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手性叔膦-酰胺不对称催化香豆素与 Morita-Baylis-Hillman 碳酸酯之间的插烯烯丙基烷基化反应

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摘要 发展了新型手性双功能叔膦-酰胺催化4-甲基香豆素化合物与外消旋Morita-Baylis-Hillman碳酸酯之间的插烯烯丙基烷基化反应, 反应条件温和, 底物适用范围广泛. 在 10～15 mol%的基于手性环己烷骨架的叔膦-酰胺催化剂 **C10** 作用下, 相应产物的产率达到 87%～99%, 对映选择性最高达 98% *ee*, 为手性香豆素衍生物的不对称合成提供了有效的方法.

关键词 烯丙基烷基化反应; 不对称催化; 手性膦; 有机催化; 插烯反应

Enantioselective Vinylogous Allylic Alkylation of Coumarins with Morita-Baylis-Hillman Carbonates Catalyzed by Chiral Phosphine-Amide

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Abstract An organocatalytic enantioselective direct vinylogous allylic alkylation between coumarins and racemic Morita-Baylis-Hillman carbonates has been developed. With 10～15 mol% a chiral cyclohexane-based phosphine-amide **C10**, a wide range of densely functionalized coumarin derivatives have been achieved in 87%～99% yields and up to 98% *ee*.

Keywords allylic alkylation; asymmetric catalysis; chiral phosphine; organocatalysis; vinylogous reaction

1 Introduction

The vinylogous reaction is arguably one of the most efficient protocols to build multifunctional allylic compounds, which are widely used in organic synthesis.[1] In the field of vinylogous reaction, the direct vinylogous asymmetric allylic alkylation (VAAA) reaction is a powerful protocol to selectively incorporate the synthetically versatile allyl group into the *γ*- or even more remote position of the vinylogous products in an efficient way. Compared to the vinylogous version of asymmetric aldol reaction, Mannich reaction and Michael addition, the VAAA reaction remains relatively less investigated. In 2009, Chen and co-workers[2a] reported the first VAAA reaction between *α*,*α*-dicyanoalkenes and racemic Morita-Baylis-Hillman (MBH) carbonates by dual organocatalysis of $(DHQD)_2AQN$ and (*S*)-BINOL. Later on, the organocatalyzed VAAA reaction has been developed by Chen[2b-2e] and other groups.[3] In these metal-free VAAA reactions, racemic MBH carbonates were used as the allylic electrophile. First, the Lewis basic catalyst (such as tertiary amines and tertiary phosphines) would perform an S_N2' attack to the MBH carbonate and generate the active intermediate **A**. There is a regioselectivity resulting from the addition of the nucleophile to intermediate **A** in S_N2 or S_N2' fashion (Scheme 1). In general, the organocatalytic VAAA reactions take place in S_N2'-S_N2' tandem process, providing branched *γ*-allylation product. On the other hand, the Jørgensen group developed a direct VAAA reaction of *α*,*β*-unsaturated aldehydes by combined organocatalysis and transition-metal catalysis, and the use of iridium catalyst led to branched products while the use of palladium catalyst led to linear products.[4] The regioselectivity of transition-metal catalyzed VAAA reaction resulted from

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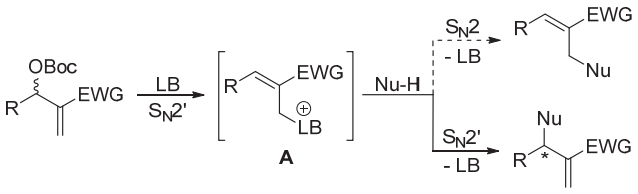
the presence of π-allyl-metal intermediate. Subsequent to Jørgensen's report, iridium- and palladium-catalyzed VAAA reaction have been disclosed.[5] Despite these advances in the past decade, the exploration of effective new catalytic system is still in demand.



Scheme 1 Regioselectivity for Lewis base-catalyzed allylic alkylation reaction

Coumarins are important motifs in numerous natural products and bioactive molecules,[6] which have attracted great attention in asymmetric catalysis recently, due to its potential vinylogous donors with an exocyclic nucleophilic site. 3-Cyano-4-methylcoumarins were firstly used as vinylogous nucleophiles for enantioselective reaction in 2010, Xie and co-workers[7] reported an enantioselective vinylogous Michael addition catalyzed by a cinchona-based primary amine. Till 2016, the next asymmetric reaction of these vinylogous nucleophiles was reported by Lautens and co-workers,[8] using a palladium-based catalytic system to promote the ring-opening reaction of oxabicycles. Since then organocatalyzed[3c,3e,9] and transition metal catalyzed[5a-5c,10] enantioselective vinylogous reactions with 3-cyano-4-methylcoumarins as the nucleophile have been demonstrated. Among the organocatalytic cases, hydrogen bond catalysis has received less attention, the only achievement was report by Singh's group[9c] very recently. *L-tert*-Leucine-derived tertiary amine thiourea was used as bifunctional catalyst in the direct vinylogous conjugate addition to maleimides, providing good yields with moderate-to-excellent enantioselectivities. It is well known that phosphines are classical nucleophilic catalysts in organic transformation.[11] Considering the high nucleophilicity, the tertiary phosphines could be effective for the electrophile of VAAA reaction. To explore the application of bifunctional catalyst in enantioselective vinylogous reaction with coumarins as the nucleophile, we investigated the VAAA reaction between 3-cyano-4-methylcoumarins and racemic MBH carbonates. Herein, we report the first phosphine-catalyzed direct VAAA reaction of coumarins, with chiral cyclohexane-based phosphine containing H-bond donor as the organocatalyst.

