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PAPER

Highly enantioselective [4 + 2] cycloadditions of allenoates and dual activated olefins catalyzed by *N*-acyl aminophosphines†

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An asymmetric organocatalytic [4 + 2] cycloaddition between α-substituted allenoates and dual activated olefins using bifunctional *N*-acyl aminophosphine catalysts is described. The use of 2-cyano acrylate derived olefins led to the first successful incorporation of an electrophile derived from an aliphatic aldehyde into this reaction.

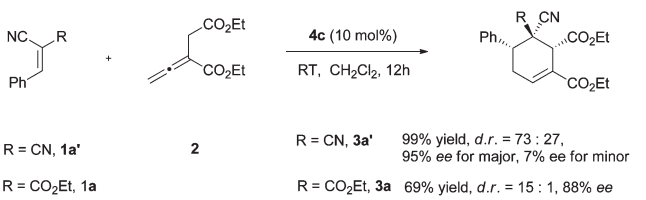
Introduction

Since Lu and co-workers' pioneering studies,[1] the phosphine-catalyzed dipole cycloaddition reaction has made tremendous progress to become a powerful strategy for the construction of a range of synthetically valuable cyclic structures from easily accessible starting materials.[2] On one hand, the incorporation of electrophiles such as electron-deficient C=C, C=N, C=O into this reaction enabled the synthesis of both carbo- and heterocycles.[3] On the other hand, based on mechanistical analysis of the proposed zwitterionic allenoate–phosphine intermediate, rational modifications in the allenoate or its surrogates have led to even more interesting and useful scope extensions of this methodology.[4–6] Particularly, Kwon and co-workers initiated the utilization of suitably substituted allenoates as four-carbon donors in this reaction, allowing for the construction of six-membered ring structures through [4 + 2] cycloadditions with this methodology,[5] which might serve as a complementary alternative to the Diels–Alder reaction. In contrast to this impressive progress, the development of asymmetric variants in this field somewhat lags behind as most successful works in this regard have been restricted to asymmetric [3 + 2] cycloadditions.[7,8]

In 2005, two years after Kwon's discovery of the non-enantioselective reaction,[5a] Fu and Wurz reported the first asymmetric α-substituted allenoate–imine [4 + 2] cycloaddition to give chiral multifunctional tetrahydropyridines catalyzed by a chiral monodentate phosphine.[5c] Recently, our group also realized this asymmetric transformation using simple amino acids-derived *N*-acyl aminophosphine catalysts.[9b] However, reports on the all-carbon version of this asymmetric [4 + 2] cycloaddition leading to chiral multifunctional cyclohexenes remains very rare,[10] although its non-enantioselective version has also been reported by Kwon & Tran in 2007.[5b] In view of the great importance of the resulting chiral cyclohexenes in the total synthesis of numerous natural and biologically active compounds,[2g] the development of an enantioselective version of this reaction is thus highly desirable. In addition, only the use of olefins derived from malononitriles and aryl aldehydes has been reported as successful electrophiles in this reaction[11] and thus there is still a need to test the suitability of other dual activated olefins, especially those capable of tolerating aliphatic aldehyde structures for this reaction. As a follow-up of our ongoing program to extend the application of these chiral *N*-acyl aminophosphine catalysts in asymmetric synthesis,[9] we present herein highly diastereoselective and enantioselective [4 + 2] cycloadditions between allenoates and dual activated olefins catalyzed by these kind of catalysts.

Results and discussion

Dual activated olefins were first introduced to [3 + 2] cycloadditions by Lu and co-workers to settle the issue of regioselectivity.[3g] In our preliminary study on the asymmetric version of the



Scheme 1 Preliminary study on the asymmetric [4 + 2] cycloaddition of α-substituted allenoate **2** and dual activated olefins.

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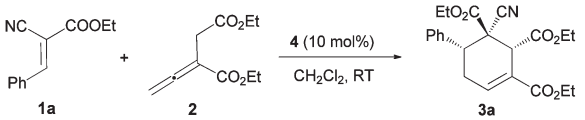
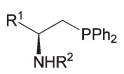
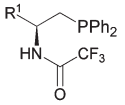
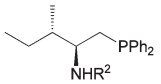
†Electronic supplementary information (ESI) available: Experimental details, copies of NMR and HPLC spectra for the cycloaddition products, X-ray crystallographic analysis of the cycloadduct **3i**. CCDC 860051. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25295c

Table 1 Screening of catalyst for the asymmetric [4 + 2] cycloaddition[a]





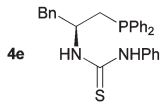




4a: R^1/R^2 = Bn/Ac
4b: R^1/R^2 = Bn/3,5-bisCF_3benzoyl
4c: R^1/R^2 = *t*-Bu/3,5-bisNO_2benzoyl
4d: R^1/R^2 = *t*-Bu/3,5-bisClbenzoyl

4f: R^1= Bn
4g:R^1= 2-(*S*)-*sec*-Bu
4h:R^1= *t*-Bu
4i: R^1= naphthalen-2-ylmethyl

