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Asymmetric Synthesis

A Phosphine-Catalyzed Novel Asymmetric [3+2] Cycloaddition of C,N-Cyclic Azomethine Imines with δ-Substituted Allenoates

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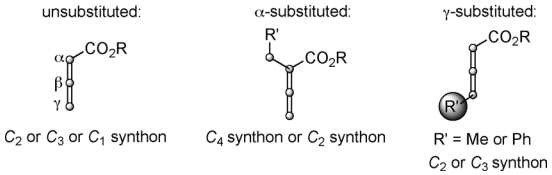
Abstract: Catalytic asymmetric [3+2] cycloadditions of C,N-cyclic azomethine imines with δ-substituted allenoates have been developed in the presence of (*S*)-Me-f-Ketal-Phos, affording functionalized tetrahydroquinoline frameworks in good yields with high diastereo- and good enantioselectivities under mild condition. The substrate scope has been also examined. This is the first time that δ-substituted allenoates have been applied as a δ,γ-C–C bond participated C_2 synthon in asymmetric synthesis.

Phosphine-catalyzed [3+2] cycloaddition of allenoates with various electron-deficient olefins has provided powerful access to a variety of useful carbocycles. This intriguing cycloaddition was first reported by Zhang and Lu in 1995.[1,2] Then, during the following decades, chemists have committed themselves to developing different types of allenoates and new reaction models based on these allenoates (Scheme 1). For example, Kwon et al. disclosed a novel phosphine-catalyzed [4+2] cycloaddition of α-substituted allenoates with imines, activated olefins or ketones, demonstrating its synthetic diversity.[3] Compared with the significant progress achieved by using unsubstituted allenoates and α-substituted allenoates, there are only a few reports on phosphine-catalyzed cycloaddition reaction employing γ-substituted allenoates.[4]

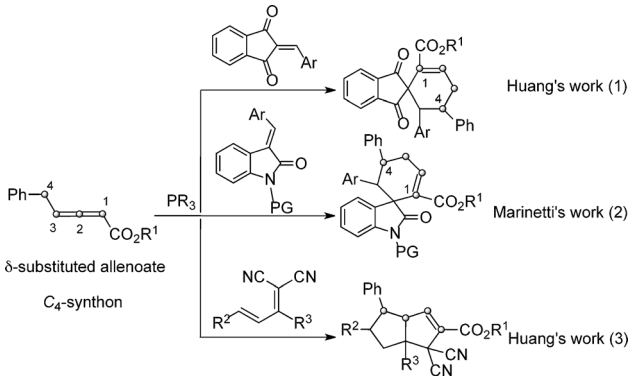


Scheme 1. Different types of allenoates.

Pioneering work on phosphine-catalyzed asymmetric Lu's [3+2] cycloaddition of allenoates with olefins was reported by Zhang in 1997.[5] Subsequently, Fu and co-workers have explored a series of axially chiral binaphthyl framework containing phosphine-catalyzed asymmetric cycloaddition of allenoates with electron-deficient olefins, affording the corresponding cycloadducts in good yields with excellent diastereo- and enantioselectivities.[6] Moreover, Marinetti and co-workers have discovered that chiral phosphines based on a planer chiral 2-phospha[3]ferrocenophane scaffold were efficient catalysts for this type of asymmetric reaction.[7] At the present stage, various multifunctional chiral phosphines derived from natural amino acids have also been realized as powerful catalysts to promote cycloaddition of allenoates with electron-deficient olefins, producing a variety of cycloadducts in good yields with high diastereo- and enantioselectivities.[8] In addition, some commercially available bidentate chiral phosphine-promoted [3+2] cycloadditions have also been reported.[9]

More recently, Huang and Marinetti's groups independently reported the phosphine-catalyzed [4+2] cycloaddition of δ-substituted allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones and 3-arylideneoxindoles, respectively [Scheme 2, Eqs. (1) and (2)]. Furthermore, Huang and co-workers developed another example of phosphine-catalyzed cascade reaction of δ-substituted allenoates to construct bicyclic-[3,3,0]octane derivatives efficiently [Scheme 2, Eq. (3)]. In these examples, δ-substituted allenoates acting as a new type of C_4 synthon exhibit a broad and perspective application prospect for this type of allenoate. However, there has been no report on the related asymmetric synthesis employing this distinctive δ-substituted allenoates until recently.[10]

