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Phosphine-catalyzed Enantioselective [3+2] Cycloadditions of γ-Substituted Allenoates with β-Perfluoroalkyl Enones

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The enantioselective construction of densely functionalized cyclopentene bearing contiguous three stereocenters has been a long-standing challenging task in organic synthesis. Herein we present a phoshine-catalyzed highly regio-, diastereo- and enantioselective [3+2] cycloaddition of γ-substituted allenoates with β-perfluoroalkyl enones, delivering a wide range of densely functionalized perfluoroalkylated cyclopentenes with three contiguous chiral stereocenters.

Introduction

Cyclopentenes (or cyclopentanes) are valuable skeletons found in many natural products and pharmaceuticals (Figure 1).[1] Among existing methodologies for their preparation, the phosphine-catalyzed [3+2] cycloaddition of allenoates with electron-deficient olefins first reported by Lu in 1995 is a powerful and straightforward strategy for the construction of functionalized cyclopentene rings.[2,3] As a result of tremendous effort from many research groups, the enantioselective Lu's [3+2] cycloaddition reaction of terminal allenoates with electron-deficient olefins have been well established over the past years.[4] However, the asymmetric [3+2] cycloaddition reaction of γ-substituted allenoates with electron-deficient olefins have been less explored, despite the stereo chemical diversity of the cycloaddition products would be dramatically increased. In 2007, the group of Miller first realized a unique "deracemization" reaction upon cycloaddition of chalcone with racemic γ-methyl allenoates but requisite the use of stoichiometric amount of chiral phosphine catalyst **A** (Scheme 1a).[4c] Subsequently, Fu and co-workers accomplished the cycloaddition reaction of racemic γ-substituted allenoates with heteroatom-bearing olefins with the use of catalytic amount of chiral phosphine **B**, furnishing a facile access to functionalized cyclopentenes with two adjacent stereo centers (Scheme 1b).[5] Recently, the group of Marinetti reported a highly enantioselective [3+2] cycloaddition of γ-substituted allenoates with benzylidenemalononitrile by utilizing chiral phosphaheli-cenes catalyst **C** (Scheme 1b).[6]

Despite these elegant progress has been made, the scope of γ-substituted allenoates and electron-deficient olefin partner

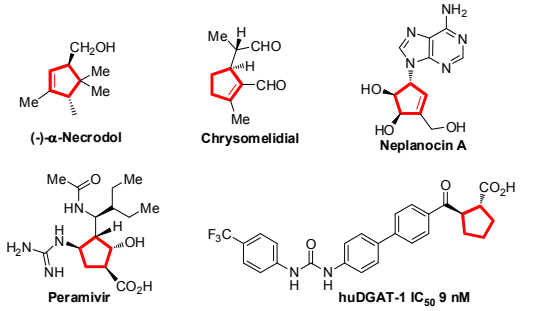
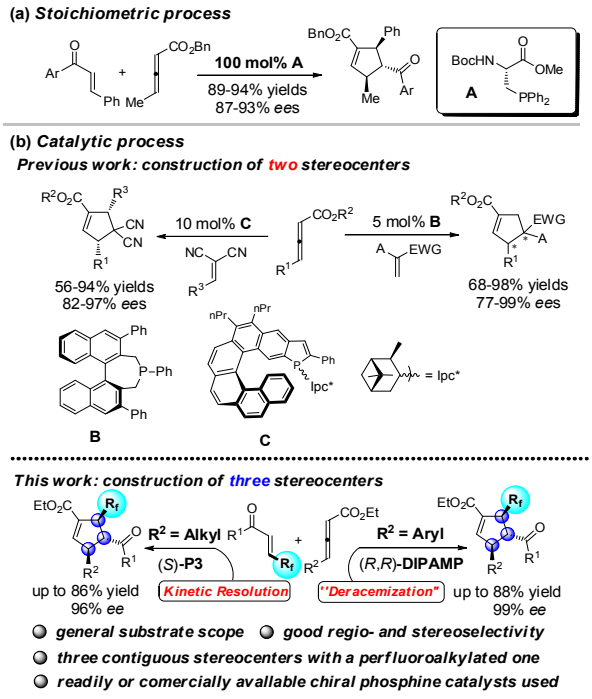


Figure 1. Selected natural products and pharmaceuticals contain cyclopentene or cyclopentane rings.



