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PAPER

Bifunctional phosphine-catalyzed cross-Rauhut–Currier/Michael/aldol condensation triple domino reaction: synthesis of functionalized cyclohexenes†

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A novel bifunctional phosphine-catalyzed reaction was developed. Cross-Rauhut–Currier, Michael and aldol reactions were successfully combined into a domino process. This method offers a powerful approach to the construction of highly substituted cyclohexene skeletons.

Introduction

Combining different organocatalytic reactions into a domino process[1] has become a fruitful concept for the synthesis of functionalized and diversified molecules,[2] and is of great value in both target-oriented and diversity-oriented synthesis.[3] These methods swiftly assemble complex molecules from simple starting materials with minimal time, and waste as well as manipulation of reaction intermediates.[4] Significant progress has been made by applying this strategy to the total synthesis of natural products and biologically active molecules.[5] The domino strategy fundamentally relies on reaction compatibility and is often realized in organocatalysis.[2]

The phosphine-catalyzed dimerization of activated alkenes, first discovered by Rauhut and Currier in 1963,[6] and coined as the Rauhut–Currier (RC) reaction,[9a] is a unique method that creates a new C–C bond between the α-position of an activated alkene and β-position of a second alkene.[6,7] To date, a number of intramolecular RC reactions, as well as enantioselective variants, have been reported.[7] In 1999, Moore revealed a unique example of an intramolecular RC reaction in the synthesis of waihoensene.[8] In 2002, Krische and Roush respectively presented detailed studies of a phosphine-catalyzed intramolecular RC reaction,[9] which was successfully used in the construction of ring systems[10] and for the total synthesis of (–)-spinosyn A,[11] (+)-harziphilone,[12] antimitotic agent FR182877,[13] (±)-ricciocarpin A and (±)-quinine.[14] Recently, elegant studies on the catalysts, domino process, asymmetric variants, and extensions of intramolecular RC reaction have been reported.[15] Despite the progress in the intramolecular manifolds, intermolecular reactions suffer from anionic polymerization or oligomerization and difficulty in controlling the selectivity of the cross-coupling.[7] Thus, effective methodologies for efficient intermolecular cross-coupling of different activated olefins are rare,[16,17] especially for the α,β-unsaturated aldehydes/ketones that will provide more functionality in the final products.[4,7a,16] More recently, great effort has been directed toward incorporating the RC reaction into domino processes to construct diverse and highly functionalized molecules with high atom efficiency, such as the RC–Wittig[18] and RC–aldol[19,20] domino reactions. These remarkable developments re-emphasize the advantages of domino processes, as well as the compatibility of the RC reaction with other reactions.

To the best of our knowledge, intermolecular RC-domino reactions have so far been confined to two-components or two-steps. Few triple domino[17c] reactions have been reported to date. Acrolein is an interesting Michael reaction acceptor that is more active than other vinyl ketones and acrylates.[11a] However, it has not been used in the RC reaction, because of its propensity to form oligomers or polymers in the presence of basic catalysts. Since Shibasaki *et al.* described the concept of multifunctional catalysis, a variety of reactions have been addressed with multifunctional organocatalysts, including the (aza)-Morita–Baylis–Hillman reaction.[21] However, efficient multifunctional organocatalysts for the RC reaction have seldom been reported. Functionalized cyclohexenes can serve as building blocks in organic synthesis and play a central role in many natural product syntheses.[22] Nevertheless, the intermolecular RC reaction has not been utilized previously for the formation of cyclohexenes. Intrigued by these elegant studies and our work concerning phosphine-catalyzed domino reactions,[23] herein, we report the Lewis base–Brønsted acid (LBBA)-catalyzed triple domino reaction for the synthesis of highly functionalized cyclohexenes (Fig. 1).

This three-component domino reaction proceeds *via* a catalyzed cross-RC/Michael/aldol condensation sequence in which three new carbon–carbon bonds are formed.

Results and discussion

We started our investigation by reacting (*E*)-ethyl-2-cyano-3-(2,4-dichlorophenyl)acrylate (**1a**) with acrolein **2** in the presence of LBBA-1 (20 mol%) (Table 1, entry 1) in $CHCl_3$. To our delight, **3a** was isolated as two stereoisomers in 34% overall yield.

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† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, IR for all new compounds **3a–3t**, chiral HPLC analyses **3a**, crystal structure of *cis*-**3a** and *trans*-**3a**. CCDC reference numbers 769828 and 769829. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05693j

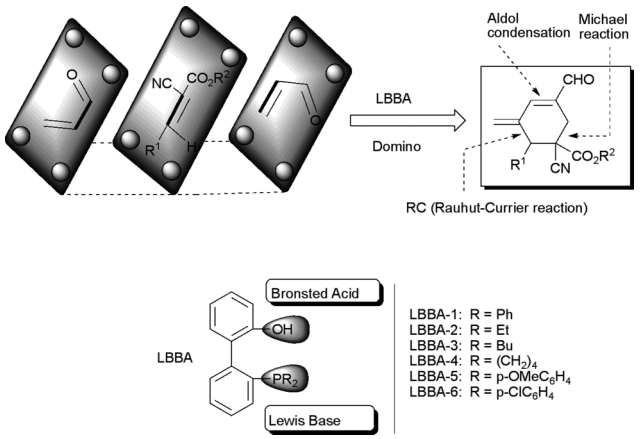


Fig. 1 Bifunctional phosphine-catalyzed triple domino reaction.

The structure and stereochemistry of **3a** were determined by a combination of NMR spectra, HRMS and single-crystal X-ray analysis (Fig. 2).[24] In attempt to improve the yield of the reaction, other reaction conditions were screened. In solvents such as THF, DMF, CH_3CN and toluene, either none or only a trace amount of product was obtained. The use of CH_2Cl_2, $CHCl_3$ led to higher yields. In addition, decreasing the concentration could further improve the yields (Table 1, entries 1, 7, 17). Stronger or weaker nucleophilic bifunctional phosphine catalysts led to lower yields (Table 1, entries 9–13). PPh_3 and PBu_3 were inefficient for this domino reaction (Table 1, entries 19 and 20).

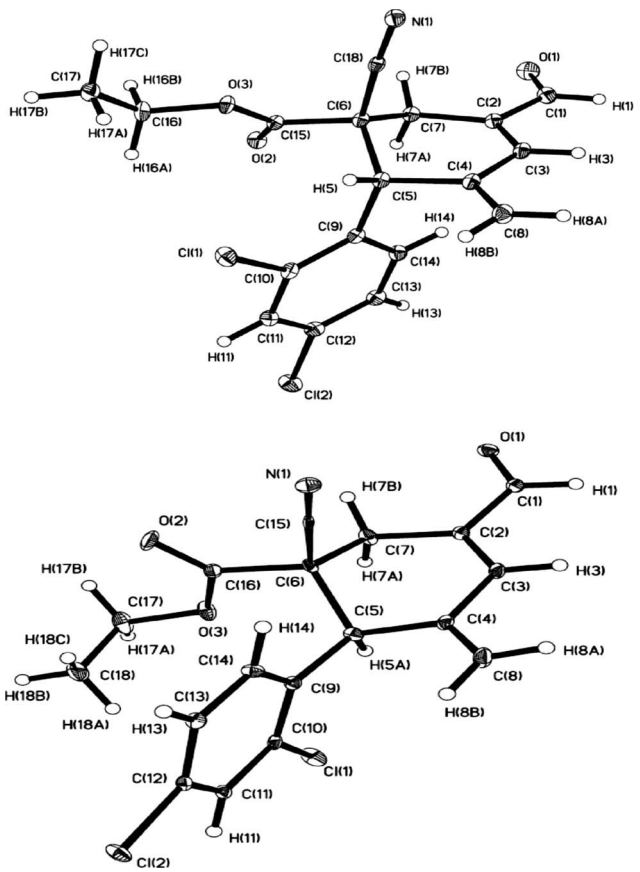
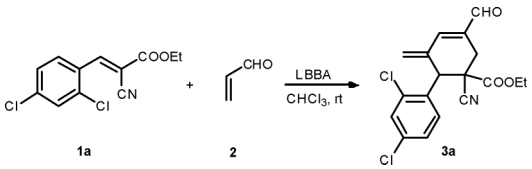


Fig. 2 X-Ray crystal structure of *cis*- and *trans*-**3a**.

