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Organocatalytic enantioselective [2 + 2] cycloadditions towards chiral fused α-trifluoromethyl azetidines†

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Access to relatively high-energy azetidines in enantioenriched form *via* a function- and diversity-oriented approach is highly desired in the field of drug discovery. Although the demands for α-trifluoromethyl azetidines with great biological potential still exist, effective strategies for the catalytic asymmetric synthesis of these chemical entities with structural diversity remain elusive. To conquer this frontier, we, herein, report the development of a building block protocol for the facile assembly of enantioenriched α-trifluoromethyl azetidines *via* peptide-mimic phosphonium salt-catalyzed asymmetric [2 + 2] cycloadditions of tethered trifluoromethyl ketimines and allenes. Of note, this methodology could allow for the enantioselective synthesis of a diverse set of six-membered ring-fused α-trifluoromethyl azetidines bearing two densely functionalized carbon stereocenters in high yields with excellent diastereo- and enantioselectivities. Besides the fundamental appeal of this strategy, scale-up experiments and representative transformations could enable its prompt application in synthetic chemistry.

Introduction

Saturated N-heterocycles constitute one of the most promising areas of research in medicinal and material applications.[1] Among the saturated ring systems, chiral four-membered rings such as azetidines and β-lactams are, surprisingly, somewhat uncommon targets, although they could serve as synthetic intermediates and typically improve toxicological benefits in biologically relevant chemical space (Fig. 1A).[2] The key reason behind unsatisfactory appreciation is that the evolvement of this class of chiral chemical compounds into pharmaceuticals can in most cases be restricted by the emergence of resistance and limited metabolic stability.[3] As such, establishing a robust and concise catalytic asymmetric method that provides a platform towards functionalized four-membered ring systems with structural diversity is desired but daunting.

As we all know, the incorporation of a trifluoromethyl group (–CF_3) into organic fragments has been one significant structural manipulation in drug design and discovery.[4] This manipulation tends to enhance the pharmacokinetic and/or pharmacological properties of compounds, thus endowing them with a favorable therapeutic profile.[5] Therefore, uncountable efforts have been put into the facile assembly of trifluoromethyl organic matter, which has enriched the landscape of fluorine chemistry.[6] Among them, a conspicuous example is the prevalence of α-trifluoromethyl amine derivatives in peptidomimetics and medicinal chemistry.[7] Of note, α-trifluoromethyl amine moieties are of particular interest since they could serve as bioisosteres for amides regardless of their unique biological relevance, which shows promise for overshadowing the metabolic sensitivity of amide bonds to amidases, esterases and proteases (Fig. 1B).[7b,d,8] The last two decades have witnessed an avalanche of exploration for the construction of α-trifluoromethyl amine scaffolds, which is in most cases concomitant to the creation of stereogenic centers.[7d,e,9] Despite significant advances, most transformations afford the α-trifluoromethyl amines in an acyclic, medium- or large-ring framework. In contrast, enantiomerically enriched α-trifluoromethylated azetidines despite having great medicinal potential have been much less exploited owing to insufficient and incomprehensible routes to their derivatives, especially using asymmetric catalysis. In this vein, foreseeable and feasible strategies towards this class of chiral skeletons have been trifluoromethylation[10] and the building block approach.[11] Trifluoromethylation is a straightforward protocol for the introduction of trifluoromethyl atoms into target skeletons, whereas a remarkable confusion occurs when it