4j: R^2 =Boc
4k: R^2 = 3,5-bisFbenzoyl
4l: R^2 = 3,5-bisCF_3benzoyl
4m:R^2 = 3,5-bisClbenzoyl



4e

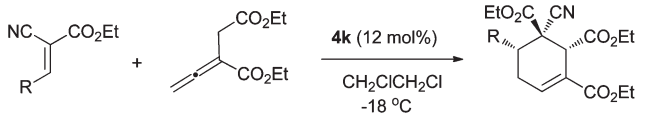
Entry	Catalyst	Time/h	Yield[b] (%)	Dr[c]	ee[d] (%)
1	**4a**	24	79	14 : 1	85
2	**4b**	12	69	15 : 1	88
3	**4c**	12	54	19 : 1	90
4	**4d**	6	91	14 : 1	92
5	**4e**	24	Trace	—	—
6	**4f**	24	35	14 : 1	83
7	**4g**	24	54	19 : 1	85
8	**4h**	12	85	19 : 1	52
9	**4i**	16	25	17 : 1	81
10	**4j**	6	82	15 : 1	73
11	**4k**	1	94	15 : 1	92
12	**4l**	2	94	15 : 1	90
13	**4m**	2	94	15 : 1	91
14[e]	**4k**	4	94	19 : 1	96

[a] All reactions were carried out with **1a** (0.08 mmol) and 2-(2-ethoxy-2-oxoethyl)-2,3-butadienoate **2** (0.16 mmol) in the presence of **4** (0.008 mmol) in 0.8 mL of CH_2Cl_2. [b] Yields of isolated products. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] The reaction was run with 12 mol% of **4k** at −18 °C in DCE.

[4 + 2] reaction using catalyst **4c** (Scheme 1), exclusive regioselectivity was observed with α-substituted allenoate **2**, which is also consistent with the finding of Kwon and co-workers.[5b] To our delight, with phenylidenemalononitrile **1a′**, the reaction occurred smoothly to give the functionalized cyclohexene product in excellent yield and enantioselectivity using catalyst **4c** (see Table 1 for its structure), albeit with unsatisfactory diastereoselectivity. However, further optimizing efforts using different catalysts to improve the diastereoselectivity with this substrate did not give satisfactory results (see the ESI† for details). We then turned our attention to the use of (*E*)-ethyl 2-cyano-3-phenylacrylate **1a**, and similarly to the observation in our previous work on the asymmetric [3 + 2] annulation reaction with this type of substrate,[9a] excellent diastereoselectivity was obtained. Moreover, it's assumed that the two different electron-deficient substituents in this type of substrate may enable different selective transformations to other useful structures. Consequently, these types of dual activated olefins were used for further studies.

Using the reaction between (*E*)-ethyl 2-cyano-3- phenylacrylate **1a** and allenoate **2** as the model reaction, we first screened a

Table 2 Enantioselective [4 + 2] cycloadditions of allenoate **2** with dual activated olefins **1** catalyzed by **4k**[a]

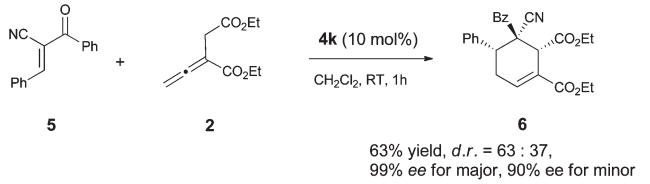


Entry	**1**, R	Product	Time/h	Yield[b] (%)	ee[c] (%)
1	**1a**, Ph	**3a**	4	94	96
2	**1b**, isopropyl	**3b**	3	92	97
3	**1c**, 2-naphthyl	**3c**	3	95	95
4	**1d**, 4-BrC_6H_4	**3d**	4	86	97
5	**1e**, 4-ClC_6H_4	**3e**	6	99	97
6	**1f**, 4-FC_6H_4	**3f**	3	80	97
7	**1g**, 3-BrC_6H_4	**3g**	4	77	95
8	**1h**, 3-ClC_6H_4	**3h**	12	87	93
9[d]	**1i**, 2-BrC_6H_4	**3i**	0.4	88	89
10[d]	**1j**, 2-FC_6H_4	**3j**	0.2	81	89
11	**1k**, 4-MeOC_6H_4	**3k**	2.5	96	95
12	**1l**, 3-MeOC_6H_4	**3l**	6	88	96
13	**1m**, 2-thienyl	**3m**	4	87	93
14	**1n**, piperonyl	**3n**	4	94	96

[a] Reactions were carried out with **1** (0.08 mmol) and **2** (0.16 mmol) in 0.8 mL of 1,2-dichloroethane. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] The reaction was conducted at room temperature.

series of catalysts with different chiral backbones and NH functionality (Table 1). Some trends in the relationship between the reaction results and the catalyst structures could be observed: the use of benzoyl group in the NH moiety is superior to the use of other protecting groups such as Boc, trifluoromethylacetyl and thiourea, which indicates the significant role of H-bonding interaction in this system; catalysts derived from L-isoleucine and L-*t*-butylleucine showed apparent advantage over other amino acid based catalysts, especially in terms of chemical yield (entries 4, 11–13). These findings are similar to those observed in our previous study on the [3 + 2] cycloadditions using these kinds of catalyst.[9a] As a compromise between catalyst availability and catalytic activity, catalyst **4k** derived from L-isoleucine was selected for further optimization of other reaction parameters (entry 13). Further investigation on temperature and solvent effect (see the ESI† for details) led to the optimum conditions for this reaction as being 12 mol% of **4k** in $ClCH_2CH_2Cl$ at −18 °C (entry 14).

