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Enantio- and Diastereoselective Organocatalytic α-Alkylation of Aldehydes with 3-Substituted 2-(Bromomethyl)acrylates

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Ⓢ *Supporting Information*

ABSTRACT: The catalytic direct α-alkylation of aldehydes with 2-(bromomethyl)acrylates has been accomplished, giving rise to α-branched and functionalized aldehydes of high diastereo- and enantiopurity. The influence of the nature of the ester group of the acrylates in reaction stereoselectivity and especially in reactivity is investigated. Optimum conditions implicate the use of phenyl acrylates in conjunction with organocatalyst **8**. Application of thus obtained adducts in synthesis is illustrated with a concise stereocontrolled preparation of trisubstituted cyclopentenes.
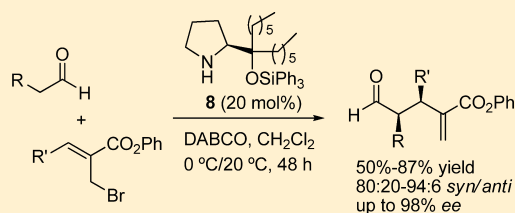
Forming new carbon−carbon bonds directly adjacent to a carbonyl group constitutes one of the most versatile tools during the construction of molecular complexity; therefore, direct, catalytic, and asymmetric methodologies for the α-alkylation of enolate equivalents are of great demand. While most traditional studies have been focused on the α-alkylation of carboxylic acid derivatives,[1] and also ketones,[2] recent works based on the in situ generation of enamines as nascent enolate equivalents,[3,4] have allowed the realization of the direct α-alkylation of aldehydes using a variety of electrophilic alkylating reagents. Namely, ω-iodoaldehydes via an intramolecular SN2 mechanism,[5,6] vinyl trifluoroborates, olefins, nitroalkanes, allylsilanes, Togni's reagent, and active bromides and iodides via radical or organophotoredox mechanisms,[7] or propargylic alcohols,[8] diarylmethanols,[9] 3-(1-arylsulfonylalkyl)indoles,[10] and benzydryl halides[11] via a SN1 pathway,[12] have been reported. In this context, and complementing the above developments, we have recently reported a mechanistically distinct enamine mediated asymmetric α-alkylation of aldehydes which relies on the use of 2-(bromomethyl)acrylates as the alkylating reagent and most likely proceeds via a SN2′ pathway.[13] Our preliminary study was largely restricted to the use of **2**, a relatively reactive alkylating reagent since the acrylate β (or 3)-position remains unsubstituted. In contrast, initial experiments soon evidenced difficulties in extending this methodology to superior, 3-substituted 2-(bromomethyl)-acrylates **5**, which logically exhibit attenuated reactivity. Furthermore, for β-substituted acrylates **5** control of the relative configuration of the resulting products becomes an additional concern of no obvious solution. Now, we have developed conditions that satisfactorily address these two limiting aspects thus expanding the range of alkylating reagents amenable for this direct and enantioselective aldehydes α-alkylation methodology.

At the outset, we were optimistic that the aldehydes alkylation protocol according to Scheme 1 would also be

Scheme 1. SN2′-Type Enamine-Mediated Asymmetric α-Alkylation of Aldehydes with 2-(Bromomethyl)acrylates
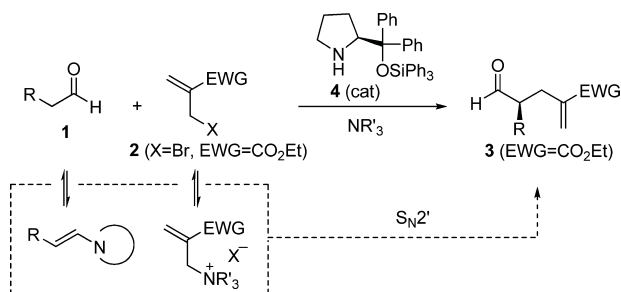
applicable to β-substituted acrylates, thus giving access to a relatively wide range of α-branched aldehyde products enantioselectively (Scheme 2). Unfortunately, this was not the case as, for example, the reaction of butyraldehyde **1A** with β-phenyl substituted acrylate **5a** in the presence of DABCO and a 20 mol % of catalyst **4** resulted unpractical (Table 1, entry 1) under several conditions examined. Reactions carried out in the presence of DMAP proceed even worse (entry 2). Similar constrains in reactivity were observed again with the ethyl acrylate **5b** which bears a *p*-chlorophenyl substituent. In this instance, however, the measured level of reaction stereoselectivity was highly promising regardless of the amine catalyst used (entries 3−5), an observation that prompted us to investigate several other reaction parameters. During the study it was eventually found that the ester group has a critical

