

Cite this: *Chem. Sci.*, 2017, 8, 4660

Received 31st March 2017

Accepted 18th April 2017

DOI: 10.1039/c7sc01432e

rsc.li/chemical-science

# Phosphine-catalyzed enantioselective [3 + 2] cycloadditions of $\gamma$ -substituted allenates with $\beta$ -perfluoroalkyl enones†

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The enantioselective construction of densely functionalized cyclopentene bearing contiguous three stereocenters has been a challenging task in organic synthesis. Herein, we present a phosphine-catalyzed highly regio-, diastereo- and enantioselective [3 + 2] cycloaddition of  $\gamma$ -substituted allenates with  $\beta$ -perfluoroalkyl enones, delivering a wide range of densely functionalized perfluoroalkylated cyclopentenones with three contiguous chiral stereocenters.

## Introduction

Cyclopentenones (or cyclopentanes) are valuable skeletons found in several natural products and pharmaceuticals (Fig. 1).<sup>1</sup> Among existing methodologies for their preparation, phosphine-catalyzed [3 + 2] cycloaddition of allenates with electron-deficient olefins was first reported by Lu in 1995 as a powerful and straightforward strategy for the construction of functionalized cyclopentene rings.<sup>2,3</sup> As a result of tremendous effort from numerous research groups, Lu's enantioselective [3 + 2] cycloaddition reaction of terminal allenates with electron-deficient olefins has been well established over the past years.<sup>4</sup> However, asymmetric [3 + 2] cycloaddition reaction of  $\gamma$ -substituted allenates with electron-deficient olefins has been less explored despite the increase in stereochemical diversity of the cycloaddition products. In 2007, Miller's group first realized a unique "deracemization" reaction upon cycloaddition of chalcone with racemic  $\gamma$ -methyl allenates but requisite the use of a stoichiometric amount of chiral phosphine catalyst **A** (Scheme 1a).<sup>4c</sup> Subsequently, Fu and co-workers have accomplished the cycloaddition reaction of racemic  $\gamma$ -substituted allenates with heteroatom-bearing olefins with the use of a catalytic amount of chiral phosphine **B**, furnishing a facile access to functionalized cyclopentenones with two adjacent stereo centers (Scheme 1b).<sup>5</sup> Recently, Marinetti and coworkers have reported a highly enantioselective [3 + 2] cycloaddition of  $\gamma$ -substituted allenates with

benzylidenemalononitrile by utilizing chiral phosphahelicenes catalyst **C** (Scheme 1b).<sup>6</sup>

Despite this progress, the scope of  $\gamma$ -substituted allenates and electron-deficient olefin partner for enantioselective Lu's annulation is very limited, and the construction of cyclopentene derivatives with three contiguous chiral stereocenters has been a major challenge but a highly desirable task. Moreover, introduction of perfluoroalkylated, particularly trifluoromethylated, stereocenters into chiral compounds have garnered 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.<sup>7</sup> During the course of our continuous interest in design, synthesis and application of novel chiral  $\beta$ -aminephosphines<sup>8,9</sup> in asymmetric catalysis and the synthesis of enantio-enriched trifluoromethylated building blocks,<sup>8d,g</sup> we envisaged that the challenging enantioselective [3 + 2] cycloadditions of  $\gamma$ -substituted allenates with  $\beta$ -perfluoroalkyl  $\alpha,\beta$ -enones might be addressed by systematic screening of known phosphines or rational design of new catalysts (Scheme 1b). In

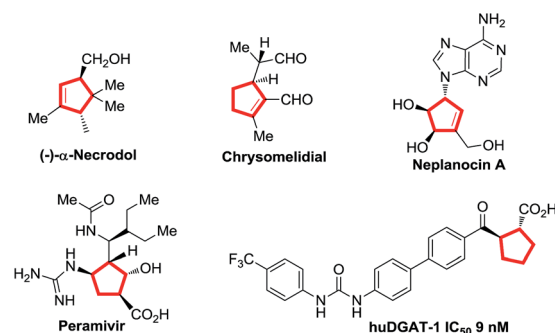
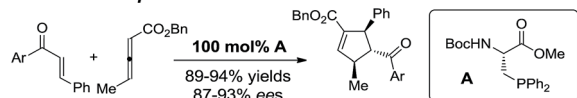


Fig. 1 Selected natural products and pharmaceuticals contain cyclopentene or cyclopentane rings.