2 Results and discussion

Initially, a model reaction between 3-cyano-4-methylcoumarin (**1a**) and racemic MBH carbonate **2a** was conducted to screen the chiral bifunctional phosphines (Figure 1). The reactions were performed at 25 ℃ in CH_2Cl_2 with 10 mol% of chiral bifunctional organocatalyst, and the results are summarized in Table 1. Phosphine-thioureas **C1** and **C2** provided a moderate enantioselectivities and low

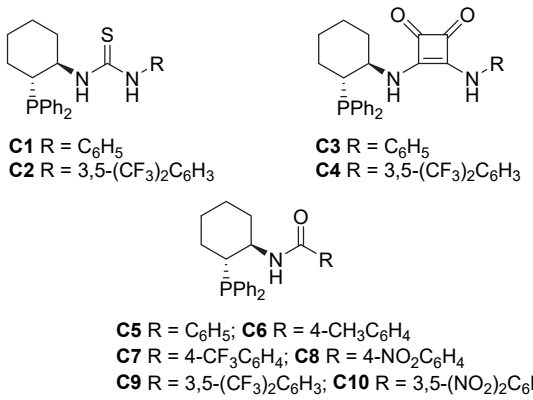
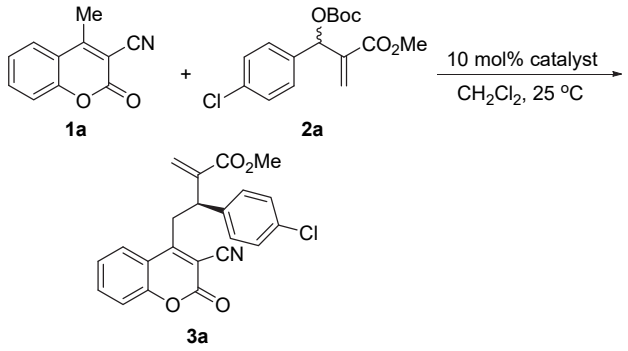


Figure 1 Structures of the chiral phosphine organocatalysts screened

Table 1 Screening of the chiral organocatalysts[a]



Entry	Catalyst	Time/h	Yield[b]/%	*ee*[c]/%
1	**C1**	24	41	72
2	**C2**	24	44	61
3	**C3**	48	47	85
4	**C4**	48	37	33
5	**C5**	10	56	84
6	**C6**	28	48	80
7	**C7**	9	87	86
8	**C8**	11	66	84
9	**C9**	8	56	48
10	**C10**	9	90	90

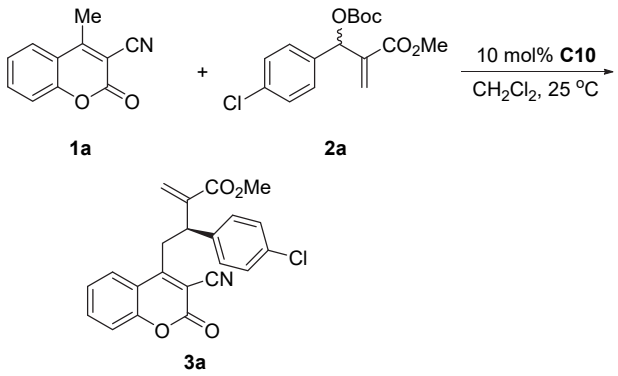
[a] The reactions were performed with 0.2 mmol of coumarin **1a**, 0.2 mmol of racemic MBH carbonate **2a**, and 10 mol% chiral catalyst in 1.0 mL of CH_2Cl_2 at 25 ℃. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC analysis.

yields (Entries 1 and 2). With phosphine-squaramide **C3**, the model reaction gave better enantioselectivities and same level of yield (Entry 3). To our surprise, the 3,5-bis-(trifluoromethyl)phenyl-containing squaramide **C4** provided poor enantioselectivity and chemical yield (Entry 4). Phosphine-amide **C5** gave better enantioselectivity and yield than phosphine-thiourea **C1** (Entry 5 vs. Entry 1). These results indicate that the Brønsted acidity of the catalyst plays an important role for the vinylogous allylic alkylation reaction. To improve the reactivity and enantioselectivity, several phosphine-amides were examined (Entries 6～8). The results suggest that the introducing of a strong electron-withdrawing group at the aromatic ring of

the amide could gave better chemical yield with similar enantioselectivity (Entries 7 and 8 vs. Entry 5). Therefore, phosphine-amides **C9** and **C10** with 3,5-bis(trifluoromethyl)phenyl group and 3,5-dinitrophenyl group were prepared and evaluated. Similar to catalysts **C2** and **C4**, the existence of a 3,5-bis(trifluoromethyl)phenyl group in the H-bond donor could not improve the results (Entry 9). Fortunately, phosphine-amide **C10** provided excellent yield and enantioselectivity (90% yield with 90% *ee*, Entry 10). As a result, phosphine **C10** was selected as catalyst for further study.