Scheme 2. Organocatalytic α-Alkylation of Aldehydes with β-Substituted 2-(Bromomethyl)acrylates
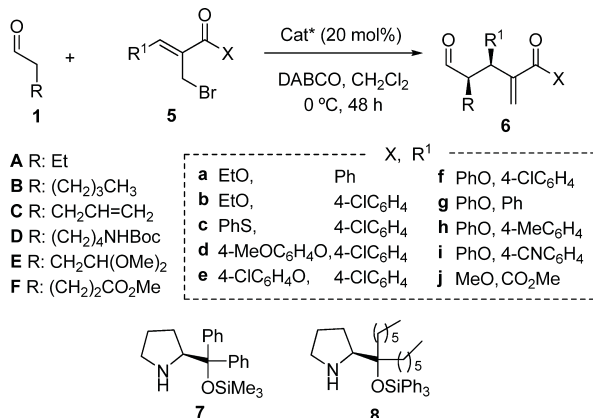
influence. Thus while thioester **5c** did not lead to any significant improvement under these conditions (entries 6–7), a considerable increase in reaction conversion was observed when phenyl ester **5f** was the alkylating partner employed: less significant with catalyst **4** (34% yield after 48 h, entry 8), but notable with catalysts **7** and **8** (60% and 67% yield, respectively, entries 9–10). Moreover, the latter two reactions proceeded with good *syn/anti* selectivity and excellent enantioselectivity for the major *syn* isomer, apparently being catalyst **8** slightly superior. Finally, it was observed that variation of the electronic nature of the ester aryl group, as in aryl acrylates **5d** and **5e**, did not provide any significant improvement and generally led to deleterious reactivity and/or selectivity (entries 11 and 12).

With the new conditions set, based on the use of *O*-phenyl acrylates, catalyst **8**, and DABCO as the coadyuvant amine base, the reaction with several aldehydes and β-substituted acrylates **5f–j** was explored (Table 2). It was gratifying to observe that the reaction proceeded with generally good yields for aldehydes bearing alkyl or alkenyl side chains (compounds **1A–C**), including those aldehydes with a carbamate, acetal, or ester functionality (compounds **1D–F**). With respect to the β-substituent of the acrylate, not only aryl, but also the ester group was tolerated (entries 5 and 9). Importantly, for the range of aldehydes and β-substituted 2-(bromoethyl) acrylates screened, the level of reaction diastereoselectivity display only

minor fluctuations in the range from 80:20 to 94:6, with ee's being around 95% or higher for the most cases. In general, a 6-fold excess aldehyde was used for optimum results; when using a 2-fold excess aldehyde reaction selectivity was maintained, but at expenses of an elapsed reaction time.

Regarding the reaction mechanism, previous work from this laboratory has provided theoretical as well as experimental evidence in support of a two step sequence for the alkylation reactions involving unsubstituted acrylate **2**. As outlined in Scheme 1, the first step would involve formation of the corresponding ammonium salt from **2** and DABCO or DMAP. Subsequent S_N2'-type displacement effected by in situ generated enamine species would then render product **3**. In the current examples with β-substituted acrylates **5**, formation of the corresponding ammonium salt **A** (Figure 1a) as reaction intermediate was confirmed in all cases by ^{1}H NMR monitoring of reaction aliquots. Interestingly, ammonium salts **B**, regioisomeric to **A**, were not observed within the limit of detection of ^{1}H NMR, a fact that further support a S_N2' type pathway for the subsequent C–C bond-forming step. On the other hand, NMR analysis also showed that both the *E*- and *Z*-configured ammonium salts **A**[14] are formed in compositions ranging from 60:40 to around 80:20 ratio in favor of *E*-**A** in all cases studied and that this ratio remains essentially unchanged at different reaction conversions for each individual case (Supporting Information). These observations seem to indicate that the reactivity of both the *E* and the *Z* ammonium salts during the key S_N2' process, is comparable. Alternatively, a scenario with differences in reactivity between the *E* and *Z* isomers, but fast *E/Z* equilibration, cannot be ruled out. On the other hand, the observed stereochemical outcome of the reaction may be explained by invoking an open (*antiperiplanar*) transition state with the enamine in its most stable, *E/s-trans*, configuration. As the stereomodels in Figure 1b show, upon this assumption the *Si*–*Si* approach would be the most favorable in order to minimize severe gauche interactions, which would nicely predict the observed sense of stereo-induction.

In order to illustrate the utility of this catalytic reaction (eq 1), an aldehyde protection–Grubbs cyclization sequence was applied to adducts **6Cf** and **6Ch** which rendered trisubstituted cyclopentenes **9** and **10** as the only isolated diastereomers in good yield and excellent enantioselectivity. Both the absolute

Table 1. Screening of the Catalyst and the Ester Group X of 5 for the Alkylation of 1A[a]

entry	X	R[1]	product	cat.	yield (%)	*syn/anti*[b]	ee[c] (%)
1	EtO	Ph	**6Aa**	4	30	90:10	98
2					<5[d]	ND	ND
3	EtO	4-ClC₆H₄	**6Ab**	4	<10[e]	81:19	99
4				7	20[e]	88:12	95
5				8	<10[e]	ND	ND
6	PhS	Ph	**6Ac**	4	24[e]	70:30	98
7				8	20[e]	70:30	95
8	PhO	4-ClC₆H₄	**6Ad**	4	34[e]	85:15	97
9				7	60	87:13	98
10				8	67	91:9	95
11	4-MeOC₆H₄O		**6Ad**	4	<10[e]	ND	ND
12	4-ClC₆H₄O		**6Ae**	4	62	85:15	ND

[a]Reactions carried out on a 0.3 mmol scale. General conditions: aldehyde (1.8 mmol), bromide (0.3 mmol), DABCO (0.3 mmol), and catalyst (20 mol %) were stirred in CH₂Cl₂ at 0 °C for 48 h. [b]Determined by ^{1}H NMR. [c]ee of major (*syn*) diastereomer determined by chiral HPLC of crude product before chromatography. [d]Using DMAP. [e]Incomplete reaction after 48 h.