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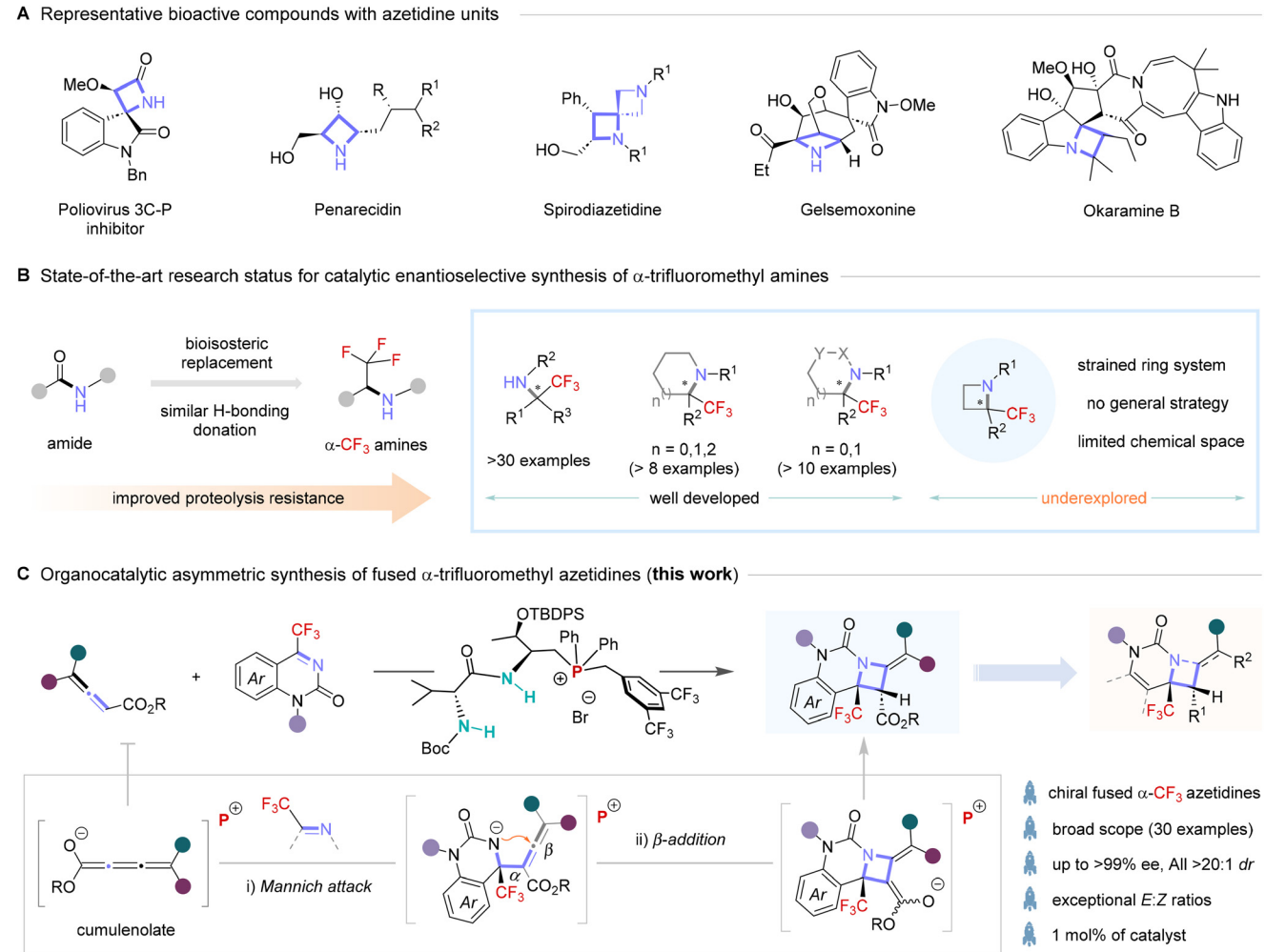


Fig. 1 Strategy for the catalytic asymmetric synthesis of chiral fused α-trifluoromethyl azetidines.

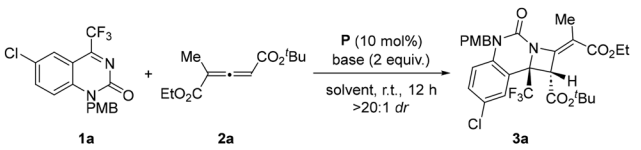
comes to the catalytic asymmetric synthesis of multiple stereogenic centers.[12] Notably, the latter features readily available and controlled transformations and trifluoromethylated building blocks, which are primed for the generation of coveted chiral entities.[13] Along this line, catalytic asymmetric [2 + 2] cycloadditions[14] of trifluoromethyl imines[15] to an appropriate two-carbon source arguably represent a concise and unified route to access chiral α-trifluoromethylated azetidines.