Subsequently, the optimization of reaction conditions (solvent, substrate concentration, reaction temperature and additive) was carried out with phosphine-amide **C10** (Table 2). In toluene, product **3a** could be obtained in good yield and enantioselectivity (Entry 1). Halogen solvents such as $CHCl_3$, CH_2Cl_2 and CH_2ClCH_2Cl gave better enantioselectivities with a shorter reaction time (Entries 2～4 vs. Entry 1). Aprotic solvents such as EtOAc and tetrahydrofuran (THF) gave similar yields and enantioselectivity at the same reaction time (Entries 5 and 6). The vinylogous allylic alkylation reaction provided a low yield and enantioselectivity in CH_3OH, probably due to side reactions and the hydrogen bonding interaction (Entry 8). The reaction became complicated in CH_3CN, so the chemical yield of product **3a** decreased obviously (Entry 7). The solvent survey results suggest that dichloromethane was the suitable solvent in terms of both reactivity and enantioselectivity (90% *ee* with 90% yield, Entry 2), and it was chosen as solvent for the subsequent study. The molar ratio of coumarin to MBH carbonate had a certain effect on the chemical yield and enantioselectivity (Entries 9 and 10 vs. Entry 2). Changing the substrate concentration from 0.1 mol/L to 0.3 mol/L in CH_2Cl_2 did not substantially affect the yield and enantioselectivity (Entries 11 and 12 vs. Entry 2). To further improve the enantioselectivity, the vinylogous allylic alkylation reaction was conducted at a lower temperature. As expected, the lower temperature gave better enantioselectivity but the reaction rate decreased significantly (Entry 13 *vs.* Entry 2). In order to increase the reaction rate at low temperature, the concentration was further increased from 0.2 mol/L to 0.4 mol/L, but there was no significant effect on the reaction rate (Entry 14 vs. Entry 13). We also attempted to improve the reaction via using additive. However, the presence of 4 Å molecular sieves did not substantially affect the yield and enantioselectivity (Entry 16 vs. Entry 14, Entry 15 vs. Entry 2). Therefore, the optimal reaction conditions have been identified as follows: 1.0 equiv. of coumarin **1** and 1.0 equiv. of racemic MBH carbonate **2** in CH_2Cl_2 (0.2 mol/L) at 25 ℃ using 10 mol% phosphine-amide **C10** as the chiral catalyst.

Table 2 Optimization of the reaction conditions[a]



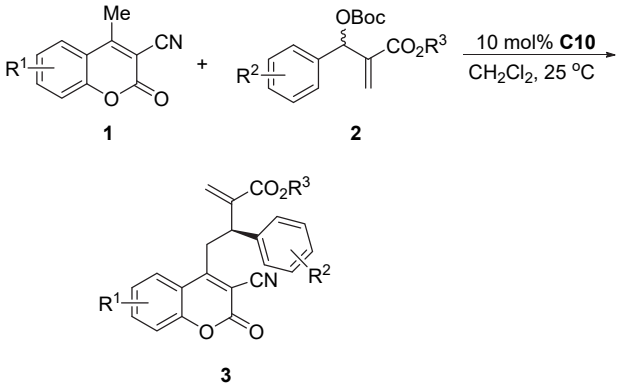
Entry	Solvent	Conc./(mol•L^{-1})	Time/h	Yield[b]/%	*ee*[c]/%
1	Toluene	0.2	24	75	77
2	CH_2Cl_2	0.2	9	90	90
3	$CHCl_3$	0.2	9	78	88
4	$ClCH_2CH_2Cl$	0.2	11	75	82
5	THF	0.2	28	69	73
6	EtOAc	0.2	28	76	71
7	CH_3CN	0.2	4	14	74
8	CH_3OH	0.2	24	14	36
9[d]	CH_2Cl_2	0.2	9	83	82
10[e]	CH_2Cl_2	0.2	9	89	89
11	CH_2Cl_2	0.3	7	86	88
12	CH_2Cl_2	0.1	24	87	86
13[f]	CH_2Cl_2	0.2	120	82	94
14[f]	CH_2Cl_2	0.4	72	81	94
15[g]	CH_2Cl_2	0.2	12	93	86
16[f,g]	CH_2Cl_2	0.4	72	81	90

[a] Unless stated otherwise, the reactions were performed with 0.2 mmol of coumarin **1a**, 0.2 mmol of racemic MBH carbonate **2a** and 10 mol% chiral catalyst **C10** in 1.0 mL of solvent at 25 ℃. [b] Isolated yield. [c] The *ee* values was determined by chiral HPLC analysis. [d] 0.3 mmol of coumarin **1a** was used. [e] 0.3 mmol of MBH carbonate **2a** was used. [f] The reaction temperature was 0 ℃. [g] 4 Å MS (30 mg) was added.

With the optimal reaction conditions in hand, the scope of the direct asymmetric vinylogous allylic alkylation was examined (Table 3). The reaction was tolerated for racemic MBH carbonates derived from different alkyl acrylates, providing high yields with excellent enantioselectivities (Entries 1～5). The MBH carbonates with a weak electron-withdrawing group were more reactive and gave better yields than that without substituent or with an electron-donating group (Entries 5, 8 and 9 vs. Entries 6 and 10). When the 4-substituent of MBH carbonate is a nitro group, only moderate yield was obtained, probably due to hydrogen bonding interaction (Entry 7). The MBH carbonate with 4-bromo provided better enantioselectivities than 4-chloro (Entry 8 vs. Entry 5). The MBH carbonate with 3-bromo provided the corresponding product with excellent yield and enantioselectivity (Entry 11). The MBH carbonate with 2-bromo also produced the desired product **3l** with excellent enantioselectivity (98% *ee*, Entry 12).

A further exploration of the substrate scope was concentrated on coumarins (Entries 13～15). The coumarin with bromo at 6- or 7-position produced the desired products **3m** and **3n**, respectively, with similar yields and excellent enantioselectivities (Entries 13 and 14). The coumarin with

Table 3 Substrate scope of the direct asymmetric vinylogous allylic alkylation of coumarins with racemic MBH carbonates[a]



Entry	R^1	R^2	R^3	Time/h	3	Yield[b]/%	ee[c]/%
1	H	4-Cl	Me	9	**3a**	90	90
2	H	4-Cl	Et	24	**3b**	89	86
3	H	4-Cl	^{n}Bu	24	**3c**	92	87
4	H	4-Cl	Bn	36	**3d**	94	88
5	H	4-Cl	^{t}Bu	24	**3e**	97	93
6	H	H	^{t}Bu	30	**3f**	85 (96)	92
7	H	4-NO_2	^{t}Bu	24	**3g**	74 (99)	96
8	H	4-Br	^{t}Bu	24	**3h**	94	94
9	H	4-F	^{t}Bu	24	**3i**	91	90
10	H	4-Me	^{t}Bu	36	**3j**	80 (93)	93
11	H	3-Br	^{t}Bu	24	**3k**	91	90
12	H	2-Br	^{t}Bu	24	**3l**	70 (93)	98
13	6-Br	4-Cl	^{t}Bu	48	**3m**	70 (89)	94
14	7-Br	4-Cl	^{t}Bu	48	**3n**	72 (87)	95
15	7-OMe	4-Cl	^{t}Bu	48	**3o**	83 (98)	90

[a] The reactions were performed with 0.2 mmol of coumarin **1**, 0.2 mmol of racemic MBH carbonate **2** and 10 mol% chiral catalyst **C10** in 1.0 mL of CH_2Cl_2 at 25 ℃. [b] Isolated yield. In the parenthesis was chemical yield using 15 mol% catalyst **C10**. [c] The *ee* values was determined by chiral HPLC analysis.