In 2011, Kwon and Guo reported the phosphine-catalyzed [3+2], [3+3], [3+4] and [3+2+3] cycloaddition of *N*,*N*-cyclic azomethine imines with different allenoates to give these cycloadducts in good yields.[3g] Later, they also developed a novel phosphine-catalyzed [3+2] and [3+4] cycloaddition of



Scheme 2. Phosphine-catalyzed cycloaddition of δ-substituted allenoates.

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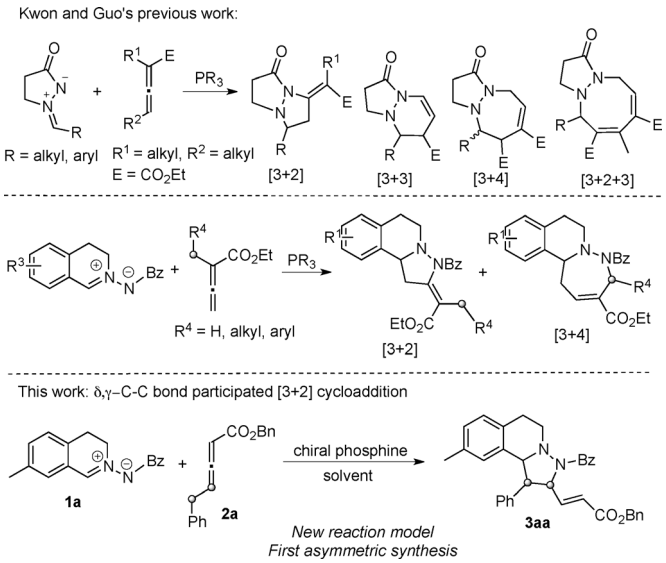
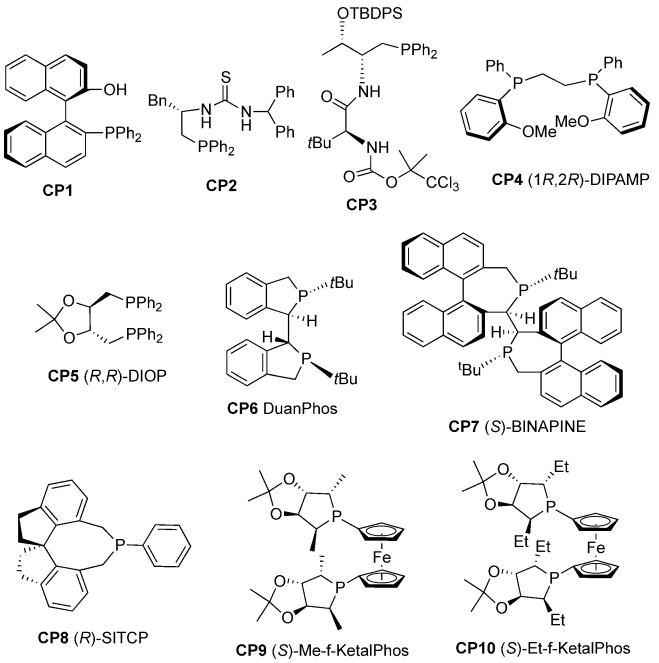
C,N-cyclic azomethine imines and allenoates (Scheme 3).[3h] As part of our ongoing interest on the phosphine-catalyzed cycloaddition of allenoates with activated olefins or others,[11] herein we report an interesting chiral phosphine-catalyzed asymmetric [3+2] cycloaddition of δ-substituted allenoates with C,N-cyclic azomethine imines,[12] furnishing the corresponding tricyclic heterocyclic compounds in good yields with high diastereo- and good enantioselectivities. The corresponding tentative reaction model is depicted in Scheme 3. This asymmetric [3+2] cycloaddition catalyzed by chiral phosphine features a new reaction model and besides, this is the first example for this type of allenoates being applied in asymmetric synthesis (Scheme 3). Since stereospecific tetrahydroisoquinolines are the "privileged" skeletons in numerous pharmaceutically important compounds that exhibit broad biological activities,[13] this phosphine-catalyzed new [3+2] cycloaddition pattern provides an efficient and useful synthetic method for the practical approach to a variety of novel functionalized tetrahydroquinoline derivatives in a shortest pathway.