Scheme 1. [3+2] cycloaddition reaction of γ-substituted allenoates and olefins.

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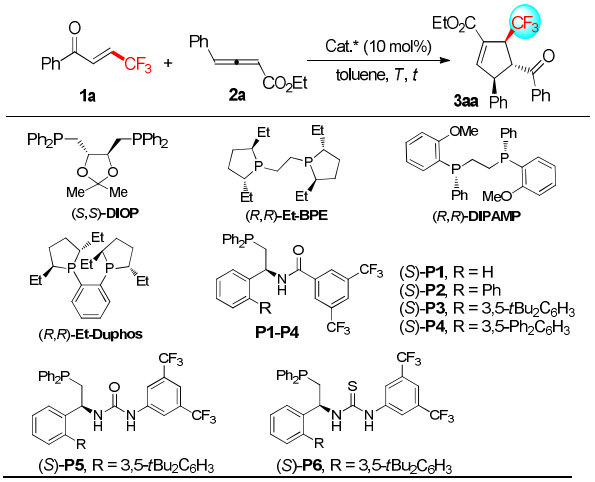
for enantioselective Lu's annulation is still very limited and the construction of cyclopentene derivatives with three contiguous chiral stereo centers has been a long-standing challenging but highly desirable task. Meanwhile, the introduction of perfluoroalkylated, especially trifluoromethylated stereo centers into chiral compounds have aroused special attention in pharmaceutical and pesticide industry since the polarity, bioavailability, metabolic stability and other properties of the parent molecules could be influenced greatly by these perfluoroalkyl groups.[7] During the course of our continuous interest in design, synthesis and application of novel chiral *β*-aminephosphines[8,9] in asymmetric catalysis and the synthesis of enantioenriched trifluoromethylated building blocks,[8d,8i] we envisaged that the challenging enantioselective [3+2] cycloadditions of *γ*-substituted allenoates with *β*-perfluoralkyl *α,β*-enones might be addressed by systematic screening of known phosphines or rational design of new catalyst (Scheme 1b). In this article, we wish to report our efforts to address this challenging reaction by identifying two phosphine catalysts, commercially available bisphosphine (*R*,*R*)-**DIPAMP** and novel multifunctional (*S*)-**P3** which developed in our group. Further control experiments showed that the reaction under the catalysis of (*R*,*R*)-**DIPAMP** is a deracemization process, while the kinetic resolution reaction was observed under the multifunc-tional phosphine catalyst.

Results and discussion

In order to validate the feasibility of the asymmetric [3+2] cycloaddition of *γ*-substituted allenoates with *β*-perfluoralkyl *α,β*-enones, allenoate **2a** and enone **1a** were exposed to a range of commercially available chiral bisphosphine catalysts (Table 1). A small amount of the desired **3aa** was observed when (*S*,*S*)-**DIOP** or (*R*,*R*)-**Et-DUPHOS** were utilized as catalysts (Table 1, entries 1-2). To our delight, (*R*,*R*)-**Et-BPE** delivered a promising level of reactivity with 64% yield and stereo induction with 39% *ee* (Table 1, entry 3). Fortunately, 86% yield of **3aa** with 89% *ee* was obtained by using the (*R*,*R*)-**DIPAMP** as catalyst (Table 1, entry 4). Noteworthy, multifunctional chiral phosphines (*S*)-**P1-P6** bearing hydrogen bond donors, such as amide and (thio) urea groups, could deliver very high chemical yield but with unacceptable enantioselectivity (Table 1, entries 5-10). Gratifyingly, the enantioselectivity was improved to 92%, albeit with a slightly lower yield when decreasing the reaction temperature from 25 °C to -20 °C (Table 1, entries 11–13). However, much lower reaction temperature was not beneficial for the enantioselectivity and reactivity any more (Table 1, entry 14). Additionally, much lower yield and enantioselectivity was observed when (*Z*)-**1a** was utilized in the reaction, indicating that the configuration of the enone also affected the reaction significantly (Table 1, entry 15). Further screening of solvents demonstrated that toluene was the best reaction medium for this transformation (see SI for details). Then the optimized reaction conditions were identified: 10 mol% (*R*,*R*)-**DIPAMP** as the catalyst and toluene as the reaction medium at -20 °C.