Having identified the optimal reaction conditions, the scope of the asymmetric [4 + 2] cycloaddition with regard to various dual activated olefins was evaluated.[12] As illustrated in Table 2, substrates with electron-withdrawing or electron-donating substituents at the *para*- or *meta* position of the benzene ring were well tolerated to provide a series of densely functionalized chiral cyclohexene derivatives with three contiguous stereogenic centers in high yields, good to excellent enantioselectivities and diastereoselectivities. For *ortho*-substituted substrates, probably due to steric reasons, the reaction needed to be run at an elevated temperature (RT) to give satisfactory yields with a slight drop in the enantioselectivity (Table 2, entries 9 and 10). Notably, in all the cases examined, excellent diastereoselectivity (dr = 19 : 1) was invariably observed, which showed an obvious advantage



Scheme 2 Asymmetric [4 + 2] cycloaddition of oxodiene **5** and α-substituted allenoate **2**.

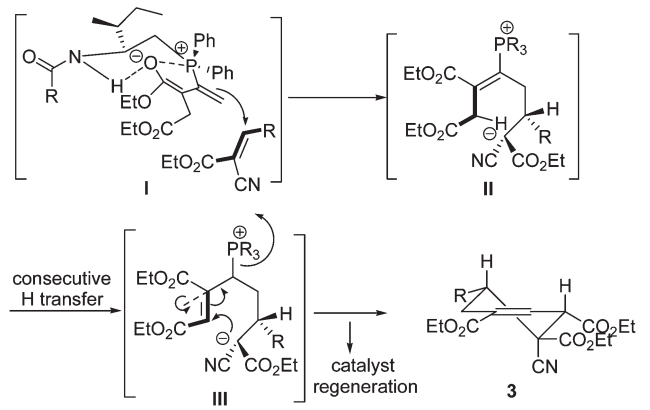


Fig. 1 A possible working mechanistic model.

over the use of olefins derived from malononitrile.[13] Especially, the very challenging substrate **1b** derived from an aliphatic aldehyde also successfully coupled with the allenoate rapidly, and the synthetically useful isopropyl cyclohexene product could be obtained in 92% yield and 97% ee (Table 2, entry 2). This result stands out as previous studies using olefins derived from aliphatic aldehydes and malononitrile failed to undergo this reaction.[5b,10] At present, we're unable to provide a rationale for this difference. It's also worth mentioning that even in the corresponding more studied [3 + 2] systems, successful examples using electrophiles derived from an aliphatic aldehyde are also very limited.[8h] The absolute configuration of the cycloadduct **3i** was determined by X-ray crystallographic analysis to be 1*R*, 2*R*, 3*R*.† The configurations of other products derived from 2-cyano acrylates were assigned by analogy.[14]

Besides 2-cyano acrylate derived activated olefins, oxodiene **5** also worked in the reaction at RT to give compound **6** with an excellent level of enantiocontrol, albeit with a poor diastereoselectivity (Scheme 2).[15]

In light of previous related studies,[5,8a,9] a tentative mechanism was proposed to explain the stereochemical results of the reaction. As illustrated in Fig. 1, a cyclic six-membered pretransition state **I**,[16] which was modified from the one originally proposed by Miller and Cowen,[8a] was held responsible for the enantioselectivity of the first addition step favoring *Re*-face attack on activated olefins. The first chiral center created in this step would induce the chirality of the second one formed in the following step. Then after consecutive proton transfers,[5] intermediate **II** would be transformed to **III** to undergo a S_N2' reaction to close the ring and regenerate the catalyst. The retention of the *E*/*Z* configuration of the dual activated olefins during this reaction is consistent with previous observations in related reactions.[7a,b] The relatively bulkier R and ester groups in the product **3** prefer to take equatorial positions, namely as in the major diastereoisomer product.

Conclusions

In conclusion, we have successfully achieved the asymmetric [4 + 2] cycloaddition of α-substituted buta-2,3-dienoate and activated alkenes, providing a range of synthetically valuable cyclohexene structures bearing three contiguous chiral centers with good to excellent diastereoselectivities and enantioselectivities. This work, together with our previous studies, demonstrates the great potential of our *N*-acyl aminophosphine catalysts in asymmetric phosphine-mediated reactions. Further studies towards a deep understanding of the reaction mechanism as well as extending the application of these readily available and air-stable phosphine catalysts are underway.