In continuation of our interest in the transformation of allenes,[16] versatile building blocks owing to their unique orthogonal cumulative π-systems, we wondered whether they could serve as two-carbon sources to undergo [2 + 2] cycloadditions with trifluoromethyl imines, particularly in a catalytic asymmetric manner. If successful, it would establish a straightforward connection towards chiral α-trifluoromethyl azetidines anchored by functionalized olefin moieties, which are primed for a variety of subsequent stereospecific transformations. However, this strategy comes with two fundamental obstacles: the unknown reactivity of such imines together with the generation of strained four-membered ring systems in which the ring strain is further increased by fusion to a second ring. Notably, both of them are susceptible to steric hindrance and substituent patterns, readily leading to competitive reaction manifolds, such as asymmetric additions[17] and/or strain-releasing cycloadditions.[18] A representative case is the phase-transfer-catalysed asymmetric reaction of *N*-arylsulfonyl imines and 1-alkylallene-1,3-dicarboxylates, which only allowed access to chiral tetrasubstituted allenes *via* an alleno-Mannich-type pathway.[17b] Inspired by our recent breakthrough of peptide-mimic phosphonium salt (PPS) catalysts and their remarkable efficacy in a variety of sought-after cycloadditions,[19] we envisaged that such a highly tunable organocatalyst system could potentially transcend the inherent chemo-, regio- and stereoselective challenges of this transformation. To test this hypothesis, we, herein, developed a novel enantioselective [2 + 2] cycloaddition reaction inspired by PPS catalysts, thus affording a library of enantioenriched fused polysubstituted α-trifluoromethyl azetidines bearing successive stereocenters (Fig. 1C). Strikingly, this reaction could tolerate cyclic trifluoromethyl ketimines and even trisubstituted allenes to yield a single diastereomer of the strained azetidine products with exceptional *E*/*Z* isomeric ratios.

Results and discussion

To commence the investigation of the [2 + 2] cycloaddition reaction, we selected cyclic trifluoromethyl ketimines (**1a**) and allenoate (**2a**) as model substrates to evaluate the conditions. Surprisingly, of the bifunctional phosphonium salts tested, peptide-mimic phosphonium salt catalysts were advantageous catalysts. In particular, when the L,D-dipeptide-based phosphonium iodide **P2**, derived from L-Val, was used, the reaction could work smoothly with 8% ee and >20 : 1 dr values (entry 2). In order to further enhance the ee value of the product, the L,D-dipeptide phosphonium iodide salts **P3–P5**, derived from different L-amino acids, were used for the model reaction. To our delight, employing the O-TBDPS-L-threonine-derived catalyst **P5** afforded the desired product in 78% yield with 12% ee. While switching **P5** to the corresponding phosphonium bromide salt **P6**, the ee value of **3a** was significantly improved due to the greater steric hindrance of the alkyl group on the phosphorus atom (entry 6). Inspired by these introductory results, our focus shifted to the architectural fine-tuning of catalyst **P6**, with a primary emphasis on steric and electronic effects (entries 7 and 8). Further increasing the steric hindrance and electron-deficient effect on the benzyl, we were pleasantly surprised to observe that the L,D-dipeptide-based phosphonium bromide salt **P8**, derived from 3,5-trifluoromethylbenzyl bromide, enhanced the enantioselectivity of product **3a** to 52% ee. To improve the stereo-controllability of the catalyst, a series of bases, solvents and reaction temperatures were screened considering their possible positive effects on weakening background reactions (see Tables S1–S4 for more details†). Among the screened reaction partners, when *n*-octane was employed as the solvent and Cs_2CO_3 (2.0 equiv.) as the base, the greatest improvement in yield and enantioselectivity was achieved by extending the reaction time at room temperature, giving the desired product **3a** in 96% yield with 98% ee (Table 1, entry 12). It is worth noting that even if we reduce the loading of catalyst **P8** to 1 mol%, the model reaction could still maintain high activity and stereoselective control (entry 17, 96% yield, >20 : 1 dr, 98% ee).

