Asymmetric Organocatalysis

DOI: 10.1002/ange.201206958

Enantioselective Synthesis of Highly Functionalized Phosphonate-Substituted Pyrans or Dihydropyrans Through Asymmetric [4+2] Cycloaddition of β,γ-Unsaturated α-Ketophosphonates with Allenic Esters**

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The phosphonate group, commonly used as a phosphate mimic in biological systems,[1] is generally regarded as a bioisostere of a carboxylic acid group in drug design.[2] In contrast to carboxylic acid, the phosphonic acid has higher acidity and stronger electrostatic interaction with the guanidine group.[3] Some drugs, such as tamiphosphor, guanidino-tamiphosphor, phosphono-zanamivir and phosphono-glycosyl acetates, which bear a phosphonic acid group instead of a carboxylic acid group, possess more inhibitory activity against the neuraminidases of the influenza viruses;[4a–c] also, phosphorus-chromones are important intermediates for producing platelet-aggregation inhibitors (Figure 1).[4d] Recently, allenoates have been found to be an attractive substrate class for Lewis base catalyzed reactions and have attracted synthetic interest.[5] A large number of phosphine-catalyzed cycloaddition reactions of allenoates have been reported after the pioneering work by Lu and co-workers in 1995.[6–8] In contrast to the well-developed phosphine-catalyzed allenoate-cycloaddition reactions, the corresponding amine-catalyzed analogues are relatively less developed and only a few examples have been reported.[9] Although this area is less explored, the development of asymmetric allenoate-cycloaddition reactions has attracted much attention.[10] The group of Masson and Zhu first reported asymmetric [2+2] cycloadditions between allenoates and imines in 2011 in the presence of cinchona-alkaloid-derived bifunctional 6′-deoxy-6′-acylaminoquinidine.[10a] Subsequently, Tong et al. and Borhan et al. also reported asymmetric [4+2] cyclization of allenoates with β,γ-unsaturated ketone to afford dihydropyran derivatives in good yields and high *ee* values using cinchona-alkaloid-derived organocatalysts.[10b,c] In this regard, we have recently reported a highly efficient 1,4-diazabicyclo-[2,2,2]octane (DABCO)-catalyzed [4+2] cycloaddition of β,γ-unsaturated α-ketophosphonates or β,γ-unsaturated α-ketoesters with allenic esters to give the corresponding highly functionalized pyran and dihydropyran derivatives in good to excellent yields and moderate to good regioselectivities under different conditions.[9n] Herein, we wish to report the asymmetric [4+2] cycloaddition of β,γ-unsaturated α-ketophosphonates with allenic esters to afford either phosphonate-substituted pyran or phosphonate-substituted dihydropyran derivatives as the major products, which are structural subunits in many natural products, drugs, and biologically active molecules,[4] in good yields and high *ee* values using different organocatalysts derived from cinchona alkaloids.

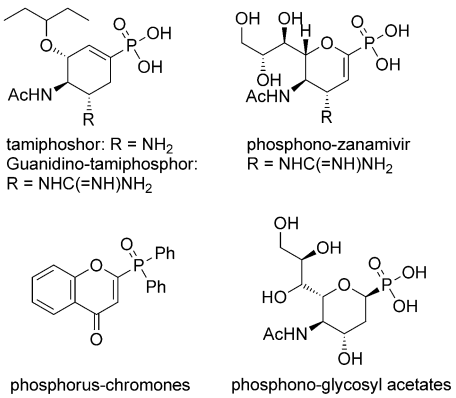

Figure 1. Phosphorus-substituted biologically active compounds.