Scheme 3. Phosphine-catalyzed asymmetric reaction employing *N,N*-cyclic azomethine imines.

We first carefully examined the reaction outcome by using benzoyl(7-methyl-3,4-dihydroisoquinolin-2-ium-2-yl)amide (**1a**) and benzyl 5-phenylpenta-2,3-dienoate (**2a**) as the model substrates catalyzed by chiral phosphines **CP1**–**CP10** (Scheme 4) in toluene.

The results are summarized in Table 1. We found that in the presence of chiral phosphine catalysts **CP1**–**7**, a novel cycloadduct **3aa** derived from the δ,γ-C–C bond of **2a** which participated in intermolecular [3+2] cycloaddition was formed in relatively low yields and enantioselectivities but almost as a single diastereomer in toluene at room temperature (Table 1, entries 2–8), and in the absence of phosphine catalyst no reaction occurred in toluene or in dichloromethane (DCM; Table 1, entry 1). When using **CP8** as the catalyst in this reaction, the desired product **3aa** was obtained in 78% yield along with

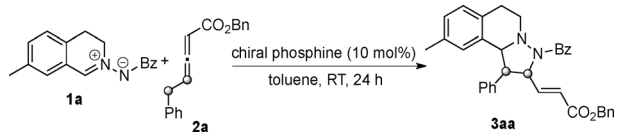


Scheme 4. Chiral phosphine catalysts.

>20:1 d.r. and 80% *ee* (Table 1, entry 9). Catalyst **CP9** [(*S*)-Me-f-KetalPhos][14] gave the highest enantioselectivity (87%) in this reaction compared to other catalysts including **CP10** (Table 1, entries 10 and 11). Subsequently, we further optimize the reaction conditions by screening of the solvent, reaction temperature and additive using **CP9** as the catalyst (Table 1, entries 12–20). The outcome revealed that using 10 mol% **CP9** as the catalyst and carrying out the reaction in *p*-xylene at room temperature served as the best condition, affording the desired product **3aa** in 81% yield after 24 h with >20:1 d.r. and 93% *ee* (Table 1, entry 18).

With the identification of the optimal reaction conditions, the generality of this (*S*)-Me-f-KetalPhos (**CP9**)-catalyzed asymmetric [3+2] cycloaddition was examined using C,N-cyclic azomethine imine **1a** and a variety of allenic esters **2**. The results are summarized in Table 2. Whether R^1 is a simple straight chain (Bn, Me) or a sterically bulky group (*t*Bu, CH_2*t*Bu), the reactions proceeded smoothly to give the corresponding cycloadducts **3aa**–**3aj** in good yields with 77–93% *ee* and >20:1 d.r. (Table 2, entries 1–4). In the case of neopentyl 5-phenylpenta-2,3-dienoate (**2d**), catalysts **CP8** and **CP9** were independently applied to the reaction, giving the desired product **3ad** in 64% yield with 80% *ee* (in parentheses), >20:1 diastereoselective ratio and in 92% yield with 77% *ee*, >20:1 diastereoselective ratio, respectively (Table 2, entry 4). δ-Substituted allenoates possessing electron-withdrawing substituents on their aromatic rings (R^2 = 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4) also gave rise to good stereoselectivities (74–77% *ee*, >20:1 d.r.) and yields (62–92%; Table 2, entries 5–8). As for substrate **2i** with electron-rich substituent on its aromatic ring (R^2 = 4-$MeOC_6H_4$), the cycloadduct **3ai** was also obtained in similar results as 65% yield and 73% *ee* (Table 2, entry 9). Changing the aromatic group to aliphatic group (R^2 = $CH_2C_6H_5$) provided the

Table 1. Optimization of reaction conditions.