Table 1: Optimization of reaction conditions [a]



Entry	Cat.	*T* (°C)	*t* (h)	Yield (%)[b]	*Ee* (%)[c]
1	(*S*,*S*)-**DIOP**	25	12	<10	--
2	(*R*,*R*)-**Et-Duphos**	25	12	<10	--
3	(*R*,*R*)-**Et-BPE**	25	8	64	39
4	(*R*,*R*)-**DIPAMP**	25	6	81	89
5	(*S*)-**P1**	25	3	79	3
6	(*S*)-**P2**	25	3	85	14
7	(*S*)-**P3**	25	3	84	40
8	(*S*)-**P4**	25	3	86	21
9	(*S*)-**P5**	25	0.5	91	31
10	(*S*)-**P6**	25	0.5	88	38
11	(*R*,*R*)-**DIPAMP**	0	6	84	90
12	(*R*,*R*)-**DIPAMP**	-10	8	81	91
13	(*R*,*R*)-**DIPAMP**	-20	12	78	92
14	(*R*,*R*)-**DIPAMP**	-25	20	63	92
15[d]	(*R*,*R*)-**DIPAMP**	-20	24	23	50

[a] Unless otherwise specified, all reactions were carried out with (*E*)-**1a** (0.1 mmol), racemic **2a** (0.15 mmol) in toluene (1 mL). [b] Yield of isolated products; d.r. and r.r. > 20:1. [c] Determined by HPLC analysis. [d] (*Z*)-**1a** was used.

With optimal reaction conditions in hand, we next investigated the scope of this enantioselective [3+2] cycloaddition reaction. Remarkably, a wide range of *β*-trifluoromethyl substituted enones containing different electron nature functional groups worked well with allenoate **2a**, delivering the highly regioselective *α*-addition products **3ba**-**3ha** in good yields with 88-94% *ee*s. However, the introduction of an *ortho* substituent such as Cl and Br to the phenyl ring of enone led to dramatic decrease in the enantioselectivity (**3ia** and **3ja)**. To our delight, naphthyl- and heteroaryl-containing substrates **1k**-**1o** are also compatible, efficiently furnishing a set of trifluoromethylated cyclopentenes containing naphthyl- and heteroaryl frameworks **3ka**-**3oa**. Additionally, the present protocol could also be readily extended to the challenging cyclohexenyl and

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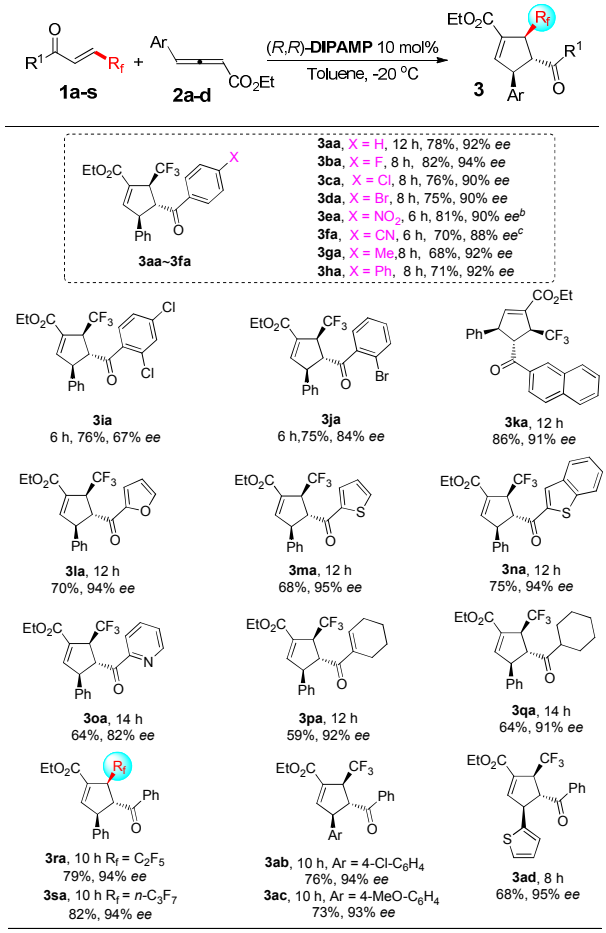
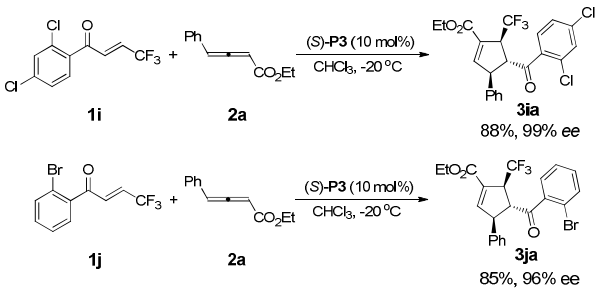
cyclohexyl based trifluoromethyl enone **1p** and **1q**. It is noteworthy that both *β*-pentafluoroethyl and *β*-heptafluoropropyl enone were particularly effective in the present transformation, delivering valuable perfluoroalkyl substituted cyclopentene **3ra** and **3sa** in good yields with 94% *ee*. Furthermore, *γ*-aryl allenoates **2b**-**2d** with substituted aryl and hetereoaryl groups are well applicable, delivering the corresponding products **3ab**-**3ad** with high regioselectivity and enantioselectivity. The absolute configuration of product **3aa** was confirmed by the single-crystal X-ray diffraction analysis.[10]