Table 2. Scope of the Aldehyde and the β-Substituted 2-(Bromomethyl)acrylate[a]

entry	aldehyde	acrylate	R[1]	product	T (°C)	yield (%)	syn/anti[b]	ee[c] (%)
1	**1A**	**5f**	4-ClC$_6$H$_4$	**6Af**	0	67[d]	91:9	95
2		**5g**	Ph	**6Ag**	0	60	94:6	98
3		**5h**	4-MeC$_6$H$_4$	**6Ah**	20	83	89:11	95
4		**5i**	4-CNC$_6$H$_4$	**6Ai**	0	65	87:13	97
5		**5j**	CO$_2$Me	**6Aj**	0	66	87:13	98
6	**1B**	**5f**	4-ClC$_6$H$_4$	**6Bf**	0	50	92:8	98
7	**1C**	**5f**	4-ClC$_6$H$_4$	**6Cf**	0	78[e]	91:9	95
8		**5h**	4-MeC$_6$H$_4$	**6Ch**	0	62	92:8	96
9		**5j**	CO$_2$Me	**6Cj**	0	64	82:18	96
10	**1D**	**5f**	4-ClC$_6$H$_4$	**6Df**	20	87	90:10	94
11	**1E**	**5f**	4-ClC$_6$H$_4$	**6Ef**	20	69	81:19	90
12	**1F**	**5f**	4-ClC$_6$H$_4$	**6Ff**	20	65	80:20	87

[a]Reactions carried out on a 0.3 mmol scale. General conditions: aldehyde (1.8 mmol), 2-(bromomethyl)acrylate (0.3 mmol), DABCO (0.3 mmol), and catalyst **8** (20 mol %) were stirred in CH$_2$Cl$_2$ for 48 h at the indicated temperature. [b]Determined by ^{1}H NMR. [c]ee of major (syn) diastereomer determined by HPLC of crude product before chromatography. [d]Using catalyst **7**. [e]Reactions carried out at 1.4 mmol scale.
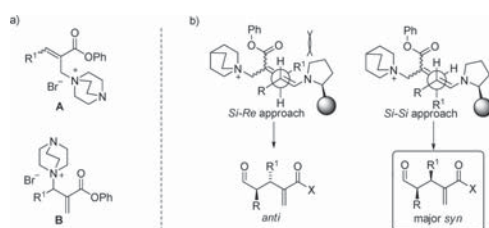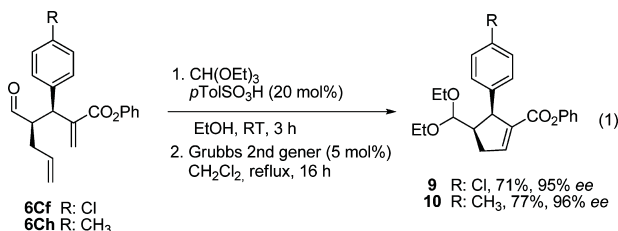

Figure 1. (a) Two possible regioisomeric ammonium salt intermediates and (b) proposed transition state models that would account for the formation of syn and anti products from **A**.

$$ \text{(1)} $$

6Cf R: Cl
6Ch R: CH$_3$

1. CH(OEt)$_3$
   pTolSO$_3$H (20 mol%)
   EtOH, RT, 3 h
2. Grubbs 2nd gener (5 mol%)
   CH$_2$Cl$_2$, reflux, 16 h

9 R: Cl, 71%, 95% ee
10 R: CH$_3$, 77%, 96% ee

and the relative configuration of **9** were unequivocally established by X-ray structure analysis. Thus configurational assignment of the precursor **6Cf** was made by correlation and for the remaining adducts by analogy assuming a uniform reaction mechanism.

In conclusion, the present catalytic system introduces an operationally simple protocol for the α-alkylation of aldehydes with β-substituted α-(bromomethyl)acrylates. A distinguishing feature of the method is that the C−C bond forming step proceeds with concomitant generation of two contiguous stereocenters with high diastereo- and enantioselectivity. The method, moreover, provides a quick entry for the stereo-controlled synthesis of trisubstituted 5-membered carbocycles, an important class of products for further elaboration.[15]

■ EXPERIMENTAL SECTION

General and Materials. All solvents were of p.a. quality and were dried by standard procedures prior to use when necessary. Materials were obtained from commercial sources and used without purification unless otherwise specified. Aldehydes were obtained from commercial sources or prepared through known procedures, purified by distillation and stored in the refrigerator at −30 °C under argon. Aldehydes **1E** and **1F** were prepared according to the procedures of Tanaka[16] and

Watanabe,[17] respectively. Aldehyde **1D** was prepared as described below. Catalyst **7** was obtained from commercial sources and immediately before use was dissolved in CH$_2$Cl$_2$ and washed with saturated NaHCO$_3$ aqueous solution. Catalysts **4** and **8** were prepared following previously reported methods.[13,18] ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz instruments. Chemical shifts are reported in ppm relative to CDCl$_3$ (δ = 7.26) for ^{1}H NMR and to the central resonances of CDCl$_3$ (δ = 77.0) for ^{13}C NMR. Analytical high performance liquid chromatography (HPLC), optical rotations, and MS spectra were recorded on standard instruments. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (0.040−0.063 mm, 230−400 mesh). Visualization (TLC) was accomplished with a solution of phosphomolybdic acid (1 g) in 100 mL of ethanol (limited lifetime), followed by heating.