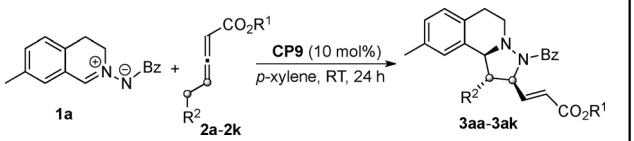
Entry[a]	Cat.*	Solvent	T [°C]	Additive	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1[e]	–	toluene or DCM	25	–	–	–	–
2	**CP1**	toluene	25	–	35	>20:1	25
3	**CP2**	toluene	25	–	26	>20:1	21
4	**CP3**	toluene	25	–	17	>20:1	6
5	**CP4**	toluene	25	–	49	>20:1	6
6	**CP5**	toluene	25	–	24	>20:1	6
7	**CP6**	toluene	25	–	58	>20:1	22
8	**CP7**	toluene	25	–	trace	–	–
9	**CP8**	toluene	25	–	78	>20:1	80
10	**CP9**	toluene	25	–	75	>20:1	87
11	**CP10**	toluene	25	–	48	>20:1	73
12	**CP9**	toluene	0	–	30	>20:1	85
13	**CP9**	DCM	25	–	79	>20:1	45
14	**CP9**	THF	25	–	70	>20:1	62
15	**CP9**	Et_2O	25	–	50	>20:1	79
16	**CP9**	benzene	25	–	86	>20:1	80
17	**CP9**	fluorobenzene	25	–	62	>20:1	70
18	**CP9**	*p*-xylene	25	–	81	>20:1	93
19	**CP9**	*p*-xylene	25	4 A MS	42	>20:1	82
20	**CP9**	*p*-xylene	25	H_2O	48	>20:1	82

[a] All reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (10 mol%) in solvent (1.0 mL), Cat* = chiral phosphine. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of crude product. [d] Determined by chiral HPLC. [e] The reaction was carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), toluene (1.0 mL) or DCM (1.0 mL) at room temperature.

corresponding product **3aj** in 57% yield with 68% *ee* and >20:1 diastereoselective ratio (Table 2, entry 10). When R^2 is hydrogen atom (R^2 = H), the reaction could not proceed efficiently to afford the corresponding product catalyzed by **CP8** or **CP9** (Table 2, entry 11). The absolute configuration of **3aa** was assigned by X-ray diffraction. The ORTEP drawing and the CIF data are summarized in the Supporting Information.[15]

Recognized δ-substituted allenoates **2a** and **2b** were more suitable for this type of [3+2] cycloaddition. We next attempted to examine the asymmetric [3+2] cycloaddition from the reaction of different azomethine imines **1** and allenoates **2a** or **2b**, and the results are summarized in Table 3. As for the substitution pattern of the C,N-cyclic azomethine imines, halogen substituents (F, Cl, Br) were all tolerated, giving the corresponding products **3bb**–**3fb** in moderate to excellent yields (72–92%) and good *ee* (68–83%). For the substrate with no substituent on their aromatic rings, tricyclic heterocyclic compound **3gb** was obtained in 72% yield with 82% *ee*. The substrates **1h**–**1j** with various electron-rich substituents on their aromatic rings were more suitable for this reaction, affording the corresponding cycloadducts **3ha**–**3ja** in good yields with 90–93% *ee*. These results suggest that the electronic properties of substituents of substrates **1** have an important influence on the reaction outcomes, especially on the control of enantioselectivity. Substrate **1** having an aliphatic group was also tested

Table 2. Scope of the asymmetric [3+2] cycloaddition to afford cycloadducts **3aa**–**3ak**.



