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Synergistically activating nucleophile strategy enabled organocatalytic asymmetric P-addition of cyclic imines†

Hongkui Zhang,‡[ac] Jian-Ping Tan,‡[ad] Xiaoyu Ren,[a] Fan Wang,[a] Jia-Yan Zheng,[a] Jiajia He,[a] Yu Feng,[c] Zhipeng Xu,*[b] Zhishan Su[a] and Tianli Wang*[a]

Herein, we present an attractive organocatalytic asymmetric addition of P-nucleophiles to five-membered cyclic *N*-sulfonyl imines facilitated by phosphonium salt catalysis, enabling the highly enantioselective synthesis of tri- and tetra-substituted cyclic phosphorus-containing benzosultams. With this protocol, various cyclic α-aminophosphonates were efficiently synthesized with high yields and exceptional enantioselectivities (up to >99% ee) under mild reaction conditions. The utility and practicality of this method were demonstrated through gram-scale reactions and straightforward elaborations. Notably, the success of this approach relies on the deliberate selection of a synergistic organocatalytic system, which helps circumvent foreseeable side effects while handling secondary phosphine oxides (SPOs). Systematic mechanistic studies, incorporating experiments and DFT calculations, have revealed the critical importance of judiciously selecting bifunctional phosphonium salt catalysts for effectively activating P-nucleophiles while stereoselectively controlling the P-attack process.

1. Introduction

The sulfonamide functional group is recognized as a pivotal pharmacophore, particularly in clinical pharmaceuticals, where optically pure five-membered benzosultams find extensive application as potent inhibitors of γ-secretase, HIV-1, aldose reductase *etc.*(Fig. 1A, I–III).[1] Cyclic *N*-sulfonyl imine, an exceptionally versatile synthetic precursor, has garnered considerable attention owing to its intriguing structures and associated properties. Chemists primarily concentrate on synthetically manipulating the electrophilic pro-chiral C=N bond of *N*-sulfonyl imines, which possess multiple heteroatoms (N, O and S), thereby frequently exhibiting or enhancing biological activities.[2] Significant advancements have occurred through the utilization of various carbon nucleophiles to react with the imine moiety, facilitating the synthesis of chiral sulfonamides in recent years. In this context, metal-catalyzed, elegantly enantioselective aryl nucleophilic additions utilizing aryl boronic acids or aryl halides as pronucleophilic reagents have been successfully developed by Zhang,[3a] Xu,[3b,c] Hayashi[3d] and Shi.[3e] Subsequently, strategies employing metal-promoted carbon-nucleophilic addition, utilizing alkyl,[4] alkenyl,[5] allyl,[6] alkynyl[7] and other[8] nucleophilic reagents, to cyclic *N*-sulfonyl imines have been extensively employed for the modular assembly of chiral *N*-substituted quaternary stereocenters. Additionally, sporadic reports in recent years have demonstrated the utilization of ketones and their derivatives to generate the enolate ion through deprotonation under alkaline conditions, facilitating participation in asymmetric nucleophilic addition with cyclic *N*-sulfonyl imines catalyzed by chiral organic bases.[9] Despite such impressive progress, significant limitations are also evident. Moreover, only C-nucleophiles have been utilized, and the majority of these cases necessitated transition metal catalysts. To our knowledge, catalytic asymmetric nucleophilic addition to five-membered cyclic *N*-sulfonyl imines using heteroatoms, particularly P-atom nucleophilic reagents, has never been reported to date, representing a significant challenge. Challenges include the potential poisoning of metal catalysts by P-nucleophiles, tautomerism between phosphine oxide species (P(v) and P(iii)), and difficulties in controlling reactivity and achieving high enantioselectivity. Notably, chiral phosphorus-containing compounds, particularly α-amino phosphates, have been widely employed as candidate pharmacological molecules (Fig. 1A, IV)[10] and/or

[a]*Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, 610064, P. R. China. E-mail: wangtl@scu.edu.cn*

[b]*College of Water Resource and Hydropower, Sichuan University, Chengdu, 610064, P. R. China. E-mail: zpxu@scu.edu.cn*

[c]*School of Materials Science & Engineering, Changzhou University, Changzhou, 213164, P. R. China*

[d]*Hunan Province Key Laboratory of Environmental Catalysis and Waste Recycling, College of Materials and Chemical Engineering, Hunan Institute of Engineering, Xiangtan, 411104, P. R. China*

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‡ H. Zhang and J.-P. Tan contributed equally to this work.

potential chiral ligands/catalysts.[11] From this perspective, the incorporation of P-atoms into *N*-sulfonyl imines to create a new structure bearing multiple hetero-atoms (*i.e.* O, S, N, and P) is intriguing yet challenging.