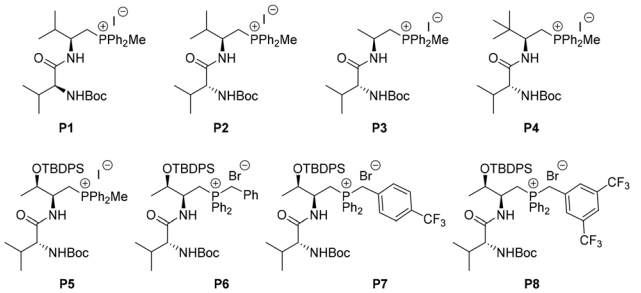
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	P	Solvent	Base	Yield[b] [%]	ee[c] [%]
1	**P1**	Xylene	Cs_2CO_3	81	5
2	**P2**	Xylene	Cs_2CO_3	82	8
3	**P3**	Xylene	Cs_2CO_3	79	4
4	**P4**	Xylene	Cs_2CO_3	85	5
5	**P5**	Xylene	Cs_2CO_3	78	12
6	**P6**	Xylene	Cs_2CO_3	73	23
7	**P7**	Xylene	Cs_2CO_3	74	34
8	**P8**	Xylene	Cs_2CO_3	80	52
9	**P8**	Toluene	Cs_2CO_3	72	37
10	**P8**	$CHCl_3$	Cs_2CO_3	77	3
11	**P8**	Et_2O	Cs_2CO_3	79	21
12[d]	**P8**	*n*-Octane	Cs_2CO_3	96	98
13[d]	**P8**	*n*-Octane	K_2CO_3	86	82
14[d]	**P8**	*n*-Octane	K_3PO_4	73	32
15[d]	**P8**	*n*-Octane	NaOH	76	16
16[d,e]	**P8**	*n*-Octane	Cs_2CO_3	Trace	—
17[d,f]	**P8**	*n*-Octane	Cs_2CO_3	96	98