Entry[a]	**2** (R^1/R^2)	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**2a**: Bn/C_6H_5	**3aa**: 81	>20:1	93
2	**2b**: *t*Bu/C_6H_5	**3ab**: 93	>20:1	91
3	**2c**: Me/C_6H_5	**3ac**: 78	>20:1	86
4[e]	**2d**: CH_2*t*Bu/C_6H_5	**3ad**: 92 (64)	>20:1	77 (80)
5	**2e**: Bn/2-BrC_6H_4	**3ae**: 90	>20:1	75
6	**2f**: Bn/3-BrC_6H_4	**3af**: 78	>20:1	74
7	**2g**: Bn/4-BrC_6H_4	**3ag**: 92	>20:1	74
8	**2h**: Bn/4-FC_6H_4	**3ah**: 62	>20:1	77
9	**2i**: Bn/4-MeOC_6H_4	**3ai**: 65	>20:1	73
10	**2j**: Bn/$CH_2C_6H_5$	**3aj**: 57	>20:1	68
11[f]	**2k**: Bn/H	**3ak**: trace	–	–

[a] All reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), **CP9** (10 mol%) in *p*-xylene (1.0 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by HPLC. [e] Neophenyl = CH_2*t*Bu, the values in parentheses were obtained by catalyzing with **CP8** (*R*)-SITCP. [f] The racemic product was obtained in 46% yield, but only trace optical product catalyzed by **CP8** or **CP9**.

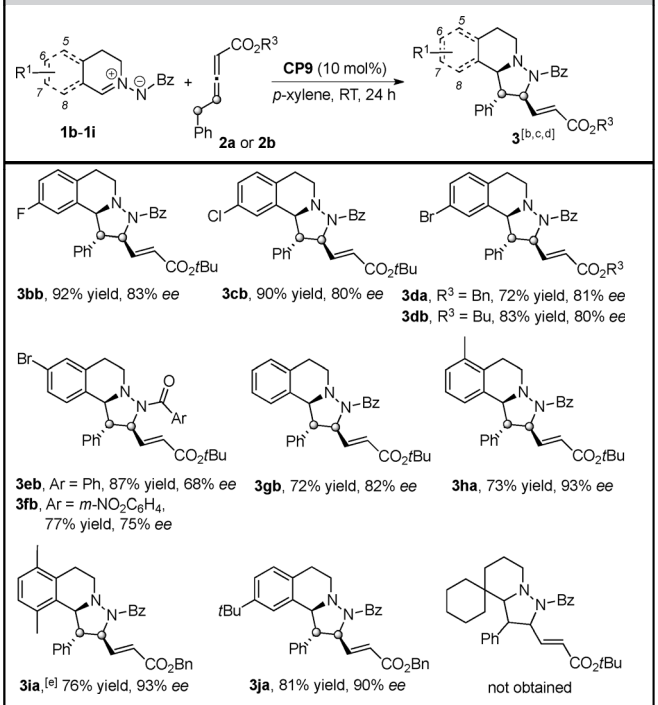
in this reaction, but the desired product could not be obtained.

A plausible mechanism for this phosphine-catalyzed novel [3+2] cycloaddition has been proposed in Scheme 5 on the basis of our experiments and the previous literature.[10,16] The reaction starts from the formation of a zwitterionic intermediate **A** between allenoate and phosphine, which would be transformed to intermediate **B** via a proton transfer.[17] Intermediate **B** acts as a 1,4-dipole and subsequently undergoes a δ-addition with C,N-cyclic azomethine imines **1** to give a zwitterionic intermediate **C**. Subsequently, a nucleophilic addition reaction initiated by nitrogen ion yields the phosphorus ylide **D**. Then an intramolecular [1,2] proton transfer is speculated to convert the phosphorus ylide **D** to another zwitterionic intermediate **E**, which, upon elimination of the phosphine catalyst, gives rise to the final [3+2] cycloaddition product **3**. A plausible transition state accounting for the stereochemical outcome of this reaction is outlined in the Supporting Information.