Returning to the issue of phosphorus nucleophiles, in general, the readily available and bench-stable secondary phosphine oxides (SPOs) were often the preferred choice due to their easy handling and relatively odorless nature.[12] In reality, a similar tautomeric equilibrium, like the textbook example of keto–enol tautomerism, can be drawn between the pentavalent oxide P(v) form and the phosphinous acid P(iii) form for such phosphorus-containing compounds.[13] The flexible tautomeric equilibrium and slippery molecular structure of SPOs make them difficult to selectively control in asymmetric reactions. With the flourishing development of asymmetric catalytic systems in recent decades, the synthetic community has witnessed the progress of the enantioselective P-addition with general imines,[14] but the gap of five-membered cyclic *N*-sulfonyl imines still needs to be filled. Considering the well-known challenge in this area, we recognize that the key to success lies in the rational design and/or selection of an efficient organocatalytic system for its powerful catalytic ability and wide application potential toward synthesis of various important chiral molecules in synthetic chemistry.[15] Given our ongoing

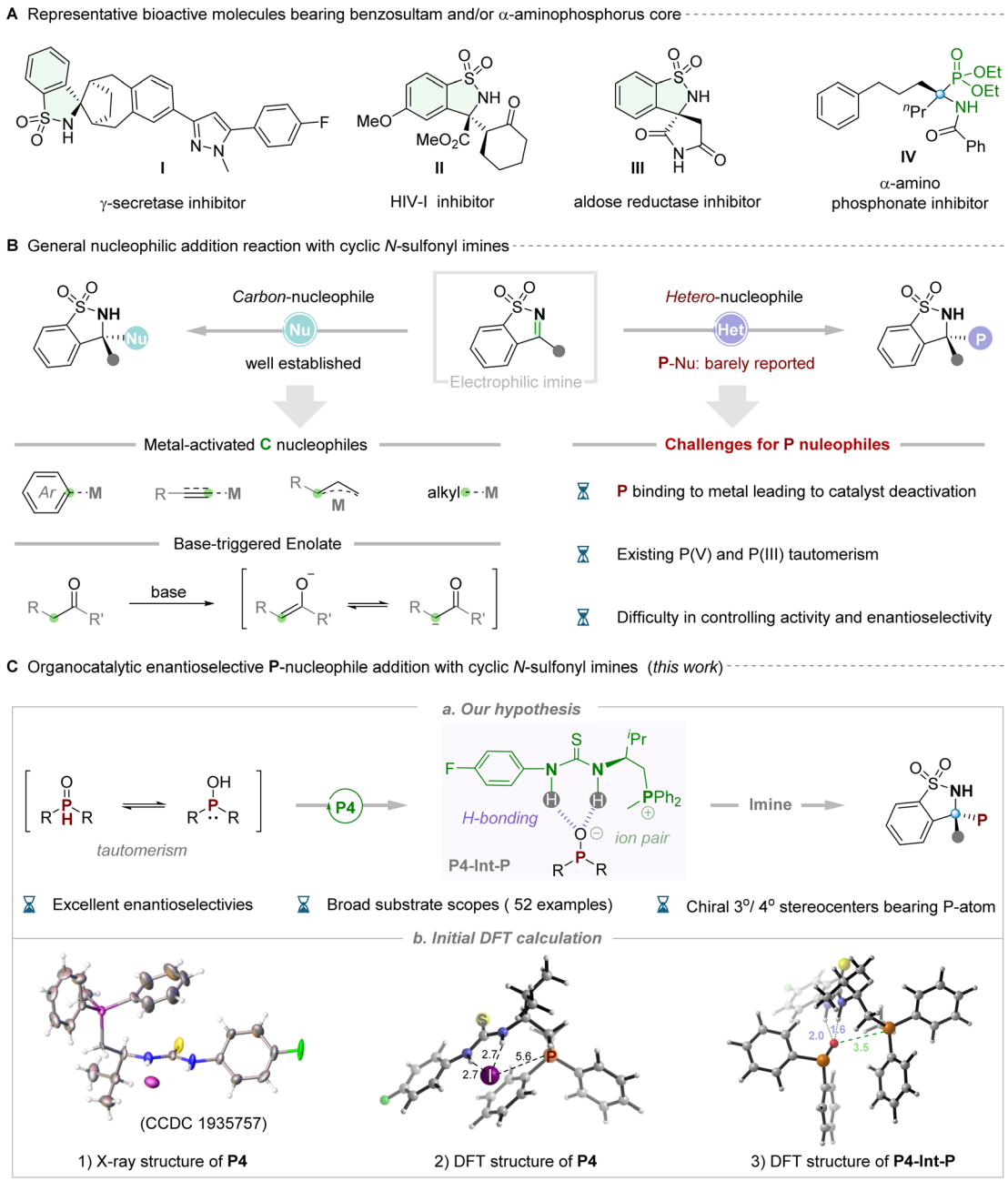


Fig. 1 Our strategy for the organocatalytic enantioselective P-nucleophilic addition of cyclic *N*-sulfonyl imines toward phosphorus-containing benzosultams.