7-methoxy gave better yield, but with lower enantioselectivity than the coumarin with 7-Br atom (Entry 15 vs. Entry 14). For some cases, when the catalyst loading was increased from 10 mol% to 15 mol%, the chemical yield is remarkably improved (Entries 6, 7, 10 and 12～15).

The absolute configuration of the vinylogous allylic alkylation product was assigned as (*R*) by comparing the HPLC chromatograms and optical rotation values of compound **3b** known in the literature.[3c] The absolute configurations of other products were assigned by analogy.

According to the experimental results and the related literatures,[3b-3d] a possible transition-state structure is proposed as shown in Figure. 2. The phosphine-amide catalyst **C10** activates the MBH carbonates through nucleophilic attack and H-bonding interaction, thereby forming an electron-deficient olefin intermediate. The resulting *tert*-butoxide is then expected to deprotonate coumarins to form a dienolate, which attacks the electron-deficient olefin intermediate through Michael addition from the *Re*-face to generate the product **3** with (*R*) configuration.

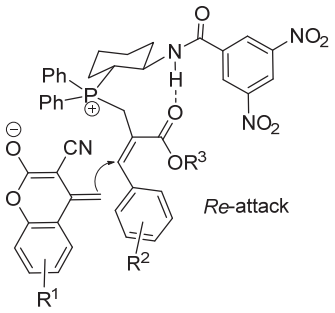


Figure 2 Proposed transition state

3 Conclusions

In conclusion, we have developed the first chiral phosphine-catalyzed enantioselective direct vinylogous allylic alkylation with coumarins as the γ-nucleophile. In the presence of 10～15 mol% chiral cyclohexane-based amide-phosphine catalyst **C10**, a wide range of densely functionalized coumarin derivatives were obtained in up to 99% yields with up to 98% *ee*.

4 Experimental section

4.1 General information

Melting points were taken on a WRS-1B digital melting-point apparatus without correction. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer, and the chemical shifts were referenced to tetramethylsilane (δ=0.00) for ^{1}H NMR and central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR. High resolution mass spectra (HRMS) were recorded on a Micromass GCT with electron spray ionization (ESI) resource. HPLC analysis was performed on a Waters equipment using Daicel Chiralpak AD-H column (λ=254 nm). Anhydrous dichloromethane, 1,2-dichloroethane, and chloroform, ethyl acetate were distilled from CaH_2. Anhydrous acetonitrile was distilled from P_2O_5. Anhydrous MeOH was distilled from magnesium-iodine. Anhydrous toluene and THF were distilled from sodium-benzophenone. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 10～40 μm. Silica gel column chromatography was performed using silica gel (300～400 mesh). Chiral bifunctional phosphine catalysts,[12] racemic Morita-Baylis-Hillman carbonates[13] and coumarins[8] were synthesized according to literature procedure.

4.2 General procedure for the preparation of catalysts **C9** and **C10**

To a solution of (1*R*,2*R*)-2-amino-1-(diphenylphosphino)-cyclohexane (0.18 mmol, 50.0 mg) in 4 mL of dry CH_2Cl_2, triethylamine (1.0 mmol) was added, then carbonyl chloride (0.21 mmol) was added drop-wise under ice-bath. The reaction mixture was stirred at 25 ℃ under N_2 atmosphere (monitored by TLC). After the reaction was

completed, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/AcOEt, V∶V=6∶1) to give the desired products **C9** and **C10**.

N-((1*R*,2*R*)-2-(diphenylphosphanyl)cyclohexyl)-3,5-bis-(trifluoromethyl)benzamide (**C9**): White solid, 80% yield, m.p. 176.6～178.9 ℃; $[\alpha]_D^{25}$ −16.6 (*c* 2.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 7.79 (s, 2H), 7.58 (t, J=7.2 Hz, 2H), 7.50～7.43 (m, 2H), 7.32～7.30 (m, 3H), 7.26～7.20 (m, 2H), 7.19～7.14 (m, 1H), 5.85 (d, J=8.4 Hz, 1H), 4.19～4.09 (m, 1H), 2.54～2.46 (m, 1H), 2.24～2.16 (m, 1H), 1.83～1.67 (m, 3H), 1.49～1.32 (m, 2H), 1.31～1.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.2, 137.3 (d, J=13.5 Hz), 136.5, 135.6 (d, J=14.6 Hz), 134.1 (d, J=20.8 Hz), 133.0 (d, J=19.8 Hz), 131.7 (d, J=33.5 Hz), 129.0 (d, J=11.3 Hz), 128.7 (d, J=7.0 Hz), 128.4 (d, J=7.5 Hz), 127.0, 124.6, 124.2, 121.5, 53.3 (d, J=16.4 Hz), 40.4 (d, J=15.4 Hz), 34.5 (d, J=7.3 Hz), 28.6 (d, J=7.8 Hz), 26.0 (d, J=6.6 Hz), 25.0; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4) δ: −7.81; IR (KBr) v: 3332, 2937, 1653, 1540, 1286, 1180, 1132, 905, 678 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{25}F_6NOP$ $[M+H]^+$ 524.1572, found 524.1572.