We initially utilized (*E*)-diisopropyl cinnamoylphosphonate **1a** (0.1 mmol, 1.0 equiv) and ethyl 2,3-butadienoate **2a** (0.12 mmol, 1.2 equiv) as the substrates, and β-isocupreidine (β-ICD, 20 mol %; see Table 1 for structure) as the catalyst in acetonitrile at room temperature to examine the reaction outcome and the result is shown in entry 1 of Table 1. It was found that the corresponding cyclic products, **3aa** and **4aa**, were obtained in 72 % combined yield and a **3aa**/**4aa** ratio of 4:1, but with low *ee* for both. To improve the reaction outcome, we screened various catalysts derived from cinchona alkaloids[11] for this reaction, and the results are summarized in Table 1. As can be seen, **C8** was the best

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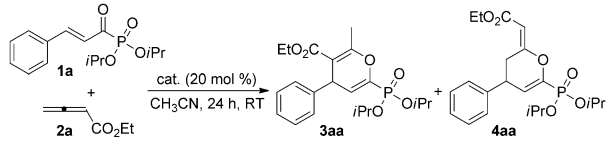
[**] We thank the Shanghai Municipal Committee of Science and Technology (11JC1402600), the National Basic Research Program of China (973)-2010CB833302, and the National Natural Science Foundation of China for financial support (21072206, 20472096, 20872162, 20672127, 21121062 and 20732008).

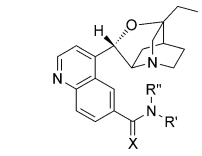
Supporting information, including spectroscopic data and HPLC traces of the compounds shown in Tables 1–3 and Scheme 1, for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206958.

Table 1: Screening of catalysts for asymmetric [4+2] cyclization.[a]

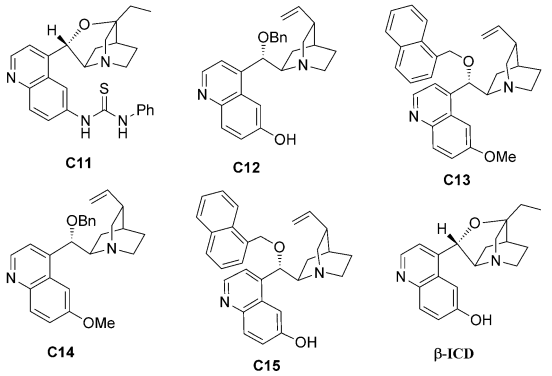


Entry	Catalyst	Yield [%][b]	**3aa**/**4aa**[c]	*ee* of **3aa** [%][d]	*ee* of **4aa** [%][d]
1	β-ICD	72	4:1	60	48
2	**C1**	73	2:1	68	45
3	**C2**	70	3:1	68	43
4	**C3**	68	3:1	67	43
5	**C4**	75	6:1	64	35
6	**C5**	65	3:1	66	32
7	**C6**	70	5:1	73	38
8	**C7**	70	6:1	62	24
9	**C8**	80	4:1	78	35
10	**C9**	65	4:1	59	19
11	**C10**	77	5:1	64	23
12	**C11**	68	1:1	60	40
13	**C12**	75	1:3	45	80
14	**C13**	90	<1:20	–	94
15	**C14**	75	1:20	–	90
16	**C15**	22	1:10	46	88

[a] All reactions were carried out using **1a** (0.10 mmol) and **2a** (0.12 mmol) at room temperature for 24 h. [b] Total yield of isolated product(s). [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase.



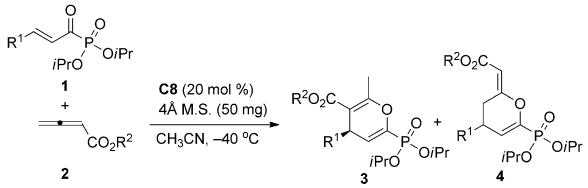
C1: R' = CH_3, R'' = H, X = O
C2: R' = CH_2CH_3, R'' = H, X = O
C3: R' = Bn, R'' = H, X = O
C4: R' = C_6H_5, R'' = H, X = O
C5: R' = CH_3, R'' = H, X = S
C6: R' = 3,5-$(MeO)_2C_6H_3$, R'' = H, X = O
C7: R' = 4-BrC_6H_4, R'' = H, X = O
C8: R' = 2-$MeOC_6H_4$, R'' = H, X = O
C9: R' = 2-naphthyl, R'' = H, X = O
C10: R' = 2,4,6-$Me_3C_6H_2$, R'' = H, X = O