progress in developing multi- and/or bi-functional phosphonium salt catalysts that have successfully addressed many synthetic challenges and significant targets,[16] we anticipate that these highly structurally tunable ion-pair catalysts with multiple hydrogen-bonding interactions with substrates will address the issue of reactivity and stereoselectivity control of P-species. Subsequently, they will participate in nucleophilic addition with cyclic *N*-sulfonyl imines to afford chiral phosphorus-containing benzosultams (Fig. 1C). Our hypothesis was rationally validated by preliminary analysis of the X-ray structure of thiourea-derived phosphonium salt catalyst **P4**. In this analysis, the iodine negative ion counterion was observed to be distant from the phosphorus cation center, resulting in weaker binding constants with the thiourea moiety, thus providing an opportunity for exchanging the negative iodine ion with the phosphate anion. Additionally, the key intermediate (**P4-Int-P**) was formed through a combination of hydrogen bonding and ion pairs within the catalyst, exhibiting stronger hydrogen bonding and electrostatic forces than catalyst **P4** according to DFT simulation (Fig. 1C, eqn (3)). We identified a novel activation mode of thiourea-derived phosphonium salt catalysts, wherein the exchanged anion not only acts as the nucleophile in enantiodetermining bond-formation but also accelerates the production of chiral phosphorus-containing benzosultams *via* hydrogen bonding in phase-transfer catalysis. This approach offers more precise control over stereoselectivity through specific association of the nucleophile with the chiral bifunctional phosphonium salt.[17]

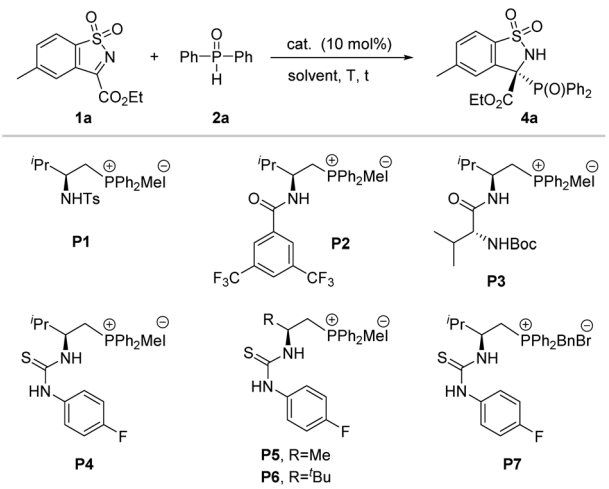
2. Results and discussion

2.1 Asymmetric P-nucleophilic addition of cyclic *N*-sulfonyl imines with secondary phosphine oxides

Inspired by the initial studies, we started our investigation to explore the feasibility of this reaction between *N*-sulfonyl cyclic ketimine **1a** and diphenylphosphine oxide **2a** in CH_2Cl_2 at room temperature in the presence of K_2CO_3. As a result, the desired racemic product **4a** was obtained with 98% yield (Table 1, entry 1). Next, when the racemic phosphonium salt **P0** was used for this reaction without addition of base, this reaction also proceeded smoothly, affording **4a** with 83% yield for 2 hours (Table 1, entry 2). The above-mentioned results implied that the strong background reaction may be involved in this system. Given our previous successful research on the enantioselective control of phosphorus-containing species in asymmetric synthesis within bifunctional phosphonium catalytic systems,[16] we chose amide-, dipeptide- and thiourea-derived phosphonium salts as candidate catalysts for their representative hydrogen-bonding and ion-pairing features. Pleasingly, all tested phosphonium salt catalysts were effective in promoting this reaction, furnishing the desired product in high yields and moderate to good enantioselectivities (entries 3–9). In particular, L-valine-derived thiourea-based **P4** was discovered to be an excellent catalyst for this transformation, affording the desired product **4a** with 93% yield and 90% ee (entry 6). To improve the enantioselectivity, we further screened the solvents (see Table S2† for more details) and proved 1,2-dichloroethane to be the best solvent, affording the desired product in excellent yield (96%) and enantioselectivity (>99% ee) (Table 1, entry 12). Additionally, we further verify the extra base will accelerate the background reaction leading to loss of enantioselectivity (entries 13 and 14). In fact, upon reducing the catalyst loading to 5 mol%, the reaction could maintain good activity, but eroded the enantioselectivity of the product slightly (Table 1, entry 15).

