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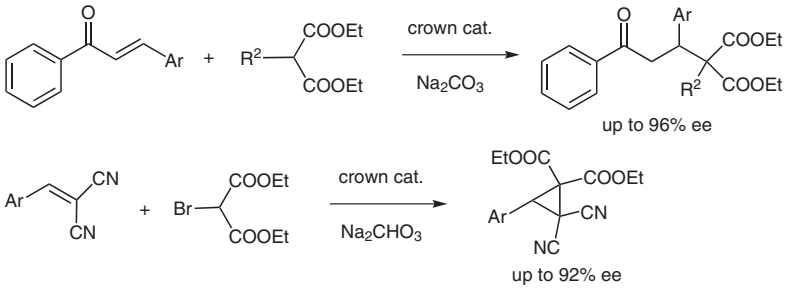
Asymmetric Michael Addition of Malonates to Enones Catalyzed by an α-D-Glucopyranoside-Based Crown Ether

Péter Bakó[*a]
Zsolt Rapi[a]
Alajos Grün[a]
Tamás Nemcsok[a]
László Hegedűs[b]
György Keglevich[a]

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, PO Box 91, 1521 Budapest, Hungary
pbako@mail.bme.hu
[b] MTA-BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8, 1111 Budapest, Hungary



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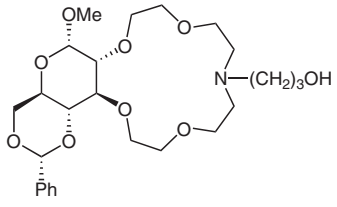
Abstract The chiral monoaza-15-crown-5 lariat ether annelated to methyl-4,6-*O*-benzylidene-α-D-glucopyranoside has been applied as a phase-transfer catalyst in several Michael addition reactions under mild conditions affording the adducts with good to excellent enantioselectivities. In the addition of α-substituted diethyl malonates to *trans*-chalcones, the substituents of the reactants had a significant impact on the yield and enantioselectivity. Among the reactions of substituted diethyl malonates, that of diethyl-2-acetoxymalonate gave the best results (up to 97% ee). New phase-transfer-catalyzed cyclopropanation reactions (MIRC reactions) of a few enones were also developed using diethyl 2-bromomalonate as the nucleophile. The corresponding chiral cyclopropane derivatives were formed with enantioselectivities up to 92% from 2-benzylidenemalononitrile starting materials, in up to 60% enantiomeric excess using 2-benzylidene-1,3-diphenyl-1,3-propanediones, and in up to 88% optical purity applying *trans*-chalcones as the starting materials.

Key words phase-transfer catalysis, sugar-based crown ethers, asymmetric Michael reactions, asymmetric cyclopropanations, enantioselectivity

The Michael addition is one of the most important C–C bond-forming reactions, and the stereoselective variants have been investigated extensively in recent years.[1] Many phase-transfer-catalyzed methods have been developed that are simple and environmentally friendly.[2] The phase-transfer-catalytic asymmetric syntheses represent an attractive approach, in which the enantioselectivity is generated by a chiral crown catalyst. Optically active crown ethers belonging to this group may incorporate a carbohydrate scaffold as the source of chirality. The attachment of a side arm with potential cation coordination sites to the crown ethers provides complexing agents called lariat ethers. Previously, chiral monoaza-15-crown-5-type lariat ethers incorporating an α-D-glucopyranoside unit and a side arm containing a heteroatom at the end were synthesized in our laboratory. They possess special complexing ability due to the flexible N-substituent. The overall complexing ability is influenced by the steric and electronic properties of the side arm.[3] The glucose-based crown ether **1** (Figure 1) proved to be an efficient catalyst in several asymmetric reactions.[4] In this paper, we describe the addition of α-substituted diethyl malonates to various electron-deficient alkenes under the phase-transfer-catalytic conditions in the presence of lariat ether **1** giving the corresponding Michael adducts or cyclopropane derivatives. The effect of the substituents of the Michael acceptors and nucleophiles on the asymmetric induction was investigated.