Scheme 2: Enantioselective [3+2] cycloadditions of *γ*-aryl substituted allenoates with *β*-perfluoro substituted enone.[a]



[a] Unless otherwise specified, all reactions were carried out with (*E*)-**1** (0.2 mmol), racemic **2** (0.3 mmol), (*R*,*R*)-**DIPAMP** (10 mol%) in toluene (2 mL) at -20 °C; isolated yield; d.r. and r.r. > 20:1. [b] r.r. = 8:1. [c] r.r. = 11:1.

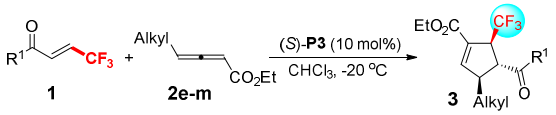
Scheme 3: (S)-**P3** catalysed enantioselective [3+2] cycloadditions of **1i** and **1j** with **2a**.



After further intensive screening of various chiral phosphine catalysts again, we were pleased to find that multifunctional phosphine (*S*)-**P3** displayed good performance in the substrates with *ortho*-substituent and the desired products **3ia** and **3ja** could be isolated in 85-88% yields with 96 and 99% *ee*, respectively (Scheme 3).

Unfortunately, the performance of (*R*,*R*)-**DIPAMP** in the cycloaddition of *γ*-alkyl substituted allenoates was not as good as that in the cases of *γ*-aryl substituted allenoates. For example, the reaction of **2e** with **1c** delivered the desired **3ce** in 67% yield but with only 86% *ee*. After further screening of a series of chiral phosphine catalysts, solvents and reaction temperature, we again found (*S*)-**P3** as a privileged catalyst for cycloaddition of *γ*-alkyl allenoates. In general, allenoates **2e**-**2g** with different alkyl substituents at the *γ* position participated in the annulation with good regio- and enantioselectivity. Additionally, diverse alkyl substituents such as benzyl, halogen and ester group were well tolerant, furnishing the corresponding cycloadducts **3ch**-**3cj** in moderate to good yields with high enantioselectivity. Further-more, allenoates with bulkyl substituents such as isopropyl, cyclopentyl and cyclohexyl at the *γ* position worked also well, delivering the desired **3ck**-**3cm** in good yields with 92-94% *ee*s. Good to excellent regioselectivity and enantioselectivity were also obtained in the cycloaddition reactions of allenoate **2g** with a wide range of *β*-trifluoromethyl substituted enones.