Having established the optimal reaction conditions in hand, we then focused on the generality of this protocol. Firstly, the scope of asymmetric P-nucleophile addition to cyclic *N*-sulfonyl imines **1** with secondary phosphine oxides was investigated (Table 2). To our delight, an array of cyclic ketimines **1** with electron-donating or electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-position of the phenyl ring moiety were found to be suitable reaction partners, furnishing the desired products (**4a–i**) in good yields and excellent enantioselectivities (98 to >99% ee). Additionally, 1-naphthyl and 2-naphthyl

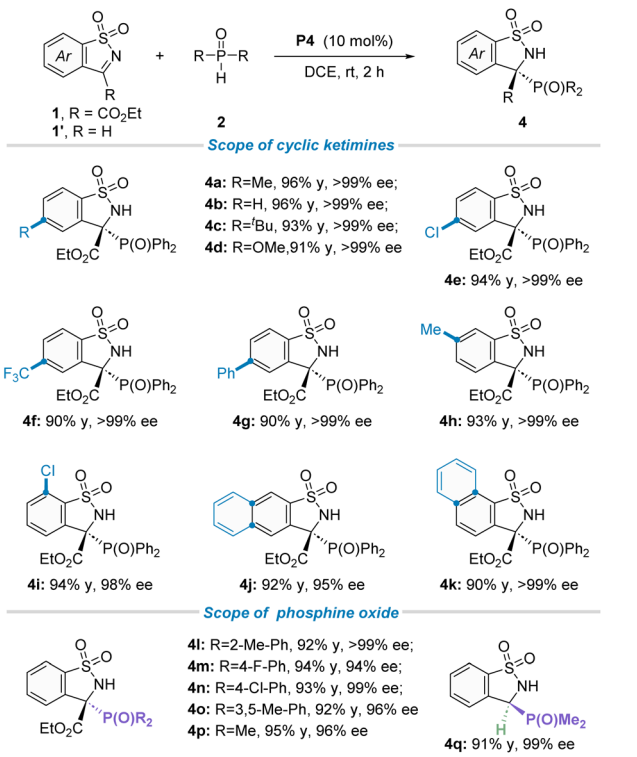
Table 1 Optimization for asymmetric P-nucleophile addition to cyclic *N*-sulfonyl imines with secondary phosphine oxides[a]



Entry	Cat.	Base (x equiv.)	Solvent	t (h)	Yield (%)[b]	ee (%)[c]
1	—	K_2CO_3 (1.0)	CH_2Cl_2	1	98	0
2	**P0**	None	CH_2Cl_2	2	83	0
3	**P1**	None	CH_2Cl_2	2	90	34
4	**P2**	None	CH_2Cl_2	2	92	53
5	**P3**	None	CH_2Cl_2	2	90	71
6	**P4**	None	CH_2Cl_2	2	93	90
7	**P5**	None	CH_2Cl_2	2	86	68
8	**P6**	None	CH_2Cl_2	2	92	86
9	**P7**	None	CH_2Cl_2	2	87	83
10	**P4**	None	$CHCl_3$	2	94	73
11	**P4**	None	Toluene	2	88	93
12	**P4**	None	**DCE**	**2**	**95**	**>99**
13[d]	**P4**	K_2CO_3 (1.0)	DCE	0.5	95	<5
14[e]	**P4**	K_2CO_3 (0.5)	DCE	1	96	75
15[f]	**P4**	None	DCE	3	92	89

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.01 mmol) in solvent (1.0 mL) at room temperature for 0.5–2.5 h, **P0** = $Ph_2Me_2P^+I^-$. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] 1.0 equivalent of K_2CO_3 was added. [e] 0.5 equivalent of K_2CO_3 was used. [f] The catalyst loading was 5 mol%. Ts = 4-Toluenesulfonyl. DCE = 1,2-Dichloroethane.

Table 2 Scope of the asymmetric P-nucleophilic addition of cyclic *N*-sulfonyl imines with secondary phosphine oxides[a]



[a] Reactions were performed with **1**/**1′** (0.1 mmol), **2** (0.12 mmol), and **P4** (0.01 mmol) in DCE (1.0 mL) at room temperature for 2 hours. All yields were isolated yields, and the ee value was determined by HPLC analysis on a chiral stationary phase.

substituted cyclic ketimines were also well tolerated under the standard reaction conditions, giving the corresponding products **4j** in 92% yield and 95% ee and **4k** in 90% yield and >99% ee, respectively. Subsequently, the generality of secondary phosphine oxides for this transformation was evaluated. As shown in Table 2 (down), for diaryl substituted phosphine oxides, the substituent group installed on the phenyl ring did not have an obvious effect on both isolated yields and stereoselectivities, offering the corresponding targets (**4l–o**) with good yields and outstanding ee values. It is worth noting that dimethyl phosphine oxide has also been proven to be a suitable phosphorus source, not only for ketimine **1a** but also for aldimine **1′a**, providing the corresponding chiral phosphorus-containing quaternary carbon center product **4p** and **3o** carbon center product **4q** with 98% ee and 99% ee, respectively. To confirm the absolute configuration of these phosphorus-containing benzosultams **4**, CD spectra were calculated by the DFT study. The S configuration could be reliably assigned to compound **4a** [19a] (see Scheme S3 in the ESI† for more details).

