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Authors: Junliang Zhang, Huamin Wang, and Weike Lu

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Ferrocene Derived Bifunctional Phosphine-Catalyzed Asymmetric Oxa-[4+2] cycloaddition of α-Substituted Allenones with Enones

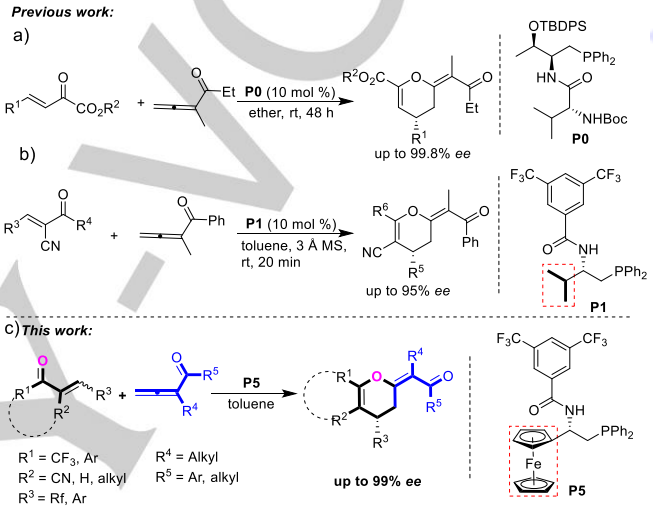
Huamin Wang, Weike Lu and Junliang Zhang*[a]

Dedication ((optional))

Abstract: An efficient ferrocene derived bifunctional phosphine-catalyzed enantioselective oxa-[4+2] cycloaddition of α-substituted allenones with a broad range of enones is investigated for the preparation of stereodefined dihydropyrans in good to excellent yields (up to 99%) and excellent enantioselectivity (up to 99% ee). Furthermore, a series of val-uable chiral polyheterocyclic frameworks can be efficiently achieved in good yields with excellent enantioselectivities.

Dihydropyrans and pyrans have attracted wide synthetic interest due to their rich appearance as important skeletons of bioactive active molecules and natural products[1]. Among them, trifluoromethylated dihydropyrans are an important class of trifluoromethylated heterocycles which emerged in a variety of biologically and pharmaceutically active molecules, for instance, antimalarial agents III[2] and NK-1 receptor antagonist IV. [3] Despite much progress has made in the synthesis of dihydropyrans and pyrans using metal-free catalysts such as N-heterocyclic carbene[4] and amine,[5] the methods for the synthesis of optically active dihydropyrans with a chiral carbon center bearing a CF_3 group are very rare[6] and is therefore highly desirable.

Recently, Lu and workers[7a] describe the first example of generating chiral pyrans via a dipeptide-based bifunc-tional phosphine (**P0**)-catalyzed annulation reaction between allenones with β,γ-unsaturated α-ketoesters (Scheme 1a). Subsequently, Lu et al.[7b] extended this protocol through the introduction of a cyano-group at the α-position of the chalcone by the use of a much simple *L*-valine-derived bifunctional phosphine (**P1**) (Scheme 1b). As part of our ongoing interest in the enantioselective synthesis of enantioenriched trifluoromethylated building blocks,[8,9f-h] and with a series of bi- or multi-functional phosphine catalysts[9] in our hand, which were developed by our group and have demonstrated their good performance in the enantioselective Rauhut-Currier reactions,[9a-e] allylation reaction[9f] and asymmetric cycloaddition,[9h,i] we became interest in the asymmetric phosphine-catalyzed oxo-[4+2] annulation of perfluoroalkylated *α,β*-enones and allenones, if success, a variety of valuable chiral perfluoroalkylated dihydropyrans will be delivered.[10] We wish to report herein an efficient ferrocene derived bifunctional phosphine catalyst **P5**, which displayed high performance in asymmetric oxo-[4+2] cycloaddition of α-substituted allenones with a broad range of enones, furnishing diverse valuable chiral functionalized 3,4-dihydropyrans in good yields and high enantioselectivity (Scheme 1c).



Scheme 1. Phosphine-Catalyzed Cycloaddition Reactions of α-Substituted Allenes.