Scheme 4: Enantioselective [3+2] cycloadditions of *γ*-alkyl substituted allenoates with *β*-perfluoro substituted enone.[a]



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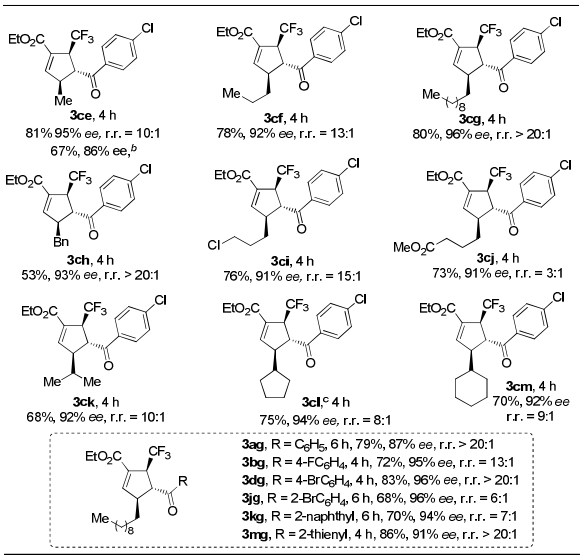
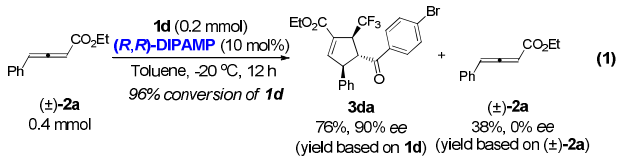
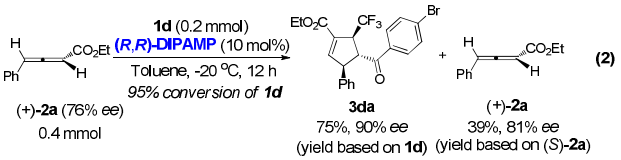


[a]Unless otherwise specified, all reactions were carried out with (*E*)-**1** (0.2 mmol), racemic **2** (0.44 mmol) , (*S*)-**P3** (10 mol%) in $CHCl_3$ (2 mL) at -20 °C. [b] toluene,-20 °C, 10 h, (*R*,*R*)-**DIPAMP** (10 mol%). [c] the regioisomer of **3cl** was isolated and its structure was confirmed by 2D-NMR analysis.

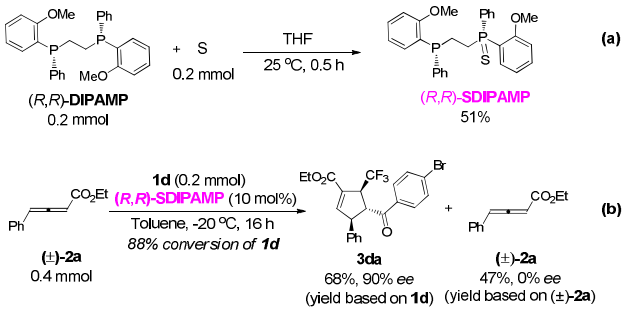
Next, we turned our attention to gain insight of the catalytic process for this [3+2] cycloaddition reaction. In the case of (*R*,*R*)-**DIPAMP** catalysed cycloaddition of **1d** and racemic **2a**, the starting material **2a** was recovered in 38% yield (based on **2a**) with 0% *ee* (Eq 1). Furthermore, when optically active allenoate (+)-**2a** (76% *ee*) was served as substrate, the *ee* of **3da** was not improved but the recovered (+)-**2a** has a higher *ee* (Eq 2). These results supported that a deracemization process was followed in the (*R*,*R*)-**DIPAMP** catalysed cycloaddition of **1d** and **2a**.





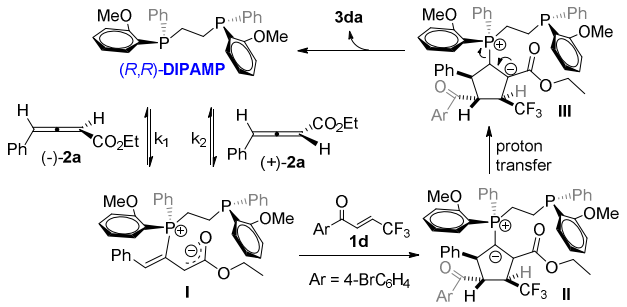
To examine the two phosphines in (*R*,*R*)-**DIPAMP** induce enantioselectivity independently or cooperatedly, (*R*,*R*)-**SDIPAMP** that containing only one nucleophilic phosphine was synthesized and subjected to the reaction of **1d** and racemic **2a** (Scheme 5). Although the reaction became slower, the enantio-selectivity of **3da** was not changed, demonstrating that the two phosphines in (*R*,*R*)-**DIPAMP** might induce enantioselectivity independently (Scheme 5b).