catalyst for the reaction, affording **3aa** and **4aa** in 80% combined yield and with **3aa** as the major product (**3aa**/**4aa** 4:1); also, *ee* values of 78% *ee* and 35% *ee* were obtained for **3aa** and **4aa**, respectively (Table 1, entry 9). Moreover, **4aa** was obtained in 90% yield and as the sole product in 94% *ee* when **C13** was used as catalyst (Table 1, entry 14). When using **C14** (an analogue of **C12** which possesses a OMe group instead of a OH group), the total yield did not change, however, the amount of product **4aa** significantly increased (Table 1, entry 15). For comparison with **C13**, catalyst **C15**, which possesses a OH group instead of a OMe group, was synthesized and was found to give the desired products in lower total yield and with less **4aa** (Table 1, entry 16).

Having identified the best organocatalyst to afford **3aa** as the major reaction product, we next carried out the reaction of **1a** and **2a** with catalyst **C8** (20 mol%) in various solvents to examine the solvent effects on this reaction, and found that CH_3CN was the solvent of choice (Supporting Information, Table SI-1, entries 1–7). Lowering the reaction temperature to −40°C allowed the isolation of **3aa** in 60% yield and 90% *ee* (**3aa**/**4aa** 5:1; Table SI-1, entries 8–10). Adding 4 Å molecular sieves (50 mg for 0.1 mmol of **1a**) improved the yield of **3aa** to 70% with 90% *ee* (Table SI-1, entry 11 and Table 2, entry 1).

Table 2: Substrate scope of the **C8**-catalyzed asymmetric [4+2] cyclization of phosphonates **1** and **2**.[a]



Entry	R^1	R^2	Product (% yield)[b]	**3**/**4**[c]	*ee* of **3** [%][d]
1	C_6H_5 (**1a**)	Et (**2a**)	**3aa** (70)	5:1	90
2	4-ClC_6H_4 (**1b**)	Et (**2a**)	**3ba** (69)	5:1	84
3	4-BrC_6H_4 (**1c**)	Et (**2a**)	**3ca** (65)	3:1	83
4	4-MeC_6H_4 (**1d**)	Et (**2a**)	**3da** (67)	4:1	90
5	4-$MeOC_6H_4$ (**1e**)	Et (**2a**)	**3ea** (75)	7:1	90
6	3-$MeOC_6H_4$ (**1f**)	Et (**2a**)	**3fa** (69)	4:1	90
7	3-MeC_6H_4 (**1g**)	Et (**2a**)	**3ga** (70)	6:1	90
8	2-$MeOC_6H_4$ (**1h**)	Et (**2a**)	**3ha** (65)	4:1	87
9	2-furyl (**1i**)	Et (**2a**)	**3ia** (68)	4:1	90
10	1-naphthyl (**1j**)	Et (**2a**)	**3ja** (70)	6:1	87
11	Me (**1k**)	Et (**2a**)	**3ka** (77)	7:1	90
12	*n*-propyl (**1l**)	Et (**2a**)	**3la** (72)	6:1	90
13	C_6H_5 (**1a**)	Bn (**2b**)	**3ab** (65)	4:1	92

[a] All reactions were carried out using **1** (0.10 mmol) and **2** (0.12 mmol) in CH_3CN 2.00 (mL) for 24 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase. Bn = benzyl.

