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Highly Enantioselective [3+2] Cycloadditions of Terminal Allenoates with β- Trifluoromethyl α,β-Enones

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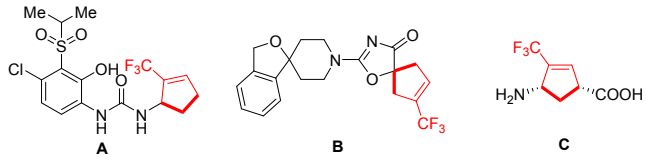
A highly enantio- and diastereoselective phosphine catalyzed [3+2] cycloadditions of terminal allenoates with β-perfluoroalkyl α,β-enones leading to a range of trifluoromethylated cyclopentenes with two contiguous chiral centers (up to 99% yield with 99% *ee*) have been disclosed. What's more, this reaction could be amenable to gram scale by utilizing only 1 mol% catalyst and also applied in the concise synthesis of trifluoromethylated DGAT-1 inhibitor.

The enantioselective introduction of trifluoromethyl group into organic molecules has become an important research field in the agrochemical and pharmaceutical industries.[1] The metabolic stability, lipophilicity and solubility of some drug candidates could be greatly influenced by the trifluoromethyl stereocenters due to its special electronic and steric properties.[2] Accordingly, tremendous efforts have been made for the incorporation of these trifluoromethyl moiety in catalytic asymmetric reactions during last few decades. Efforts in this area could be generally divided into two aspects. The first strategy involve entioselectively introducing trifluoromethyl group into prochiral substrate.[3] The second category involves the asymmetric functionalization of trifluoromethyl-containing building blocks.[4] Notably, the second approach is well suited for some readily available trifluoromethyl containing substrates, such as trifluoromethylated carbonyls, imines and Michael acceptors.



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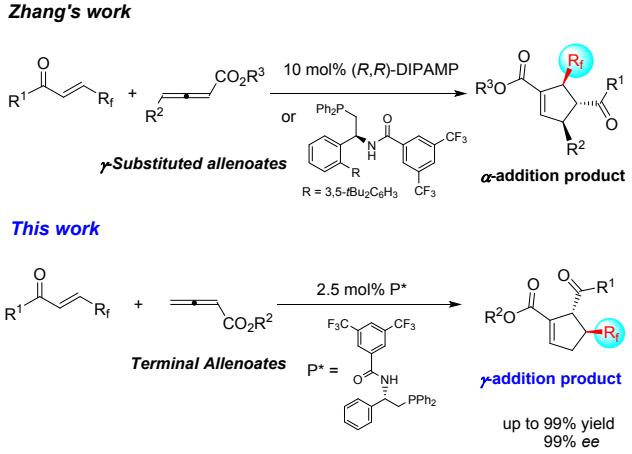
Electronic Supplementary Information (ESI) available: Experimental details, analytical data, NMR spectra of products. See DOI: 10.1039/x0xx00000x

Figure 1. Bioactive molecules featuring with trifluoromethylated cyclopentene skeleton.

On the other hand, cyclopentene and its derivatives are key structural motif in in many natural products and active pharmaceuticals.[5] Over the last few decades, enantioselective construction of cyclopentene skeletons has garnered considerable attention and a set of synthetic methodologies have been well developed. Among the existing synthetic methods, Lu's [3+2] annulation of activated alkenes with allenoates is a highly efficiency, yet straightfoward strategy for the synthsis of functionalized cyclopentene rings.[6,7] However, to the best of our knowledge, reports concerning chiral phosphine catalysed Lu's [3+2] annulations for the construction of trifluoromethylated cyclopentene skeleton are relatively limited. In 2017, Zhang and co-workers reported a phosphine catalyzed enantioselective [3+2] annulation of γ-substituted allenoates with β-trifluoromethyl α,β-enones afford to a set of trifuoromethylated cyclopentenes.[8] Inspired by Zhang's work and with regard to the significance of trifuoromethylated cyclopentenes in bioactive molecules (Figure 1),[9] we would like to further explore the asymmetric [3+2] cycloaddition reaction of terminal allenotes with β-trifluoromethyl α,β-enones and expand its synthetic application (Scheme 1).