2.2 Asymmetric P-nucleophilic addition of cyclic *N*-sulfonyl imines with phosphites

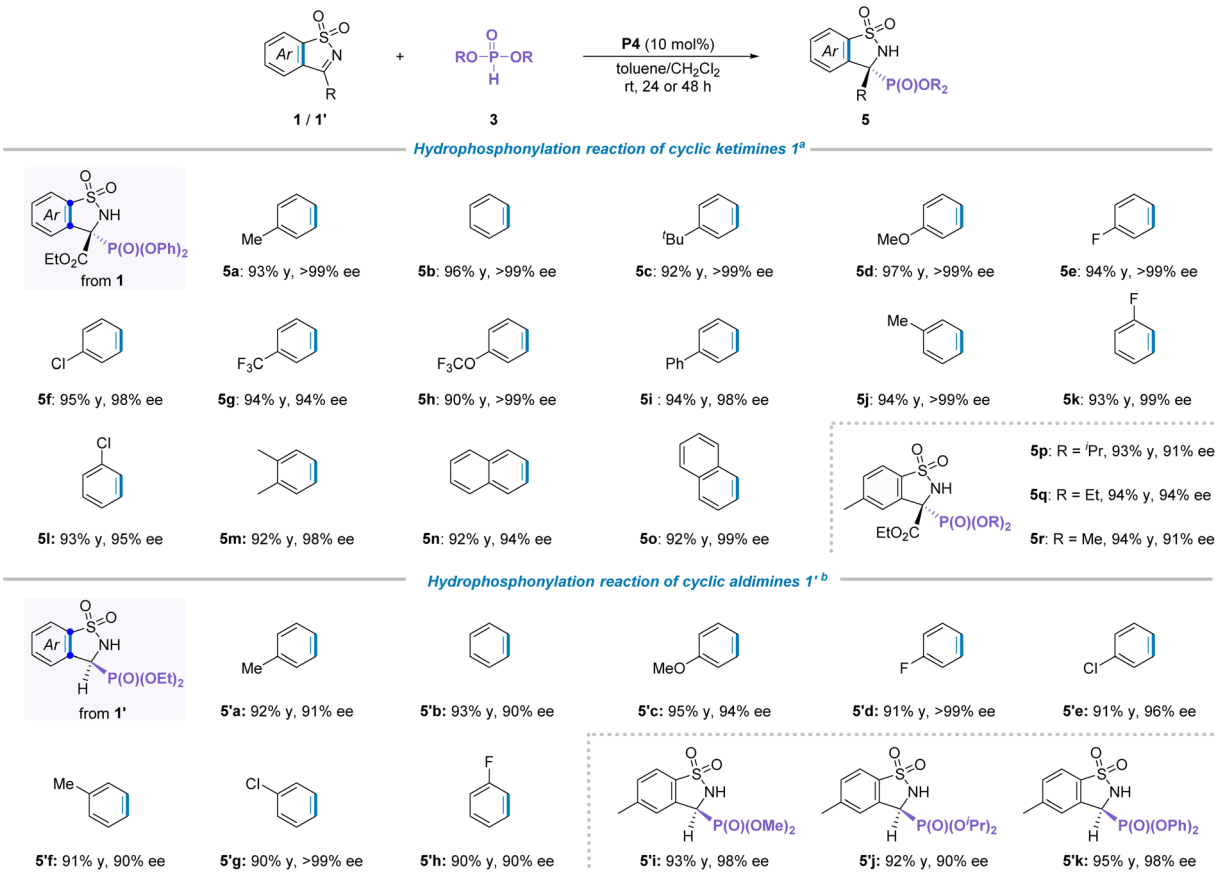
Different types of phosphoryl species have distinct chemical properties and pharmacological activities.[18] Particularly, α-amino phosphates and their derivatives usually demonstrated important physiological activity in life.[19] Therefore, the generality of phosphites as P-nucleophiles added to cyclic *N*-sulfonyl imines was explored. Inspired by the above successful results, the hydrophosphonylation reaction between cyclic ketimine **1a** and diphenyl phosphite **3a** to evaluate catalytic effects in the presence of **P4** and 1,2-dichloroethane (DCE) at room temperature was studied, and results show that the desired addition product **5a** was obtained in 94% yield and 88% ee. After a series of quick screening of optimization, toluene was found to be the most suitable solvent, affording the corresponding product in 96% yield with >99% ee (see Tables S3 and S4 in the ESI† for more details).