Table 1 Screening catalysts and conditions for the domino reaction[a]

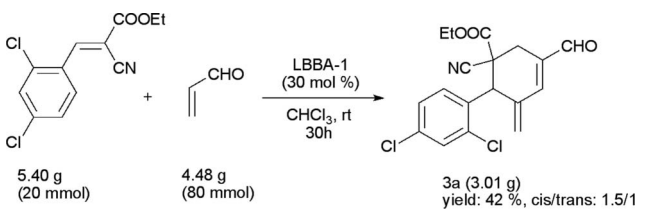


1a 2 3a

Entry	Solvent	Cat. (mol%)	*V*/ml	Yield (%)[b]
1	$CHCl_3$	LBBA-1 (20)	2	34
2	THF	LBBA-1 (20)	2	—
3	DMF	LBBA-1 (20)	2	—
4	CH_3CN	LBBA-1 (20)	2	Trace
5	Toluene	LBBA-1 (20)	2	11
6	CH_2Cl_2	LBBA-1 (20)	2	31
7	$CHCl_3$	LBBA-1 (20)	5	42
8[c]	$CHCl_3$	LBBA-1 (20)	5	41
9	$CHCl_3$	LBBA-2 (20)	5	Trace
10	$CHCl_3$	LBBA-3 (20)	5	Trace
11	$CHCl_3$	LBBA-4 (20)	5	Trace
12	$CHCl_3$	LBBA-5 (20)	5	36
13	$CHCl_3$	LBBA-6 (20)	5	38
14	$CHCl_3$	LBBA-1 (30)	5	51
15	$CHCl_3$	LBBA-1 (50)	5	42
16	$CHCl_3$	LBBA-1 (100)	5	46
17[d]	$CHCl_3$	LBBA-1 (30)	10	58
18[e]	$CHCl_3$	LBBA-1 (30)	20	52
19[d]	$CHCl_3$	PPh_3 (30)	10	Trace
20[d]	$CHCl_3$	PBu_3 (30)	10	—

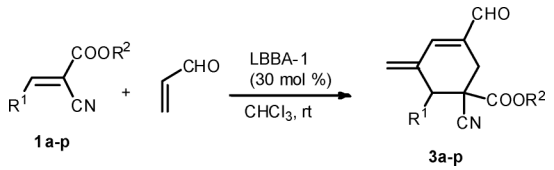
[a] All reactions were performed on a 0.5 mmol scale and carried out for 24 h. The ratio of **1a**/**2** is 1 : 3.0. [b] Product isolated by flash chromatography. [c] The ratio of the **1a**/**2** is 1 : 5.0. [d] Acrolein (1.50 mmol) in $CHCl_3$ (5 ml) was added to a mixture of catalyst LBBA or PR_3 (R = Ph, Bu) (0.15 mmol, 30 mol%), **1a** (0.5 mmol) in $CHCl_3$ (5 ml). [e] Acrolein (1.50 mmol) in $CHCl_3$ (10 ml) was added to a mixture of catalyst LBBA (0.15 mmol, 30 mol%), **1a** (0.5 mmol) in $CHCl_3$ (10 ml).

A variety of activated alkenes **1** were tolerated under the optimized reaction conditions (Table 2). The electronic characteristics of the substituent on the phenyl ring have little effect on the yields and the diastereoselectivities. Furyl- and naphthyl-substituted activated alkenes **1** were also successfully employed in this reaction. Although the domino process afforded the final products in moderate overall yield (30–66%), this corresponded to an average yield of 67–87% per bond formed. Under optimized conditions, the reaction can be performed on a 20 mmol scale to obtain a 42% yield of **3a** (Scheme 1). Although activated allenes[7a,17c] and silyloxyallenes[17a] have been investigated in place of alkenes in Rauhut–Currier reactions, conjugated dienes have seldom been employed in a similar capacity.[17b] We questioned whether it would be possible to extend the present multicomponent triple domino transformation to conjugated diene compounds under the same conditions. As outlined in Fig. 3, the



Scheme 1 The reaction on a 20 mmol scale.

Table 2 Scope of the domino reactions in the presence of LBBA-1[a]



1a-p 3a-p

Entry	R^1	R^2	Time/h	Yield (%)[b]	*cis*/*trans*[c]
1	2,4-ClC_6H_3	Et	24	58(**3a**)	1.5/1
2	2,4-ClC_6H_3	Me	24	51(**3b**)	1.4/1
3	2,4-ClC_6H_3	Bu-*t*	72	45(**3c**)	1.7/1
4	2-Cl-C_6H_4	Et	28	45(**3d**)	1.2/1
5	3-Cl-C_6H_4	Et	24	53(**3e**)	4/1
6[e]	4-Cl-C_6H_4	Et	48	43(**3f**)	5/1
7	2-Br-C_6H_4	Et	24	42(**3g**)	2/1
8	4-Br-C_6H_4	Et	24	48(**3h**)	2.9/1
9	4-F-C_6H_4	Et	25	52(**3i**)	7/1
10	3-Me-C_6H_4	Et	72	54(**3j**)	3/1
11	C_6H_5	Et	40	65(**3k**)	5/1
12[d]	4-OMe-C_6H_4	Et	72	35(**3l**)	5/1
13	2-Me-C_6H_4	Me	72	41(**3m**)	1.2/1
14	4-Me-C_6H_4	Et	72	59(**3n**)	3/1
15	2-Naphthyl	Et	72	66(**3o**)	2.5/1
16	2-Furyl	Et	72	30(**3p**)	>20/1

[a] See experimental procedure for reaction conditions. [b] Isolated yield. [c] Determined through NMR spectroscopic analysis and comparison with the NMR spectra of *cis*-**3a** and *trans*-**3a**. [d] 45 mol% catalyst was used.

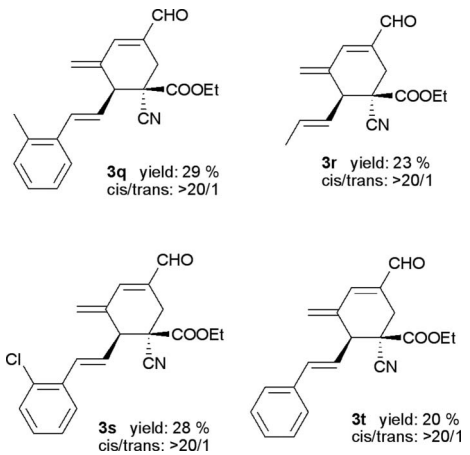
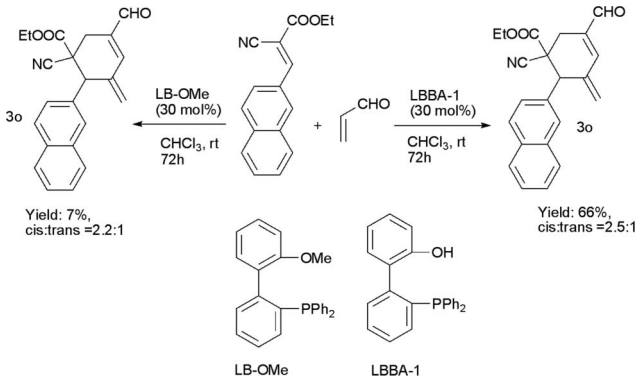


Fig. 3 Triple domino reaction of conjugated dienes **1** with acrolein **2**.