Preparation of Aldehyde 1D. The following procedure adapted from Cushman et al.[19] was employed. CH$_2$Cl$_2$ (100 mL) and (COCl)$_2$ (3.9 mL, 46 mmol, 1.5 equiv) were successively placed in an oven-dried three-necked flask, and the solution was cooled to −60 °C under dry Ar. DMSO (4.8 mL, 68 mmol) in CH$_2$Cl$_2$ (15 mL) was added at a rate where a temperature below −60 °C was maintained. The mixture was then stirred for ca. 5 min followed by dropwise addition of a solution of the N-Boc aminohexanol (31 mmol) in CH$_2$Cl$_2$ (25 mL) over a period of ca. 5 min. The mixture was stirred for an additional 25 min, then rapidly quenched with Et$_3$N (22 mL, 0.16 mol). The obtained white slurry was stirred for ca. 5 min and then allowed to warm to room temperature. The reaction mixture was washed with water (300 mL) and the aqueous layer was extracted with Et$_2$O (300 mL). The combined organic layers were washed with brine (2 × 200 mL). The residue was subjected to flash chromatography (eluent: n-hexane/ethyl acetate 5:1), yielding a colorless oil (yield 90%) with physical and spectroscopic data coincident with previously reported.[19]

Preparation of 2-(Bromomethyl)acrylates 5e−i. A three-step sequence was applied following procedures adapted from literature.[20,21] Acryloylchloride (7.28 g, 80 mmol) in dichloromethane (10 mL) was added within 0.5 h to a solution of the corresponding aryl alcohol (80 mmol) and triethylamine (10.1 g, 100 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 24 h, then washed with water (2 × 30 mL) and extracted with dichloromethane (2 × 10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexane/EtOAc 95:5) to give the aryl acrylate as a colorless oil. Ten mmol of this acrylate was added to a solution of DABCO (360 mg, 3 mmol) and the corresponding aldehyde (5 mmol) in DMF (5 mL), and the reaction mixture was stirred at room temperature for 60 h. The reaction product was extracted with dichloromethane (100 mL) and washed with water (3 × 100 mL). The organic layer was dried over anhydrous MgSO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash

silica gel column chromatography (hexane/EtOAc 8:2) to give the corresponding Baylis−Hillman adducts. To a solution of thus obtained adduct (3 mmol) in dichloromethane (10 mL) LiBr (6 mmol) and previously prepared NaHSO$_4$·SiO$_2$[22] (300 mg) were added. The mixture was stirred at room temperature and the reaction was monitored by TLC. On completion the mixture was filtered and the filtrate was concentrated and subjected to flash column chromatography over silica gel (hexane/EtOAc 95:5 to 90:10).

Data of 5e. Starting from 4-chlorophenol (step 1, 10 mmol) and 4-chlorobenzaldehyde (step 2): overall yield 65%; white solid; mp 70.8 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.95 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.3, 149.2, 143.1, 139.2, 136.2, 132.3, 131.0, 130.4, 129.3, 128.5, 122.9, 26.0; HRMS C$_{16}$H$_{11}$BrCl$_2$O$_2$ [M + H]$^+$ calcd 386.9380, found 386.9377.

Data of 5f. Starting from phenol (step 1, 30 mmol) and 4-chlorobenzaldehyde (step 2): overall yield 65%; white solid; mp 77 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.99 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.52−7.35 (m, 4H), 7.33−7.21 (m, 3H). 4.49 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.4, 150.7, 142.7, 138.8, 136.0, 132.4, 131.0, 129.4, 129.2, 125.9, 121.5, 26.9; HRMS C$_{16}$H$_{12}$BrClO$_2$ [M + H]$^+$ calcd 352.9780, found 352.9766.

Data of 5g. Starting from phenol (step 1, 10 mmol) and benzaldehyde (step 2); overall yield 58%; white solid; mp 58−60 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (s, 1H), 7.65 (d, J = 6.8 Hz, 2H), 7.54−7.40 (m, 5H), 7.30−7.20 (m, 3H), 4.51 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.7, 150.8, 144.3, 134.0, 128.9, 125.9, 121.6, 26.6; HRMS C$_{16}$H$_{13}$BrO$_2$ [M + H]$^+$ calcd 317.0177, found 317.0180.

Data of 5h. Starting from phenol (step 1, 10 mmol) and 4-methylbenzaldehyde (step 2): overall yield 63%; white solid; mp 68 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.83 Hz 2H), 7.36−7.20 (m, 5H), 4.56 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.9, 150.9, 144.5, 140.5, 131.2, 130.0, 129.7, 129.4, 127.4, 125.8, 121.6, 26.9, 21.4; HRMS C$_{17}$H$_{15}$BrO$_2$ [M + H]$^+$ calcd 331.0332, found 331.0334.

Data of 5i. Starting from phenol (step 1, 10 mmol) and 4-cyanobenzaldehyde (step 2): overall yield 14%; white solid; mp 106.3 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.98 (s, 1H), 7.75 (dd, J = 8.4, 20.9 Hz, 4H), 7.44 (t, J = 7.8 Hz, 2H), 7.33−7.18 (m, 3H), 4.41 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.1, 150.7, 141.5, 138.5, 132.6, 131.3, 129.9, 129.6, 126.2, 121.4, 118.1, 115.3, 113.3, 25.2; HRMS C$_{17}$H$_{12}$BrNO$_2$ [M + H]$^+$ calcd 342.0144, found 342.0130.