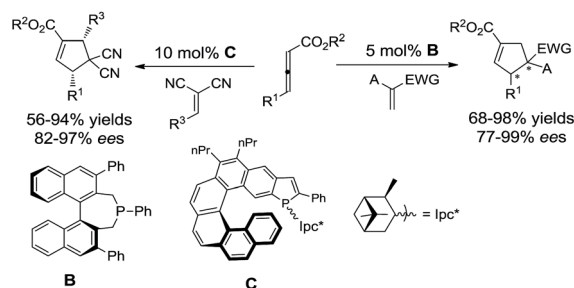
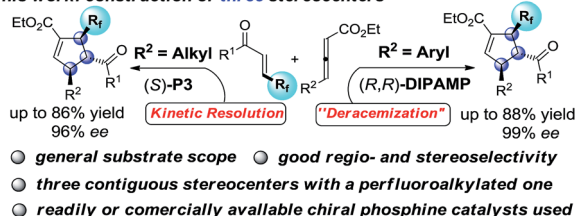
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† Electronic supplementary information (ESI) available: Experimental details, analytical data, NMR spectra of products. CCDC 1503840 (3aa). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc01432e

## (a) Stoichiometric process



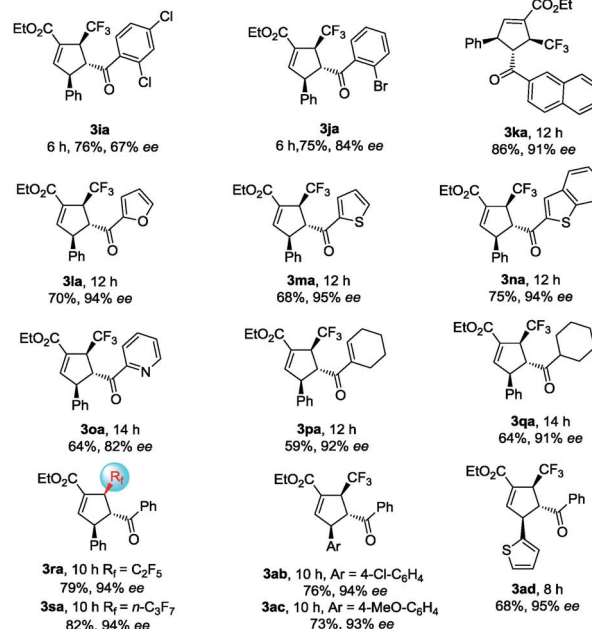
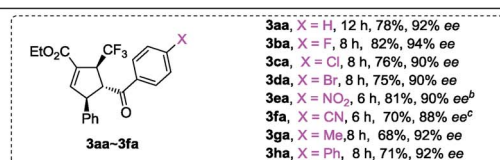
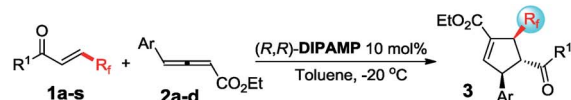
## (b) Catalytic process

Previous work: construction of **two** stereocentersThis work: construction of **three** stereocentersScheme 1 [3 + 2] cycloaddition reaction of  $\gamma$ -substituted allenoates and olefins.

the present study, we report our efforts in addressing this challenging reaction by identifying two phosphine catalysts, commercially available bisphosphine (*R,R*)-**DIPAMP** and novel multifunctional (*S*)-**P3** which have been developed in our group. Further control experiments have shown that the reaction under the catalysis of (*R,R*)-**DIPAMP** was a deracemization process, while the kinetic resolution reaction was observed under the multifunctional phosphine catalyst (Scheme 1).

## Results and discussion

In order to validate the feasibility of the asymmetric [3 + 2] cycloaddition of  $\gamma$ -substituted allenoates with  $\beta$ -perfluoroalkyl  $\alpha,\beta$ -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** was utilized as the catalyst (Table 1, entries 1 and 2). Interestingly, (*R,R*)-**Et-BPE** exhibited a promising level of reactivity with 64% yield and stereoselectivity with 39% ee (Table 1, entry 3). Fortunately, 86% yield of **3aa** with 89% ee was obtained using (*R,R*)-**DIPAMP** as a catalyst (Table 1, entry 4). It can be noted that multifunctional chiral phosphines (*S*)-**P1**–**P6** bearing hydrogen bond donors, such as amide and (thio) urea groups, could deliver higher 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 enantioselectivity and



[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 2 Enantioselective [3 + 2] cycloadditions of  $\gamma$ -aryl substituted allenoates with  $\beta$ -perfluoro substituted enone<sup>a</sup>.

reactivity (Table 1, entry 14). In addition, much lower yield and enantioselectivity was observed when (*Z*)-**1a** was utilized in the reaction, indicating that the configuration of 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 ESI† 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.