With the identified optimal reaction conditions in hand, we then set out to explore the generality for the scope of this hydrophosphonylation transformation. Firstly, a wide range of cyclic ketimines **1** bearing different substituent groups were investigated (Table 3a). As a result, neither the electronic properties nor the positions of the substituents on the aromatic ring of cyclic imines had an observable influence on the isolated yield and stereoselectivity of the products (**5a–5o**). Subsequently, the ester groups of phosphites with different sized substituent groups, including methyl, ethyl and isopropyl, were examined. To our delight, all these tested substrates were well compatible with the standard conditions, providing the corresponding products in good yields and enantioselectivities. Afterwards, when the cyclic aldimines **1′** as a model electrophilic reagent combined with diethyl phosphite for this reaction, the optimal solvent was changed to CH_2Cl_2 with addition of 2.0 equivalents of Cs_2CO_3 at room temperature in the presence of **P4** (see Table S4† for more details). Under these standard reaction conditions, the compatibility for the substituent group was evaluated. As illustrated in Table 3b, a diverse array of cyclic aldimines **1′** regardless of the positions and electronic properties of the substituents on the phenyl ring were perfectly compatible with the standard reaction conditions, providing the corresponding products **5′a–′h** in high isolated yields (90–95%) with excellent enantioselectivities (90 to >99%). Moreover, other types of phosphite esters, such as dimethyl, diisopropyl and diphenyl phosphite were also suitable for the reaction and the corresponding adducts **5′i–k** were obtained in good yield and ee values. Besides, the absolute configuration of compounds **5** was assigned as *S* on the basis of analysis of CD spectra calculated by the DFT method.[20a] The absolute configuration of product **5′** was rationally assigned to be *S* by comparing the optical rotation of the same compound with previously reported results[20b] (see the ESI for more details, Scheme S2†).

2.3 Asymmetric P-nucleophilic addition of CF_3-substituted cyclic *N*-sulfonyl amines

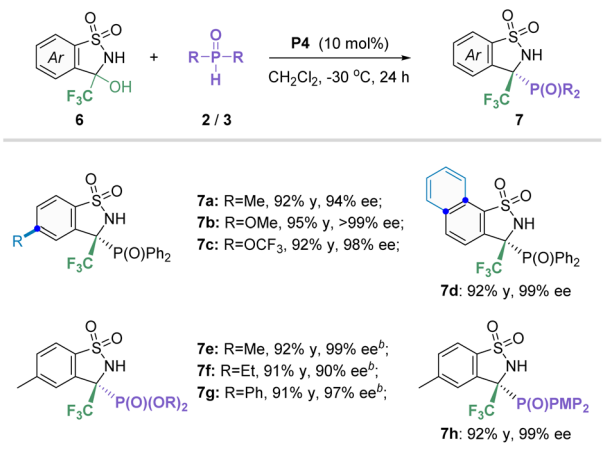
It is a universally accepted fact that the introduction of a trifluoromethyl group into *N*-heterocyclic molecules can further bring positive effects in the development of agrochemicals or pharmaceuticals.[21] Thus, the preparation of the privileged CF_3-substituted benzosultam that also contains a useful phosphorus atom is an important endeavor in the synthetic

Table 3 Scope of the asymmetric P-nucleophilic addition of cyclic *N*-sulfonyl imines with phosphites[a,b]



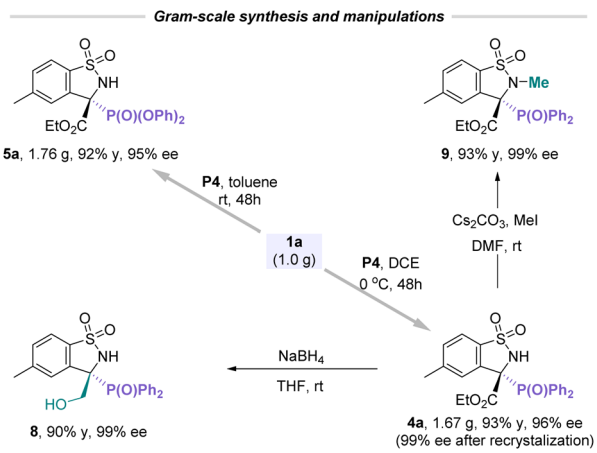
[a] Reactions were performed with cyclic ketimines **1** (0.1 mmol), **3** (0.12 mmol), and **P4** (0.01 mmol) in toluene (2.0 mL) at room temperature for 24 hours. All yields were isolated yields, and the ee value was determined by HPLC analysis on a chiral stationary phase. [b] Reactions were performed with cyclic aldimines **1'** (0.1 mmol), **3** (0.12 mmol), **P4** (0.01 mmol) and Cs_2CO_3 (0.2 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 48 hours.

Table 4 Asymmetric P-nucleophilic addition of CF_3-substituted cyclic *N*-sulfonyl amines[a]



[a] Reactions were performed with **6** (0.1 mmol), **2/3** (0.12 mmol), and **P4** (0.01 mmol) in CH_2Cl_2 (3.0 mL) at −30 °C for 24 hours. Isolated yield. The ee value was determined by HPLC analysis on a chiral stationary phase. [b] At room temperature for 48 hours.

community. Based on the previous literature,[22] we envisaged that α-hydroxy, α-trifluoromethyl substituted sulfonamide will *in situ* generate sulfimide easily, which could serve as a good electrophilic reagent.[23] According to the above successful findings, we set out to carry out studies on asymmetric P-



Scheme 1 Scale-up synthesis and manipulation of the product.