Preparation of 5j. (Adapted from the literature.[23]) A mixture of dimethyl methylmaleate (1.58 g, 10 mmol), N-bromosuccinimide (2.67 g, 15 mmol), and a catalytic amount of AIBN (33 mg, 0.20 mmol) in carbon tetrachloride (50 mL) was gently refluxed for 12 h in a 100 mL round-bottom flask. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl$_4$ (4 mL × 2); the combined organic layer was washed with water (15 mL) and brine (10 mL) and then dried over Na$_2$SO$_4$. The organic layer was concentrated in vacuo to furnish a thick yellow oil, which was purified by flash column chromatography on silica gel (hexane/ethyl acetate 90:10). The product's physical and chemical characterization data were coincident with the reported data.[23]

General Procedure for the Catalytic α-Alkylation of Aldehydes with 5. A solution of the corresponding 2-(bromomethyl)-3-(aryl)acrylate **5** (0.3 mmol) and DABCO (39 mg, 0.315 mmol) in CH$_2$Cl$_2$ (1 mL) was stirred at room temperature for 30 min and then was cooled to the specified temperature (Table 2). To this cooled solution were successively added freshly distilled aldehyde **1** (6 equiv) and catalyst **8** (0.06 mmol, 20 mol %). The mixture was stirred at specified temperature and time (see below), then diluted with dichloromethane (10 mL), washed with H$_2$O (10 mL), HCl 1 N (10 mL) and brine (10 mL), and dried with anhydrous MgSO$_4$. The solvent was evaporated under vacuum and the crude material was purified by flash chromatography (eluent EtOAc/Hex from 2:98 to 10:90).

(3S,4R)-Phenyl 3-(4-chlorophenyl)-4-formyl-2-methylene-hexanoate (6Af) (Entry 1, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (106 mg, 0.3 mmol),

DABCO (39 mg, 0.315 mmol), and butanal (0.16 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a colorless oil. Yield: 67% (69 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.61 (d, J = 4.2 Hz, 1H), 7.39−7.21 (m, 7H), 7.01−6.99 (m, 2H), 6.61 (s, 1H), 5.94 (s, 1H), 4.25 (d, J = 11.5 Hz, 1H), 2.98−2.88 (m, 1H), 1.53−1.43 (m, 2H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.2, 164.8, 150.6, 141.0, 137.9, 130.0, 128.9, 125.9, 121.5, 56.3, 45.4, 21.2, 11.0. The diastereomeric ratio (91:9) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 254 nm (hexane/[i]PrOH in the ratio of 90/10, flow rate = 0.5 mL/min, t$_R$ = 15.8 min (minor), t$_R$ = 16.6 min (major)); HRMS C$_{20}$H$_{20}$ClO$_3$ [M + H]$^+$ calcd 343.1101, found 343.1089.

(3S,4R)-Phenyl 4-Formyl-2-methylene-3-phenylhexanoate (6Ag) (Entry 2, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-phenylacrylate (95 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and butanal (0.16 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a colorless oil. Yield: 60% (55 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.59 (d, J = 4.3 Hz, 1H), 7.35−7.17 (m, 7H), 7.21−7.18 (m, 1H), 6.96 (d, 2H, J = 7.6 Hz), 6.57 (s, 1H), 5.92 (s, 1H), 4.25 (d, 1H, J = 11.5 Hz), 2.95−2.89 (m, 1H), 1.50−1.43 (m, 2H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.7, 165.0, 150.7, 141.3, 139.3, 129.4, 128.7, 127.2, 125.8, 121.5, 56.7, 46.0, 21.2, 11.1. The diastereomeric ratio (94:6) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack AS-H column at 210 nm (hexane/[i]PrOH in the ratio of 98/2, flow rate = 0.5 mL/min, t$_R$ = 19.9 major, t$_R$ = 22.0 min); HRMS C$_{20}$H$_{20}$O$_3$ [M + H]$^+$ calcd 309.1491, found 309.1504.

(3S,4R)-Phenyl 4-Formyl-2-methylene-3-p-tolylhexanoate (6Ah) (Entry 3, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-p-tolylacrylate (99 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and butanal (0.16 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a colorless oil. Yield: 83% (80 mg). Spectroscopical data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.59 (d, J = 4.3 Hz, 1H), 7.41−7.30 (m, 2H), 7.28−7.10 (m, 5H), 7.02−6.95 (m, 2H), 6.56 (s, 1H), 5.91 (s, 1H), 4.23 (d, J = 11.5 Hz, 1H), 2.97−2.85 (m, 1H), 2.34 (s, 3H) 1.53−1.41 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.8, 165.0, 150.8, 141.5, 136.8, 136.2, 129.3, 128.5, 126.9, 125.7, 121.5, 56.6, 45.6, 21.1, 21.0, 11.1. The diastereomeric ratio (89:11) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack AS-H column at 254 nm (hexane/iPrOH in the ratio of 95:5, flow rate = 0.5 mL/min t$_R$ = 18.5 min (major), t$_R$ = 21.0 min (minor)); HRMS C$_{21}$H$_{22}$O$_3$ [M + H]$^+$ calcd 322.1569, found 322.1584.