1

Figure 1 Lariat ether **1** incorporating a methyl-α-D-glucopyranoside unit

Methyl-α-D-glucopyranoside-based catalyst introduced by us was found to be efficient in addition of 2-substituted diethyl malonates **3a–d** to *trans*-chalcones **2a–j**. These reactions were studied in the presence of chiral catalysts in a few reports. For example, La–BINOL complexes,[5] L-proline derivatives,[6] chiral amino alcohol–Al complexes,[7] pyrrolidylalkyl ammonium hydroxide, and chiral ammonium salts[8] were investigated as the catalysts. A number of asymmetric syntheses were described using chiral phase-transfer catalysis.[1d,2h,9]

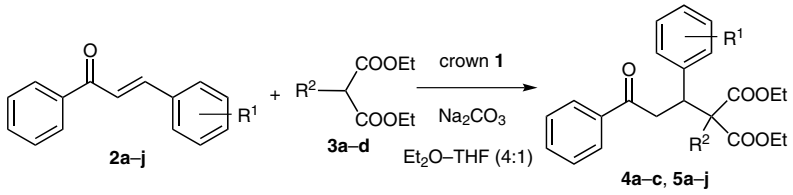
Recently, cinchona alkaloids type quaternary ammonium salts were applied successfully in catalytic asymmetric reactions.[10]

In our experiments, the conjugate addition of substituted diethyl malonates **3a**–**d** to *trans*-chalcones **2a**–**j** was carried out in a solid–liquid two-phase system employing the starting materials in a 1:4 mixture of THF and diethyl ether as the solvent using 15 mol% of crown ether **1** and two equivalents of dry Na_2CO_3 as the solid phase at ambient temperature. Products **4a**–**c** and **5a**–**j** were obtained by preparative TLC, and the enantiomeric purity was measured by chiral HPLC.[11a] The experiments are shown in Table 1.

In the case of substituents R^2 = Et, Bu, NO_2, Ph, and Bn, chalcone **2a** did not enter into reaction with the corresponding diethyl malonates. The reaction of diethyl malonate (R^2 = H) with chalcone (R^1 = H) provides the corresponding Michael adduct with 63% yield and 62% enantioselectivity.

As can be seen from Table 1, the keto-diester products (**4a**,**b** and **5a**–**j**) could be obtained (with one exception **4c**) in moderate to good yields (40–78%). Catalyst **1** induced only a modest enantiomeric excess in the reaction of chalcone **2a** with diethyl 2-acetamidomalonate (**3a**), diethyl 2-methylmalonate (**3b**), and diethyl 2-allylmalonate (**3c**). The enantiomeric excesses were 46%, 31%, and 63%, respectively (Table 1, entries 1–3). Surprisingly, the enantiomeric excess was increased to 96%, when diethyl 2-acetoxymalonate (**3d**) was used as the nucleophile (Table 1, entry 4).[11b] Then we wished to study the effect of the nature and the position of the R^1 substituents of the chalcones **2a**–**j** on the enantioselectivity using diethyl 2-acetoxymalonate **3d** (Table 1, entries 4–13). It can be seen that in the cases investigated, the R^1 substituents, with one exception, decreased the extent of the asymmetric induction as compared to the unsubstituted instance (**2a**). In the reaction of 2-, 3-, and 4-nitrochalcones **2b**–**d** with malonate **3d**, enantiomeric excesses of 72%, 81%, and 89%, respectively, were observed (Table 1, entries 5–7), while with the 2-, 3-, and 4-chlorochalcones **2e**–**g**, enantiomeric excesses of 15%, 81% and 88%, respectively, were detected (Table 1, entries 8–10). The methoxy-substituted adducts **5h**–**j** were obtained in enantiomeric excesses of 39%, 72%, and 97%, respectively (Table 1, entries 11–13). It can be seen that the *ortho* and *meta* substituents cause a significant decrease in the enantiomeric excesses (Table 1, entries 5, 6, 8, 9, 11, and 12), while, within the above series, the maximum enantiomeric excesses were obtained with the *para*-substituted chalcones (Table 1, entries 7, 10, and 13). This tendency seems to be independent on the nature of the substituent. Electron-withdrawing and electron-donating groups have a similar effect. The conclusion can be