Experimental

General methods

The ^{1}H NMR spectra were recorded on a DPX-300 or Varian EM-360 (300 MHz). ^{13}C NMR spectra were recorded on a DPX-300 (300 MHz) or DPX-400 (400 MHz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS equipment using chiral columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm. IR spectra were recorded on a Perkin-Elmer 983G instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

General procedure for the asymmetric [4 + 2] cycloadditions

To a flame-dried test tube with a magnetic stir bar was added α-cyanoacrylates or analogs **1** (0.08 mmol), catalyst **4** (0.0096 mmol) and 1,2-dichloroethane (0.8 mL) at room temperature. The solution was allowed to stir for 10 min at −18 °C before α-substituted 2,3-butadienoate **2** (0.16 mmol) was added *via* micro-syringe in one portion, which was followed by vigorously stirring at −18 °C. After the reaction was complete (indicated by TLC), the mixture was directly purified by column chromatography on silica gel (petroleum ether–ethyl acetate as the eluent) to furnish the corresponding product.

(1*R*,3*S*)-Diethyl 2,2-dicyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-3,4-dicarboxylate (3a′)[5b]

99% yield as a 73 : 27 mixture of *cis* and *trans* isomers; *cis* isomer: Colorless, crystalline solid. m.p. = 101–103 °C; $[\alpha]_D^{26}$ −97.7 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 5H), 7.40–7.38 (m, 1H), 4.36 (d, *J* = 18.6 Hz, 2H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.17 (m, 1H), 3.28 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.13 (dd, *J* = 20.8, 12.0 Hz, 1H), 2.75 (d, *J* = 19.6 Hz, 1H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H);

enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H column, hexane–*i*-PrOH 80 : 20, flow rate 0.60 mL min^{-1}; t_{major} = 18.4 min, t_{minor} = 27.5 min, λ = 254 nm).

Trans isomer: Light yellow solid. m.p. = 120–122 °C; $[\alpha]_D^{26}$ −24.3 (c = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47–7.42 (m, 5H), 7.40–7.38 (m, 1H), 4.39–4.21 (m, 5H), 3.84 (dd, J = 10.9, 5.6 Hz, 1H), 3.03–2.93 (ddt, J = 20.2, 11.1, 2.1 Hz, 1H), 2.88–2.77 (dt, J = 20.2, 5.2 Hz, 1H), 1.37 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H); enantiomeric excess: 7%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.75 mL min^{-1}; t_{major} = 12.8 min, t_{minor} = 8.9 min, λ = 254 nm).

(1*R*,2*R*,3*R*)-Triethyl 2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3a)

Yield: 94%; Viscous, colorless oil; $[\alpha]_D^{26}$ −76.4 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.34–7.32 (m, 3H), 7.19 (m, 1H), 4.43 (m, 1H), 4.29–4.11 (m, 4H), 3.99 (q, J = 7.0 Hz, 2H), 3.28 (dd, J = 12.3, 5.0 Hz, 1H), 3.08 (dd, J = 19.3, 12.8 Hz, 1H), 2.62 (d, J = 19.3 Hz, 1H), 1.31–1.24 (m, 6H), 0.93 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.7, 166.9, 165.7, 138.5, 136.7, 128.7, 128.6, 128.4, 126.8, 115.3, 62.9, 61.9, 61.0, 53.6, 50.1, 46.3, 29.6, 14.1, 13.9, 13.5; **IR (film)**: 2984, 2931, 2240, 1744, 1661, 1456, 1372, 1241, 1184, 1093, 1037, 738; **HRMS (ESI)**: calcd for $[M + Na]^+$ ($C_{22}H_{25}NaNO_6$) requires 422.1580, found 422.1577; enantiomeric excess: 96%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.75 mL min^{-1}; t_{major} = 15.0 min, t_{minor} = 10.4 min, λ = 220 nm).

(1*R*,2*R*,6*R*)-Triethyl 1-cyano-6-isopropylcyclohex-3-ene-1,2,3-tricarboxylate (3b)

Yield: 92%; Viscous, colorless oil; $[\alpha]_D^{26}$ −10.0 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (m, 1H), 4.42–4.32 (m, 2H), 4.25–4.16 (m, 5H), 2.51 (m, 2H), 2.10 (dt, J = 10.5, 4.3 Hz, 1H), 1.84 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.28–1.25 (m, 6H), 1.09 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.8, 167.8, 165.8, 138.9, 126.5, 115.6, 63.2, 61.9, 60.9, 51.8, 50.9, 45.3, 28.9, 22.9, 22.5, 16.5, 14.1, 14.0, 13.9; **IR (film)**: 2979, 2240, 1745, 1662, 1468, 1372, 1233, 1180, 1110, 1069, 1035, 860, 760, 728; **HRMS (ESI)**: calcd for $[M + Na]^+$ ($C_{19}H_{27}NaNO_6$) requires 388.1736, found 388.1735; enantiomeric excess: 97%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.65 mL min^{-1}; t_{major} = 10.5 min, t_{minor} = 9.2 min, λ = 254 nm).