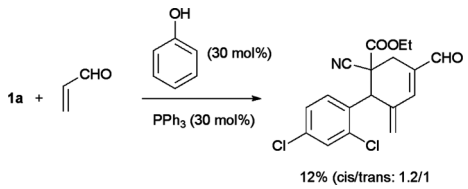
domino reactions proceeded well for both aliphatic and aromatic conjugated dienes and provided the corresponding products with high diastereoselectivity, albeit with a slightly lower yield.

Notably, the phenolic hydroxyl group on the LBBA is important, because when the *O*-methylated catalyst (LB-OMe) was employed, the rate of the reaction decreased, giving the **3o** only in 7% yield (Scheme 2).

In addition, the reaction was also carried out by combination of PPh_3 and phenol. **3a** could also be obtained in 12% yield with lower diastereoselectivity (*cis*/*trans*: 1.2 : 1) after 20 h (Scheme 3). This indicated that not only are the phenolic and phosphine groups both necessary, but also that being at an appropriate distance from each other and on the same molecule facilitates the catalysis.

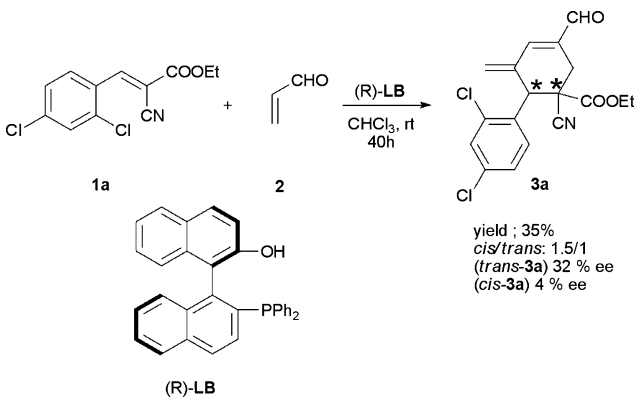


Scheme 2 The comparison of catalytic reactivity between LBBA-1 and LB-OMe.



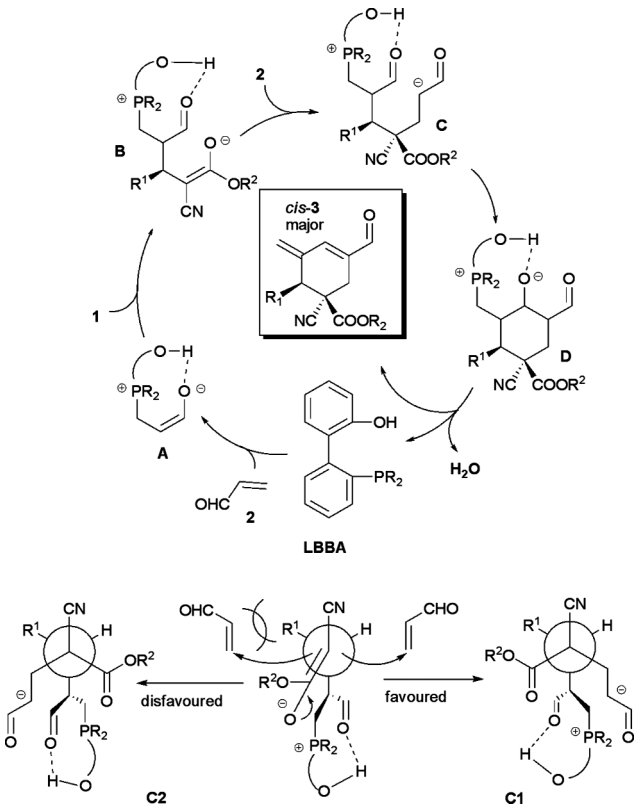
Scheme 3 The reaction carried out by combination of PPh_3 and phenol.

Preliminary studies on the asymmetric variant of this reaction tested with the optically pure bifunctional catalyst **LB**.[21a] We obtained a promising 32% and 4% enantiomeric excess for *trans*- and *cis*-**3a**, respectively (Scheme 4).



Scheme 4 Asymmetric annulation.

The detailed mechanism of this triple domino reaction has not been clarified. A possible mechanism for the formation of cyclohex-1-ene-carbaldehyde derivatives **3** is presented in Scheme 5. In the first step, **2** reacts with catalyst LBBA to give the zwitterionic phosphonium intermediate **A**. The phenolic OH serves as a Brønsted acid to stabilize intermediate **A** through an intramolecular hydrogen bond. The RC reaction then occurs, producing intermediate **B**. Subsequent Michael addition of intermediate **B** to another molecular of acrolein gives intermediate **C** (**C1** or **C2**). Intramolecular aldol condensation then takes place (**C1**–**D**), producing **3** *via* dehydration, and regenerating LBBA to complete the catalytic cycle. As shown in the Newman projection, the steric repulsions between R^1 and acrolein suggest that the generation of intermediate **C1** is favoured and hence **3** with a diastereoselectivity for the *cis*-isomer is obtained.



Scheme 5 Possible mechanism for the formation of **3**.

Conclusions

In conclusion, we have developed a bifunctional phosphine-catalyzed cross-Rauhut–Currier/Michael/aldol condensation domino reaction to provide highly functionalized cyclohexene carbaldehydes from simple, inexpensive starting materials. The possibility to perform the developed cascade in gram-scale reactions has also been demonstrated. This work could open up new opportunities to develop domino reactions. Experiments designed to explore the scope, limitations and applications in organic synthesis are ongoing and will be reported in due course.

Experimental

General

All solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were was recorded at 100 MHz. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm calibrated to tetramethylsilane as an external reference. The data with an asterisk (*) indicate peaks of the minor diastereomer (*trans*). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet. HRMS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on a RY-I apparatus and are reported uncorrected. Catalysts **LBBA**,[23] **(*R*)-LB**[21] and activated alkenes and conjugated dienes were prepared according to known methods.[25]

Preparation of the catalyst LB-OMe

LBBA-1 (717 mg, 2.00 mmol) in $CHCl_3$ (10 ml) was added 30% hydrogen peroxide (3.0 ml) at 0 °C, and stirred for 2 h. The organic phase was washed with 3 × 10 ml of water and dried ($MgSO_4$), and finally concentrated, without further purification giving 2′-(diphenylphosphoryl)biphenyl-2-ol 740 mg (99%). To a mixture of 2′-(diphenylphosphoryl)biphenyl-2-ol (708.67 mg, 2.00 mmol) and K_2CO_3 (1014 mg, 8.00 mmol) in acetone (12 ml), was added MeI (140 mg, 8.00 mmol), and the mixture was refluxed for 5 h. After being cooled to room temperature, the mixture was filtered though Celite, and the solid was washed with Et_2O, without further purification, to give 2-(diphenylphosphinyl)- 2′-methoxyl-1,1′-biphenyl 760 mg (99%). Then to a mixture of 2-(diphenylphosphinyl)- 2′-methoxyl-1,1′-biphenyl (768 mg, 2.00 mmol) and Et_3N (4040 mg, 40.00 mmol) in xylene (50 ml) was added $HSiCl_3$ (1350 mg, 10.00 mmol) at 0 °C. The reaction mixture was stirred at 120 °C for 5 h. After being cooled to room temperature, the mixture was diluted with Et_2O and quenched with a small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and the solid was washed with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude phosphine was purified by silica gel column chromatography, giving **LB-OMe** 382 mg (52%). White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (t, J = 6.3, 1H), 7.18 (s, 11H), 7.11 – 6.96 (m, 4H), 6.81 (td, J = 7.3, 3.1, 1H), 6.72 (dd, J = 8.0, 2.3, 1H), 6.71 (s, 1H), 3.41 – 3.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.5, 144.1, 143.8, 137.4, 137.3, 136.6, 136.5, 136.0, 135.9, 133.1, 132.7, 132.5, 130.2, 129.3, 129.3, 127.9, 127.7, 127.2, 127.1, 127.1, 127.0, 126.3, 118.8, 109.1, 53.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ = –13.04. mp = 175–176 °C. IR (KBr): 3051, 2962, 2832, 1968, 1896, 1583, 1433, 1249, 1090, 1027, 743, 697, 508 cm^{-1}. **HRMS** (ESI/[M + Na]$^{+}$) Cacld. for: $C_{25}H_{21}OPNa$ 369.1403, found 369.1399.