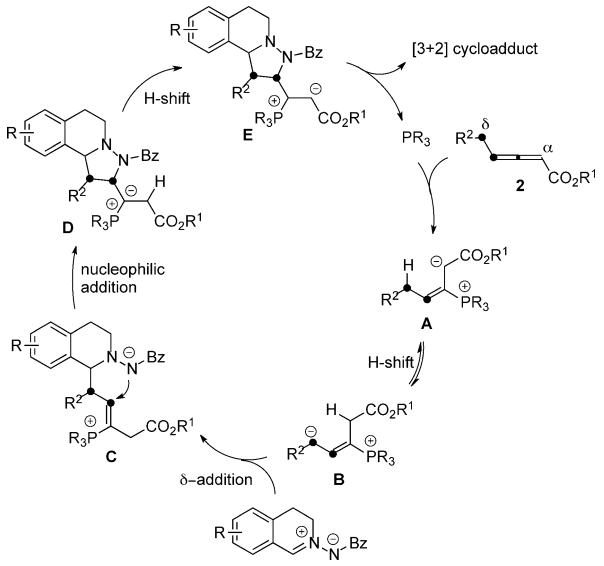
The deuterium-labeling experiment was carried out under standard conditions by adding D_2O (10 equiv) into the reaction of azomethine **1g** and allenoate **2b** in the presence of 10 mol% PPh_3. As shown in Scheme 6, a partially deuterated product **3gb′** was obtained in 40% yield and 10:1 d.r., along with 41% deuterium incorporation at C4-position, 50% deuterium incorporation at C5-position and 56% deuterium incorporation at C6-position, further confirming the proton-transfer process in the above proposed mechanism (Scheme 6).

We also tested *N*,*N*′-cyclic azomethine imine **4** or compound **5** in this reaction catalyzed by triphenylphosphine or **CP9**. However, no desired products were obtained under the standard conditions [Scheme 7, Eqs. (1) and (2)]. Enlarging the reaction scale to 264 mg (1.0 mmol) afforded **3aa** in 380 mg, 72%

Table 3. Substrate scope of azomethine imines **1b–1i**.[a]



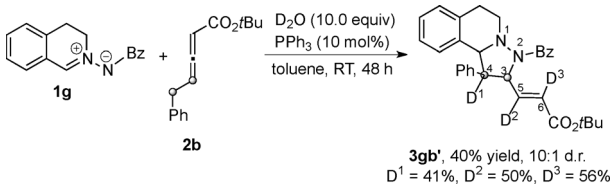
[a] All reactions were carried out with **1b–1j** (0.1 mmol), **2a** or **2b** (0.15 mmol), **CP9** (10 mol%) in *p*-xylene (1.0 mL) at room temperature. [b] Isolated yield. [c] The diastereoselectivities were determined by ^{1}H NMR spectroscopy of crude product, all products with d.r. $>$20:1. [d] Determined by chiral HPLC. [e] Using **CP8** (10 mol%) as catalyst; using **CP9** as catalyst only trace product could be obtained.



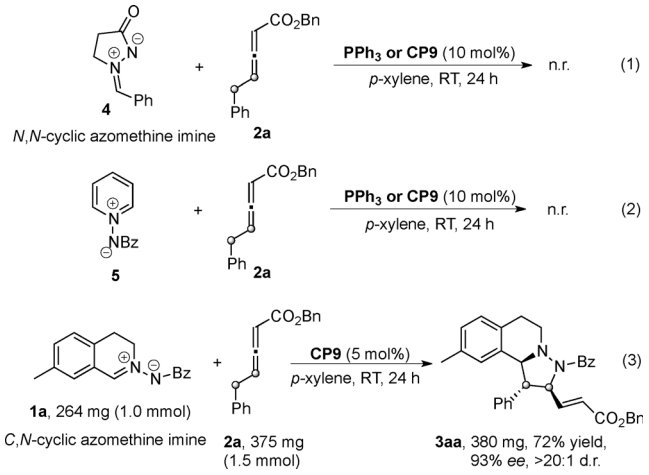
Scheme 5. A plausible mechanism.

yield, $>$20:1 d.r. and 93% *ee* under the standard conditions [Scheme 7, Eq. (3)].

In summary, we report the first example of highly diastereoselective and enantioselective cycloaddition of azomethine imines and δ-substituted allenic esters catalyzed by chiral



Scheme 6. Deuterium-labeling experiment.



Scheme 7. The examination of the substrate scope using other azomethine imines and the reaction outcome on an enlarged reaction scale.

phosphine **CP9** [(*S*)-Me-f-KetalPhos] for construction of tetrahydroquinolines. The novelty of this study is that this type of allenoates can be used as a δ,γ-C–C bond participated C_2 synthon in the phosphine-catalyzed asymmetric [3+2] cycloaddition with azomethine imines. Under the present catalytic system, the desired products can be obtained in 57–92% yields with 68–93% *ee* values, and $>$20:1 d.r. values. These stereospecific tetrahydroquinoline frameworks are difficult to access by using other synthetic methods. Further exploration of δ-substituted allenic esters in other types of reactions and their asymmetric synthesis are ongoing in our laboratory.