(1*R*,2*R*,6*R*)-Triethyl 1-cyano-6-(naphthalen-2-yl)cyclohex-3-ene-1,2,3-tricarboxylate (3c)

Yield: 95%; Viscous, colorless oil; $[\alpha]_D^{26}$ −102.2 (c = 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83–7.82 (m, 4H), 7.53–7.48 (m, 3H), 7.22 (m, 1H), 4.48 (m, 1H), 4.29–4.16 (m, 4H), 3.93–3.84 (m, 2H), 3.45 (dd, J = 12.3, 4.2 Hz, 1H), 3.20 (m, 1H), 2.68 (dt, J = 19.3, 4.5 Hz, 1H), 1.33–1.23 (m, 6H), 0.77 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.7, 167.0, 165.8, 138.5, 134.1, 133.3, 133.2, 128.6, 128.1, 127.9, 127.6, 126.9, 126.5, 125.7, 115.4, 63.0, 62.0, 61.1, 53.6, 50.2, 46.4, 29.7, 14.2, 13.9, 13.4; **IR (film)**: 3057, 2983, 2933, 2245, 1748, 1660, 1600, 1466, 1372, 1265, 1091, 1030, 860; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{26}H_{27}NaNO_6$) requires 472.1736, found 472.1730; enantiomeric excess: 95%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 43.6 min, t_{minor} = 20.6 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 4′-bromo-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3d)

Yield: 86%; Viscous, colorless oil; $[\alpha]_D^{26}$ −69.1 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.17 (m, 1H), 4.40 (m, 1H), 4.28–4.15 (m, 4H), 4.03 (q, J = 7.1 Hz, 2H), 3.26 (dd, J = 12.3, 4.2 Hz, 1H), 3.03 (m, 1H), 2.61 (dt, J = 19.3, 4.5 Hz, 1H), 1.31–1.23 (m, 6H), 1.01 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 166.8, 165.6, 138.1, 135.7, 131.9, 130.1, 126.9, 122.8, 115.1, 63.2, 62.0, 61.1, 53.3, 50.1, 45.7, 29.4, 14.1, 13.9, 13.5; **IR (film)**: 2983, 2933, 2250, 1745, 1660, 1589, 1489, 1372, 1239, 1183, 1080, 1033, 855, 827, 765; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{22}H_{24}NaBrNO_6$) requires 500.0685, found 500.0679; enantiomeric excess: 97%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 29.2.0 min, t_{minor} = 17.7 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 4′-chloro-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3e)

Yield: 99%; Viscous, colorless oil; $[\alpha]_D^{26}$ −79.3 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.19 (m, 1H), 4.42 (m, 1H), 4.28–4.15 (m, 4H), 4.04 (q, J = 7.0 Hz, 2H), 3.28 (dd, J = 12.3, 4.1 Hz, 1H), 3.04 (dd, J = 20.5, 10.8 Hz, 1H), 2.62 (dt, J = 19.3, 4.5 Hz, 1H), 1.32–1.24 (m, 6H), 1.01 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 166.8, 165.6, 138.0, 135.2, 134.7, 129.8, 129.0, 127.0, 115.1, 63.2, 62.0, 61.1, 53.4, 50.1, 45.6, 29.6, 14.1, 13.9, 13.6; **IR (film)**: 2983, 2929, 2245, 1743, 1660, 1494, 1466, 1372, 1239, 1184, 1094, 1026, 833, 765, 733; **HRMS (ESI)**: calcd for $[M + Na]^+$ ($C_{22}H_{24}ClNaNO_6$) requires 456.1190, found 456.1188; enantiomeric excess: 97%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 22.2 min, t_{minor} = 15.1 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 2-cyano-4′-fluoro-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3f)

Yield: 80%; Viscous, colorless oil; $[\alpha]_D^{26}$ −90.7 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.18 (m, 1H), 7.06–7.01 (m, 2H), 4.41 (m, 1H), 4.28–4.15 (m, 4H), 4.02 (q, J = 7.0 Hz, 2H), 3.29 (dd, J = 12.3, 4.3 Hz, 1H), 3.03 (m, 1H), 2.61 (dt, J = 19.4, 4.5 Hz, 1H), 1.31–1.23 (m, 6H), 1.00 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.6, 166.9, 165.7, 164.1 (d, J_{C-F} = 247 Hz), 138.2, 132.5 (d, J_{C-F} = 3.7 Hz), 130.2 (d, J_{C-F} = 8.0 Hz), 126.9, 115.8 (d, J_{C-F} = 21.8 Hz), 115.2, 63.1, 62.0, 61.1, 53.6, 50.1, 45.5, 29.7, 14.1, 13.9, 13.6;

^{19}F NMR ($CDCl_3$, 282 MHz) δ −113.5; **IR (film)**: 2984, 2934, 2245, 1744, 1660, 1605, 1512, 1466, 1373, 1237, 1183, 1098, 1031, 843, 766, 730; **HRMS (ESI)**: calcd for $[M + Na]^+$ ($C_{22}H_{24}FNaNO_6$) requires 440.1485, found 440.1489; enantiomeric excess: 97%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 18.8 min, t_{minor} = 14.3 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 3′-bromo-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3g)