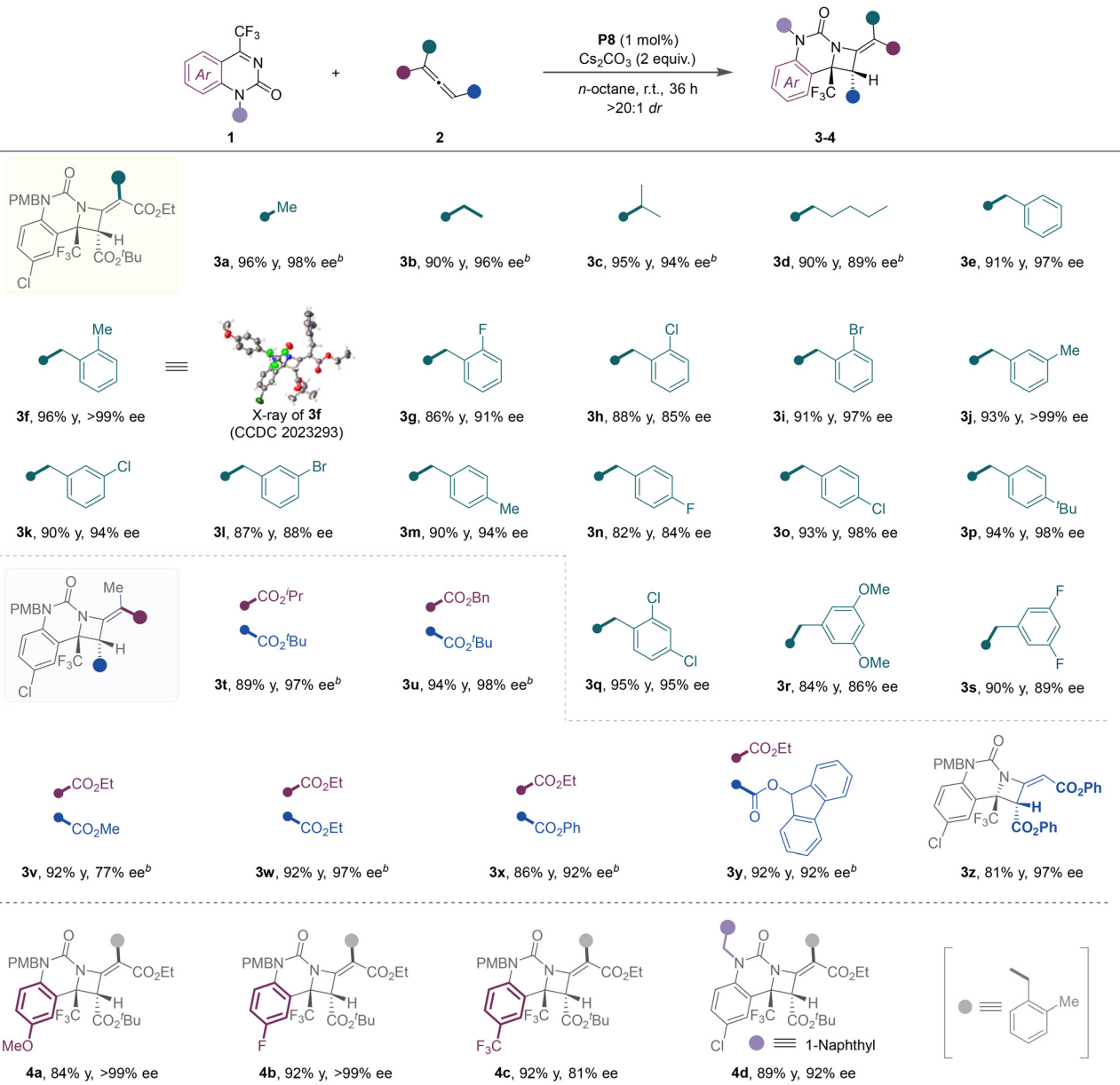
[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.11 mmol), base (0.20 mmol), and **P** (0.01 mmol) in solvent (1 mL) at room temperature for 12 h. All >20 : 1 dr and dr values were determined by ^{1}H NMR of the crude product. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was carried out for 72 h. [e] At 0 °C. [f] With 1 mol% of **P8**.



With optimal conditions established, we then explored the substrate scope with respect to asymmetric [2 + 2] annulation to construct a series of fused-azetidine skeletons. As highlighted in Table 2, the reaction conditions tolerated various alkyl substituted allenoates to provide the desired chiral azetidines in excellent yields with up to 98% ee and >20 : 1 dr (**3a–3e**). Subsequently, to further validate the utility and generality of the current reaction systems, we investigated the electronic effect on the benzene ring of benzyl substituted allenoates. Generally, different functional groups, containing either electron-neutral, -donating or -withdrawing groups, at the *ortho*-, *meta*-, or *para*-position on the phenyl ring of the benzyl substituted allene moiety were well tolerated under the current optimized conditions, thus furnishing the corresponding products in good yields with excellent stereoselectivities (**3f–3p**, up to 96% yield, up to >99% ee, all >20 : 1 dr). Also, the influence of the poly-substituted pattern on the aromatic ring was assessed, and these substrates also reacted smoothly under the standard reaction conditions, providing the corresponding products **3q–3s** with high yields and stereoselectivities (84–95% yield, 86–95% ee, >20 : 1 dr). Notably, to our delight, the [2 + 2] cycloaddition reaction can also be successfully applied to other types of allenic esters to afford polycyclic azetidines in good to excellent yields with high enantio- and diastereoselectivities (**3t–3z**, 81–94% yields, 77%–98% ee, >20 : 1 dr). The substrate scope with respect to trifluoromethyl ketimines was explored next (Table 2, bottom). Variation of the imine moiety afforded the desired products **4a–4d**, all giving excellent outcomes (up to 92% yield, up to >99% ee, >20 : 1 dr). Besides, the relative and absolute configurations of chiral azetidines were unambiguously established by X-ray crystallographic analysis of **3f** (CCDC 2023293†).[20]