β-Trifluoromethylated enone **1f** and allenone **2a** were selected as the model substrates for screening the reac-tion conditions (Table 1) and the chiral phosphine catalysts (Figure 1). Gratifyingly, catalyst **P1**, used in previous Lu's work,[7b] could indeed catalyze the cycloaddition reaction in toluene at room temperature to furnish the desired trifluoroalkylated 3,4-dihydropyran in 95% yield with acceptable *ee* (Table 1, entry 1). The replacement of the side iso-propryl group of **P1** with the phenyl, structured as **P2**, led to a similar ee (Table 1, entry 2). Further introduction of a phenyl group at the ortho-position of phenyl in **P2** would give a much lower *ee* (Table 1, entries 3). However, the bulkier 3,5-di-tert-butylphenyl group located to the phenyl ring would deliver better enantioselectivity to 90% *ee* (Table 1, entries 4). In an effort to further enhance enantioselectivity, we are pleased to find that ferrocene derived catalyst **P5** which could be easily prepared using our previously developed protocol,[9g] could improve the *ee* to 93% of the product in a better yield (Table 1, entry 5). The variation of the 3,5-bis(trifluoro-methyl)benzoyl derived amide to tert-butanesulfinamide led to much lower enantioselectivity, indicating that the amide moiety plays crucial role in inducing enantioselectivity (Table 1, entry 6). Employing commercially available chiral ferrocene phosphine **P7** exhibited no catalytic activities (Table 1, entry 7). Further studies showed that toluene was

H. Wang, W, Lu, Prof. Dr. J. Zhang*
Shanghai Key Laboratory of Green Chemistry and Chemical Processes,
School of Chemistry and Molecular Engineering,
East China Normal University
Shanghai, 200062 (P. R. China)
E-mail: jlzhang@chem.ecnu.edu.cn
http://faculty.ecnu.edu.cn/s/1811/main.jspy

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the optimal solvent and variation of the reaction temperature did not lead to obvious improvements (Table 1, entries 8-14).

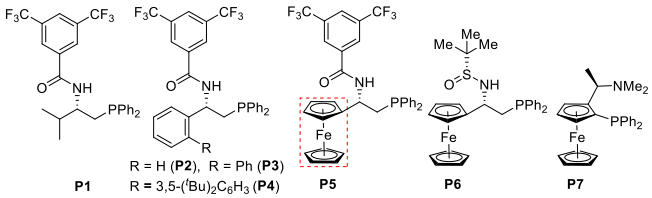
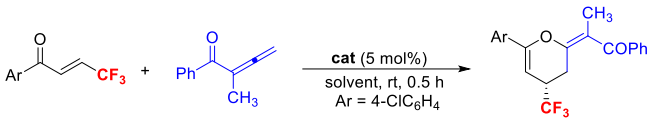


Figure 1. Phosphine catalysts employed in this study.

Table 1: Optimization Reaction Conditions[a]



1f 2a 3fa

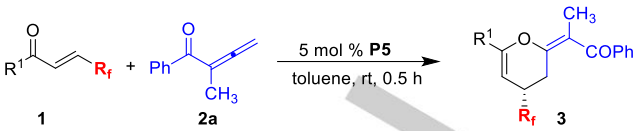
Entry	Cat	Solvent	Yield [%][b]	*Ee* [%][c]
1	**P1**	toluene	95	83
2	**P2**	toluene	95	80
3	**P3**	toluene	90	66
4	**P4**	toluene	92	90
5	**P5**	toluene	96	93
6[d]	**P6**	toluene	40	-54
7	**P7**	toluene	n.r.	--
8	**P5**	DCM	90	88
9	**P5**	$CHCl_3$	94	92
10	**P5**	THF	80	74
11	**P5**	MeCN	40	57
12	**P5**	acetone	50	57
13[e]	**P5**	toluene	95	93
14[f]	**P5**	toluene	94	94

[a] Reaction conditions: **1f** (0.1 mmol), **2a** (0.12 mmol), and the catalyst (0.005 mmol) in the solvent specified (1 mL) at room temperature for 0.5 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 12 h. [e] at 0 °C for 1 h. [f] at -20 °C for 10 h.