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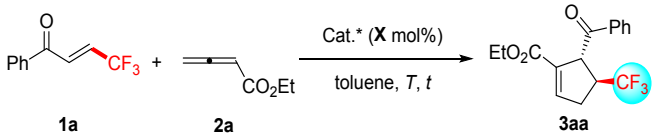
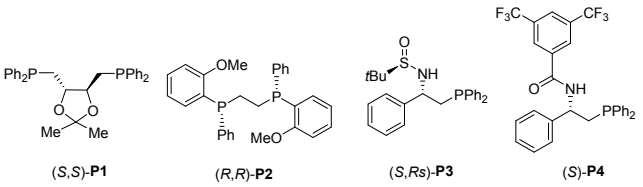
Scheme 1. [3+2] cycloaddition reactions of allenes with diverse electron-deficient olefins.

Our study was initiated by exploring the performance of commercially available chiral phosphine catalyst (*S*,*S*)-**P1** and (*R*,*R*)-**P2** in the cycloaddition of allenoate **2a** and enone **1a**. Unfortunately, these two phosphine catalysts did not offer satisfactory enantioselectivity (Table 1, entries 1-2). Inspired by previous studies,[10] the hydrogen-bonding interactions play vital influence on the enantioselectivity and reactivity in chiral phosphine catalysis, we then envisaged that multifunctional phosphine which contains hydrogen-bonding donor might be helpful for the improvement of enantioselectivity. To our delight, the desired **3aa** was obtained in excellent yield with high regioselectivity and good enantioselectivity under the catalysis of (*S*)-**P4**,[11] (Table 1, entry 4). Further improvement in *ee* was achieved by lowering the reaction temperature to -20 °C (Table 1, entries 5-8). Gratifyingly, lowering the catalyst loading of (*S*)-**P4** to 2.5 mol% proved to be feasible and both the efficiency and enantioselectivity were maintained (Table 1, entries 9-10).

Table 1: Optimization of reaction conditions for the enantioselective [3+2] cycloaddition reaction.[a]



1a **2a** **3aa**



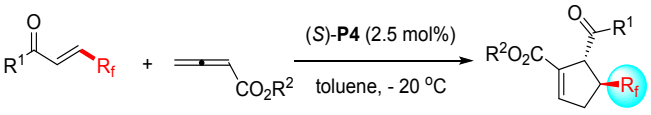
(*S*,*S*)-**P1** (*R*,*R*)-**P2** (*S*,*Rs*)-**P3** (*S*)-**P4**

Entry	Cat.	X	*T* (°C)	*t* (h)	Yield (%)[b]	*ee* (%)[c]
1	(*S*,*S*)-**P1**	5	25	0.5	76	23
2	(*R*,*R*)-**P2**	5	25	0.5	83	76
3	(*S*,*Rs*)-**P3**	5	25	0.5	90	34
4	(*S*)-**P4**	5	25	0.5	96	90
5	(*S*)-**P4**	5	0	0.5	96	93
6	(*S*)-**P4**	5	-15	1	96	94
7	(*S*)-**P4**	5	-20	1	96	97
8	(*S*)-**P4**	5	-25	1.5	96	97
9	(*S*)-**P4**	2.5	-20	1	96	97
10	(*S*)-**P4**	1	-20	12	41	96

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol) in solvent (1 mL). [b] Yield of isolated products; both diastereo- and regioselectivity were >20:1. [c] Determined by HPLC analysis using a chiral stationary phase.