N-((1*R*,2*R*)-2-(diphenylphosphanyl)cyclohexyl)-3,5-dinitrobenzamide (**C10**): Yellow solid, 85% yield, m.p. 240.6～241.3 ℃; $[\alpha]_D^{25}$ −82.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (t, J=2.0 Hz, 1H), 8.51 (d, J=2.0 Hz, 2H), 7.58 (t, J=7.2 Hz, 2H), 7.49～7.43 (m, 2H), 7.35～7.28 (m, 3H), 7.22 (t, J=7.2 Hz, 2H), 7.11 (t, J=7.2 Hz, 1H), 6.07 (d, J=8.0 Hz, 1H), 4.21～4.09 (m, 1H), 2.58～2.48 (m, 1H), 2.26～2.14 (m, 1H), 1.88～1.68 (m, 3H), 1.50～1.38 (m, 2H), 1.38～1.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.2, 148.3, 137.7, 137.4 (d, J=14.0 Hz), 135.3 (d, J=14.5 Hz), 134.1 (d, J=20.6 Hz), 133.1 (d, J=19.8 Hz), 129.1, 128.8 (d, J=6.9 Hz), 128.7, 128.5 (d, J=7.8 Hz), 126.8, 120.7, 53.8 (d, J=16.5 Hz), 40.5 (d, J=15.8 Hz), 34.5 (d, J=7.5 Hz), 28.6 (d, J=7.6 Hz), 26.0 (d, J=7.0 Hz), 25.0; ^{31}P NMR (162 MHz, $CDCl_3$, 85% H_3PO_4) δ: −7.69; IR (KBr) v: 3365, 2937, 1660, 1540, 1353, 1317, 1089, 913 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{25}N_3O_5P$ $[M+H]^+$ 478.1526, found 478.1522.

4.3 General procedure for the enantioselective vinylogous allylic alkylation

To a solution of catalyst **C10** (9.6 mg, 10 mol%) and racemic MBH carbonate **2** (0.2 mmol) in 1.0 mL of CH_2Cl_2 was added coumarin **1** (0.2 mmol) at 25 ℃; and the resulting mixture was stirred at this temperature until the reaction completed (monitored by TLC). The mixture was purified by column chromatography on silica gel (petroleum ether/AcOEt as eluent) to give the desired product **3**.

Methyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3a**): White solid, 70.8 mg, 90% yield, 90% *ee*. m.p. 135.9～136.6 ℃; $[\alpha]_D^{25}$ −102.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93 (dd, J=8.0, 1.6 Hz, 1H), 7.74～7.66 (m, 1H), 7.47～7.40 (m, 1H), 7.38 (dd, J=8.4, 1.2 Hz, 1H), 7.28～7.21 (m, 2H), 7.12～7.06 (m, 2H), 6.49 (s, 1H), 5.83 (d, J=1.2 Hz, 1H), 4.37 (dd, J=10.0, 5.2 Hz, 1H), 3.76 (dd, J=13.2, 5.6 Hz, 1H), 3.73 (s, 3H), 3.53 (dd, J=12.8, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.5, 163.3, 156.4, 153.4, 141.0, 136.8, 135.1, 133.7, 129.5, 129.0, 126.7, 126.2, 125.5, 117.9, 117.1, 113.4, 103.2, 52.3, 46.2, 36.6; IR (neat) v: 2951, 2229, 1719, 1600, 1556, 1140, 1105, 756 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{16}{}^{35}ClNNaO_4$ $[M+Na]^+$ 416.0660, found 416.0656. HPLC analysis (V∶V=50∶50, *n*-hexane/EtOH as eluent, 0.9 mL/min): t_R = 8.31 min (major), 12.94 min (minor).

Ethyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3b**): Pale-yellow solid, 72.6 mg, 89% yield, 86% *ee*. m.p. 158.0～158.6 ℃; $[\alpha]_D^{25}$ −91.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.94 (dd, J=8.0, 1.2 Hz, 1H), 7.75～7.66 (m, 1H), 7.48～7.40 (m, 1H), 7.38 (d, J=8.4 Hz, 1H), 7.31～7.19 (m, 2H), 7.09 (d, J=8.4 Hz, 2H), 6.49 (s, 1H), 5.81 (d, J=0.8 Hz, 1H), 4.38 (dd, J=10.0, 5.6 Hz, 1H), 4.25～4.08 (m, 2H), 3.76 (dd, J=12.8, 5.2 Hz, 1H), 3.53 (dd, J=12.8, 10.0 Hz, 1H), 1.24 (t, J=7.2 Hz, 3H); HPLC analysis (V∶V=50∶50, *n*-hexane/EtOH as eluent, 0.9 mL/min): t_R=7.73 min (major), 14.84 min (minor).

Butyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3c**): Pale-yellow oil, 80.2 mg, 92% yield, 87% *ee*. $[\alpha]_D^{25}$ −97.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (dd, J=8.4, 1.6 Hz, 1H), 7.75～7.65 (m, 1H), 7.46～7.40 (m, 1H), 7.38 (dd, J=8.4, 1.2 Hz, 1H), 7.28～7.21 (m, 2H), 7.08 (dt, J=8.4, 2.8 Hz, 2H), 6.49 (s, 1H), 5.81 (d, J=1.2 Hz, 1H), 4.37 (dd, J=10.4, 5.6 Hz, 1H), 4.18～4.04 (m, 2H), 3.75 (dd, J=12.8, 5.2 Hz, 1H), 3.53 (dd, J=13.2, 10.4 Hz, 1H), 1.65～1.54 (m, 2H), 1.38～1.24 (m, 2H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 163.4, 156.4, 153.4, 141.4, 136.9, 135.1, 133.6, 129.5, 128.9, 126.4, 126.2, 125.5, 117.9, 117.2, 113.4, 103.2, 65.2, 46.1, 36.7, 30.4, 19.0, 13.6; IR (neat) v: 2959, 2229, 1712, 1600, 1556, 1139, 1105, 754 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}{}^{35}ClNHO_4$ $[M+H]^+$ 436.1310, found 436.1307; HPLC analysis (V∶V=50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=9.08 min (major), 19.03 min (minor).

Benzyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3d**): White solid, 88.3 mg, 94% yield, 88% *ee*. m.p. 175.4～176.4 ℃; $[\alpha]_D^{25}$ −89.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (dd, J=8.4, 1.6 Hz, 1H), 7.72～7.64 (m, 1H), 7.40～7.28 (m, 5H), 7.25～7.17 (m, 4H), 7.05 (dt, J=8.4, 2.8 Hz, 2H), 6.53 (s, 1H), 5.84 (d, J=1.2 Hz, 1H), 5.18 (d, J=12.4 Hz, 1H), 5.10 (d, J=12.4 Hz, 1H), 4.37 (dd, J=10.4, 5.2 Hz, 1H), 3.75 (dd, J=12.8, 5.2 Hz, 1H), 3.53 (dd, J=12.8, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 163.2, 156.3, 153.4, 141.1, 136.8, 135.2, 135.1, 133.7, 129.5, 129.0, 128.6, 128.4, 128.1, 127.0, 126.2, 125.5, 67.1, 46.2, 36.5; IR (neat) v: 2964, 2229, 1731, 1706,

1179, 1020, 742, 699 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{20}{}^{35}ClNHO_4$ $[M+H]^+$ 470.1154, found 470.1152; HPLC analysis (V∶V = 50 ∶ 50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R = 9.79 min (major), 16.38 min (minor).

tert-Butyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3e**): White solid, 84.5 mg, 97% yield, 93% *ee*. m.p. 149.0～149.5 ℃; $[\alpha]_D^{25}$ −98.5 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (dd, J=8.4, 1.6 Hz, 1H), 7.74～7.66 (m, 1H), 7.46～7.39 (m, 1H), 7.38 (dd, J=8.4, 1.2 Hz, 1H), 7.26～7.21 (m, 2H), 7.10～7.03 (m, 2H), 6.38 (s, 1H), 5.70 (d, J=1.2 Hz, 1H), 4.34 (dd, J=10.0, 5.6 Hz, 1H), 3.73 (dd, J=12.8, 5.2 Hz, 1H), 3.51 (dd, J=12.8, 10.0 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 163.6, 156.4, 153.3, 142.8, 137.4, 135.1, 133.4, 129.4, 128.8, 126.3, 125.6, 125.5, 117.8, 117.3, 113.3, 103.1, 81.7, 45.9, 36.7, 27.8; IR (neat) v: 2980, 2230, 1731, 1600, 1556, 1366, 1138, 755 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}{}^{35}ClNNaO_4$ $[M+Na]^+$ 458.1129, found 458.1133; HPLC analysis (V∶V= 50∶50, *n*-hexane/EtOH as eluent, flow rate: 0.9 mL/min): t_R = 5.84 min (major), 7.89 min (minor).

tert-Butyl (*R*)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylene-3-phenylbutanoate (**3f**): White solid, 68.2 mg, 85% yield, 92% *ee*. m.p. 183.3～183.9 ℃; $[\alpha]_D^{25}$ −74.9 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (dd, J= 8.0, 1.2 Hz, 1H), 7.71～7.64 (m, 1H), 7.43～7.38 (m, 1H), 7.36 (dd, J=8.4, 1.2 Hz, 1H), 7.29～7.17 (m, 3H), 7.14～7.06 (m, 2H), 6.38 (s, 1H), 5.72 (d, J=1.2 Hz, 1H), 4.36 (dd, J=9.6, 5.6 Hz, 1H), 3.74 (dd, J=12.8, 5.6 Hz, 1H), 3.53 (dd, J=12.4, 10.0 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 164.0, 156.6, 153.3, 143.2, 138.9, 134.9, 128.7, 128.0, 127.6, 126.4, 125.4, 117.7, 117.4, 113.4, 103.1, 81.6, 46.5, 36.9, 27.8; IR (neat) v: 2980, 2229, 1735, 1702, 1599, 1557, 1138, 757, 698 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{23}NNaO_4$ $[M+Na]^+$ 424.1519, found 424.1520; HPLC analysis (V∶V=50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R = 7.28 min (major), 8.64 min (minor).

tert-Butyl (*R*)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylene-3-(4-nitrophenyl)butanoate (**3g**): Colorless oil, 88.3 mg, 99% yield, 96% *ee*. $[\alpha]_D^{25}$ −107.8 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.14 (dt, J=8.4, 2.8 Hz, 2H), 7.86 (dd, J=8.4, 2.0 Hz, 1H), 7.77～7.68 (m, 1H), 7.44 (dd, J=7.6, 1.2 Hz, 1H), 7.40 (dd, J=8.0, 1.2 Hz, 1H), 7.34 (dt, J=4.8, 2.8 Hz, 2H), 6.45 (s, 1H), 5.79 (d, J=1.2 Hz, 1H), 4.47 (dd, J=9.6, 5.6 Hz, 1H), 3.80 (dd, J=13.2, 6.0 Hz, 1H), 3.58 (dd, J=13.2, 10.0 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.8, 162.9, 156.2, 153.4, 147.2, 146.7, 141.9, 135.4, 129.0, 126.3, 126.0, 125.6, 123.9, 118.0, 117.1, 113.2, 103.2, 82.1, 46.3, 36.2, 27.8; IR (neat) v: 2980, 2230, 1731, 1715, 1600, 1518, 1344, 1139, 756 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}N_2NaO_6$ $[M+Na]^+$ 469.1370, found 469.1367; HPLC analysis (V∶V = 50 ∶ 50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R = 10.45 min (major), 15.79 min (minor).