General procedure for the synthesis of cyclohexene carbaldehydes (3a)

Acrolein (84 mg, 1.50 mmol) in $CHCl_3$ (5 ml) was added dropwise to a solution of (*E*)-ethyl-2-cyano-3-(2,4-dichlorophenyl) acrylate (135 mg, 0.50 mmol) and catalyst LBBA-1 (53 mg, 0.15 mmol) in $CHCl_3$ (5 ml). The stirring was maintained at room temperature until completion of the reaction (the reaction was monitored by TLC). The solvent was removed under reduced pressure to give a residue. The residue was purified by flash column chromatography (petroleum ether/EtOAc 10 : 1) to yield **3a**: 105 mg, 58%; colorless solid; *cis*-**3a**/*trans*-**3a** = 1.5/1. **3b–3t** were produced under the same conditions.

The reaction can be performed in 20 mmol scale

Acrolein (4.5 g, 80.00 mmol) in $CHCl_3$ (50 ml) was added dropwise to a solution of (*E*)-ethyl-2-cyano-3-(2,4-dichlorophenyl) acrylate (5.5 g, 20.00 mmol) and catalyst LBBA-1 (2.1 g, 12.00 mmol) in $CHCl_3$ (50 ml) over 2 h. The stirring was maintained at room temperature for 30 h. The solvent was removed under reduced pressure to give a residue. The residue was purified by flash column chromatography (petroleum ether/EtOAc 10 : 1) to yield **3a**: 3.0 g, 42%; colorless solid; *cis*/*trans* = 1.5 : 1.

The procedure for the asymmetric synthesis of cyclohexene carbaldehydes (3a)

Acrolein (84 mg, 1.50 mmol) in $CHCl_3$ (5 ml) was added dropwise to a solution of (*E*)-ethyl-2-cyano-3-(2,4-dichlorophenyl) acrylate (135 mg, 0.50 mmol) and catalyst LB (68 mg, 0.15 mmol) in $CHCl_3$ (5 ml). The stirring was maintained at room temperature until completion of the reaction (the reaction was monitored by TLC). The solvent was removed under reduced pressure to give a residue. The residue was purified by flash column chromatography (petroleum ether/EtOAc 10 : 1) to yield **3a**. Yield: 35%, *cis*/*trans*: 1.5/1. *trans*-**3a**: 32% ee, $[\alpha]_D^{20} = 22$ ($c = 0.1$ in $CHCl_3$); *cis*-**3a**: 4% ee, $[\alpha]_D^{20} = 11$ ($c = 0.2$ in $CHCl_3$).

***trans*-Ethyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*trans*-3a)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.74 (dd, $J = 8.5$, 2.9 Hz, 1H), 7.56 – 7.42 (m, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.27 (d, $J = 1.4$ Hz, 1H), 5.73 (s, 1H), 4.99 (s, 1H), 4.73 (d, $J = 1.4$ Hz, 1H), 4.19 – 3.99 (m, 2H), 3.23 (dd, $J = 17.8$, 3.5 Hz, 1H), 3.05 (d, $J = 17.8$ Hz, 1H), 1.06 (td, $J = 7.1$ Hz, 3.5, 3H).

^{13}C NMR (101 MHz, CDCl3) δ = 191.6, 166.5, 145.8, 139.8, 136.2, 135.1, 134.9, 132.2, 130.0, 129.8, 128.0, 126.7, 117.5, 63.4, 48.3, 46.6, 32.2, 13.6. m.p. 156–158 °C; IR (KBr): 2983, 2926, 2720, 2244, 1744, 1681, 1587, 1474, 1253, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{15}Cl_2NO_3Na$ 386.0321, found 386.0324.

***cis*-Ethyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*cis*-3a)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.70$ (s, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.34 (s, 1H), 7.17 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 5.79 (s, 1H), 5.58 (s, 1H), 5.03 (s, 1H), 4.33 – 3.97 (m, 2H), 3.10 (d, $J = 19.0$ Hz, 1H), 2.90 (d, $J = 19.0$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.6, 165.6, 145.7, 140.3, 135.4, 134.9, 134.8, 133.6, 129.9, 129.6, 127.9, 118.3, 63.5, 46.4, 46.2, 25.9, 13.7. m.p. 117–119 °C. IR (KBr): 2982, 2928, 2718, 2243, 1744, 1680, 1475, 1249, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{15}Cl_2NO_3Na$ 386.0321, found 386.0322.

***trans*-Methyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*trans*-3b)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.66$ (s, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.49 (s, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.28 (s, 1H), 5.74 (s, 1H), 5.01 (s, 1H), 4.75 (s, 1H), 3.65 (s, 3H), 3.25 (d, $J = 17.7$ Hz, 1H), 3.06 (d, $J = 17.8$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.6, 167.1, 145.9, 139.7, 136.1, 135.1, 134.8, 132.1, 129.9, 129.9, 128.1, 127.0, 117.4, 54.0, 48.2, 46.5, 32.1. m.p. 170–172 °C; IR (KBr): 2924, 2850, 2722, 2354, 2245, 1748, 1680, 1630, 1475, 1255, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{17}H_{13}Cl_2NO_3Na$ 372.0165, found 372.0170.

***cis*-Methyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*cis*-3b)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.71$ (s, 1H), 7.42 (d, $J = 2.1$ Hz, 1H), 7.36 (s, 1H), 7.17 (dd, $J = 8.5$, 2.1 Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 1H), 5.81 (s, 1H), 5.59 (s, 1H), 5.01 (s, 1H), 3.78 (s, 3H), 3.09 (d, $J = 18.8$ Hz, 1H), 2.87 (d, $J = 18.8$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.6, 166.1, 145.7, 140.1, 135.4, 135.0, 134.7, 133.3, 129.9, 129.5, 128.2, 128.0, 118.3, 53.9, 46.3, 46.1, 29.7, 25.6. m.p. 120–122 °C; IR (KBr): 2955, 2923, 27178, 2244, 1749, 1682, 1435, 1257 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{17}H_{13}Cl_2NO_3Na$ 372.0165, found 372.0171.

***trans*-*tert*-Butyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*trans*-3c).** ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.59$ (s, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.42 (s, 1H), 7.28 (d, $J = 8.3$ Hz, 1H), 7.20 (s, 1H), 5.64 (s, 1H), 4.88 (s, 1H), 4.59 (s, 1H), 3.15 (d, $J = 17.7$ Hz, 1H), 2.94 (d, $J = 17.8$ Hz, 1H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 190.8$, 164.3, 144.9, 138.9, 135.3, 134.1, 133.9, 131.2, 129.0, 128.6, 126.8, 125.4, 116.9, 84.0, 48.0, 45.7, 31.3, 26.3. oil; IR (KBr): 3157, 3055, 2928, 2716, 2241, 1744, 1683, 1478, 1253, 1160 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{20}H_{19}NO_3Cl_2Na$ 414.0634, found 414.0629.