(3S,4R)-Phenyl 3-(4-cyanophenyl)-4-formyl-2-methylene-hexanoate (6Ai) (Entry 4, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-(4-cyanophenyl)acrylate (103 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and butanal (0.16 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a colorless oil. Yield: 65% (65 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.60 (d, J = 3.9 Hz, 1H), 7.63 (dd, J = 1.7, 6.6 Hz, 2H), 7.47−7.17 (m, 5H), 6.97 (dd, J = 1.1, 7.5 Hz, 2H), 6.64 (s, 1H), 5.97 (s, 1H), 4.31 (d, J = 11.6 Hz, 1H), 3.03−2.92 (m, 1H), 1.55−1.36 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.5, 164.5, 150.4, 145.0, 140.2, 135.5, 132.4, 129.5, 128.0, 126.0, 121.3, 118.5, 111.2, 55.8, 46.0, 21.1, 10.9. The diastereomeric ratio (87:13) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 254 nm (hexane/iPrOH in the ratio of 90/10, flow rate = 0.5 mL/min, t$_R$ = 40.2 min (major), t$_R$ = 45.4 min (minor)); HRMS C$_{21}$H$_{19}$NO$_3$ [M + H]$^+$ calcd 334.1443, found 334.1436.

(3R,4R)-Methyl 3-(Methoxycarbonyl)-4-formyl-2-methylene-hexanoate (6Aj) (Entry 5, Table 2). Starting from dimethyl

bromomethylfumarate (72 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and butanal (0.16 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 90/10) to give the title compound as a colorless oil. Yield: 66% (45 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.59 (d, J = 2.6 Hz, 1H), 6.43 (s, 1H), 5.82 (s, 1H), 4.00 (d, J = 8.7 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.90−2.80 (m, 1H), 1.81−1.69 (m, 2H), 0.93 (t, J = 3.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.0, 171.9, 166.3, 136.1, 128.7, 54.7, 52.3, 45.8, 20.5, 11.5. The diastereomeric ratio (87:13) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 209.8 nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min, t_R = 48.8 min (mayor), t_R = 53.3 min (minor)); HRMS C$_{11}$H$_{16}$O$_5$ [M + H]$^+$ calcd 229.1076, found 229.1075.

(3S,4R)-Phenyl 3-(4-Chlorophenyl)-4-formyl-2-methyleneoctanoate (6Bf) (Entry 6, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (106 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and hexanal (0.22 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 98/2) to give the title compound as a yellow oil. Yield: 50% (57 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.56 (d, J = 4.7 Hz, 1H), 7.36−7.18 (m, 7H), 6.99 (d, J = 8.4 Hz, 2H), 6.58 (s, 1H), 5.91 (d, J = 0.9 Hz, 1H), 4.20 (d, J = 11.5 Hz, 1H), 3.01−2.91 (m, 1H), 1.38−1.06 (m, 6H), 0.92−0.86 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.3, 150.6, 141.0, 138.0, 133.1, 130.1, 126.0, 121.5, 54.9, 45.8, 28.7, 22.5, 13.7. The diastereomeric ratio (92:8) was determined by ^{1}H NMR.The enantiomeric excess was determined by HPLC with Chiralpack IB column at 210 nm (hexane/^{i}PrOH in the ratio of 99/1, flow rate = 0.5 mL/min, t_R = 15.9 min, t_R = 18.2 major); HRMS C$_{22}$H$_{24}$ClO$_3$ [M + H − C$_6$H$_5$O]$^+$ calcd 277.0995, found 277.1002.

(3S,4R)-Phenyl 3-(4-Chlorophenyl)-4-formyl-2-methylenehept-6-enoate (6Cf) (Entry 7, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (106 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and 4-pentenal (0.18 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a yellow oil. Yield: 78% (84 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.63 (d, J = 3.6 Hz, 1H), 7.39−7.29 (m, 4H), 7.25−7.18 (m, 3H), 7.00−6.96 (m, 2H), 6.58 (s, 1H), 5.91 (d, J = 1.0 Hz, 1H), 5.63 (dt, J = 8.5, 8.5, 17.1 Hz, 1H), 5.08−4.92 (m, 2H), 4.28 (d, J = 11.4 Hz, 1H), 3.14 (dd, J = 3.6, 11.4 Hz, 1H), 2.19 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.8, 164.7, 150.6, 140.8, 137.6, 135.6, 133.3, 130.0, 129.4, 128.9, 127.3, 125.9, 121.4, 118.1, 54.1, 45.3, 32.5. The diastereomeric ratio (91:9) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 254 nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate =0.5 mL/min, t_R = 22.0 min, t_R = 25.1 major); HRMS C$_{21}$H$_{20}$ClO$_3$ [M + H − C$_6$H$_5$O]$^+$ calcd 261.0682, found 261.0682.