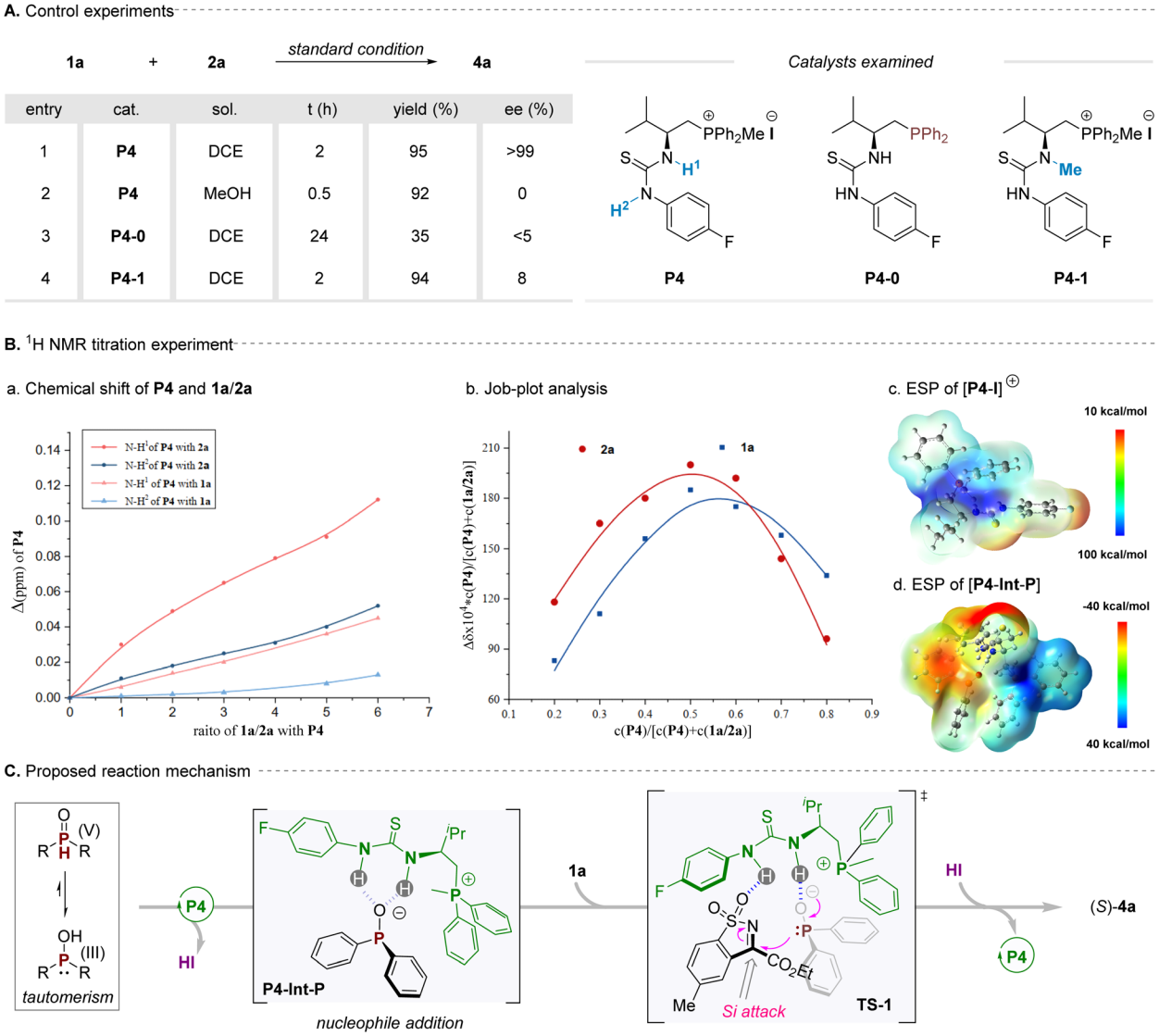
nucleophile addition between CF_3-substituted cyclic *N*-sulfonyl amines and P-nucleophiles in the presence of a phosphonium salt catalyst (Table 4). After a quick survey of the reaction conditions, the target product **7a** was obtained with 92% yield and 94% ee under the **P4** catalyst in CH_2Cl_2 at −30 °C for 48 h (see Table S5 in the ESI† for more details on conditions optimization). Subsequently, the scope of *in situ* generated CF_3-containing cyclic imine **6** with secondary phosphine oxides was investigated. To our delight, different aryl substituent groups with electron-donating or -withdrawing as well as naphthyl could well tolerate the standard conditions, affording the corresponding products **7b–d** in high yields (92–95%) and excellent enantioselectivities (94–99% ee). Furthermore, various phosphites including diaryl and dialkyl phosphites were also found to be good reaction partners, offering the desired products **7e–h** in satisfactory yields and enantioselectivities (91–92% yields, 90–99% ee).