***cis*-*tert*-Butyl-1-cyano-6-(2,4-dichlorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (*cis*-3c)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.62$ (s, 1H), 7.38 (d, $J = 1.8$ Hz, 1H), 7.22 (s, 1H), 7.11 (dd, $J = 8.5$, 1.9 Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 1H), 5.67 (s, 1H), 5.50 (s, 1H), 5.00 (s, 1H), 3.03 (d, $J = 19.1$ Hz, 1H), 2.92 (d, $J = 18.8$ Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 190.9$, 163.3, 144.7, 139.3, 134.1, 134.0, 133.7, 133.0, 128.8, 128.5, 126.9, 126.4, 117.8, 84.3, 45.9, 44.5, 26.4, 26.3, 25.4. oil; IR (KBr): 3158, 3055, 2928, 2718, 2243, 1745, 1686, 1475, 1244, 1167 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{20}H_{19}NO_3Cl_2Na$ 414.0634, found 414.0630.

***trans*-Ethyl-6-(2-chlorophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (*trans*-3d)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.66$ (s, 1H), 7.80 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.45 (dd, $J = 7.7$, 1.6 Hz, 1H), 7.40 – 7.28 (m, 3H), 5.72 (d, $J = 2.1$ Hz, 1H), 5.01 (d, $J = 1.7$ Hz, 1H), 4.79 (s, 1H), 4.06 (qq, $J = 10.7$, 7.1 Hz, 2H), 3.24 (d, $J = 17.7$ Hz, 1H), 3.08 (d, $J = 17.8$ Hz, 1H), 1.00 (t, $J = 7.1$ Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.7, 166.7, 146.1, 140.1, 135.4, 134.9, 133.5, 130.0, 129.7, 129.2, 127.6, 126.7, 117.8, 63.2, 48.4, 47.1, 32.3, 13.5. m.p. 161–162 °C; IR (KBr): 2982, 2926, 2719, 2243, 1743, 1681, 1435, 1252, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{16}ClNO_3Na$ 352.0711, found 352.0715.

***cis*-Ethyl-6-(2-chlorophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (*cis*-3d)**

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.64$ (s, 1H), 7.37 – 7.30 (m, 1H), 7.28 (d, $J = 1.5$ Hz, 1H), 7.23 – 7.05 (m, 2H), 6.86 (dd, $J = 7.7$, 1.5 Hz, 1H), 5.71 (s, 1H), 5.53 (s, 1H), 5.04 (s, 1H), 4.19 – 3.96 (m, 2H), 3.02 (d, $J = 18.7$ Hz, 1H), 2.88 (d, $J = 18.7$ Hz, 1H), 1.17 (t, $J = 7.2$ Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 190.8$, 164.7, 144.9, 139.6, 134.5, 133.9, 133.0, 129.0, 128.6, 127.7, 126.8, 126.5, 117.6, 62.4, 45.6, 45.5, 24.7, 12.6. m.p. 146–148 °C; IR (KBr): 2981, 2927, 2720, 2243, 1743, 1681, 1435, 1251, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{16}ClNO_3Na$ 352.0711, found 352.0713.

cis-Ethyl-6-(3-chlorophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (_cis_-3e)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 9.65* (s, 1H), 7.37 (d, J = 2.0 Hz, 2H), 7.27 (s, 1H), 7.00 – 6.91 (m, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.84 (s, 1H), 5.79* (s, 1H), 5.62 (s, 1H), 5.30* (s, 1H), 5.23* (s, 1H), 4.40 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 4.09 – 4.02* (m, 2H), 3.17* (d, J = 17.7 Hz, 1H), 3.09 (d, J = 18.6 Hz, 1H), 3.00* (d, J = 17.9 Hz, 1H), 2.70 (d, J = 18.6 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.01* (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.8, 191.6*, 167.0*, 165.6, 146.0*, 145.8, 140.1*, 139.9, 138.5, 137.3*, 135.6, 134.8, 134.6*, 130.2, 130.1*, 128.9*, 128.8, 128.4, 128.0, 127.5*, 126.1, 118.4, 117.3*, 63.4, 63.3*, 51.7*, 51.6, 49.1*, 47.1, 31.2*, 24.3, 13.9, 13.6*; IR (KBr): 2983, 2936, 2722, 2243, 1746, 1683, 1431, 1242, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{16}ClNO_3Na$ 352.0711, found 352.0715.

cis-Ethyl-6-(4-chlorophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (_cis_-3f)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.28 – 7.20 (m, 1H), 6.94 (d, J = 8.5 Hz, 1H), 5.82 (s, 1H), 5.60 (s, 1H), 4.41 (s, 1H), 4.25 – 3.99 (m, 1H), 3.08 (d, J = 18.8 Hz, 1H), 2.70 (dd, J = 18.8, 1.9 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.8, 165.6, 145.9, 140.2, 135.6, 135.1, 134.7, 129.4, 129.1, 127.8, 118.4, 63.3, 51.4, 47.1, 24.3, 13.9. oil, IR (KBr): 2981, 2927, 2719, 2242, 1748, 1682, 1492, 1243, 1161 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{16}ClNO_3Na$ 352.0711, found 352.0710.

***trans*-Ethyl-6-(2-bromophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (*trans*-3g)**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 5.66 (s, 1H), 4.92 (s, 1H), 4.70 (s, 1H), 4.11 – 3.77 (m, 2H), 3.18 (d, J = 17.8 Hz, 1H), 3.02 (d, J = 17.8 Hz, 1H), 0.92 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.7, 165.6, 145.1, 139.0, 134.1, 133.9, 132.4, 129.0, 128.1, 127.2, 125.8, 125.4, 116.8, 62.2, 49.0, 47.4, 31.3, 12.5. m.p. 152–154 °C; IR (KBr): 2963, 2927, 2720, 2244, 1743, 1681, 1431, 1252, 1162, 1054 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{16}BrNO_3Na$ 396.0206, found 396.0198.

cis-Ethyl-6-(2-bromophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (_cis_-3g)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.64 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 5.71 (s, 1H), 5.55 (s, 1H), 5.05 (s, 1H), 4.20 – 3.95 (m, 2H), 3.04 (d, J = 18.7 Hz, 1H), 2.92 (d, J = 18.7 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.8, 164.6, 144.9, 139.5, 135.7, 134.3, 132.5, 128.8, 127.6, 127.2, 126.8, 123.9, 117.6, 62.4, 48.1, 45.4, 24.9, 12.6. m.p. 157–159 °C; IR (KBr): 2983, 2928, 2721, 2244, 1744, 1680, 1470, 1242, 1164, 1022 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{16}BrNO_3Na$ 396.0206, found 396.0201.

cis-Ethyl-6-(4-bromophenyl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate. (_cis_-3h)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (s, 1H), 9.65* (s, 1H), 7.52* (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.36 (s, 1H), 6.89 (d, J = 8.0 Hz, 2H), 5.82 (s, 1H), 5.60 (s, 1H), 4.39 (s, 1H), 4.23 – 4.12 (m, 2H), 3.16* (d, J = 17.7 Hz, 1H), 3.08 (d, J = 18.6 Hz, 1H), 2.98* (d, J = 17.7 Hz, 1H), 2.70 (d, J = 18.6 Hz, 1H), 1.27 (t, J = 7.4 Hz, 3H), 1.02* (t, J = 7.2 Hz, 3H).NMR (101 MHz, $CDCl_3$) δ = 191.8, 191.7*, 167.1*, 165.6, 146.0*, 145.8, 140.3*, 1402, 135.6*, 135.6, 134.8, 132.1, 132.0*, 129.8, 127.8, 127.4*, 122.9*, 122.8, 118.4, 117.4*, 63.3, 51.5*, 51.5, 49.1, 47.0, 29.7*, 24.4, 13.9, 13.6*. oil; IR (KBr): 2982, 2932, 2850, 2722, 2243, 1745, 1683, 1488, 1244, 1162, 1011 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{16}BrNO_3Na$ 396.0206, found 396.0201.