tert-Butyl (*R*)-3-(4-bromophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3h**): Colorless oil, 90.3 mg, 94% yield, 94% *ee*. $[\alpha]_D^{25}$ −92.9 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (dd, J=8.0, 1.2 Hz, 1H), 7.74～7.66 (m, 1H), 7.46～7.34 (m, 4H), 7.01 (dt, J=8.4, 2.0 Hz, 2H), 6.38 (s, 1H), 5.70 (d, J=1.2 Hz, 1H), 4.33 (dd, J=10.0, 5.6 Hz, 1H), 3.73 (dd, J=12.8, 5.6 Hz, 1H), 3.51 (dd, J=12.8, 10.0 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.2, 163.6, 156.4, 153.3, 142.7, 138.0, 135.1, 131.8, 129.8, 126.3, 125.7, 125.5, 121.6, 117.9, 117.3, 113.4, 103.2, 81.8, 46.0, 36.6, 27.8; IR (neat) v: 2979, 2229, 1731, 1712, 1601, 1366, 1139, 755 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ $[M+Na]^+$ 502.0624, found 502.0625; HPLC analysis (V∶V= 50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R = 8.87 min (major), 11.73 min (minor).

tert-Butyl (*R*)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-3-(4-fluorophenyl)-2-methylenebutanoate (**3i**): Colorless oil, 76.3 mg, 91% yield, 90% *ee*. $[\alpha]_D^{25}$ −85.8 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (dd, J=8.0, 1.6 Hz, 1H), 7.74～7.65 (m, 1H), 7.45～7.39 (m, 1H), 7.38 (dd, J=8.4, 1.2 Hz, 1H), 7.14～7.03 (m, 2H), 6.99～6.91 (m, 2H), 6.38 (s, 1H), 5.71 (d, J=1.6 Hz, 1H), 4.34 (dd, J= 10.0, 5.2 Hz, 1H), 3.72 (dd, J=12.8, 5.6 Hz, 1H), 3.50 (dd, J=12.8, 10.4 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.3, 163.7, 162.0 (d, J=245.1 Hz), 156.4, 153.3, 143.1, 135.0, 134.6, 129.7 (d, J=8.0 Hz), 126.3, 125.5, 125.2, 117.9, 117.3, 115.6 (d, J=21.4 Hz), 113.3, 103.2, 81.7, 45.9, 36.9, 27.8; IR (neat) v: 2978, 2229, 1731, 1711, 1600, 1366, 1138, 754 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}FNKO_4$ $[M+K]^+$ 458.1165, found 458.1168; HPLC analysis (V∶V = 50 ∶ 50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R = 5.74 min (major), 7.55 min (minor).

tert-Butyl (*R*)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylene-3-(*p*-tolyl)butanoate (**3j**): Colorless oil, 66.5 mg, 80% yield, 93% *ee*. $[\alpha]_D^{25}$ −52.0 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.97 (dd, J=8.4, 1.6 Hz, 1H), 7.71～7.64 (m, 1H), 7.45～7.38 (m, 1H), 7.36 (dd, J=8.4, 1.2 Hz, 1H), 7.06 (d, J=8.0 Hz, 2H), 6.99 (dd, J=6.4, 2.4 Hz, 2H), 6.35 (s, 1H), 5.69 (d, J=1.2 Hz, 1H), 4.34 (dd, J=9.6, 5.6 Hz, 1H), 3.72 (dd, J=12.8, 5.6 Hz, 1H), 3.51 (dd, J=12.8, 10.0 Hz, 1H), 2.28 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 164.1, 156.7, 153.3, 143.4, 137.3, 135.7, 134.8, 129.4, 127.9, 126.5, 125.4, 117.7, 117.5, 113.5, 103.1, 81.5, 46.2, 37.1, 27.8, 21.0; IR (neat, cm^{-1}): v 2977, 2229, 1731, 1712, 1600, 1327, 1137, 755. HRMS (ESI) calcd for $C_{26}H_{25}NNaO_4$ $[M+Na]^+$ 438.1676, found 438.1676; HPLC analysis (V∶V=50∶50, *n*-hexane/EtOH as eluent, 0.9 mL/min): t_R = 5.75 min (major), 6.83 min (minor).

tert-Butyl (*R*)-3-(3-bromophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3k**): Colorless oil, 87.4 mg, 91% yield, 90% *ee*; $[\alpha]_D^{25}$ −59.5 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.86 (dd, J=8.0, 1.6 Hz, 1H), 7.74～7.65 (m, 1H), 7.46～7.32 (m, 3H), 7.26 (t, J= 2.0 Hz, 1H), 7.15 (t, J=7.6 Hz, 1H), 7.10 (dt, J=8.0, 1.6

Hz, 1H), 6.40 (s, 1H), 5.71 (d, J=1.6 Hz, 1H), 4.32 (dd, J=10.0, 6.4 Hz, 1H), 3.72 (dd, J=12.8, 6.0 Hz, 1H), 3.52 (dd, J=12.8, 9.6 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.1, 163.5, 156.4, 153.4, 142.5, 141.5, 135.1, 131.0, 130.7, 130.2, 126.7, 126.2, 126.0, 125.5, 122.7, 117.9, 117.3, 113.3, 103.2, 81.8, 46.2, 36.5, 27.8; IR (neat) v: 2976, 2229, 1730, 1712, 1600, 1556, 136 6, 1138, 754 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ $[M+Na]^+$ 502.0624, found 502.0622; HPLC analysis (V∶V=90∶10, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=21.63 min (major), 25.98 min (minor).