Scheme 5: Synthesis of (*R*,*R*)-**SDIPAMP** and its application in the asymmetric [3+2] cycloaddition of **2a** and **1d**.



Based on the abovementioned results and previous reports [11], a plausible catalytic cycle for (*R*,*R*)-**DIPAMP** catalysed asymmetric [3+2] cycloaddition reaction of *γ*-aryl allenoates with trifluoromethyl enones is illustrated in Scheme 6. The zwitterionic intermediate **I** was formed through nucleophilic addition of (*R*,*R*)-**DIPAMP** to racemic **2a**. The deracemization process results from the same nucleophilic attack rate ($K_1 = K_2$) of (*R*,*R*)-**DIPAMP** to the two enantiomers of allenoates **2a**. The subsequent [3+2] cycloaddition favours *α*-addition to provide intermediate **II** which then undergoes proton transfer to provide intermediate **III**. Finally, (*R*,*R*)-**DIPAMP** and cyclopeantene **3da** were released from intermediate **III**.

Scheme 6: Possible catalytic cycle for (*R*,*R*)-**DIPAMP** catalysed asymmetric [3+2] cycloaddition.



In contrast to (*R*,*R*)-**DIPAMP**, a clearly kinetic resolution reaction takes place with the use of the multifunctional chiral phosphine (*S*)-**P3** as catalyst since the (+)-**2a**[12] and (+)-**2g**[13] was recovered in 76% *ee* (in toluene, 77% *ee* in $CHCl_3$) and 81% *ee* respectively (Eqs 3 and 4). In order to confirm the possible hydrogen-bonding interaction during the catalytic process, (*S*)-**P7** without hydrogen-bonding donor was synthesized and subjected to the cycloaddition reaction (Scheme 7), the conversion decreased dramatically even under higher catalyst loading and higher reaction temperature. What's more, the *ee* value of recovered **2g** was vanished (Scheme 7b). These results clearly demonstrated that the hydrogen-bonding donor in (*S*)-**P3** is crucial for the enantioselectively formation of cycloaddition product via a nice kinetic resolution process.

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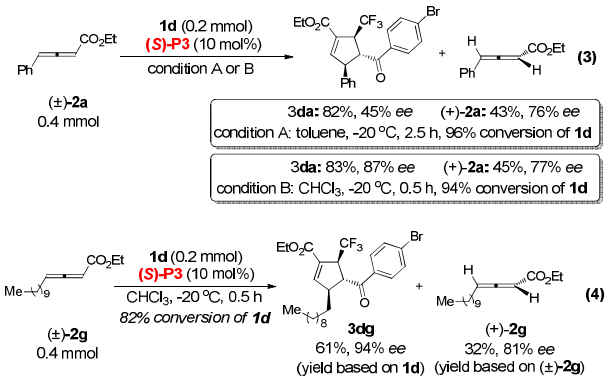
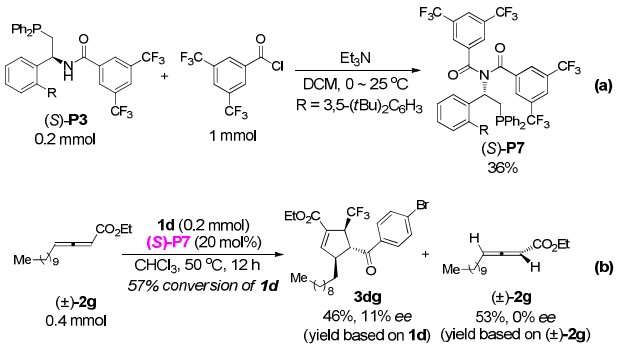
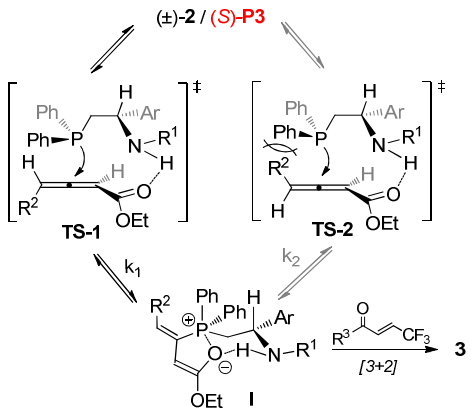


Scheme 7: Synthesis of (*S*)-**P7** and its application in the asymmetric [3+2] cycloaddition of **2g** and **1d**.