2.4 Scaled-up synthesis and transformation of the product

To further validate the scalability and practicality of this catalytic asymmetric protocol, the gram-scale experiments for the P-nucleophile addition with cyclic *N*-sulfonyl imines proceeded smoothly under the corresponding conditions, providing manifold corresponding products such as **4a** and **5a** with comparable yields without loss of enantioselectivities (Scheme 1). Moreover, the direct reduction of the ester group of **4a** using $NaBH_4$ furnished β-hydroxyl-functionalized compound **8** in excellent yield and enantioselectivity. In addition, the free N–H installed on the chiral benzosultams could be readily *N*-methylated with iodomethane to afford α-aminophosphonate **9** in high yield and without any loss of the enantiomeric purity, which provides a possibility for further modification on drug molecules.

2.5 Mechanistic investigations

To gain insight into the mechanism for this reaction, a series of control experiments were carried out to understand the reaction



Scheme 2 Mechanistic experiments and plausible reaction mechanism.

mechanism, particularly towards the chiral control (Scheme 2A). Firstly, the reaction between cyclic ketimine **1a** and diphenylphosphine oxide **2a** was performed with bifunctional phosphonium salt **P4** in DCE at room temperature for 24 h, affording the corresponding product **4a** in 95% yield with >99% ee. When the polar solvent methanol was used, the enantioselectivity of the corresponding product decreased dramatically, which was probably mainly due to hydrogen bonding in systems being weakened or even destroyed (Scheme 2A, entry 2). Besides, when the optimal phosphonium salt catalyst **P4** was changed to its corresponding trivalent phosphine (**P4-0**) under the standard conditions for the reaction, the yield and selectivity of the reaction decreased remarkably, giving a nearly racemic product only with 35% isolated yield (Scheme 2A, entry 3), which also indicated that the ion pairing of the phosphonium salt played an important role in the reaction. Additionally, one of the N–H bonds of the **P4** was blocked to form a new methylated catalyst **P4-1**, which was further used as the catalyst for this model reaction, and the enantioselectivity of the product decreased obviously, with only 8% ee being obtained for the target (Scheme 2A, entry 4). These preliminary results clearly suggested that the H-bonding and ion-pair interactions in this catalytic system are critical factors for asymmetric induction. Subsequently, the ^{1}H NMR titration experiments were performed for gaining further insights to the mechanism, particularly towards the origins of chirality induction for this reaction (Scheme 2B). In this vein, titration of P-nucleophile **2a** to the optimal catalyst **P4** led to a distinct chemical shift change in the position of both of the thiourea-NH signals of the catalyst. In contrast, upon titration of cyclic *N*-sulfonyl imine substrate **1a** with **P4**, less pronounced changes were observed. Additionally, Job plot analysis of the addition of **1a** or **2a** to **P4** indicated a 1 : 1 ratio binding model between the catalyst and substrate (Scheme 2B, b). The above results evidently indicated that the bifunctional phosphonium salt **P4** was inclined to combine with the phosphite anion *via* double H-bonding and ion pair activation. Of note, given the observation that the iodide ion is relatively far from the phosphonium cation *via* the analysis of X-ray crystal structure for catalyst **P4** (Fig. 1C, b1), we envisaged the iodide ion was easily disengaged from the phosphonium salt and could serve as a Brønsted base to remove the proton of P-nucleophiles. Simultaneously, the phosphonium cation particularly possesses a semi-enclosed cavity with an electropositive region as demonstrated by its computed electrostatic potential (ESP) map (Scheme 2B, c), which would be combined with anion species *via* ion pair interattraction, forming a possible **P4-Int-P** intermediate, which was also reasonably validated by its electrostatic potential (ESP) map result (Scheme 2B, d). On the basis of these observations, a plausible reaction mechanism of this reaction was proposed in Scheme 2c; the key success for this high reactivity and enantioselectivity for this transformation is the adaptive assembly of the bifunctional phosphonium salt catalyst with P-nucleophiles *via* H-bonding and ion-pair interactions.

3. Conclusions

In conclusion, we have successfully completed the first highly enantioselective P-nucleophilic addition of five-membered cyclic *N*-sulfonyl imines by a tunable bifunctional ion-pair catalyst with multiple-hydrogen-bond interaction ability. Under this protocol, three libraries of structurally and functionally diverse enantioenriched cyclic quaternary/tertiary phosphorus-containing benzosultam compounds were efficiently prepared with high isolated yields and excellent enantioselectivities under mild reaction conditions. The key to success is the rational choice of an efficient organocatalytic system that not only avoids predictable side effects upon manipulating SPOs, but also ingeniously reins in the P-nucleophiles with powerful H-bonding and ion-pair interactions. The utility and the practicality of this reaction were demonstrated by gram-scale preparation and facile elaborations. Systematic mechanistic studies including experiments and DFT calculations elucidated the judicious choice of bifunctional phosphonium salt catalysts is critical for the ingenious stereoselective reining in of the P-nucleophiles. This finding is expected to stimulate a more extensive exploration of the catalytic asymmetric construction of phosphorus-containing heterocyclic compounds in synthetic chemistry.

Data availability

All the experimental data are provided in the ESI.† Crystallographic data for P4 has been deposited and available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under NO. 1935757 and can be obtained from **https://www.ccdc.cam.ac.uk**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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