(3S,4R)-Phenyl 4-Formyl-2-methylene-3-p-tolylhept-6-enoate (6Ch) (Entry 8, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-p-tolylacrylate (99 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and 4-pentenal (0.18 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 95/5) to give the title compound as a colorless oil. Yield: 62% (62 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.63 (d, J = 3.8 Hz, 1H), 7.34 (t, J = 7.7 Hz 2H), 7.22−7.11 (m, 4H), 7.00−6.96 (m, 2H), 6.83 (d, J = 7.6 Hz, 1H), 6.55 (s, 1H), 5.90 (d, J = 1.0 Hz, 1H), 5.65 (dt, J = 8.6, 17.2 Hz, 1H), 4.98 (dd, J = 6.1, 26.2 Hz, 2H), 4.25 (d, J = 11.4 Hz, 1H), 3.13 (dd, J = 3.9, 11.3 Hz, 1H), 2.34 (s, 3H), 2.38−2.30 (m, 1H), 2.21 (t, J = 6.8, Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.5, 165.0, 150.7, 141.4, 133.9, 129.5, 125.8, 121.5, 120.8, 117.8, 115.3, 54.6, 45.6, 32.7, 21.0. The diastereomeric ratio (92:8) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 254 nm (hexane/^{i}PrOH in the ratio of

97/3, flow rate = 0.5 mL/min, t_R = 15.5 min, t_R = 19.2 major); HRMS C$_{22}$H$_{22}$O$_3$ [M + H]$^+$ calcd 335.1647, found 335.1663.

(3R,4R)-Methyl 4-Formyl-3-methoxycarbonyl-2-methylene-hept-6-enoate (6Cj) (entry 9, Table2). Starting from dimethyl bromomethylfumarate (72 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol), and 4-pentenal (0.18 mL, 1.8 mmol), the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 98/2) to give the title compound as a colorless oil. Yield: 64% (46 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl3) δ 9.65 (d, J = 1.8 Hz, 1H), 6.43 (s, 1H), 5.81 (s, 1H), 5.78−5.65 (m, 1H), 5.07 (dd, J = 1.5, 5.3 Hz, 2H), 4.00 (d, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.10−3.02 (m, 1H), 2.57−2.50 (m, 1H), 2.37−2.31 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.6, 171.8, 166.1, 135.8, 134.2, 129.1, 127.4, 118.1, 52.4, 45.9, 31.3. The diastereomeric ratio (82:18) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 209.8 nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min, t_R = 37.5 min (minor), t_R = 44.7 min (major)); HRMS C$_{12}$H$_{17}$O$_5$ [M + H]$^+$ calcd 241.1076, found 241.1083.

(3S,4R)-Phenyl 8-(tert-Butoxycarbonylamino)-3-(4-chloro-phenyl)-4-formyl-2-methyleneoctanoate (6Df) (Entry 10, Table 2). Starting from (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (106 mg, 0.3 mmol), DABCO (39 mg, 0.315 mmol) and 6-(N-Boc-amino)hexanal (387 mg, 1.8 mmol). The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 87% (127 mg). Spectroscopic data of the major diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.60 (d, J = 4.2 Hz, 1H), 7.38−7.23 (m, 7H), 7.00 (d, J = 7.4 Hz, 2H), 6.61 (s, 1H), 5.95 (s, 1H), 4.23 (d, J = 11.5 Hz), 3.18−3.09(m, 1H), 3.07−2.96 (m, 2H), 1.51−1.48 (m, 2H), 1.47 (s, 3H), 1.46 (s, 6H), 1.41−1.31 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.0, 164.7, 155.9, 150.6, 140.9, 137.8, 133.2, 129.4, 129.0, 127.6, 126.0, 121.4, 70.8, 54.8, 45.8, 40.1, 30.0, 28.4, 27.7, 23.8. The diastereomeric ratio (90:10) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 254 nm (hexane/^{i}PrOH in the ratio of 80/20, flow rate =0.5 mL/min, t_R = 42.5 min (major), t_R = 46.2 min (minor); HRMS C$_{27}$H$_{33}$ClNO$_5$ [M + H − C$_5$H$_{10}$O$_2$]$^+$ calcd 368.1417, found 368.1416.

(3S,4R)-Phenyl 3-(4-Chlorophenyl)-4-formyl-6,6-dimethoxy-2-methylenehexanoate (6Ef) (Entry 11, Table 2). Starting from 4,4-dimethoxybutanal (3 mmol, 3 equiv), (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (176 mg, 0.5 mmol), and DABCO (56.1 mg, 0.51 mmol) at room temperature for 60 h according to the general procedure: yield 69% (140 mg) (diastereomeric ratio 5:1); ^{1}H NMR (major diastereoisomer) (300 MHz, CDCl$_3$) δ 9.67 (d, J = 3.3 Hz, 1H), 7.40−7.18 (m, 7H), 7.00−6.96 (m, 2H), 6.59 (s, 1H), 5.97 (d, 1H, J = 0.9 Hz), 4.26−4.20 (m, 2H), 3.24 (s, 3H), 3.22 (s, 3H), 1.90−1.80 (m, 2H), 1.63−1.53 (m, 1H); ^{13}C NMR (major diastereoisomer) (75 MHz, CDCl$_3$) δ 202.5, 164.6, 150.6, 140.6, 137.8, 133.2, 130.0, 129.9, 129.4, 128.9, 127.5, 125.9, 121.4, 103.0, 54.2, 53.3, 50.2, 46.1, 32.5. The diastereomeric ratio (81:19) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC with Chiralpack IA column at 254 nm (hexane/^{i}PrOH in the ratio of 98/2, flow rate = 0.5 mL/min, t_R = 31.9 min (major), t_R = 46.7 min (minor)).