Table 1 Asymmetric Addition of α-Substituted Diethyl Malonates to *trans*-Chalcones in the Presence of Lariat Ether **1**



Entry	Chalcone	R^1	Malonate	R^2	Time (h)	Yield (%)[a]	$[\alpha]_D^{22}$[b]	ee (%)[c]
1	**2a**	H	**3a**	NHAc	220	**4a** 55	6.7	46
2	**2a**	H	**3b**	Me	160	**4b** 65	19.9	31
3	**2a**	H	**3c**	$CH_2CH{=}CH_2$	220	**4c** 27	18.5	63
4	**2a**	H	**3d**	OAc	170	**5a** 72	9.4	96
5	**2b**	2-O_2N	**3d**	OAc	70	**5b** 60	14.7	72
6	**2c**	3-O_2N	**3d**	OAc	30	**5c** 78	20.1	81
7	**2d**	4-O_2N	**3d**	OAc	25	**5d** 73	3.4	89
8	**2e**	2-Cl	**3d**	OAc	140	**5e** 45	14.6	15
9	**2f**	3-Cl	**3d**	OAc	72	**5f** 61	14.9	81
10	**2g**	4-Cl	**3d**	OAc	40	**5g** 76	13.6	88
11	**2h**	2-MeO	**3d**	OAc	220	**5h** 40	22.1	39
12	**2i**	3-MeO	**3d**	OAc	72	**5i** 57	15.9	72
13	**2j**	4-MeO	**3d**	OAc	72	**5j** 73	13.8	97

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, *c* 1.
[c] The enantioselectivities were determined by chiral HPLC analysis.

drawn from the above phenomenon that the steric effects play a more important role in the development of asymmetric induction than the electronic effects.

Among the substituted chalcones, the 4-methoxy adduct **5j** formed with the highest enantioselectivity (97% ee).[11c] The Michael adducts formed in the above experiments have a positive optical rotation which strongly suggests that the *R*-enantiomer is formed,[12] but the absolute configuration still have to be proved.

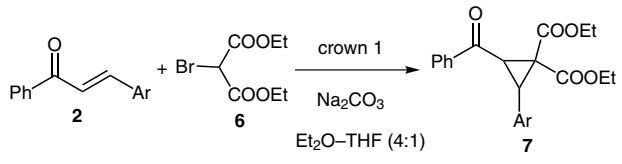
In the next part, new solid–liquid phase-transfer reactions are presented affording chiral cyclopropane derivatives in the presence of glucopyranoside-based macrocycle **1**.

The cyclopropane ring is an important building moiety for a large number of biologically active compounds, therefore the development of novel methods to make available new cyclopropane families is a challenge. The Michael initiated ring closure (MIRC) reaction represents an elegant approach which has been applied extensively for the construction of cyclopropane derivatives. The MIRC reaction strategy may also be utilized through a one-pot multicomponent reaction which has gained interest among the synthetic organic chemists recently.[13]

Surprisingly, the use of chiral phase-transfer catalysts in the synthesis of asymmetric cyclopropane derivatives has so far been limited to only a few cases.[14] Previously Waser and Herchl investigated the asymmetric reaction of 2-bromomalonate with *trans*-chalcones furnishing cyclopropane derivatives in the presence of cinchona alkaloid derived phase-transfer catalysts.[15]