To showcase the application potential of this method, we carried out mmol-scale experiments with **1a** and **2f** under stan-

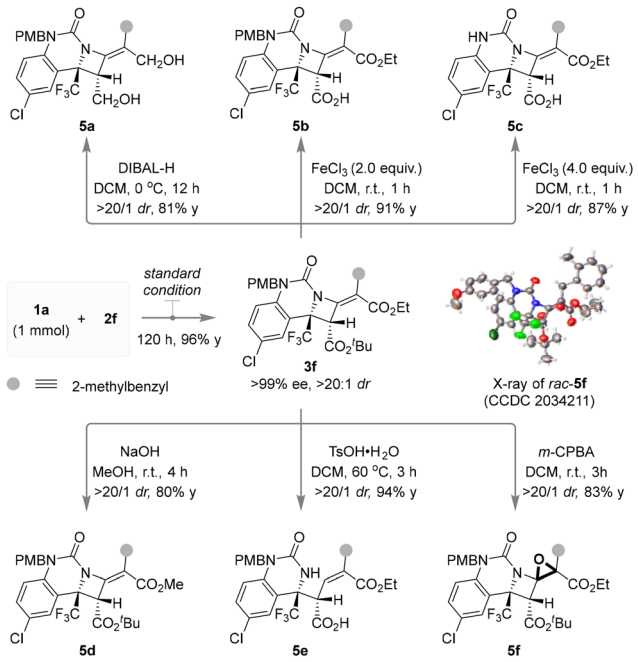
Table 2 Scope of substrates[a]



[a] Reactions were performed with **1** (0.10 mmol), **2** (0.11 mmol), Cs_2CO_3 (0.20 mmol), and **P8** (0.001 mmol) in *n*-octane (1 mL) at r.t. for 36 h. All >20 : 1 dr and dr values were determined by ^{1}H NMR. Isolated yields. The ee values were determined by HPLC. [b] At r.t. for 72 h.

dard conditions, affording the desired product **3f** without any loss of yield and enantioselectivity. In the meantime, the diversified synthetic elaboration of **3f** is also fulfilled (Scheme 1). First, **3f** can be converted to dihydroxy substituted azetidine **5a** in 81% yield by reduction. Then the corresponding carboxyl substituted azetidine **5b** can be gained by hydrolysis. Interestingly, when we increase the amount of $FeCl_3$ used, the PMB protecting group can be removed simultaneously to afford hydrolysis product **5c**. Additionally, we found that the *tert*-butyl ester of **3f** can undergo an ester exchange reaction to form **5d** in good yield, and the component of azetidine can be cleaved under the action of *p*-toluenesulfonic acid, and the spiro-azetidine-oxirane compound **5f** was obtained by means of epoxidation. These transformations can be carried out efficiently while maintaining the chirality of the corresponding products.

To shed some light on this enantioselective [2 + 2] reaction, preliminary mechanistic studies were conducted (Fig. 2). We first prepared the methylated phosphonium salt catalysts **P8-1** and **P8-2**. When the methylated phosphonium salts **P8-1** and **P8-2** were used, nearly racemic products were obtained, accompanied by a significant decrease in yields (Fig. 2A,



Scheme 1 Scale-up synthesis and transformation.