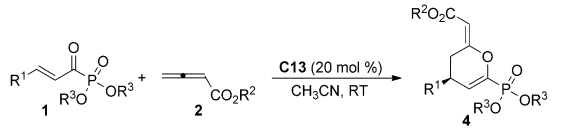
Having established the optimal reaction conditions for the formation of **3aa** as the major product, we surveyed the scope of the reaction by varying the structure of phosphonates **1** and allenoates **2**. As shown in Table 2, regardless of whether electron-donating or electron-withdrawing groups were introduced in *ortho*-, *meta*- or *para*-positions of the benzene rings of **1**, these substrates were equally well-tolerated in the reaction, giving the corresponding major products **3** in good yields and high *ee* values (Table 2, entries 2–8). Heterocyclic substrate **1i** was also suitable in this reaction, and gave **3ia** as the major product in 68% yield and 90% *ee* (Table 2, entry 9). The substrate **1j**, in which R^1 is a 2-naphthyl group, was also tolerated in this reaction, providing the corresponding major product **3ja** in 70% yield with 87% *ee* (Table 2, entry 10). As for substrates **1k** and **1l**, in which R^1 is an aliphatic group, the reactions also proceeded smoothly to give the desired major products **3ka** and **3la** in 77% yield with 90% *ee* and 72% yield with 90% *ee*, respectively (Table 2, entries 11 and 12). Changing the ester moiety of allenic esters **2** from OEt to

OBn provided a similar outcome, furnishing the desired major product **3ab** in 65% yield and 92% *ee* (Table 2, entry 13). Products **3** have been assigned an *S* configuration by X-ray diffraction analysis of **3ja** (Supporting Information, Figure SI-1).[13] The structure of **3** is closely related with phosphorus-chromones.[4d]

Furthermore, the results shown in entry 14 of Table 1 encouraged us to further screen various solvents in the reaction of **1a** and **2a** with **C13** as the catalyst. The examination of solvent effects revealed that CH_3CN was the best solvent for this reaction, providing **4aa** as the sole product in 90% yield and 94% *ee* (Supporting Information, Table SI-2, entries 1–8). Lowering the reaction temperature to 0°C or −15°C and reducing the catalyst loading to 10 mol% did not improve the reaction outcomes (Table SI-2, entries 9–11).

Under the optimized conditions to produce **4aa** as the sole reaction product in good yield and high *ee* value, the reaction scope was investigated by using various phosphonates **1** with several allenic esters **2**; the results of these experiments are summarized in Table 3. As can been seen, the reactions produced cycloadducts **4** in high yields and high enantiomeric excesses for a wide range of substrates **1** with various aromatic groups, heteroaromatic rings, alkyl or naphthyl groups (Table 3, entries 1–12). When the ester moiety of the phosphonates was changed from O*i*Pr to OMe or O*t*Bu, the reactions also proceeded smoothly to give the desired products **4ma** and **4na** in 87% yield with 93% *ee* and 83% yield with 95% *ee*, respectively (Table 3, entries 13 and 14). Changing the ester moiety of allenic esters **2** from OEt to OBn provided a similar outcome, affording the desired product **4ab** in 85% yield and 96% *ee* (Table 3, entry 15).

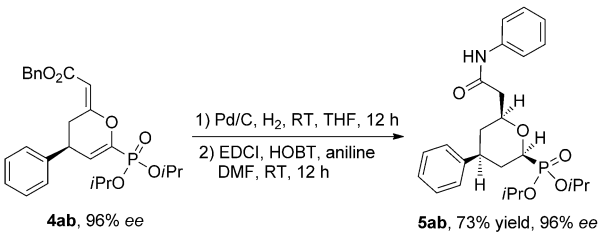
Table 3: Substrate scope of the **C13**-catalyzed asymmetric [4+2] cyclization of phosphonates **1** and **2**.[a]



