the P^{III} could be easily oxidized by *m*-CPBA, S_8 and Se powder to the corresponding P^V compounds in acceptable yields with minimal erasure of er values under mild condition (**4a**-**4c**). The oxazole was smoothly synthesized from the aldehydes by employing TosMIC[36] under a basic condition (**4d**). A reductive esterification process of the remaining aldehyde to access **4e** in 50% yield and with little loss of er. Efficient synthesis of trans olefins was accomplished via the HWE[37] reaction, yielding **4f** with Z/E values of 1:10. Combining *p*-Anisidine with **3a** through a reductive amination reaction to afford **4g** in acceptable er with moderate yield. Interestingly, a reductive silicification reaction of **3a** was accomplished efficiently by employing Et_3SiH as reductant in the presence of catalytic $B(C_6F_5)_3$. Furthermore, **3a** underwent an achiral NHC catalytic oxidative condition, a phenol esterification product **4i** were obtained smoothly with outstanding yield and er value. Noteworthily, the product **4j** is a chiral P-centric version of SadPhos[38] which have been proven by Zhang et al as a chiral ligand in several asymmetric synthesis, it could be easily synthesized from **3a** via reductive amination reaction along with a nucleophilic addition with PhMgBr, and as well as its analogues, it may become a latent ligand in metal-mediated organic synthesis.

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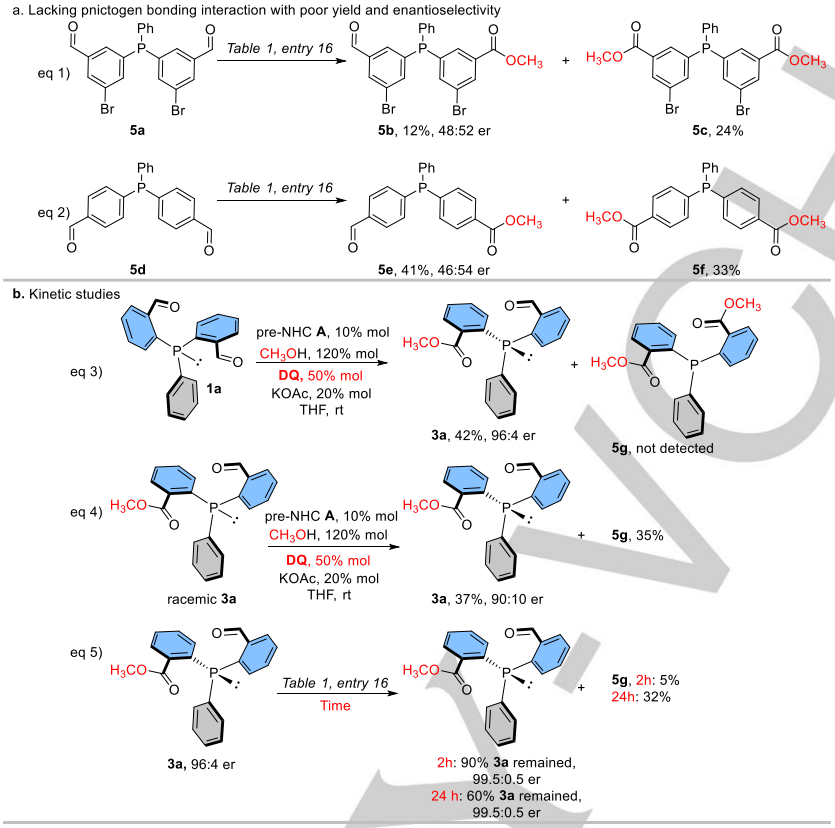
Scheme 3. Mechanism investigation