In our experiment, the reaction of 1.5 equivalents of diethyl 2-bromomalonate **6** with 1.0 equivalent *trans*-chalcones **2** resulted in chiral cyclopropane derivatives using a 4:1 mixture of THF–diethyl ether as the solvent in the presence of dry Na_2CO_3 (used in twofold excess) as the base, and employing 15 mol% of the crown ether **1** at room temperature as described above (Table 2).[11a]

Table 2 Phase-Transfer-Catalyzed MIRC Reaction of Diethyl 2-Bromomalonate (**6**) with Chalcones **2**



Entry	Ar	Chalcone	Time (d)	Yield (%)[a]	$[\alpha]_D^{22}$[b]	ee (%)[c]
1	Ph	**2a**	8	**7a** 28	17.5	88
2	4-$O_2NC_6H_4$	**2d**	12	**7d** 33	33.0	42
3	4-ClC_6H_4	**2g**	12	**7g** 52	35.4	55

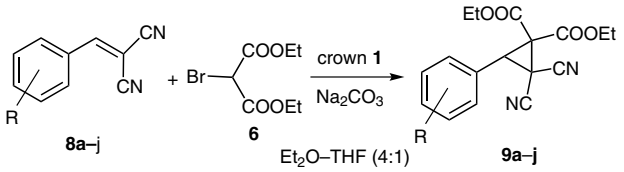
[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, *c* 1.
[c] The enantioselectivities were determined by chiral HPLC analysis.

The *trans* isomer of the corresponding cyclopropane derivatives was formed with high diastereoselectivity (up to 98%). The diastereoselectivity was determined by ^1H NMR spectroscopy utilizing the literature data.[16]

It can be seen from Table 2 that the cyclopropane diesters **7** were formed in low yields and in enantioselectivities of 42–88%. The unsubstituted derivative **7a** was obtained in the highest enantioselectivity (88%, Table 2, entry 1).[17a] The *para* substituents decreased the extent of the asymmetric induction: the 4-nitro and 4-chloro derivatives **7d** and **7g** were formed in enantiomeric excesses of 42% and 55%, respectively (Table 2, entries 2 and 3). The lower yields are probably the consequence of the dimerization side reaction of the bromomalonate.[15]

As a new model reaction, the asymmetric cyclopropanation of 2-benzylidene-malononitriles **8a**–**j** with diethyl 2-bromomalonate (**6**) was also elaborated by us, in which the glucose-based lariat ether **1** generated the asymmetric induction. The optically active cyclopropane derivatives **9a**–**j** were prepared under similar solid–liquid phase-transfer catalytic conditions shown above (Table 3).

Table 3 Scope of the Phase-Transfer-Catalyzed MIRC Reaction of Diethyl 2-Bromomalonate (**6**) with 2-Benzylidenemalononitriles (BMN) **8a**–**j**



Entry	R	BMN	Time (h)	Yield (%)[a]	$[\alpha]_D^{22}$[b]	ee (%)[c]
1	H	**8a**	20	**9a** 82	–9.6	32
2	2-Me	**8b**	24	**9b** 74	–1.0	17
3	3-Me	**8c**	24	**9c** 71	–20.1	71
4	4-Me	**8d**	24	**9d** 74	–17.3	92
5	2-Cl	**8e**	24	**9e** 44	0	0
6	3-Cl	**8f**	14	**9f** 47	–8.0	79
7	4-Cl	**8g**	14	**9g** 41	–18.2	39
8	2-O_2N	**8h**	16	**9h** 84	–41.0	21
9	3-O_2N	**8i**	24	**9i** 59	–6.0	24
10	4-O_2N	**8j**	24	**9j** 54	–7.0	75

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, *c* 1.
[c] The enantioselectivities were determined by chiral HPLC analysis.