On the basis of the above control experiments and recent excellent mechanistic studies[11] on the [3+2] cycloaddition allenoates with electron-deficient olefins, a tentative proposed catalytic cycle for (*S*)-**P3** catalysed asymmetric [3+2] cycloaddition reaction of racemic allenoate with trifluoromethyl enone is shown in Scheme 8. (-)-**2** might has a preferable configuration which facilitate the hydrogen-bonding interactions of N-H and carbonyl group (Scheme 8, **TS-1**). On the other hand, the nucleophilic attack of (*S*)-**P3** with (+)-**2** might be suppressed by the steric interactions of the bulky R^2 group with the phenyl moiety (Scheme 8, **TS-2**). Accordingly, the different nucleophilic attack rate ($K_1 > K_2$) of (*S*)-**P3** to the two enantiomers of allenoates **2** contributes to the kinetic resolution process. Noteworthy, further experimental and theoretical studies are required to gain insight of this kinetic resolution process.

Scheme 8: Possible catalytic cycle for (*S*)-**P3** catalysed asymmetric [3+2] cycloaddition reaction of racemic allenoate with trifluoromethyl enone.



Conclusions

In conclusion, we have developed a highly regio-, diastereo- and enantioselective [3+2] cycloaddition of γ-substituted allenoates with β-perfluoroalkyl enones with the use of (*R*,*R*)-**DIPAMP** or (*S*)-**P3** as catalyst, which provides a facile access to a wide range of trifluoromethylated cyclopentenes with three contiguous chiral centers (up to 88% yield with 99% *ee*). In the case of γ-aryl allenoate, commercially available chiral phosphine (*R*,*R*)-**DIPAMP** was identified to be the most efficient catalyst. In contrast, our developed multifunctional phosphine (*S*)-**P3** displayed high performance in the asymmetric cycloaddition of γ-alkyl allenoates with trifluoromethyl enones. Additionally, control experiments demonstrated that under the catalysis of (*R*,*R*)-**DIPAMP**, racemic allenoate reacted with trifluoromethyl enone through a "deracemization" process, whereas a clearly kinetic resolution reaction takes place with the use of the multifunctional chiral phosphine (*S*)-**P3** as catalyst due to the hydrogen-bonding interaction between catalyst and the allenoate. Efforts toward other transformations of allenoate under the catalysis of our developed catalysts **P1**-**P6** are currently underway and will be reported in due course.

Acknowledgements

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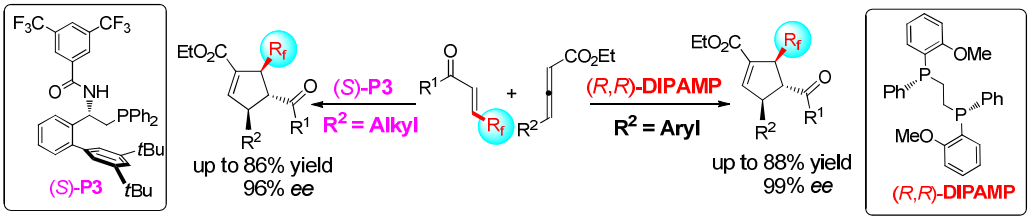

- ***general substrate scope***
- ***three contiguous stereocenters with a perfluoroalkylated one***
- ***good regio- and stereoselectivity***
- ***readily or comercially avallable chiral phosphine catalysts***

The enantioselective construction of densely functionalized cyclopentene bearing contiguous three stereocenters has been a long-standing challenging task in organic synthesis. Herein we present a phoshine-catalyzed highly regio-, diastereo- and enantioselective [3+2] cycloaddition of γ-substituted allenoates with β-perfluoroalkyl enones, delivering a wide range of densely functionalized perfluoroalkylated cyclopentenes with three contiguous chiral stereocenters.