tert-Butyl (*R*)-3-(2-bromophenyl)-4-(3-cyano-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3l**): White solid, 67.2 mg, 70% yield, 98% *ee*. m.p. 176.7～177.3 ℃; $[\alpha]_D^{25}$ −84.9 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.83 (dd, J=8.8, 1.6 Hz, 1H), 7.71～7.63 (m, 1H), 7.48 (dd, J=7.6, 1.6 Hz, 1H), 7.43～7.33 (m, 4H), 7.10 (td, J=8.0, 1.6 Hz, 1H), 6.47 (s, 1H), 5.73 (d, J=1.6 Hz, 1H), 4.89 (dd, J=10.4, 5.2 Hz, 1H), 3.76 (dd, J=12.8, 5.2 Hz, 1H), 3.44 (dd, J=12.8, 10.4 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 163.0, 156.5, 153.2, 143.0, 138.9, 134.9, 133.0, 129.1, 129.0, 128.1, 126.0, 125.5, 125.3, 125.2, 118.0, 117.6, 113.2, 103.2, 81.7, 44.2, 36.9, 27.7; IR (neat) v: 2981, 2226, 1720, 1598, 1555, 1142, 1081, 759 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ $[M+Na]^+$ 502.0624, found 502.0623; HPLC analysis (V∶V=90∶10, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=23.76 min (major), 26.29 min (minor).

tert-Butyl (*R*)-4-(6-bromo-3-cyano-2-oxo-2*H*-chromen-4-yl)-3-(4-chlorophenyl)-2-methylenebutanoate (**3m**): Pale-yellow solid, 72.1 mg, 70% yield, 94% *ee*. m.p. 168.9～169.4 ℃; $[\alpha]_D^{25}$ −217.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (dd, J=7.2, 2.0 Hz, 1H), 7.56 (dd, J=8.0, 2.0 Hz, 2H), 7.29～7.22 (m, 2H), 7.08 (dt, J=8.4, 2.8 Hz, 2H), 6.37 (s, 1H), 5.66 (d, J=1.2 Hz, 1H), 4.29 (dd, J=10.0, 5.6 Hz, 1H), 3.70 (dd, J=12.8, 5.6 Hz, 1H), 3.48 (dd, J=13.2, 10.0 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.4, 163.1, 155.8, 153.4, 142.6, 137.1, 133.6, 129.6, 129.5, 129.1, 129.0, 127.3, 126.0, 121.1, 116.3, 113.2, 103.2, 81.9, 46.0, 36.8, 27.8; IR (neat) v: 2978, 2229, 1729, 1712, 1596, 1545, 1366, 1138, 824 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{21}{}^{79}Br^{35}ClNNaO_4$ $[M+Na]^+$ 536.0234, found 536.0226; HPLC analysis (V∶V=50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=6.49 min (major), 10.85 min (minor).

tert-Butyl (*R*)-4-(7-bromo-3-cyano-2-oxo-2*H*-chromen-4-yl)-3-(4-chlorophenyl)-2-methylenebutanoate (**3n**): White solid, 74.1 mg, 72% yield, 95% *ee*. m.p. 168.0～170.5 ℃; $[\alpha]_D^{25}$ −212.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dd, J=7.6, 1.6 Hz, 1H), 7.56 (dd, J=8.0, 2.0 Hz, 2H), 7.29～7.22 (m, 2H), 7.08 (dt, J=8.4, 2.8 Hz, 2H), 6.37 (s, 1H), 5.66 (d, J=1.2 Hz, 1H), 4.29 (dd, J=10.0, 5.6 Hz, 1H), 3.70 (dd, J=12.8, 5.6 Hz, 1H), 3.48 (dd, J=12.8, 10.0 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.3, 163.1, 155.8, 153.4, 142.6, 137.1, 133.6, 129.6, 129.5, 129.0, 128.9, 127.3, 126.0, 121.0, 116.3, 113.2, 103.1, 81.9, 46.0, 36.7, 27.8; IR (neat) v: 2978, 2229, 1732, 1712, 1596, 1545, 1366, 1138, 823 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{21}{}^{79}Br^{35}ClNNaO_4$ $[M+Na]^+$ 536.0234, found 536.0236; HPLC analysis (V∶V=50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=6.53 min (major), 10.88 min (minor).

tert-Butyl (*R*)-3-(4-chlorophenyl)-4-(3-cyano-7-methoxy-2-oxo-2*H*-chromen-4-yl)-2-methylenebutanoate (**3o**): Yellow solid, 77.3 mg, 83% yield, 90% *ee*. m.p. 160.9～161.4 ℃; $[\alpha]_D^{25}$ −89.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, J=2.4 Hz, 1H), 7.31～7.22 (m, 4H), 7.11 (dt, J=8.4, 2.8 Hz, 2H), 6.36 (s, 1H), 5.63 (d, J=1.2 Hz, 1H), 4.38 (dd, J=10.8, 5.2 Hz, 1H), 3.94 (s, 3H), 3.74 (dd, J=12.8, 5.2 Hz, 1H), 3.47 (dd, J=12.8, 10.4 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 163.3, 156.8, 156.7, 147.8, 142.8, 136.9, 133.6, 129.7, 128.9, 126.0, 123.3, 118.8, 117.6, 113.7, 108.2, 103.3, 81.9, 56.2, 46.1, 37.1, 27.9; IR (neat) v: 2976, 2229, 1728, 1702, 1562, 1280, 1165, 1040, 836 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{24}{}^{35}ClNNaO_5$ $[M+Na]^+$ 488.1235, found 488.1236; HPLC analysis (V∶V=50∶50, *n*-hexane/*i*-PrOH as eluent, 0.9 mL/min): t_R=6.43 min (major), 9.13 min (minor).

Supporting Information Copies of NMR spectra for phosphines **C9** and **C10**, as well as NMR spectra and HPLC chromatograms for products **3**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

References

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