With the optimized reaction conditions in hand, we examine the scope and limitation of this reaction using various β-perfluoroalkylated *α,β*-enone **1**, and the results are listed in Table 2. In general, the reaction could proceed smoothly to produce the desired adducts in good yields with high enantioselectivities regardless of the structure of enones with different aryl or heteroaryl groups (Table 2, entries 1-23). The absolute configuration of **3ta** was established by single crystal X-ray diffraction analysis[11] (see ESI). It was particularly gratifying that reducing the catalyst loading to 2.5 mol%, the reaction still delivers high yield of **3sa** on a 3.0 mmol scale without affecting the excellent stereoselectivity. Finally, changing the trifluoromethyl group to C_2F_5 and C_3F_7 groups in substrates **1** were also applicable in the present asymmetric cycloaddition transformation, furnishing valuable perfluoroalkylated dihydropyran **3xa-3ya** in high *ee* (Table 2, 24 and 25). The use of Z-isomer of **1a** afforded the **3aa** with the same absolute configuration as the reaction of E-isomer of **1a** but in a relatively lower yield (Table 2, entry 26).

Next, we examined the reaction scope with a series of allenones, and the results are shown in Table 3. Several electron-withdrawing or -donating substituents were tolerant at the different positions of the aromatic ring, providing the

Table 2: Investigation the scope of β-perfluoroalkyl enone component[a]

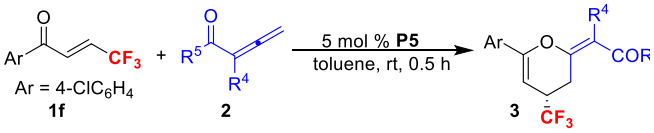


1 2a 3

Entry	1, R^1/R_f	Yield [%][b]	*Ee* [%][c]
1	**1a**, Ph/CF_3	**3aa**, 97	94
2	**1b**, 4-MeC_6H_4/CF_3	**3ba**, 96	92
3	**1c**, 4-MeOC_6H_4/CF_3	**3ca**, 95	94
4	**1d**, 4-PhC_6H_4/CF_3	**3da**, 95	92
5	**1e**, 4-FC_6H_4/CF_3	**3ea**, 85	93
6	**1f**, 4-ClC_6H_4/CF_3	**3fa**, 91	93
7	**1g**, 4-BrC_6H_4/CF_3	**3ga**, 91	92
8	**1h**, 4-IC_6H_4/CF_3	**3ha**, 86	91
9	**1i**, 4-O_2NC_6H_4/CF_3	**3ia**, 98	90
10	**1j**, 4-NC_6H_4/CF_3	**3ja**, 93	91
11	**1k**, 4-MeO_2SC_6H_4/CF_3	**3ka**, 92	90
12	**1l**, 4-$CF_3C_6H_4$/CF_3	**3la**, 98	92
13	**1m**, 2-BrC_6H_4/CF_3	**3ma**, 97	92
14	**1n**, 3-BrC_6H_4/CF_3	**3na**, 96	94
15	**1o**, 2-O_2NC_6H_4/CF_3	**3oa**, 98	91
16	**1p**, 3-O_2NC_6H_4/CF_3	**3pa**, 97	93
17	**1q**, 3,4-$Cl_2C_6H_3$/CF_3	**3qa**, 99	94
18	**1r**, 1-naphthy/CF3	**3ra**, 86	94
19[c]	**1s**, 2-naphthy/CF3	**3sa**, 96	92
20	**1t**, 2-benzothienyl/CF_3	**3ta**, 95	95
21	**1u,** 2-furyl/CF_3	**3ua**, 96	92
22	**1v,** 2-thienyl/CF_3	**3va**, 98	94
23	**1w,** 2-pyridyl/CF_3	**3wa**, 90	93
24	**1x,** Ph/C_2F_5	**3xa**, 95	90
25	**1y,** Ph/C_3F_7	**3ya**, 97	91
26	**(*Z*)-1a**	**3aa**, 70	94

[a] Reactions were performed with **1** (0.2 mmol), **2a** (0.24 mmol), and **P5** (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Isolated yield. [c] 3.0 mmol scale and 2.5 mol% **P5**.