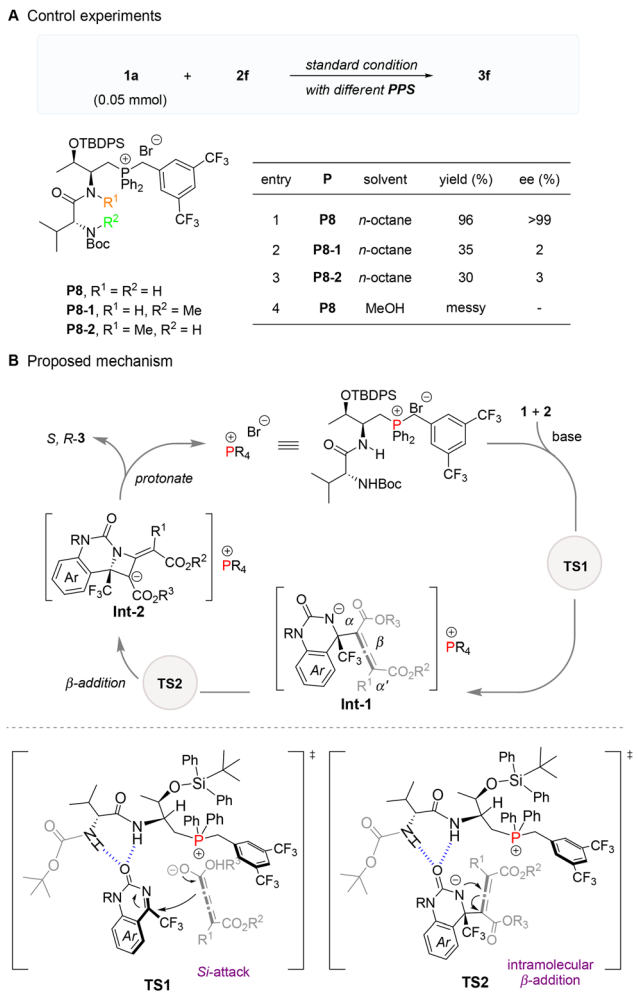


Fig. 2 Mechanistic insights and the proposed reaction mechanism.

entries 1–3). Furthermore, performing the reaction in methanol failed to produce the desired product. These preliminary results highlight the critical roles of hydrogen bonding and ion-pairing interactions within catalysis. Based on these findings and our prior investigations,[19] a plausible reaction mechanism was proposed (Fig. 2B). In the presence of the **P8** catalyst, the deprotonated allenoate **2a** easily undergoes Mannich addition with cyclic trifluoromethyl ketimine **1a** to form **Int 1**, which is stabilized by hydrogen bonding and ion-pairing interactions. Such a catalyst–substrate complex is amenable to proceeding with an intramolecular *N*-attack at the β-position of the allene moiety, allowing the entry of **Int 2**. Finally, asymmetric protonation occurs, thereby yielding the target enantioenriched α-trifluoromethyl azetidine **3** along with the release of catalyst **P8**.

Conclusions

In summary, we have disclosed a general and efficient PPS-catalyzed asymmetric [2 + 2] cycloaddition reaction between α-trifluoromethyl ketimines and trisubstituted allenes. With this protocol, a variety of structurally intriguing six-membered ring-fused α-trifluoromethylated azetidines were constructed in high yields and with excellent diastereo- and enantioselectivities. In this process, allenes serve as two-carbon synthons, which not only ensure the facile formation of the first densely functionalized carbon stereocenter, but also are supposed to deliver the stereogenic center to which ester moieties are attached. Notably, the obtained azetidine products anchored by functionalized olefin moieties were readily transformed into a series of high-valued derivatives *via* simple operation. Given the catalytic asymmetric [2 + 2] cycloaddition still being an elusive objective, it is envisaged that this versatile organocatalytic system could be harnessed in the enantioselective synthesis of other challenging four-membered ring systems.

Data availability

All data included in this study are available upon request by contacting the corresponding author (*i.e.* Prof. Tianli Wang, email: wangtl@scu.edu.cn).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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20 Deposition numbers 2023293 (for **3f**) and 2034211 (for rac-**5f**) contain the supplementary crystallographic data for this paper.†