With a set of optimal conditions (2.5 mol% (*S*)-**P4**, toluene as the solvent) in hand, our efforts concentrated on investigating the scope of this enantioselective [3+2] cycloaddition reaction. Remarkably, a wide range of β-trifluoromethyl substituted enones containing electron-rich or electron-poor functional groups were universally worked well with allenoate **2a**, delivering the highly selective γ-addition products **3aa**-**3ja** in excellent yields with 95-99% *ee*s (Table 2, entries 1-10). Moreover, the introduction of an *ortho* substituent such as F, Cl and Br to the phenyl ring of enone was well tolerated and the corresponding **3ka**-**3ma** were isolated in 96-98% yields with excellent enantioselectivity (Table 2, entries 11-13). Notably, the high performance of (*S*)-**P1** was not impeded by the naphthyl- and heteroaryl-containing substrates **1n**-**1q** (Table 2, entries 14-17). β-Trifluoromethyl α,β-enones contain cyclohexyl (**1r**) and cyclohexenyl (**1s**) also proceeded smoothly to furnish the desired cyclopentene, albeit with relatively lower enantioselectivity (Table 1, Entry 18 and 19). Different terminal allenoates such as methyl allenoate **2b** and benzyl allenoate **2c** were also applicable, affording **3ab**-**3ac** in high yields with 94-96% *ee*s (Table 2, entries 20-21). Finally, both β-pentafluoroethyl and β-heptafluoropropyl enone were particularly effective in the present asymmetric [3+2] cycloaddition transformation, delivering valuable perfluoro substituted cyclopentene **3ta**-**3ua** in high *ee* (Table 2, entries 22-23). The absolute configuration of product **3pa** was confirmed by the single-crystal X-ray diffraction analysis.[12] Absolute configuration of other trifluoromethylated cyclopentene were assigned by analogy.

Table 2: Enantioselective [3+2] cycloadditions of allenoates with β-perfluoro substituted enone catalysed by (*S*)-**P4**.[a]



1 **2** **3**

Entry	R^1/R_f (**1**)	R^2 (**2**)	**3**	Yield (%)[b]	*ee* (%)[c]
1	C_6H_5/CF_3 (**1a**)	Et (**2a**)	**3aa**	96	97
2	4-$NO_2C_6H_4/CF_3$ (**1b**)	**2a**	**3ba**	99	99
3	4-CNC_6H_4/CF_3 (**1c**)	**2a**	**3ca**	95	99
4	4-$CF_3C_6H_4/CF_3$ (**1d**)	**2a**	**3da**	95	98
5	4-FC_6H_4/CF_3 (**1e**)	**2a**	**3ea**	96	98
6	4-ClC_6H_4/CF_3 (**1f**)	**2a**	**3fa**	97	97
7	4-BrC_6H_4/CF_3 (**1g**)	**2a**	**3ga**	96	98
8	4-MeC_6H_4/CF_3 (**1h**)	**2a**	**3ha**	94	95
9	4-$MeOC_6H_4/CF_3$ (**1i**)	**2a**	**3ia**	95	95
10	4-PhC_6H_4/CF_3 (**1j**)	**2a**	**3ja**	95	99
11	2-FC_6H_4/CF_3 (**1k**)	**2a**	**3ka**	97	98
12	2,4-$Cl_2C_6H_3/CF_3$ (**1l**)	**2a**	**3la**	98	99
13	2-BrC_6H_4/CF_3 (**1m**)	**2a**	**3ma**	96	95
14	2-naphthyl/CF_3 (**1n**)	**2a**	**3na**	95	97
15	2-furyl/CF_3 (**1o**)	**2a**	**3oa**	94	95
16	2-thienyl/CF_3 (**1p**)	**2a**	**3pa**	95	96
17	Benzothiophene/CF_3(**1q**)	**2a**	**3qa**	96	99
18	cyclohexyl/CF_3(**1r**)	**2a**	**3ra**	90	61
19	1-cyclohexenyl/CF_3(**1s**)	**2a**	**3sa**	82	84
20	**1a**	Me (**2b**)	**3ab**	95	96
21	**1a**	Bn (**2c**)	**3ac**	92	94
22	C_6H_5/C_2F_5 (**1t**)	**2a**	**3ta**	95	96
23	C_6H_5/C_3F_7 (**1u**)	**2a**	**3ua**	97	98