In order to understanding the potential effects of pnictogen bonding interactions, we synthesized a substrate **5a** and **5d**, wherein formyl groups were positioned at the meta- and para-positions of the P atom, under standard catalytic conditions, the results exhibited extremely low ee value and yield of the mono-ester product, with a notable increase in the formation of the di-ester product (Scheme 3a, eq 1-2). We attribute these declines to the possibility of the remote formyl moieties did not form intramolecular PnB interactions with the phosphorus atom. These results reveal the crucial role of inherent PnB non-covalent character in conformational accommodation and selectivity of carbene to the formyl group. Subsequently, a series of control experiments were subsequently conducted to probe the mechanism of this esterification process. When the reaction was performed by employing 0.5 equivalent **DQ** under the optimized condition, the target product **3a** were generated in 42% yield possessing 92% ee and without observation of di-ester product **5g**, based on this result, we considered that the first desymmetrization is the major contributor to the enantioselectivity control[39] (Scheme 3b, eq 3). Moreover, treatment of racemic **3a** with 0.5 equivalent oxidant under the standard condition afforded di-ester product **5g** in 35% yield, along with the remained **3a** in 37% yield accompanied 80% ee (Scheme 3b, eq 4). Meanwhile, enantioenriched **3a** (with 92% ee) subjected to standard condition again, showed roughly 5% **5g** detection, with residual **3a** displaying higher ee value (99%) without erasing even after 24 hours, albeit the yield of di-ester **5g** increased to 32% (Fig 3b, eq 5), based on these two experiments, the results suggested that **1a** converted to major enantiomer **3a** is much faster than the rate of **1a** produce to minor enantiomer[40]. Besides, the outcome of equations 4-5 disclosed that the speed of *R*-**3a** reacted with carbene is faster than *S*-**3a**.

In summary, we have successfully implemented a synergistic system utilizing neutral pnictogen Bond (PnB) interactions and chiral carbene for the enantioselective synthesis of P^{III} compounds. Our protocol takes advantage of intramolecular pnictogen bonds installed in substrates to modulate substrate conformation and differentiate carbene reactivity. Moreover, the Lewis acidic PnB interaction have been proven through the X-ray and NCI analysis. Control experiments have disclosed that substrates lacking PnB interactions exhibited poor regio- and stereo- selectivity in standard condition, with the di-ester being the major product. In particular, our strategy features mild conditions, broad functional group tolerance and excellent optical purities. The obtained enantioenriched phosphorus products could be easily transferred to a series of platform molecules with latent applications in catalysis and biological investigations. We aspire to offer a fresh perspective through the integration of non-covalent interactions into asymmetric synthesis and reaction control.

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Keywords: Pnictogen Bond • *N*-heterocyclic carbene • Synergistic catalysis • P^{III}-Stereogenic Compounds

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Layout 2:

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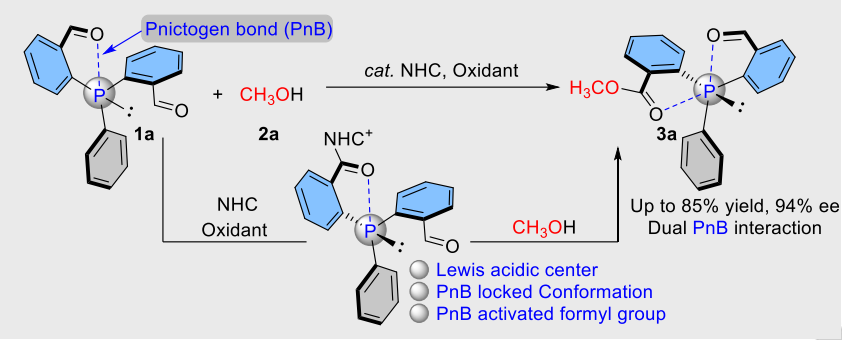

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Carbene-catalyzed and Pnictogen Bond-assisted Access to P^{III}-Stereogenic Compounds

A catalytic approach for the asymmetric synthesis of chiral P^{III} compounds by combining intramolecular PnB interactions and carbene catalysis was developed. The Lewis acidic P center simultaneously activate the bonded formyl group and stabilize the conformation of Breslow intermediates, it may help to achieve high stereo and regio-selectivities. Following the oxidation of the Breslow intermediate, nucleophile facilitates recycling of NHC to generate enantioenriched trivalent phosphorus compounds.