cis-Ethyl-1-cyano-6-(4-fluorophenyl)-3-formyl-5-methylenecyclohex-3-enecarboxylate (_cis_-3i)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 9.65* (s, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.01 – 6.95 (m, 3H), 5.82 (s, 1H), 5.78 (d, J = 2.0 Hz, 1H), 5.60 (s, 1H), 5.30* (s, 1H), 5.21* (d, J = 1.5 Hz, 1H), 4.42 (s, 1H), 4.17 (qd, J = 7.1, 1.3 Hz, 2H), 4.03* (t, J = 7.3 Hz, 2H), 3.17* (d, J = 17.7 Hz, 1H), 3.08 (d, J = 18.6 Hz, 1H), 2.99* (d, J = 16.7 Hz, 1H), 2.71 (d, J = 20.1 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.00* (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.8, 191.7*, 165.7, 161.4*, 146.1*, 145.9, 140.7*, 140.5, 135.6, 134.8*, 132.5, 132.5*, 129.9, 129.8, 127.7, 127.3*, 118.5, 116.1, 115.9*, 115.8, 115.7*, 63.2, 63.2*, 51.4*, 51.3, 47.2, 24.3, 13.9, 13.6*. m.p. 118–123 °C, IR (KBr): 2985, 2931, 2850, 2722, 2243, 1748, 1681, 1427, 1244, 1163, 845 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{16}FNO_3Na$ 336.1006, found 336.1004.

cis-Ethyl-2-cyano-4-formyl-3′-methyl-6-methylene-1,2,3,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate (_cis_-3j)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.63 (s, 1H), 9.57* (s, 1H), 7.32 – 7.28 (m, 1H), 7.20 (s, 1H), 7.11 – 7.05 (m, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.72 (s, 1H), 5.73 (s, 1H), 5.69* (s, 1H), 5.53 (s, 1H), 5.19* (s, 1H), 4.32 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.08* (d, J = 17.5 Hz, 1H), 2.99 (d, J = 18.8 Hz, 1H), 2.66 (d, J = 18.4 Hz, 1H), 2.28* (s, 3H), 2.20 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H), 0.88* (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.0, 190.9*, 166.3*, 164.8, 145.4*, 145.3, 139.7*, 139.7, 137.6, 137.4*, 135.5*, 134.6, 134.1*, 133.7*, 128.3, 127.8, 127.7, 127.6*, 126.6, 126.4*, 124.0*, 123.9, 117.8, 116.63*, 62.0, 62.0*, 51.1, 46.2, 23.2, 23.0*, 20.4, 12.8, 12.5*. oil; IR (KBr): 2983, 2928, 2871, 2724, 2242, 1745, 1686, 1445, 1246, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{19}H_{19}NO_3Na$ 332.1257, found 332.1251.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-phenylcyclohex-3-enecarboxylate (_cis_-3k)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 9.65* (s, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.29 – 7.25 (m, 3H), 7.04 – 6.92 (m, 2H), 5.81 (s, 1H), 5.77* (d, J = 1.9 Hz, 1H), 5.61 (s, 1H), 5.24* (s, 1H), 4.43 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.99* (qd, J = 7.1, 2.3 Hz, 2H), 3.16* (d, J = 17.7 Hz, 1H), 3.07 (d, J = 18.6 Hz, 1H), 2.74 (dd, J = 18.5, 1.5 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H), 0.94* (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.9, 191.8*, 167.3*, 165.8,

146.3*, 146.2, 140.8*, 140.7, 136.6, 135.7, 135.2*, 134.8*, 128.9, 128.8, 128.7*, 128.6*, 128.1, 127.6*, 127.4, 118.7, 117.6*, 63.1, 63.0*, 52.3*, 52.1, 49.3*, 47.3, 24.3, 13.8, 13.6*. m.p. 157–160 °C, IR (KBr): 2984, 2930, 2827, 2720, 2242, 1747, 1679, 1427, 1246, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{17}NO_3Na$ 318.1101, found 318.1108.

cis-Ethyl-1-cyano-3-formyl-6-(4-methoxyphenyl)-5-methylenecyclohex-3-enecarboxylate (*cis*-3l)

NMR (400 MHz) δ = 9.70 (s, 1H), 9.64* (s, 1H), 7.35 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.79 (s, 1H), 5.76* (s, 1H), 5.60 (s, 1H), 5.30* (s, 1H), 5.26* (s, 1H), 4.39 (s, 1H), 4.17 (qd, J = 7.1 Hz, 1.5, 2H), 4.05 – 3.98* (m, 2H), 3.81* (s, 3H), 3.76 (s, 3H), 3.15* (d, J = 17.6 Hz, 1H), 3.06 (d, J = 18.5 Hz, 1H), 2.99* (d, J = 17.6 Hz, 1H), 2.72 (dd, J = 18.5, 1.6 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz) δ = 192.0, 191.8*, 167.4*, 165.9, 159.8*, 159.6, 146.4*, 146.2, 141.1*, 141.0, 135.6, 129.2, 128.9, 127.4, 127.3*, 118.8, 114.2, 114.1*, 63.1, 63.0*, 55.3*, 55.2, 51.5*,51.5, 47.3, 24.3, 13.9, 13.7*. oil, IR (KBr): 2959, 2928, 2840, 2718, 2242, 1748, 1686, 1513, 1252, 1181, 1031 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{17}NO_3Na$ 348.1206, found 348.1207.

trans-Methyl-1-cyano-3-formyl-5-methylene-6-*o*-tolylcyclohex-3-enecarboxylate (*trans*-3m)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1H), 7.66 – 7.52 (m, 1H), 7.20 – 7.09 (m, 3H), 5.64 (s, 1H), 4.98 (s, 1H), 4.28 (s, 1H), 3.47 (s, 3H), 3.16 (d, J = 17.7 Hz, 1H), 2.97 (d, J = 17.6 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.8, 167.0, 145.6, 139.7, 136.4, 133.7, 132.8, 129.8, 127.3, 126.3, 126.1, 125.8, 117.0, 52.7, 47.4, 45.8, 31.5, 18.6. m.p. 138–139 °C; IR (KBr): 2957, 2922, 2851, 2719, 2244, 1745, 1679, 1435, 1259, 1162 cm^{-1};**HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{18}H_{17}NO_3Na$ 348.1101, found 318.1109.