Yield: 77%; Viscous, colorless oil; $[\alpha]_D^{26}$ −115.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.26–7.22 (m, 1H), 7.17–7.16 (m, 1H), 4.42 (m, 1H), 4.28–4.15 (m, 4H), 4.05 (m, 2H), 3.25 (dd, *J* = 12.6, 4.3 Hz, 1H), 3.03 (dd, *J* = 19.3, 10.8 Hz, 1H), 2.61 (dt, *J* = 19.1, 4.5 Hz, 1H), 1.31–1.23 (m, 6H), 1.01 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 166.8, 165.6, 138.9, 138.0, 131.9, 131.8, 130.4, 126.9, 126.7, 122.7, 115.0, 63.2, 62.1, 61.1, 53.4, 50.1, 45.8, 29.4, 14.1, 13.9, 13.6; **IR (film)**: 2982, 2246, 1744, 1661, 1473, 1372, 1304, 1241, 1184, 1031, 858, 790; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{22}H_{24}NaBrNO_6$) requires 500.0685, found 500.0683; enantiomeric excess: 95%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 28.4 min, t_{minor} = 15.7 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 3′-chloro-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3h)

Yield: 87%; Viscous, colorless oil; $[\alpha]_D^{26}$ −84.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.33 (m, 4H), 7.17 (m, 1H), 4.42 (m, 1H), 4.28–4.15 (m, 4H), 4.06–3.99 (m, 2H), 3.26 (dd, *J* = 12.3, 4.2 Hz, 1H), 3.05 (dd, *J* = 20.8, 12.8 Hz, 1H), 2.62 (dt, *J* = 18.9, 4.5 Hz, 1H), 1.31–1.25 (m, 6H), 1.00 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 166.8, 165.6, 138.7, 138.0, 134.6, 130.1, 128.9, 128.8, 127.0, 126.3, 115.0, 63.2, 62.1, 61.1, 53.4, 50.1, 45.8, 29.4, 14.1, 13.9, 13.6; **IR (film)**: 2982, 2928, 2856, 2266, 1746, 1660, 1596, 1572, 1473, 1441, 1372, 1238, 1184, 1089, 1028, 858, 792, 700; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{22}H_{24}ClNaNO_6$) requires 456.1190, found 456.1186; enantiomeric excess: 93%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 25.1 min, t_{minor} = 14.7 min, λ = 220 nm).

(1*S*,2*R*,3*R*)-Triethyl 2′-bromo-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3i)

Yield: 88%; Colorless, crystalline solid. m.p. = 88–90 °C; $[\alpha]_D^{26}$ −91.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.37 (t, *J* = 7.1 Hz, 1H), 7.18–7.14 (m, 2H), 4.45 (m, 1H), 4.27–4.20 (m, 4H), 4.11–4.06 (m, 1H), 4.02–3.97 (m, 2H), 2.83 (dd, *J* = 19.3, 12.0 Hz, 1H), 2.67 (dt, *J* = 19.6, 6.0 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.4, 166.0, 165.7, 138.6, 136.7, 133.5, 129.8, 128.0, 127.2, 125.0, 122.7, 115.8, 63.2, 62.0, 61.1, 52.3, 50.8, 44.1, 30.7, 14.1, 13.9, 13.5; **IR (film)**: 2983, 2240, 1746, 1658, 1471, 1371, 1303, 1238, 1184, 1089, 1029, 856, 758; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{22}H_{24}NaBrNO_6$) requires 500.0685, found 500.0681; enantiomeric excess: 89%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.60 mL min^{-1}; t_{major} = 20.1 min, t_{minor} = 12.4 min, λ = 220 nm).

(1*S*,2*R*,3R)-Triethyl 2-cyano-2′-fluoro-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3j)

Yield: 81%; Viscous, colorless oil; $[\alpha]_D^{26}$ −71.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78–7.74 (t, *J* = 7.3 Hz, 1H), 7.33–7.27 (m, 1H), 7.20–7.17 (m, 2H), 7.07–7.02 (t, *J* = 9.1 Hz, 1H), 4.46 (m, 1H), 4.28–4.16 (m, 4H), 4.08–3.99 (m, 2H), 3.82 (dd, *J* = 12.3, 4.3 Hz, 1H), 3.82 (dd, *J* = 19.3, 10.8 Hz, 1H), 2.61 (dt, *J* = 19.4, 4.5 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 166.4, 165.7, 161.4 (d, J_{C-F} = 248 Hz), 138.4, 130.0 (d, J_{C-F} = 8.8 Hz), 128.4 (d, J_{C-F} = 2.9 Hz), 127.1, 124.8 (d, J_{C-F} = 3.7 Hz), 124.4 (d, J_{C-F} = 14.0 Hz), 115.8 (d, J_{C-F} = 23.4 Hz), 115.5, 63.1, 62.0, 61.1, 52.7, 50.4, 37.3, 30.0, 14.1, 13.9, 13.5; **^{19}F NMR** ($CDCl_3$, 282 MHz) δ −117.8; **IR (film)**: 2984, 2935, 2242, 1745, 1660, 1492, 1457, 1373, 1239, 1192, 1100, 1032, 857, 763; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{22}H_{24}FNaNO_6$) requires 440.1485, found 440.1484; enantiomeric excess: 89%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.60 mL min^{-1}; t_{major} = 16.9 min, t_{minor} = 12.5 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 2-cyano-4′-methoxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3k)