[a] Unless otherwise specified, all reactions were carried out with **1** (0.2 mmol), **2** (0.24 mmol) , (*S*)-**P4** (2.5 mol%) in toluene (2 mL) at -20 °C for 1.5 h; [b] Isolated yield; diastereoselectivity and regioselectivity for all

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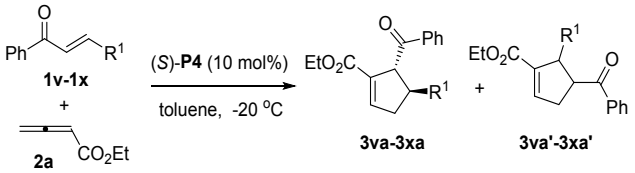
examples were more than 20:1; determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis.

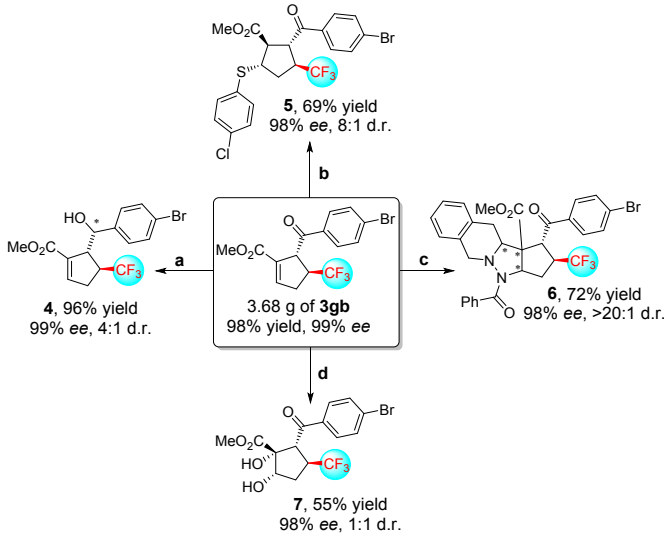
Table 3: Enantioselective [3+2] cycloadditions of allenoates with enone catalysed by (*S*)-**P4**.[a]



Entry	R^1	3	3/3' ratio	Yield 3+3' (%)[b]	*ee* (%)[c]
1	Me (**1v**)	**3va**	**13:1**	64	22
2	Ph (**1w**)	**3wa**	**5:1**	72	11
3	4-$NO2C_6H_4$ (**1X**)	**3xa**	**20:1**	83	6

[a] Unless otherwise specified, all reactions were carried out with **1** (0.2 mmol), **2** (0.24 mmol) , (*S*)-**P4** (10 mol%) in toluene (2 mL) at -20 °C for 8 h; [b] Isolated yield; [c] Determined by chiral HPLC analysis.

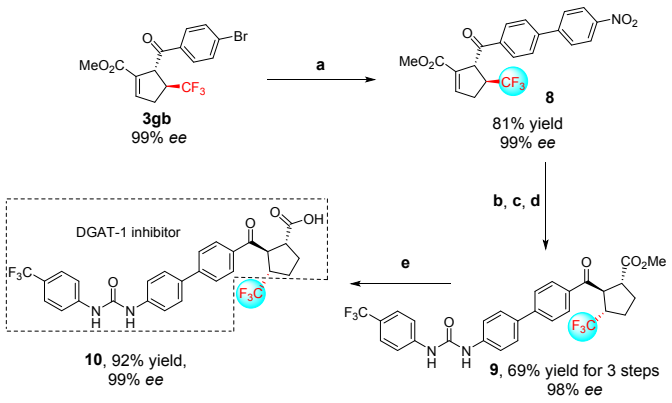
Following the above successful experiments, the [3+2] cycloaddition reactions of enones (**1v**-**1x**) with allenoates **2a** were studied (Table 3). In the presence of a 10 mol % chiral phosphine (*S*)-**P4**, enones **1v**-**1x** were able to convert to the desired cyclopentenes **3va**-**3xa** through preferential *γ*-addition in moderate yields with poor enantioselectivities (Table 3, Entry 1-3). These results demonstrated that the chiral phosphine (*S*)-**P4** was not a suitable catalyst for the [3+2] annulation reactions of this type Michael acceptors.