cis-Methyl-1-cyano-3-formyl-5-methylene-6-*o*-tolylcyclohex-3-enecarboxylate. (*cis*-3m)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 7.34 (s, 1H), 7.21 – 7.16 (m, J = 5.5, 1.7 Hz, 2H), 7.14 – 7.06 (m, 1H), 6.81 (d, J = 7.7 Hz, 1H), 5.75 (s, 1H), 5.49 (s, 1H), 4.74 (s, 1H), 3.65 (s, 3H), 3.08 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.0, 165.4, 145.4, 140.2, 134.8, 134.5, 134.1, 130.2, 127.3, 126.2, 126.1, 125.8, 117.9, 52.4, 45.6, 45.4, 28.7, 24.8, 18.8. m.p. 135–137 °C; IR (KBr): 2955, 2922, 2851, 2719, 2243, 1752, 1678, 1435, 1249, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Cacld. for: $C_{18}H_{17}NO_3Na$ 318.1101, found 318.1109.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-*p*-tolylcyclohex-3-enecarboxylate (*cis*-3n)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.62 (s, 1H), 9.57* (s, 1H), 7.28 (s, 1H), 7.10* (d, J = 8.1 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H), 5.72 (s, 1H), 5.68* (d, J = 1.6 Hz, 1H), 5.52 (s, 1H), 5.18* (s, 1H), 4.33 (s, 1H), 4.16 – 4.01 (m, 2H), 3.97 – 3.89* (m, 2H), 2.98 (d, J = 19.0 Hz, 1H), 2.65 (d, J = 18.5 Hz, 1H), 2.28* (s, 3H), 2.22 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H), 0.90* (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9, 190.8*, 166.3*, 164.8, 145.4, 145.2*, 139.8, 137.5, 134.7, 133.8*, 132.6, 131.1*, 128.6, 128.4*, 126.8, 126.4, 126.3*, 117.8, 116.7*, 62.0, 50.8, 48.74*, 46.2, 30.1*, 23.3, 20.1*, 20.0, 12.8, 12.5*. oil; IR (KBr): 2984, 2927, 2859, 2722, 2242, 1746, 1682, 1513, 1244, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{19}H_{19}NO_3Na$ 332.1257, found 332.1257.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-(naphthalen-2-yl)cyclohex-3-enecarboxylate (*cis*-3o)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.67 (s, 1H), 9.59* (s, 1H), 7.82 – 7.69 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.35 (d, J = 1.8 Hz, 1H), 6.99 (dd, J = 8.5 Hz, 1.2, 1H), 5.76 (s, 1H), 5.70* (s, 1H), 5.56 (s, 1H), 5.21* (s, 1H), 5.16* (s, 1H), 4.53 (s, 1H), 4.10 – 4.00 (m, 2H), 3.83* (q, J = 7.0 Hz, 2H), 3.14* (d, J = 17.7 Hz, 1H), 3.03 (d, J = 18.6 Hz, 1H), 2.97* (d, J = 18.9 Hz, 1H), 2.73 (d, J = 18.5 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H), 0.69* (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.0, 190.8*, 166.3*, 164.8, 145.3*, 145.3, 139.8*, 139.6, 134.7, 133.8*, 133.0, 132.2*, 132.1*, 132.1, 131.9, 131.6*, 127.8, 127.5, 127.0*, 126.9, 126.8, 126.6, 126.53*, 125.7, 125.6, 125.4*, 124.2, 117.7, 116.7*, 62.1, 62.0*, 51.3*, 51.2, 48.3*, 46.4, 28.7*, 23.5, 12.8, 12.4*. oil; IR (KBr): 3058, 2983, 2917, 2721, 2245, 1782, 1600, 1250, 1244, 1162, 749 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{22}H_{19}NO_3Na$ 368.1257, found 363.1253.

cis-Ethyl-1-cyano-3-formyl-6-(furan-2-yl)-5-methylenecyclohex-3-enecarboxylate (*cis*-3p)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.64 (s, 1H), 7.28 (d, J = 0.7 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 6.32 – 6.23 (m, 1H), 6.04 (d, J = 3.2 Hz, 1H), 5.83 (s, 1H), 5.68 (s, 1H), 4.58 (s, 1H), 4.42 – 4.15 (m, 2H), 3.06 (d, J = 18.4 Hz, 1H), 2.65 (d, J = 18.4 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.1, 165.8, 149.6, 144.7, 143.0, 138.2, 135.6, 127.2, 118.1, 110.6, 109.3, 63.4, 46.2, 46.1, 25.1, 13.9. oil, IR (KBr): 2984, 2938, 2835, 2723, 2243, 1749, 1680, 1426, 1251, 1165 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{16}H_{15}FO_4Na$ 308.0893, found 303.0898.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-(2-methylstyryl)cyclohex-3-enecarboxylate (*cis*-3q)

^{1}H NMR (400 MHz, CDCl3) δ 9.55 (s, 1H), 7.21 – 7.17 (m, 1H), 7.14 – 7.02 (m, 4H), 6.66 (d, J = 15.5 Hz, 1H), 5.73 – 5.65 (m, 2H), 5.61 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.89 (d, J = 8.2 Hz, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.84 (d, J = 18.5 Hz, 1H), 2.21 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ = 191.0, 164.9, 143.6, 138.8, 134.5, 134.0, 133.9, 132.4, 129.3, 127.2, 125.3, 125.2, 124.9, 123.4, 117.2, 62.2, 49.4, 45.4, 24.4, 18.7, 13.0. oil. IR (KBr): 2961, 2928, 2851, 2321, 2241, 1745, 1684, 1449, 1252, 1016 cm^{-1}; HRMS (ESI/[M + Na]$^+$) Calcd. for: $C_{21}H_{21}NO_3Na$ 358.1414, found 358.1417.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-((*E*)-prop-1-enyl)cyclohex-3-enecarboxylate (*cis*-3r)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.52 (s, 1H), 7.04 (s, 1H), 5.61 – 5.51 (m, 1H), 5.11 (ddd, J = 14.9, 7.9, 1.3 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.66 (d, J = 7.9 Hz, 1H), 2.92 (d, J = 18.3 Hz, 1H), 2.73 (d, J = 18.0 Hz, 1H), 1.59 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.1, 165.0, 149.5, 143.8, 139.0, 130.8, 124.9, 123.6, 117.4, 62.1, 49.0, 24.0, 21.1, 17.0, 13.0.

oil IR (KBr): 2966, 2928, 2854, 2320, 2245, 1743, 1687, 1443, 1252, 1029 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{20}H_{18}ClNO_3Na$ 282.1101, found 282.1107.

cis-Ethyl-6-(2-chlorostyryl)-1-cyano-3-formyl-5-methylenecyclohex-3-enecarboxylate (*cis*-3s)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.55 (s, 1H), 7.30 (dd, J = 6.0, 3.3, 1H), 7.26 (dd, J = 6.0, 3.3 Hz, 1H), 7.12 (dd, J = 6.0, 3.3, 3H), 6.83 (d, J = 15.6 Hz, 1H), 5.78 (dd, J = 15.6, 8.5 Hz, 1H), 5.72 (s, 1H), 5.62 (s, 1H), 4.30 – 4.19 (m, 2H), 3.94 (d, J = 8.4 Hz, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.81 (d, J = 18.9 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.0, 164.8, 143.4, 138.3, 133.9, 132.9, 132.1, 130.5, 128.7, 128.4, 126.0, 126.0, 125.7, 124.7, 117.1, 62.4, 49.4, 45.3, 24.2, 13.0. oil. IR (KBr): 2984, 2936, 2836, 2724, 2350, 2243, 1746, 1684, 1572, 1242, 1162 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{20}H_{18}ClNO_3Na$ 378.0867, found 378.0863.

cis-Ethyl-1-cyano-3-formyl-5-methylene-6-styrylcyclohex-3-enecarboxylate (*cis*-3t)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.56 (s, 1H), 7.27 – 7.17 (m, 1H), 7.10 (s, 1H), 6.42 (d, J = 15.6 Hz, 1H), 5.82 (dd, J = 15.4, 8.1 Hz, 1H), 5.70 (s, 1H), 5.59 (s, 1H), 4.30 – 4.17 (m, 1H), 3.87 (d, J = 7.9 Hz, 1H), 2.99 (d, J = 18.6 Hz, 1H), 2.81 (d, J = 18.6 Hz, 1H), 1.25 (t, J = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.1, 164.9, 143.6, 138.6, 134.6, 134.2, 133.9, 127.7, 127.7, 127.4, 125.6, 125.5, 125.5, 121.7, 117.2, 62.3, 49.3, 45.3, 24.3, 13.1. oil. IR (KBr): 2981, 2928, 2851, 2728, 2375, 2243, 1745, 1684, 1447, 1249, 1164 cm^{-1}; **HRMS** (ESI/[M + Na]$^+$) Calcd. for: $C_{20}H_{19}NO_3Na$ 344.1257, found 344.1260.