Yield: 96%; Viscous, colorless oil; $[\alpha]_D^{26}$ −94.5 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.18 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.41 (m, 1H), 4.28–4.15 (m, 4H), 4.02 (q, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 3.25 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.04 (dd, *J* = 17.8, 10.8 Hz, 1H), 2.59 (dt, *J* = 19.3, 4.5 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.8, 167.0, 165.8, 159.8, 138.7, 129.5, 128.6, 126.8, 115.4, 114.1, 63.0, 61.9, 61.0, 55.3, 53.8, 50.1, 45.5, 29.7, 14.1, 13.9, 13.6; **IR (film)**: 2984, 2936, 2838, 2242, 1742, 1612, 1515, 1463, 1372, 1248, 1184, 1032, 837; **HRMS (ESI)**: calcd for $[M + Na]^+$($C_{23}H_{27}NaNO_7$) requires 452.1685, found 452.1686; enantiomeric excess: 95%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 20.6 min, t_{minor} = 15.3 min, λ = 220 nm).

(1*R*,2*R*,3*R*)-Triethyl 2-cyano-3′-methoxy-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2,3,4-tricarboxylate (3l)

Yield: 88%; Viscous, colorless oil; $[\alpha]_D^{26}$ −83.2 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.3 Hz, 1H), 7.18 (m, 1H), 6.97 (m, 2H), 6.87 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.43 (m, 1H), 4.28–4.15 (m, 4H), 4.04 (m, 2H), 3.80 (s, 3H), 3.25 (dd, *J* = 12.3, 4.3 Hz, 1H), 3.06 (dd, *J* = 19.4, 12.6 Hz, 1H), 2.62 (dt, *J* = 19.4, 4.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz,

3H), 0.98 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.7, 166.9, 165.8, 159.8, 138.4, 129.8, 129.8, 126.8, 120.7, 115.4, 114.3, 113.9, 63.0, 62.0, 61.0, 55.3, 53.5, 50.1, 46.3, 29.6, 14.1, 13.9, 13.6; **IR (film)**: 2983, 2933, 2245, 1745, 1660, 1602, 1491, 1463, 1372, 1233, 1184, 1094, 1035, 861, 788; **HRMS (ESI)**: calcd for $[M + Na]^+(C_{23}H_{27}NaNO_7)$ requires 452.1685, found 452.1684; enantiomeric excess: 96%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 31.0 min, t_{minor} = 16.2 min, λ = 220 nm).

(1*S*,2*R*,6*S*)-Triethyl 1-cyano-6-(thiophen-2-yl)cyclohex-3-ene-1,2,3-tricarboxylate (3m)

Yield: 87%; Viscous, colorless oil; $[\alpha]_D^{26}$ −81.6 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 7.00 (m, 1H), 4.38 (m, 1H), 4.28–4.19 (m, 4H), 4.15–4.07 (m, 2H), 3.64 (dd, J = 12.0, 4.2 Hz, 1H), 3.06 (dd, J = 19.3, 12.3 Hz, 1H), 2.62 (dt, J = 19.5, 6.1 Hz, 1H), 1.31–1.24 (m, 6H), 1.10 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.5, 167.0, 165.6, 138.7, 137.9, 127.0, 126.9, 126.8, 125.5, 114.9, 63.3, 62.0, 61.1, 54.4, 49.8, 41.7, 31.2, 14.1, 13.9, 13.7; **IR (film)**: 2984, 2931, 2237, 1748, 1661, 1466, 1372, 1250, 1238, 1186, 1032, 855, 712; **HRMS (ESI)**: calcd for $[M + Na]^+(C_{20}H_{23}NaNSO_6)$ requires 428.1144, found 428.1142; enantiomeric excess: 93%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.70 mL min^{-1}; t_{major} = 17.6 min, t_{minor} = 15.1 min, λ = 220 nm).

(1*R*,2*R*,6*R*)-Triethyl 6-(benzo[*d*][1,3]dioxol-5-yl)-1-cyanocyclohex-3-ene-1,2,3-tricarboxylate (3n)

Yield: 94%; Viscous, colorless oil; $[\alpha]_D^{26}$ −89.3 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (m, 1H), 6.92 (m, 1H), 6.81 (m, 2H), 5.95 (s, 2H), 4.40 (m, 1H), 4.26–4.15 (m, 4H), 4.06 (m, 2H), 3.21 (dd, J = 12.3, 4.0 Hz, 1H), 3.00 (dd, J = 20.9, 12.3 Hz, 1H), 2.59 (dt, J = 19.3, 4.5 Hz, 1H), 1.31–1.23 (m, 6H), 1.06 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 168.7, 167.0, 165.7, 148.0, 147.8, 138.5, 130.3, 126.8, 122.2, 115.3, 108.5, 108.4, 101.3, 63.1, 62.0, 61.0, 53.7, 50.1, 45.9, 29.8, 14.1, 13.9, 13.7; **IR (film)**: 2983, 2938, 2906, 2247, 1747, 1660, 1505, 1492, 1370, 1301, 1253, 1184, 1038, 934, 813; **HRMS (ESI)**: calcd for $[M + Na]^+(C_{23}H_{25}NaNO_8)$ requires 466.1478, found 466.1477; enantiomeric excess: 96%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.65 mL min^{-1}; t_{major} = 29.1 min, t_{minor} = 20.8 min, λ = 220 nm).