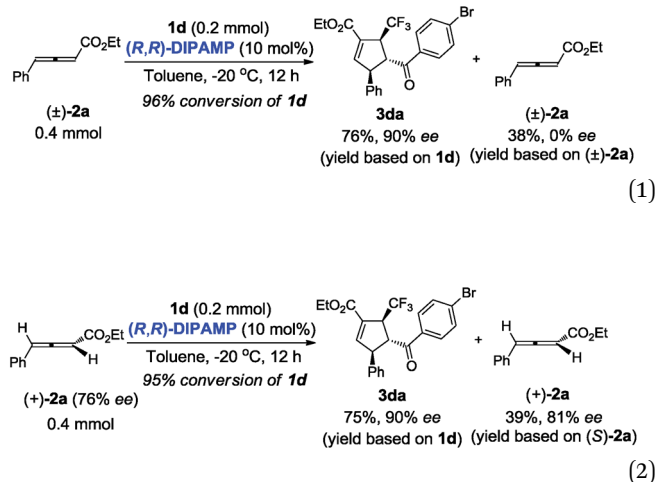
Under optimal reaction conditions, we investigated the scope of the enantioselective [3 + 2] cycloaddition reaction (Scheme 2). Remarkably, a wide range of  $\beta$ -trifluoromethyl substituted enones containing different electron nature functional groups worked well with allenoate **2a**, thereby resulting in a highly regioselective  $\alpha$ -addition products **3ba–3ha** in good yields with 88–94% ee. 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**



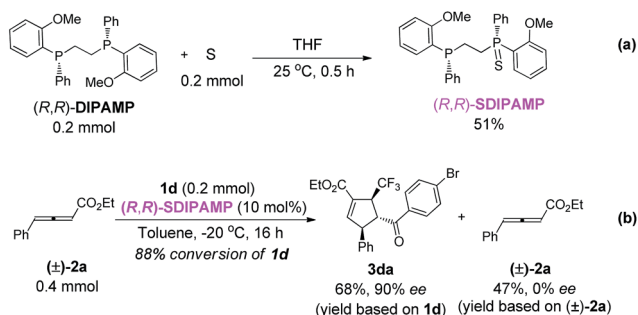


in the annulation process with good regio- and enantioselectivity. In addition, diverse alkyl substituents such as benzyl, halogen and ester group were well tolerant, furnishing the corresponding cycloadducts **3ch–3ej** in moderate to good yields with high enantioselectivity. Furthermore, allenates with bulky substituents such as isopropyl, cyclopentyl and cyclohexyl at  $\gamma$  position worked well, thereby forming the desired **3ck–3cm** in good yields with 92–94% ee. Good to excellent regioselectivity and enantioselectivity were also obtained in the cycloaddition reactions of allenate **2g** with a wide range of  $\beta$ -trifluoromethyl substituted enones (Scheme 4).

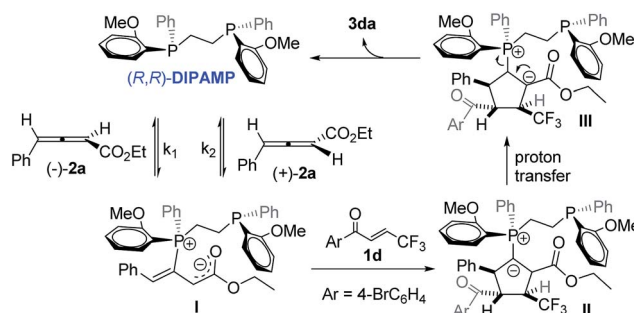
Next, we turned our attention to gain insight into catalytic process for the proposed [3 + 2] cycloaddition reaction. In case of (*R,R*)-**DIPAMP** catalysed cycloaddition of **1d** and racemic **2a**, the starting material **2a** was recovered in 38% yield (based on **2a**) with 0% ee (eqn (1)). Furthermore,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



To examine both the phosphines in (*R,R*)-**DIPAMP** induce enantioselectivity independently or cooperatively, (*R,R*)-**SDIPAMP** that contained only one nucleophilic phosphine was synthesized and subjected to the reaction of **1d** and racemic **2a**



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

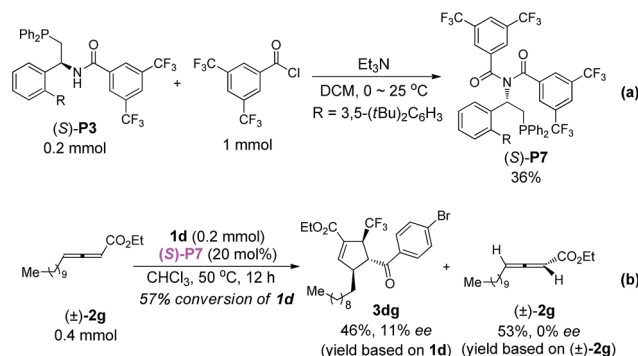


Scheme 6 Possible catalytic cycle for (*R,R*)-**DIPAMP** catalysed asymmetric [3 + 2] cycloaddition.

(Scheme 5). Although the reaction became slower, enantioselectivity of **3da** remained unchanged, demonstrating that both the phosphines in (*R,R*)-**DIPAMP** might induce enantioselectivity independently (Scheme 5b).