Entry	R^1	R^2	R^3	Product (% yield)[%][b]	*ee* of **4** [%][c]
1	C_6H_5 (**1a**)	Et (**2a**)	*i*Pr	**4aa** (90)	94
2	4-ClC_6H_4 (**1b**)	Et (**2a**)	*i*Pr	**4ba** (92)	92
3	4-BrC_6H_4 (**1c**)	Et (**2a**)	*i*Pr	**4ca** (91)	91
4	4-MeC_6H_4 (**1d**)	Et (**2a**)	*i*Pr	**4da** (93)	95
5	4-$MeOC_6H_4$ (**1e**)	Et (**2a**)	*i*Pr	**4ea** (90)	95
6	3-$MeOC_6H_4$ (**1f**)	Et (**2a**)	*i*Pr	**4fa** (88)	94
7	3-MeC_6H_4 (**1g**)	Et (**2a**)	*i*Pr	**4ga** (89)	95
8	2-$MeOC_6H_4$ (**1h**)	Et (**2a**)	*i*Pr	**4ha** (91)	93
9	2-furyl (**1i**)	Et (**2a**)	*i*Pr	**4ia** (85)	90
10	1-naphthyl (**1j**)	Et (**2a**)	*i*Pr	**4ja** (87)	94
11	Me (**1k**)	Et (**2a**)	*i*Pr	**4ka** (87)	94
12	*n*-propyl (**1l**)	Et (**2a**)	*i*Pr	**4la** (85)	94
13	C_6H_5 (**1m**)	Et (**2a**)	Me	**4ma** (87)	93
14	C_6H_5 (**1n**)	Et (**2a**)	*t*Bu	**4na** (83)	95
15	C_6H_5 (**1a**)	Bn (**2b**)	*i*Pr	**4ab** (85)	96

[a] All reactions were carried out using **1** (0.10 mmol) and **2** (0.12 mmol) in CH_3CN (2.00 mL) for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

Product **4ab** can be easily transformed into tetrahydropyran **5ab** as a single stereoisomer after hydrogenation with Pd/C in THF and condensation with aniline in 73% yield and 96% *ee* in two steps. The crystal structure of **5ab** has been determined by X-ray diffraction and the ORTEP drawing is shown in Figure SI-2 in the Supporting Information,[13] which provides information on the absolute stereochemistry of products **4** (*S* configuration) as well (Scheme 1). The structure of **5ab** is also very similar to that of phosphono-glycosyl acetates.[3a]

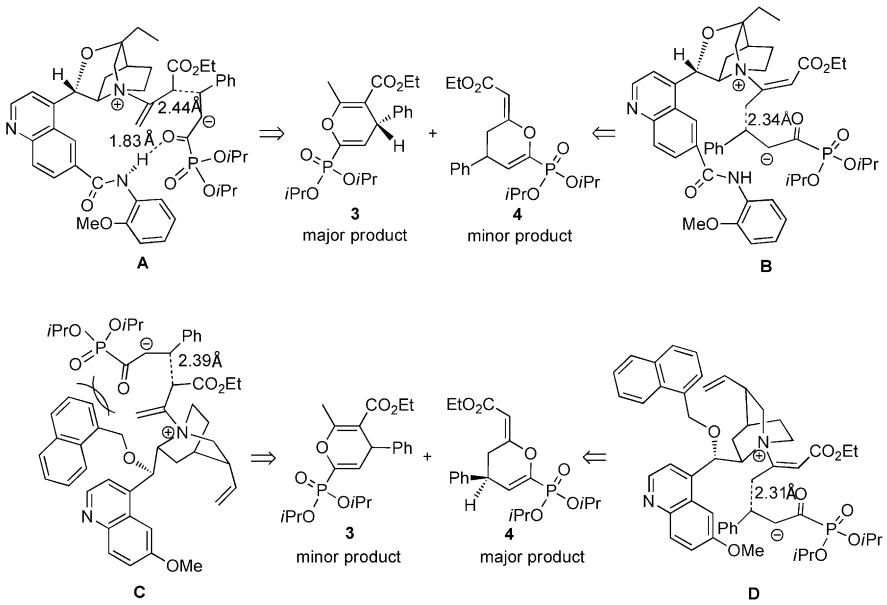


4ab, 96% *ee* — **5ab**, 73% yield, 96% *ee*

Scheme 1. Transformation of Product **4ab**. Bn = benzyl, DMF = dimethylformamide, EDCI = N′-(ethylcarbonimidoyl)-N,N-dimethyl 1,3-propanediamine, HOBT = hydroxybenzotriazole.