Scheme 2. Synthetic transformations of **3gb**: (a) $NaBH_4$, THF/H_2O, 0 °C, 1h; (b) 4-chlorothiophenol, DABCO, DCM, 25 °C, 12 h; (c) benzoyl(3,4-dihydroisoquinolin-2-ium-2-yl)amide, toluene, 100 °C, 8 h; (d) $RuCl_3$, $NaIO_4$, CH_3CN/H_2O/EtOAc, 0 °C, 0.5 h.

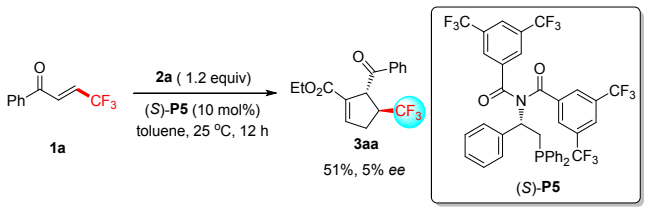
A gram-scale [3+2] cycloaddition reaction of **1g** and **2b** was then conducted, which proceeded smoothly with the use of only 1 mol% catalyst and delivered 3.68 g of **3gb** in 98% yield with 99% *ee* (Scheme 2). Additionally, the synthetic utility of **3gb** was showcased and a wide range of other chiral building blocks could be easily prepared. The selective reduction of carbonyl group provided an effective access to valuable chiral alcohol **4**. Transformations involving the C=C double bond of **3gb**, such as Michael addition with thiophenol, dipolar cycloaddition reaction with 1,3-dipole and dihydroxylation were carried out and the corressponding synthetic valuable frameworks **5**, **6** and **7** were furnished without loss of enantiopurity.

Most importantly, a creative and concise synthetic strategy for trifluoromethylated DGAT-1 inhibitor **10** was successfully developed (Scheme 3).[13] Starting from **3gb**, the Suzuki coupling reaction worked well and gave compound **8** in 81% yield. The urea-based compound **9** was subsequently obtained in 69% yield (overall yield for three steps) from **8** via sequential hydrogenation, isocyanate coupling and PCC oxidation. Finally, hydrolysis of the ester group gave the target molecule **10** in high yield without loss of enantiopurity.



Scheme 3. Concise synthetic strategy for trifluoromethylated DGAT-1 inhibitor: (a) $Pd(PPh_3)_4$, 4-nitro-phenylboronic acid, KF, DME/toluene/EtOH/ H_2O, 60 °C, 36 h; (b) Pd/C, MeOH, 25 °C, 24 h; (c) 4-(trifluoromethyl)phenyl isocyanate, THF, 25 °C, 1 h; (d) PCC, DCM, 25 °C, 2 h; (e) LiOH, THF/H_2O, 25 °C, 3 h.

In order to conform the possible hydrogen-bonding interactions during the catalytic process, (*S*)-**P5** without hydrogen-bonding donor was synthesized and utilized in the [3+2] cycloaddition reaction of **1a** and **2a** (Scheme 4). When (*S*)-**P5** was employed as the catalyst, the enantioselective [3+2] cycloaddition reaction proceeded much slower with dramaticlly decreased enantioselectivity demonstrated that the hydrogen-bonding donors in the chiral phosphine catalyst were vital for both reactivity and enantioselectivity of this [3+2] cycloaddition reaction.



Scheme 4. Performance of (*S*)-**P5** in the enantioselective [3+2] cycloaddition reaction of **1a** and **2a**.