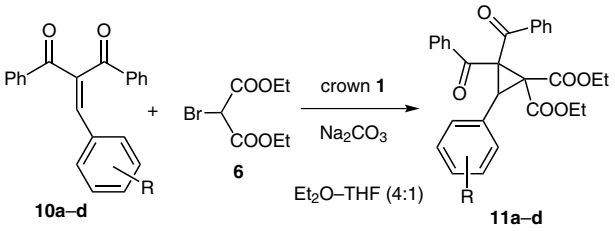
The yields of 41–84% suggest that with 14–24 hours reaction time, the base-catalyzed dimerization of bromomalonate **6** was suppressed.[15]

One can see from the data of Table 3 that in the reaction of unsubstituted benzylidene-malononitrile, cyclopropane derivative **9a** was formed in a modest enantioselectivity of

32%. However, the enantioselectivity depended strongly on the substituent of the benzylidene-malononitrile. Some substituents decreased, while others increased the enantioselectivity. The 2-, 3-, and 4-methyl-substituted cyclopropane derivatives **9b**–**d**) were formed in 17%, 71%, and 92% enantioselectivities, respectively (Table 3, entries 2–4). In the case of the 2-, 3-, and 4-chloro-substituted model compounds **9e**–**g**) enantioselectivities 0%, 79%, and 39%, respectively, were detected (Table 3, entries 5–7). The 2-, 3-, and 4-nitro-substituted cyclopropane derivatives **9h**–**j** were obtained in enantioselectivities of 21%, 24%, and 75%, respectively (Table 3, entries 8–10). One can see that in the case of Me and NO_2 substituents, the tendency is similar to that observed with the previous model: The farer the substituent is located from the reaction center, the higher the extent of the asymmetric induction is. The highest enantioselectivies (92% and 75%) were detected starting from the 4-methyl and the 4-nitro derivatives **8d**–**j** (Table 3, entries 4 and 10).[17b] The situation is different with the chloro substituent, as in the case the 3-chloro derivative **9f** was formed with the highest enantioselectivity (79%). It is noteworthy that in the reaction of the 2-chloro derivative, crown ether **1** was inefficient as a chiral inductor. It is possible that in certain cases the steric effects are dominating, while in other cases, the electronic effects determine the extent of asymmetric induction.

The asymmetric cyclopropanation of 2-benzylidene-1,3-diphenylpropane-1,3-diones **10a**–**d** with diethyl 2-bromomalonate (**6**) is a new reaction, in which the glucose-based lariat ether **1** was found as an efficient catalyst under solid–liquid phase-transfer conditions described above (Table 4).[11a]

Table 4 The MIRC Reaction of Diethyl 2-Bromomalonate (**6**) with 2-Benzylidene-1,3-diphenylpropane-1,3-diones (BDP)



Entry	R	BDP	Time (d)	Yield (%)[a]	$[\alpha]_D^{22,b}$	ee (%)[c]
1	H	**10a**	8	**11a** 52	68.9	60
2	3-MeO	**10b**	17	**11b** 46	77.5	49
3	4-MeO	**10c**	7	**11c** 31	63.5	56
4	4-O_2N	**10d**	7	**11d** 50	10.4	5

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, *c* 1.
[c] The enantioselectivities were determined by chiral HPLC analysis.

It can be seen from Table 4 that in the reaction of diethyl 2-bromomalonate (**6**) with unsubstituted **10a** and with its 3- and 4-methoxy derivatives **10b**,**c** the cyclopropane diesters **11a**–**c** were obtained in yields of 31–52%, and in enantioselectivities of 60%, 49%, and 56%, respectively.[17c] In the case of the 4-nitro substituent, the corresponding product **11d** was formed in only a 5% enantioselectivity. If the 4-methoxy and 4-nitro models are compared, the dramatic decrease in the enantioselectivity may refer to the decisive role of electronic effects.