Based on the above experimental results and our previous mechanistic studies on the formation of racemic cycloaddition products,[9n] we have done theoretical investigations on transition state (TS) models **A**–**D** (Scheme 2), which have been proposed as the key transition states for the formation of products **3** and **4**. These TS structures (see Figure 2) were optimized at the mPW1K/6-31G(d) level of theory, and their relative energies were calculated at the mPW1K/6-31+G(2d)//mPW1K/6-31G(d) level of theory.[12] When **C8** is used in the reaction, the energy of key TS **A**, which leads to product **3**, and involves a hydrogen bond between the CONH moiety in **C8** and the carbonyl group and phosphonate moiety in substrate **1**, is lower than that of the TS **B** leading to product **4** by 18.2 kJ mol^{-1}. Thus, when **C8** is used as the catalyst, product **3** is the major product. When **C13**, which lacks a hydrogen bond donor, is used as the catalyst, it cannot form hydrogen bonds with the substrates. Furthermore, we determined that the energy of the key TS **C** leading to product **3** is higher than that of the TS **D** leading to product **4** by 6.4 kJ mol^{-1}, owing to the steric repulsion between the naphthyl moiety of **C13** and the phosphonate group of **1**.

In conclusion, we have developed a novel asymmetric [4+2] cycloaddition of β,γ-unsaturated α-ketophosphonates with allenic esters catalyzed by organocatalysts derived from cinchona alkaloids, which affords the corresponding major adducts (phosphonate-substituted functionalized pyran or dihydropyran derivatives) in high yields and enantioselectivities. Calculations indicate that stereocontrol is determined by hydrogen-bonding effects or steric interactions. Cinchona-alkaloid-derived organocatalysts which possess either a hydrogen bond donor or a sterically bulky group can give different cycloadducts. These reactions differ from previous [4+2] cycloadditions through steric interactions;[10b,c] herein, we first report that different types of cycloadducts can be afforded through hydrogen-bonding interactions or pure steric repulsion. These corresponding phosphonate-substituted function-



Scheme 2. Key transition state models. Relative energies ΔH_{298}(kJ mol^{-1}): **A** 0.0, **B** 18.2; **C** 6.4, **D** 0.0.