(1*R*,2*R*,3*S*)-Diethyl 2-benzoyl-2-cyano-1,2,3,6-tetrahydro-[1,1′-biphenyl]-3,4-dicarboxylate (6)

63% yield as a 63 : 37 mixture of *cis* and *trans* isomers; *cis* isomer: Viscous, colorless oil; $[\alpha]_D^{26}$ −117.5 (c = 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.35 (m, 3H), 7.25–7.17 (m, 8H), 4.71 (m, 1H), 4.27 (q, J = 7.0 Hz, 2H), 4.11 (m, 2H), 3.51 (dd, J = 12.3, 4.1 Hz, 1H), 3.21 (m, 12.8 Hz, 1H), 2.66 (dt, J = 19.3, 4.6 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.6, 169.1, 165.8, 138.2, 137.1, 136.7, 129.1, 129.0, 128.7, 128.1, 127.7, 127.3, 117.7, 62.0, 61.0, 56.4, 51.8, 47.5, 29.4, 14.2, 13.7; **IR (film)**: 3063, 2983, 2235, 1737, 1597, 1451, 1374, 1250, 1182, 1133, 1094, 1031, 970, 748; **HRMS (ESI)**: calcd for $[M + Na]^+(C_{26}H_{25}NaNO_5)$ requires 454.1630, found 454.1631; enantiomeric excess: 99%, determined by HPLC (Chiralpak OD column, hexane–*i*-PrOH 80 : 20, flow rate 0.50 mL min^{-1}; t_{major} = 24.4 min, t_{minor} = 16.4 min, λ = 220 nm).

Trans isomer: Viscous, colorless oil; $[\alpha]_D^{26}$ −165.4 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 1H), 7.34–7.25 (m, 8H), 7.21–7.17 (m, 2H), 4.51 (m, 1H), 4.33–4.22 (q, J = 7.1 Hz, 2H), 4.07 (m, 1H), 3.96 (m, 1H), 3.54 (dd, J = 11.5, 4.3 Hz, 1H), 3.12 (dd, J = 18.6, 11.5 Hz, 1H), 2.65 (dt, J = 18.9, 5.1 Hz, 1H), 1.38–1.34 (t, J = 7.0 Hz, 3H), 1.00–0.96 (t, J = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.5, 168.7, 166.2, 138.4, 136.9, 136.7, 132.8, 129.5, 129.2, 128.8, 127.7, 127.1, 121.7, 61.9, 61.0, 53.6, 51.8, 48.0, 27.7, 14.2, 13.5, 13.5; **IR (film)**: 3062, 2982, 2928, 2240, 1722, 1677, 1596, 1449, 1373, 1259, 1187, 1104, 1030, 739; **HRMS (ESI)**: calcd for $[M + Na]^+$ ($C_{26}H_{25}NaNO_5$) requires 454.1630, found 454.1632; enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column, hexane–*i*-PrOH 80 : 20, flow rate 0.50 mL min^{-1}; t_{major} = 23.7 min, t_{minor} = 18.2 min, λ = 254 nm).

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10 As this manuscript is ready for submission, a paper describing asymmetric [4 + 2] cycloaddition between α-substituted allenoate and arylidenemalononitrile appeared: F. Zhong, X. Han, Y. Wang and Y. Lu, *Chem. Sci.*, 2012, DOI: 10.1039/c2sc00963c.

11 In ref. 10, olefins derived from malononitrile and isatin were also used successfully in this reaction.

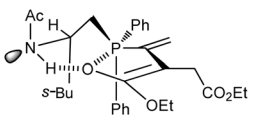
12 Other allenoates bearing H or Ph instead of an ester group at the β′ atom were also examined but poor conversions (<10%) were obtained, which might be ascribed to the weaker anion-stabilizing ability of these substituents. See ref. 5 for similar phenomena.

13 See Table S1 in the ESI† and ref. 10 for comparison.

14 See the ESI† for details.

15 (*Z*)-Ethyl 2-nitro-3-phenylacrylate and dimethyl 2-benzylidenemalonate were also studied but gave no reaction in this system. Oxodiene **5** worked as a 1,4-amphiphilic reagent in Cinchona alkaloids catalyzed [4 + 2] annulation of non-substituted allenoate: X. Wang, T. Fang and X. Tong, *Angew. Chem., Int. Ed.*, 2011, **50**, 5361. The configurations of products **6** were determined by NOESY spectra. See the ESI† for details.

16 We thank one of our reviewers for proposing an alternative half-chair conformation (see below). In this model, the *s*-butyl group and the acyl group on the nitrogen atom take axial positions to minimize the possible enhanced *gauche* interaction between these two substituents due to the more planar nature of the sp^3 hybridized nitrogen atom in our proposed chair-like pretransition state.



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