Table 3: Investigation the scope of allenone component[a]



1f 2 3

Entry	**2**, R^4/R^5	**3**,Yield [%][b]	*Ee* [%][c]
1	**2b**, CH_3/4-MeC_6H_4	**3fb**, 97	93
2	**2c**, CH_3/4-FC_6H_4	**3fc**, 98	93
3	**2d**, CH_3/4-ClC_6H_4	**3fd**, 98	91
4	**2e**, CH_3 /4-BrC_6H_4	**3fe**, 97	91
5	**2f**, CH_3/3-ClC_6H_4	**3ff**, 60	91
6	**2g**, CH_3/2-benzodioxole	**3fg**, 92	92
7	**2h**, CH_3/CH_3	**3fh**, 76	93
8	**2i**, CH_3/ C_2H_5	**3fi**, 73	99
9	**2j**, Bn /CH_3	**3fj**, 50	97

[a] Reactions were performed with **1f** (0.2mmol), **2** (0.24 mmol), and **P5** (0.01 mmol) in toluene (1.0 mL) at room temperature. [b] Isolated yields. [c] Determined by HPLC analysis on a chiral stationary phase.

corresponding products in 60-98% yield with excellent enantioselectivities (Table 3, entries 1-6). The halogens in the products provide a handle for further transformations. In addition, allenone **2** with only alkyl substituents (**2h-2j**) in general gave higher *ees* (Table 3, entries 7-9).

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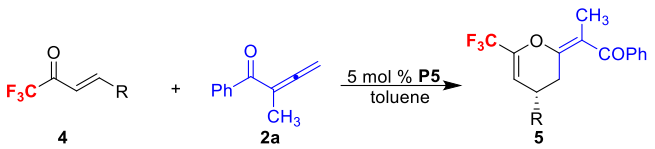
Table 4: Investigation the scope of trifluoromethyl enone component[a]

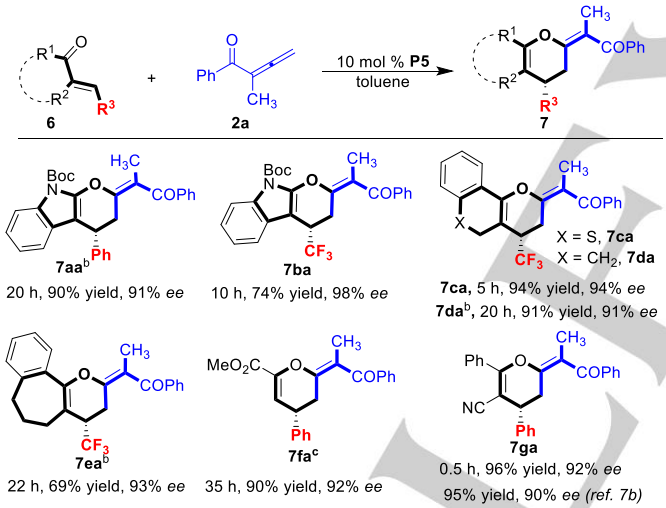


Entry	**4**, R	**5**, Yield [%][b]	*Ee* [%][c]
1	**4a**, Ph	**5aa**, 94	90
2[d]	**4b**, 4-$CH_3C_6H_5$	**5ba**, 95	90
3[d]	**4c**, 4-BrC_6H_5	**5ca**, 97	91
4[d]	**4d**, 3,4,5-$(OMe)_3C_6H_2$	**5da**, 95	90

[a] Reactions were performed with **5** (0.2 mmol), **2a** (0.24 mmol), and **P5** (0.01 mmol) in toluene (1.0 mL) at room temperature for 0.5 h. [b] Isolated yields. [c] Determined by HPLC analysis on a chiral stationary phase. [d] at 0 °C for 12 h.

We next examined the reactivity of *1,1,1*-trifluorobut-*3*-en-2-ones for the preparation of 6-(trifluoromethyl) dihydropyrans (Table 4). An array of trifluoromethyl enone, irrespective of methyl, methoxy, and halogen substituents on the aromatic ring, reacted well with **2a** to produce the corresponding products in good yields with 90%-91% *ee* values (Table 4, entries 1-4).