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Notes and references

1 For general review on domino reaction, see for example: (*a*) D. Enders, C. Grondal and M. R. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*b*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; (*c*) H.-C. Guo and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*e*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131.

2 J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498.

3 C. A. Evans and S. J. Miller, *J. Am. Chem. Soc.*, 2003, **125**, 12394.

4 D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861.

5 For selected examples see: (*a*) L. Zu, J. Wang, H. Li, H. Xie, W. Jiang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 1036; (*b*) P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404.

6 M. M. Rauhut and H. Currier,(American Cyanamid Co.), *U. S. Patent* 3,074,999, 1963; *Chem Abstr.*1963581124a.

7 For general review on RC reaction, see for example: (*a*) C. E. Aroyan, A. Dermenci and S. J. Miller, *Tetrahedron*, 2009, **65**, 4069; (*b*) J. L. Methot and W. R. Roush, *Adv. Synth. Catal.*, 2004, **346**, 1035.

8 J.-K. Erguden and H. W. Moore, *Org. Lett.*, 1999, **1**, 375.

9 (*a*) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.*, 2002, **124**, 2402; (*b*) S. A. Frank, D. J. Mergott and W. R. Roush, *J. Am. Chem. Soc.*, 2002, **124**, 2404.

10 (*a*) D. J. Mergott, S. A. Frank and W. R. Roush, *Org. Lett.*, 2002, **4**, 3157; (*b*) J. L. Methot and W. R. Roush, *Org. Lett.*, 2003, **5**, 4223.

11 (*a*) S. M. Winbush, D. J. Mergott and W. R. Roush, *J. Org. Chem.*, 2008, **73**, 1818; (*b*) D. J. Mergott, S. A. Frank and W. R. Roush, *Proc. Natl. Acad. Sci. USA* 2004, **101**, 11955.

12 L. M. Stark, K. Pekari and E. J. Sorensen, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 12064.

13 J. L. Methot and W. R. Roush, *Org. Lett.*, 2003, **5**, 4223.

14 (*a*) K. Agapiou and M. J. Krische, *Org. Lett.*, 2003, **5**, 1737; (*b*) P. Webber and M. J. Krische, *J. Org. Chem.*, 2008, **73**, 9379.

15 (*a*) P. M. Brown, N. Käppel and P. J. Murphy, *Tetrahedron Lett.*, 2002, **43**, 8707; (*b*) B. G. Jellerichs, J.-R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 7758; (*c*) M. Couturier, F. Ménard, J. A. Ragan, M. Riou, E. Dauphin, B. M. Andresen, A. Ghosh, K. Dupont-Gaudet and M. Girardin, *Org. Lett.*, 2004, **6**, 1857; (*d*) A. L. Luis and M. J. Krische, *Synthesis*, 2004, **15**, 2579; (*e*) M. E. Krafft and T. F. N. Haxell, *J. Am. Chem. Soc.*, 2005, **127**, 10168; (*f*) R. K. Thalji and W. R. Roush, *J. Am. Chem. Soc.*, 2005, **127**, 16778; (*g*) M. E. Krafft, K. A. Seibert, T. F. N. Haxell and C. Hirosawa, *Chem. Commun.*, 2005, 5772; (*h*) M. E. Krafft and K. A. Seibert, *Synlett*, 2006, 3334; (*i*) M. E. Krafft, T. F. N. Haxell, K. A. Seibert and K. A. Abboud, *J. Am. Chem. Soc.*, 2006, **128**, 4174; (*j*) M. E. Krafft and J. A. Wright, *Chem. Commun.*, 2006, 2977; (*k*) C. E. Aroyan and S. J. Miller, *J. Am. Chem. Soc.*, 2007, **129**, 256; (*l*) F. Seidel and J. A. Gladysz, *Synlett*, 2007, 986; (*m*) P. M. Brown, N. Käppel, P. J. Murphy and M. B. Hursthouse, *Tetrahedron*, 2007, **63**, 1100; (*n*) F. O. Seidel and J. A. Gladysz, *Adv. Synth. Catal.*, 2008, **350**, 2443; (*o*) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, Daniel Könning, R. M. de Figueiredo and M. Christmann, *Org. Lett.*, 2009, **11**, 4116; (*p*) C. E. Aroyan, A. Dermenci and S. J. Miller, *J. Org. Chem.*, 2010, **75**, 5784; (*q*) Y. Qiao, S. Kumar and W. P. Malachowski, *Tetrahedron Lett.*, 2010, **51**, 2636.

16 (*a*) X. Sun, S. Sengupta, J. L. Petersen, H. Wang, J. P. Lewis and X. Shi, *Org. Lett.*, 2007, **9**, 4495; (*b*) L. Cai, B. Zhang, G. Wu, H. Song and Z. He, *Chem. Commun.*, 2011, **47**, 1045.

17 (*a*) T. E. Reynolds, M. S. Binkley and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 2449; (*b*) P. Shanbhag, P. R. Nareddy, M. Dadwal, S. M. Mobin and I. N. N. Namboothiri, *Org. Biomol. Chem.*, 2010, **8**, 4867; (*c*) C. A. Evans and S. J. Miller, *J. Am. Chem. Soc.*, 2003, **125**, 12394; (*d*) C. Zhong, Y. Chen, J. L. Petersen, N. G. Akhmedov and X. Shi, *Angew. Chem., Int. Ed.*, 2009, **48**, 1279.

18 N. T. McDougal and S. E. Schaus, *Angew. Chem., Int. Ed.*, 2006, **45**, 3117.

19 J. Wang, H. Xie, H. Li, L. Zu and W. Wang, *Angew. Chem., Int. Ed.*, 2008, **47**, 4177.

20 W. Yao, Y. Wu, G. Wang, Y. Zhang and C. Ma, *Angew. Chem., Int. Ed.*, 2009, **48**, 9713.

21 (*a*) Y. Wei and M. Shi, *Acc. Chem. Res.*, 2010, **43**, 1005 and the references cited therein; (*b*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680–3681; (*c*) K. Matsui, K. Tanaka, A. Horii, S. Takizawa and H. Sasai, *Tetrahedron: Asymmetry*, 2006, **17**, 578; (*d*) S. Takizawa, N. Inoue, S. Hirata and H. Sasai, *Angew. Chem., Int. Ed.*, 2010, **49**, 9725.

22 For the utilization of functionalized cyclohexene see: Y. S. Tran and O. Kwon, *J. Am. Chem. Soc.*, 2007, **129**, 12632 and the references cited therein.

23 (*a*) X. Meng, Y. Huang and R. Chen, *Chem.–Eur. J.*, 2008, **14**, 6852; (*b*) X. Meng, Y. Huang and R. Chen, *Org. Lett.*, 2009, **11**, 137; (*c*) X. Meng, Y. Huang, H. Zhao, P. Xie, J. Ma and R. Chen, *Org. Lett.*, 2009, **11**, 991; (*d*) P Xie, Y. Huang and R. Chen, *Org. Lett.*, 2010, **12**, 3768; (*e*) J. Ma, Y. Huang and R. Chen, *Org. Biomol. Chem.*, 2011, **9**, 1791; (*f*) J. Ma, P. Xie, C. Hu, Y. Huang and R. Chen, *Chem.–Eur. J.*, 2011, **17**, 7418.

24 CCDC-769828(*trans*-**3a**), 769829 (*cis*-**3a**) contain the supplementary crystallographic data for this paper†.

25 (*a*) Q. Sun, L. Shi, Z. Ge, T. Chen and R. Li, *Chin. J. Chem.*, 2005, **23**, 745; (*b*) Y. Uozumi, A. Tanahashi, S.-Y. Lee and T. Hayashi, *J. Org. Chem.*, 1993, **58**, 1945.