We have developed the asymmetric conjugate addition of α-substituted diethyl malonates to a few enones in the presence of an α-D-glucopyranoside-based monoaza-15-crown-5-type lariat ether **1** under solid–liquid phase-transfer conditions. The addition of α-substituted diethyl malonates to *trans*-chalcones furnished chiral Michael adducts with modest to good yields and with variable enantioselectivities. The substituents had a considerable impact on the outcome of the reactions. Moreover, we found correlation between the enantioselectivity and substituents of the chalcone. The best enantioselectivity was obtained with diethyl 2-acetoxymalonate, while from among the Michael acceptors, the 4-substituted chalcones were the most suitable. The latter phenomenon may refer to the role of steric effect on the asymmetric induction.

We have developed three new cyclopropanation reactions under solid–liquid phase-transfer-catalytic conditions. The MIRC reaction of diethyl 2-bromomalonate with *trans*-chalcones, with 2-benzylidenemalononitriles, and with 2-benzylidene-1,3-diphenyl-1,3-propanediones resulted in the formation of chiral cyclopropane derivatives with variable yields and enantioselectivities depending on the substituents in the aromatic ring.

Acknowledgment

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(11) (a) **General Procedure for the Michael Additions**
Unsaturated compound (1 mmol), substituted malonate (1.5 mmol), and the crown ether (0.15 mmol) were dissolved in a mixture of anhydrous THF (0.6 mL) and Et_2O (2.4 mL) and dry Na_2CO_3 (2 mmol) was added. The reaction mixture was stirred at r.t. After completion of the reaction, the organic phase was concentrated in vacuo, and the residue was taken up in CH_2Cl_2 (10 mL), washed with cold 10% HCl (3 × 10 mL), then with H_2O (10 mL), dried (Na_2CO_3 and Na_2SO_4), and concentrated. The crude product was purified by preparative TLC using silica gel and hexane–EtOAc (5:1) as the eluent. The enantioselectivities were determined by chiral HPLC analysis using a Chiralpack AD-H column, (20 °C, 256 nm, hexane–*i*-PrOH = 90:10, 0.8 mL/min) in comparison with authentic racemic materials.
(b) Compound **5a**: yield 72%; $[\alpha]_D^{22}$ + 9.4 (*c* 1, $CHCl_3$); ee 96%; t_r (major enantiomer) = 9.9 min, t_r (minor enantiomer) = 13.2 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.5 Hz, 2 H, ArH), 7.53 (t, *J* = 7.5 Hz, 1 H, ArH), 7.43 (t, *J* = 7.5 Hz, 2 H, ArH), 7.35 (d, *J* = 7.5 Hz, 2 H, ArH), 7.26–7.20 (m, 3 H, ArH), 4.37 (dd, *J* = 8.5, 4.0 Hz, 1 H, PhH), 4.24–4.16 (m, 2 H, OCH_2), 4.02–3.89 (m, 2 H, OCH_2), 3.67 (dd, *J* = 16.0, 4.0 Hz, 1 H, $COCH_2$), 3.59 (dd, *J* = 17.5, 8.5 Hz, 1 H, $COCH_2$), 2.23 (s, 3 H, $COCH_3$), 1.23 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.06 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3) ppm. HRMS: *m/z* calcd for $C_{24}H_{26}O_7$: 426.1679; found: 426.1680.
(c) Compound **5j**: yield 73%; $[\alpha]_D^{22}$ + 13.8 (*c* 1, $CHCl_3$); ee 97%; t_r (major enantiomer) = 24.9 min, t_r (minor enantiomer) = 22.8 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 7.5, 1.0 Hz, 2 H, ArH), 7.53 (t, *J* = 7.5 Hz, 1 H, ArH), 7.43 (t, *J* = 7.5 Hz, 2 H, ArH), 7.26 (d, *J* = 8.5 Hz, 2 H, ArH), 6.77 (d, *J* = 8.5 Hz, 2 H, ArH), 4.31 (dd, *J* = 8.5, 4.0 Hz, 1 H, ArCH), 4.24–4.15 (m, 2 H, OCH_2), 4.06–3.92 (m, 2 H, OCH_2), 3.75 (s, 3 H, $ArOCH_3$), 3.71 (dd, *J* = 18.0, 4.0 Hz, 1 H, $COCH_2$), 3.56 (dd, *J* = 18.0, 9.0 Hz, 1 H, $COCH_2$), 2.23 (s, 3 H, $COCH_3$), 1.23 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.10 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3) ppm. HRMS: *m/z* calcd for $C_{25}H_{28}O_8$: 456.1784; found: 456.1785.