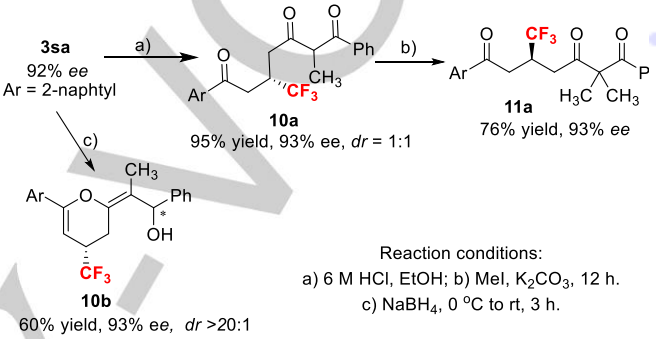
Table 5: Further investigation the scope of enone bearing without perfluoroalkyl group[a]



[a] Reactions were performed with **6** (0.2 mmol), **2a** (0.24 mmol), and **P5** (0.02 mmol) in toluene (1.0 mL) at room temperature. Yields are isolated yield. Enantiomeric excesses are determined by HPLC analysis on a chiral stationary phase. [b] at 0 °C. [c]at -50 °C.

Inspired by the above success, we turned to further explore the indolinone substituted *α,β*-enones bearing a CF_3 or Ph group have also been successfully utilized to construct the chiral cyclic frameworks in excellent enantioselectivities and good yields (Table 5). The six or seven-membered benzocyclic *α,β*-enone substrate were well tolerated, and the corresponding products were isolated in good to excellent yields and enantioselectivities. Importantly, these polyheterocyclic compounds might be further applicable to access more complicated functionalized or polycyclic molecules that are useful in medicinal and material chemistry. Gratifyingly, the reaction of *β,γ*-unsaturated *α*-keto ester with **2a** could also produce the desired product 7fa in 90% yield with 92% *ee* with the 10 mol% of catalyst at -50 °C. This catalyst system could be also applicable to the reaction of *α*-cyano-enone, furnishing the desired product **7ga** in 96% yield with 92% *ee*, a similar result to Lu's catalyst.[7b]

To demonstrate the synthetic utility of the products, two transformations of the representative **3sa** were demonstrated (Scheme 2), Ring opening of **3sa** through treatment with HCl in ethanol provided 1,3,7-triketone **10a**, followed by methylation reaction affording the gem-dimethyl ketone **11a**. The chiral trifluoromethylated 3,4-dihydropyran **3sa** was treated with $NaBH_4$ in THF for 3 h, giving the reduction product **10b** in 60% yield as a single diastereomer.



Scheme 2. Further Synthetic Transformations of **3sa**.

In summary, we have developed a highly effective phosphine-catalyzed asymmetric [4+2] cycloaddition of α-substituted allenones with a range of perfluoroalkyl enones to afford a wide variety of CF_3-containing dihydropyrans in high yields with excellent enantioselectivities (90−99% ee). Meanwhile, a series of benzocyclic *α,β*-enones have also been successfully utilized to construct a diverse range of chiral polycyclic molecules frameworks in high enantioselectivities. The method is also applicable to *β,γ*-unsaturated *α*-keto ester and *α*-cyano-enone. Further elaboration of the approach to the syntheses of bioactive natural products and molecules are under way and will be reported in due course.

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Keywords: chiral phosphines • oxa-cycloaddition reaction • dihydropyrans • polyheterocyclic • allenones

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[11] The X-ray crystal structure information is available at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 1548565 (**3ta**).

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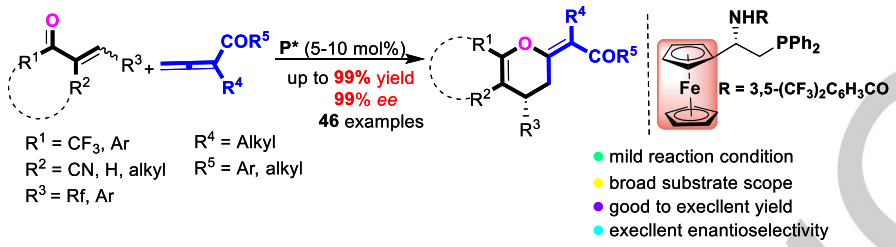

An efficient ferrocene derived bifunctional phosphine-catalyzed enantioselective oxa-[4+2] cycloaddition of α-substituted allenones with a broad range of perfluoroalkyl enones is investigated for the preparation of stereodefined fluoroalkylated dihydropyrans in good to excellent yields (up to 99%) and excellent enantioselectivity (up to 99% *ee*). Furthermore, a series of valuable chiral fluoroalkylated polyheterocyclic frameworks can be efficiently achieved in good yields with excellent enantioselectivities.

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