(3S,4R)-7-Methyl 1-Phenyl 3-(4-chlorophenyl)-4-formyl-2-methyleneheptanedioate (6Ff) (Entry 12, Table 2). Starting from methyl 5-oxopentanoate (3 mmol, 3 equiv), (Z)-phenyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate (176 mg, 0.5 mmol), and DABCO (56.1 mg, 0.51 mmol) at room temperature for 60 h according to the general procedure: yield 65% (132 mg) (diastereomeric ratio 4:1); ^{1}H NMR (major diastereoisomer) (300 MHz, CDCl$_3$) 9.59 (d, J = 4.0 Hz, 1H), 7.37−7.30 (m, 3H), 7.27−7.21 (m, 4H), 6.99 (d, J = 8.4, 9.7 Hz, 2H), 6.60 (s, 1H), 5.94 (s, 1H), 4.24−4.21(m, 1H), 4.08 (t, J = 6.1 Hz, 2H), 3.68 (s, 3H) 2.44−2.38 (m, 2H), 1.74−1.70 (m, 2H); ^{13}C NMR (major diastereoisomer) (75 MHz, CDCl$_3$) δ 202.4, 172.8, 164.6, 150.5, 140.6, 137.3, 133.3, 129.0, 121.4, 63.9, 53.8, 51.6, 51.5, 46.0, 30.8, 28.0, 22.9, 21.4, 20.1. The diastereomeric ratio (80:20) was determined by ^{1}H NMR. The

enantiomeric excess was determined by HPLC with Chiralpack AS-H column at 210 nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min, t_R = 53.3 min (major), t_R = 60.0 min (minor)); HRMS $C_{22}H_{21}ClO_5$ [M + H − C_6H_5O]$^+$ calcd 308.0815, found 308.0794.

Ring-Closing Metathesis. Synthesis of Cyclopentenes 9 and 10. Triethyl orthoformate (429 μL, 2.58 mmol) and pTsOH·H$_2$O (32.7 mg, 0.17 mmol, 20 mol %) were added to a solution of the corresponding adduct **6C** (0.86 mmol) in EtOH (6 mL). The mixture was stirred for 3 h at room temperature. After dilution with dichloromethane (10 mL), the mixture was washed with 1% aqueous NaOH (10 mL) and brine (10 mL), and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), and evaporation of the solvent under reduced pressure gave a brown oil of protected adduct, which was used as such in the next step. To a solution of this diethyl acetal protected aldehyde (0.8 mmol) in dry dichloromethane (6 mL) and under argon atmosphere was added Grubbs' second-generation catalyst (35 mg, 5 mol %). The reaction mixture was refluxed for 12 h (50 °C), diluted with dichloromethane (10 mL), and filtered through a small pad of silica gel (with dichloromethane rinsing). Evaporation of the solvent under reduced pressure gave an oil that was purified through column chromatography (eluent EtOAc/hexane 1:9).

(4R,5S)-Phenyl 5-(4-chlorophenyl)-4-(diethoxymethyl)-cyclopent-1-enecarboxylate (9): overall yield from **6Cf** (0.86 mmol) 322 mg, 71%; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.33−7.11 (m, 8H), 6.94−6.90 (m, 1H), 4.26 (dd, J = 9.0, 1.8 Hz, 1H), 3.90 (d, 1H, J = 9.0 Hz), 3.55−3.42 (m, 3H), 3.12−3.00 (m, 1H), 2.96−2.86 (m, 1H), 2.71−2.54 (m, 2H), 1.15 (t, 3H, J = 6.9 Hz), 1.11 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.2, 150.5, 145.6, 139.3, 137.5, 132.4, 130.0, 129.1, 128.1, 125.5, 121.3, 103.2, 62.1, 60.4, 50.5, 46.5, 34.3, 15.4, 15.0. The enantiomeric excess was determined by HPLC with Chiralpack AY-H column at 254 nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min, t_R = 16.3 min (major), t_R = 26.2 min (minor)); HRMS $C_{23}H_{25}ClO_4$ [M − C_2H_5O]$^+$ calcd 355.1101, found 355.1098.

(4R,5S)-Phenyl 4-(diethoxymethyl)-5-p-tolylcyclopent-1-enecarboxylate (10): overall yield from **6Ch** (0.62 mmol): 173 mg, 77%; mp 81−83 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.31−7.22 (m, 2H), 7.17−7.03 (m, 5H), 6.95−6.90 (m, 2H), 4.24 (d, 1H, J = 8.9 Hz), 3.91 (d, 1H, J = 9.1 Hz), 3.56−3.40 (m, 3H), 3.09−2.97 (m, 1H), 2.90 (dq, 1H, J = 7.1, 14.1 Hz), 2.64−2.59 (m, 2H), 2.31 (s, 3H), 1.16−1.08 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.4, 150.6, 145.1, 139.8, 135.5, 128.7, 125.4, 121.5, 103.5, 62.1, 60.3, 50.7, 46.7, 34.4, 21.0, 15.5, 15.1. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 254 nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min, t_R = 15.5 min (major), t_R = 19.2 min (min)); HRMS $C_{24}H_{28}O_4$ [M−C_2H_5O]$^+$ calcd 335.1647, found 335.1631.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Selected NMR spectra, HPLC chromatograms, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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