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(16) The corresponding coupling constants of 7.5 Hz (δ = 4.12 ppm, *J* = 7.5 Hz and δ = 3.89 ppm, *J* = 7.5 Hz) observed for the *trans* isomer are in agreement with the literature data. The corresponding constants would be *J* = 9.9 Hz in both cases for the *cis* compound. See: (a) Makosza, M.; Kwast, A. *Tetrahedron* **1991**, *41*, 5001. (b) Sun, Y.; Yang, G.; Shen, Y.; Hua, Z.; Chai, Z. *Tetrahedron* **2013**, *69*, 2733.

(17) (a) Compound **7a**: yield 28%; $[\alpha]_D^{22}$ +17.5 (*c* 1, $CHCl_3$); ee 88%; t_r (major enantiomer) = 5.0 min, t_r (minor enantiomer) = 9.3 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.5 Hz, 2 H, ArH), 7.62 (t, *J* = 7.5 Hz, 1 H, ArH), 7.51 (t, *J* = 7.5 Hz, 2 H, ArH), 7.33–7.26 (m, 5 H, ArH), 4.14 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.12 (d, *J* = 7.5 Hz, 1 H, COC*H*), 4.00 (q, *J* = 7.0 Hz, 2 H, OCH_2), 3.89 (d, *J* = 7.5 Hz, 1 H, PhCH), 1.11 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.99 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. HRMS: *m/z* calcd for $C_{22}H_{22}O_5$: 366.1467; found: 366.1470.
(b) Compound **9d**: yield 74%; $[\alpha]_D^{22}$ –17.3 (*c* 1, $CHCl_3$); ee 92%; t_r (major enantiomer) = 4.3 min, t_r (minor enantiomer) = 5.0 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.0 Hz, 2 H, ArH), 7.20 (d, *J* = 8.0 Hz, 2 H, ArH), 4.42 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.30–4.20 (m, 2 H, OCH_2), 3.92 (s, 1 H, ArCH), 2.35 (s, 3 H, $ArCH_3$), 1.38 (t, *J* = 7.0 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H) ppm. HRMS: *m/z* calcd for $C_{18}H_{18}N_2O_4$: 326.1267; found: 326.1270.
(c) Compound **11a**: yield 52%; $[\alpha]_D^{22}$ +68.9 (*c* 1, $CHCl_3$); ee 60%; t_r (major enantiomer) = 11.9 min, t_r (minor enantiomer) = 41.1 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.5 Hz, 2 H, ArH), 7.44 (d, *J* = 7.5 Hz, 2 H, ArH), 7.33 (d, *J* = 7.0 Hz, 2 H, ArH), 7.26–7.19 (m, 5 H, ArH), 7.14 (t, *J* = 7.5 Hz, 2 H, ArH), 7.10 (t, *J* = 7.5 Hz, 2 H, ArH), 5.64 (s, 1 H, PhCH), 4.47–4.40 (m, 1 H, OCH_2), 4.38–4.29 (m, 1 H, OCH_2), 3.87–3.80 (m, 1 H, OCH_2), 3.64–3.57 (m, 1 H, OCH_2), 1.35 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.84 (t, *J* = 7.0 Hz, 3 H, CH_3). HRMS: *m/z* calcd for $C_{29}H_{26}O_6$: 470.1729; found: 470.1733.