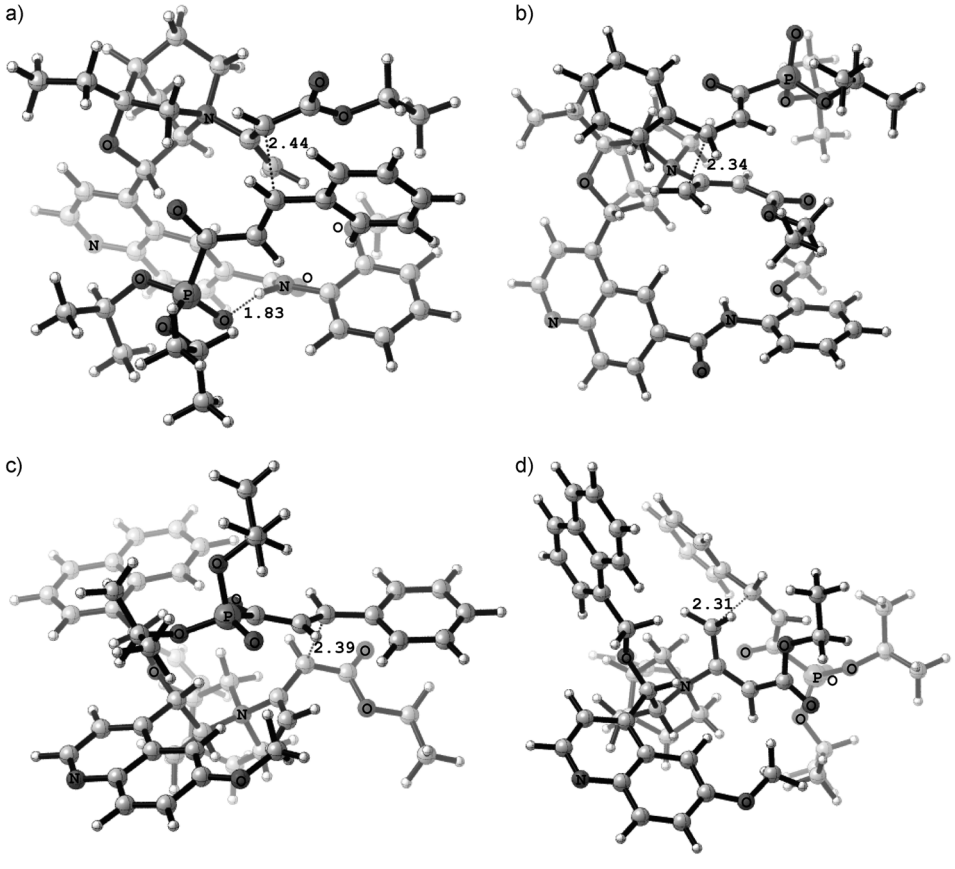


Figure 2. Optimized structures of key transition states.

alized pyran and dihydropyran derivatives are important structural subunits in many natural products, drugs, and biologically active molecules.[4] Efforts are currently underway to use the cinchona-alkaloid-derived catalysts in other asymmetric reactions and to apply this new methodology to the synthesis of biologically active products.

Experimental Section

General Procedure: Under an argon atmosphere, allenoate **2** (0.12 mmol) was added to a solution of β,γ-unsaturated α-ketophosphonates **1** (0.1 mmol) and catalyst **C8** or **C13** (0.02 mmol) in CH_3CN (2.0 mL) and stirred at either −40 °C or room temperature for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate 4:1 → 2:1) to provide compound **3** or **4**, as desired.

Ethyl-6-(diisopropoxyphosphoryl)-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (**3aa**): a slightly yellow liquid (28.6 mg, 70 %); this is a known compound;[9n] ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 1.09 (t, J = 6.8 Hz, 3H), 1.31 (d, J = 6.4 Hz, 6H), 1.35 (d, J = 6.4 Hz, 3H), 1.37 (d, J = 6.4 Hz, 3H), 2.40 (s, 3H), 3.97–4.06 (m, 2H), 4.44 (d, J = 4.8 Hz, 1H), 4.65–4.73 (m, 2H), 6.10 (dd, J = 10.4 Hz, 4.8 Hz, 1H), 7.18–7.22 (m, 3H), 7.28–7.30 ppm (m, 2H); $[\alpha]_D^{20}$ = −100.8 (c = 0.95, CH_2Cl_2; 90 % *ee*); Chiralcel AD-H, *n*-hexane/*i*PrOH = 95:5, 0.6 mL min^{-1}, 254 nm, t_{major} = 16.02 min, t_{minor} = 19.55 min.

(*E*)-Ethyl-2-(6-(diisopropoxyphosphoryl)-4-phenyl-3,4-dihydro-2*H*-pyran-2-ylidene)acetate (**4aa**): a slightly yellow liquid (36.7 mg, 90 %); this is a known compound;[9n] ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 1.23 (t, J = 7.2 Hz, 3H), 1.35 (d, J = 6.3 Hz, 6H), 1.39 (d, J = 6.3 Hz, 6H), 3.10 (dd, J = 16.8 Hz, 9.9 Hz, 1H), 3.64–3.71 (m, 2H), 4.07–4.16 (m, 2H), 4.71–4.80 (m, 2H), 5.65 (s, 1H), 6.27 (dd, J = 10.2 Hz, 6.9 Hz, 1H), 7.19–7.26 (m, 3H), 7.30–7.35 ppm (m, 2H); $[\alpha]_D^{20}$ = −151.1 (c 0.70, CH_2Cl_2) (94 % *ee*); Chiralcel AD-H, *n*-hexane/*i*PrOH = 95:5, 0.6 mL min^{-1}, 254 nm, t_{major} = 30.15 min, t_{minor} = 27.52 min.

Received: August 28, 2012
Published online: October 8, 2012

Keywords: asymmetric catalysis · cycloaddition · cinchona alkaloids · dihydropyrans · organocatalysis

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