Based on the above control experiment and previous mechanistic studies on the [3 + 2] annulation of allenoates with electron-deficient alkenes,[14] proposed catalytic cycle for (S)-**P4**

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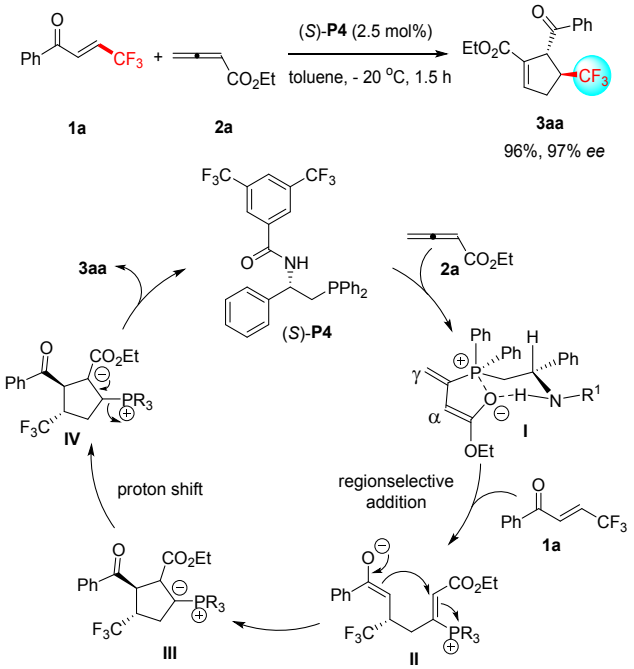
catalyzed asymmetric [3 +2] cycloaddition of terminal allenoate with trifluoromethyl enone is shown in Scheme 5. Nucleophilic attack of chiral phosphine catalyst (*S*)-**P4** on allenoate **2a** generates zwitterionic intermediate **I** which stabilized by hydrogen-bonding interactions of N–H and carbonyl group. Intermediate **II** was then created from the less hindered γ-addition. The subsequent intramolecular Michael addition, followed by proton transfer and release of catalyst, afford the final [3+2] cycloaddition product **3aa**.



Scheme 5. Proposed mechanism.

In conclusion, we have developed a highly enantio- and diastereoselective phosphine catalyzed [3+2] cycloadditions of terminal allenoates with β-perfluoroalkyl α,β-enones. Diverse trifluoromethylated cyclopentenes were delivered in good yields with high regio-, diastereo-, and enantioselectivities. The synthetic utilities of this methodology were further demonstrated by the concise synthesis of trifluoromethylated DGAT-1 inhibitor and other valuable building blocks. Efforts toward the chiral phosphine catalyzed other asymmetric transformations is currently underway in our group and will be reported in due course.

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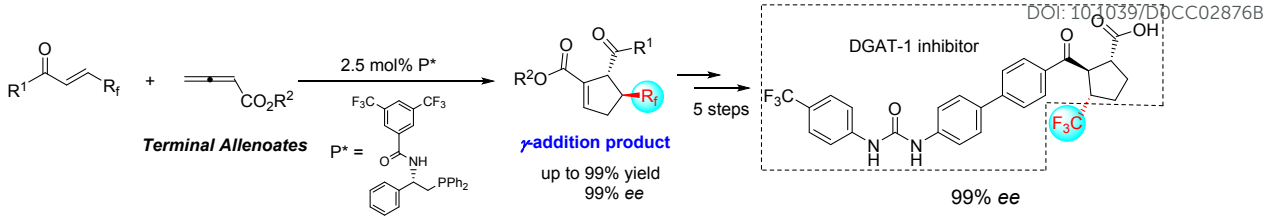

A highly enantio- and diastereoselective phosphine catalyzed [3+2] cycloadditions of terminal allenoates with β-perfluoroalkyl α,β-enones leading to a series of trifluoromethylated cyclopentenes with two contiguous chiral centers (up to 99% yield with 99% *ee*) have been disclosed. This reaction could be amenable to gram scale by utilizing only 1 mol% catalyst and also applied in the concise synthesis of trifluoromethylated DGAT-1 inhibitor.

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