Experimental Section

General procedure for the phosphine-catalyzed asymmetric [3+2] cycloaddition

Azomethine imine **1a** (0.1 mmol), (*S*)-Me-f-KetalPhos **CP9** (0.01 mmol), and anhydrous *p*-xylene (1.0 mL) were added into a Schlenk tube, then δ-substituted allenic ester **2a** (0.15 mmol) was added slowly. The reaction mixture was stirred at room temperature for 24 h (TLC monitored) under argon atmosphere. The reaction mixture was then concentrated on a rotary evaporator under reduced pressure and the residue was subjected to purification by column chromatography (PE/AcOEt = 10:1 ~ 6:1) to afford the corresponding product **3aa**.

(*E*)-Benzyl 3-(3-benzoyl-9-methyl-1-phenyl-1,2,3,5,6,10b-hexahydropyrazolo[5,1-a]isoquinolin-2-yl)acrylate (3aa)

White solid, 81% yield, 42 mg; M.p.: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.93 (d, J = 6.8 Hz, 2H), 7.46–7.24 (m, 13H), 7.13

(dd, $J_1 = 7.0$ Hz, $J_2 = 15.6$ Hz, 1H), 6.98–6.90 (m, 2H), 6.04 (d, $J = 15.6$ Hz, 1H), 5.85 (s, 1H), 5.31 (t, $J = 7.6$ Hz, 1H), 5.16 (d, $J = 12.0$ Hz, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 4.37 (d, $J = 10.8$ Hz, 1H), 3.51 (dd, $J_1 = 9.2$ Hz, $J_2 = 10.0$ Hz, 1H), 3.27–3.18 (m, 2H), 3.02–2.94 (m, 1H), 2.70 (d, $J = 16.0$ Hz, 1H), 1.99 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.5$, 166.0, 147.1, 137.3, 135.7, 135.1, 134.8, 132.8, 130.5, 129.4, 129.0, 128.72, 128.65, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.3, 121.3, 69.8, 68.0, 66.4, 58.3, 49.9, 29.0, 20.8 ppm; HRMS calcd for $C_{35}H_{33}N_2O_3^{+1}$ $[M+H]^+$: 529.2486, found: 529.2475; $[\alpha]_D^{20} = -28.6$ ($c = 0.35$, $CHCl_3$) for 93% *ee*; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column, hexane/*i*PrOH = 80:20, 0.6 mL min^{-1}, 214 nm, $t_{minor} = 52.987$ min, $t_{major} = 23.313$ min.

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Keywords: cycloaddition · azomethine imines · chiral phosphine · enantioselectivity · substituted allenoates

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Asymmetric Synthesis

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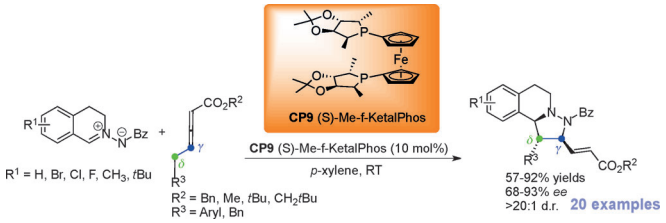
A Phosphine-Catalyzed Novel Asymmetric [3+2] Cycloaddition of C,N-Cyclic Azomethine Imines with δ-Substituted Allenoates



Another round: Catalytic asymmetric [3+2] cycloaddition of C,N-cyclic azomethine imines with δ-substituted allenoates have been developed in the presence of (*S*)-Me-f-KetalPhos, affording functionalized tetrahydroquinoline frameworks in good yields with high diastereo- and good enantioselectivities under mild conditions. This is the first example to apply δ-substituted allenoates as a δ,γ-C–C bond participated C_2 synthon in asymmetric synthesis.