Based on the abovementioned results and earlier reports,<sup>11</sup> a plausible catalytic cycle for (*R,R*)-**DIPAMP** catalysed asymmetric [3 + 2] cycloaddition reaction of  $\gamma$ -aryl allenates with trifluoromethyl enones has been illustrated in Scheme 6. The zwitterionic intermediate **I** was formed through nucleophilic addition of (*R,R*)-**DIPAMP** to racemic **2a**. The deracemization process resulted from the same nucleophilic attack rate ( $K_1 = K_2$ ) of (*R,R*)-**DIPAMP** to both the enantiomers of allenates **2a**. The subsequent [3 + 2] cycloaddition favoured  $\alpha$ -addition to provide intermediate **II**, which then underwent proton transfer to provide intermediate **III**. Finally, (*R,R*)-**DIPAMP** and cyclopentene **3da** were released from intermediate **III**.

In contrast to (*R,R*)-**DIPAMP**, a kinetic resolution reaction takes place with multifunctional chiral phosphine (*S*)-**P3** as the catalyst and (+)-**2a**<sup>12</sup> and (+)-**2g**<sup>13</sup> is recovered in 76% ee (in toluene, 77% ee in  $\text{CHCl}_3$ ) and 81% ee respectively (eqn (3) and (4)). In order to confirm the possible hydrogen-bonding interaction during the catalytic process, (*S*)-**P7** without hydrogen-bond donor was synthesized and subjected to the cycloaddition reaction (Scheme 7). The conversion decreased dramatically under higher catalyst loading and higher reaction temperature. The ee value of the recovered **2g** also vanished (Scheme 7b). These results demonstrated that the hydrogen-

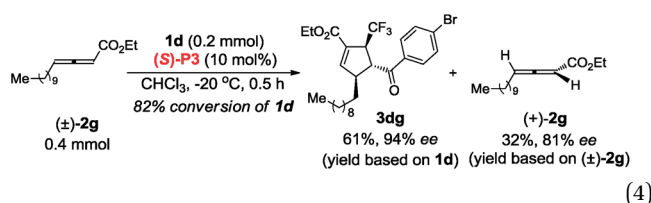
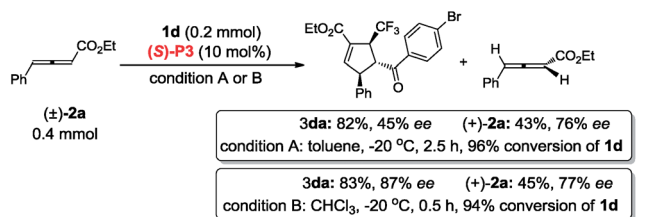


Scheme 7 Synthesis of (*S*)-**P7** and its application in the asymmetric [3 + 2] cycloaddition of **2g** and **1d**.

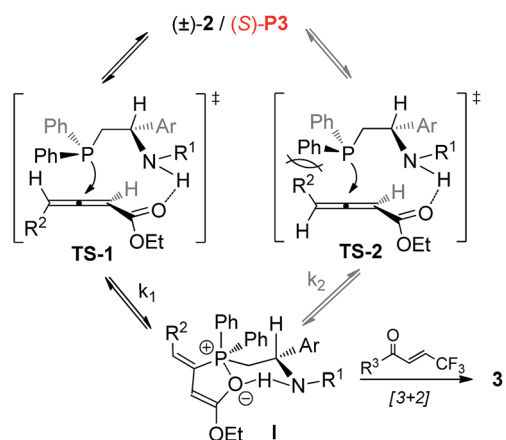




bond donor in (*S*)-**P3** was crucial for enantioselective formation of cycloaddition product *via* kinetic resolution process.



On the basis of above control experiments and recent excellent mechanistic studies<sup>11</sup> on the [3 + 2] cycloaddition of allenates with electron-deficient olefins, a tentatively proposed catalytic cycle for (*S*)-**P3** catalysed asymmetric [3 + 2] cycloaddition reaction of racemic allenates with trifluoromethyl enone is shown in Scheme 8. (–)-**2** might prefer a configuration that would facilitate 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 interaction of the bulky *R*<sup>2</sup> group with the phenyl moiety (Scheme 8, **TS-2**). Accordingly, different nucleophilic attack rates (*K*<sub>1</sub> > *K*<sub>2</sub>) of (*S*)-**P3** to both the enantiomers of allenates **2** contribute to the kinetic resolution process. It should be noted that further experimental and theoretical studies are required to gain insights into kinetic resolution process.



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

## Conclusions

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

## Acknowledgements

We are grateful to 973 Programs (2015CB856600), the National Natural Science Foundation of China (21372084, 21425205, 21672067) and the Changjiang Scholars and Innovative Research Team in University (PCSIRT) for financial supports.

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