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Asymmetric conjugate addition to alkylidene malonates

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Abstract—Dialkylzinc and trialkylaluminium reagents undergo conjugate addition to alkylidene malonates with 0.5% copper triflate as catalyst. The reaction could be made enantioselective by completing the reaction in the presence of 0.5–1.0 mol% of chiral phosphorus ligand. Enantiomeric excesses (e.e.s) of up to 73% could be attained with a ligand prepared from TADDOL and 2-naphthylcyclohexanol.

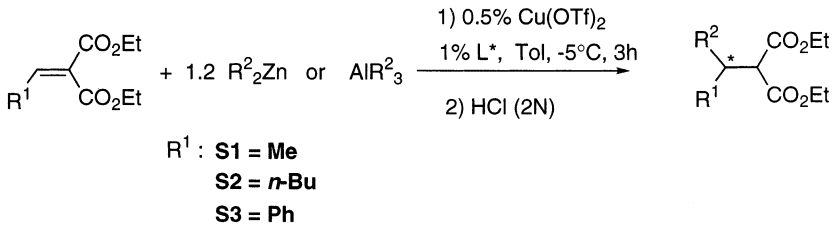
1. Introduction

The conjugate addition of organocopper reagents to Michael acceptors is an essential synthetic methodology[1] and as such asymmetric versions of this reaction have been widely studied.[2] In the copper-catalysed reactions, we have shown that dialkylzinc may be used as the primary organometallic reagent and that an accelerating effect is exerted by ligands such as trivalent phosphorus agents (both achiral and chiral ligands).[3] We have also demonstrated that a range of different substrates may be used as Michael acceptors in this conjugate addition reaction.[3] Following our initial report on the asymmetric version of the copper-catalysed conjugate addition of diorganozincs,[4] several groups have developed different chiral ligands and applied this reaction to various substrates.[5] Having described the enantioselective 1,4-addition to various enones[6] and nitroalkenes,[7] we turned our attention to alkylidene malonates. These substrates are good Michael acceptors for organoaluminium reagents[8] and the Cu-catalysed reaction of organomanganese[9] and organozinc[3] reagents. More recently, Evans reported the enantioselective conjugate addition of silyl enolates,[10] and Jorgensen reported the enantioselective Friedel–Crafts alkylation with heteroaromatic compounds.[11]

We report herein the first asymmetric conjugate addition (Scheme 1) of dialkylzinc and triethylaluminium reagents onto aryl- and alkylidene malonates by using catalytic copper/homochiral phosphorus ligand system. A number of ligands (**L1**–**L5**) and conditions and the effects upon the yield and selectivity of the process were examined in this study.

2. Results and discussion

It should be noted that the experimental conditions of this reaction compare favourably with those established for organomanganese[9] and organoaluminium[8] reagents with respect to the catalyst loading, the yield and the mildness and generality of the procedure. In addition, the presence of a phosphorus ligand offers the opportunity to introduce enantioselectivity into the process.



Scheme 1. Asymmetric conjugate addition reaction.

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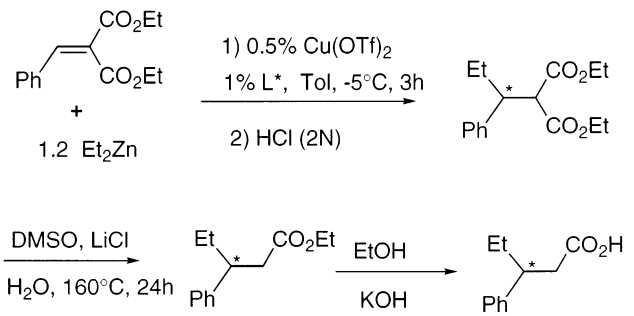
Three substrates were tested, **S1** bearing a small methyl substituent, **S2** with a larger *n*-butyl group, and **S3** with a phenyl substituent. These are representative of most of the classes encountered in the literature. Of the organometallic reagents, Et_2Zn (most often used), Bu_2Zn and Me_2Zn were tested, but Et_3Al was the only organoaluminium reagent studied.

The e.e.s of the conjugate adducts was determined by either gas chromatography, HPLC or supercritical fluid chromatography (SFC) analyses. In some cases, a Krapcho[12] degradation had to be carried out to obtain baseline separation of the peaks. The absolute configuration was determined by comparison of the optical rotation of the monoacids[13] formed after saponification of the corresponding monoester (Scheme 2).



Scheme 2.

Several ligands were tested which are representative of the classes we had previously developed. The first class of ligands we examined were the TADDOL derived ligands **L1**–**L7** (Table 1). Ligand **L1**,[14] in which the TADDOL moiety is the only asymmetric centre, has recently been shown to give very good asymmetric induction in conjugate addition reactions to nitroalkenes.[7] However, only moderate induction was observed for the reactions of **S1** (20% e.e.) and **S3** (15% e.e.) and even lower selectivity (8% e.e.) was seen in the reaction of **S2**. A decrease in the yield to 55% was also seen in the reaction of **S2**.

The next ligands studied bear additional chirality at the exocyclic moiety, and therefore a matched or mismatched combination may arise. **L2**, used by Pfaltz[15] and Seebach[16] in asymmetric catalysis, gave nearly the same result as **L1**, with a very low e.e. of 6% in the conjugate addition to **S2** with a low yield (62%) and poor selectivity in the reactions of **S1** and **S3** (19 and 22% e.e., respectively). Ligand **L3**, containing a (+)-Fenchol residue, gave an encouraging result with 30% e.e. and quantitative yield in the reaction of **S2**. However, low selectivities of 10% e.e. were obtained in the equivalent reactions of **S1** and **S3**.

We decided to use TADDOL ligands containing a chiral substituted cyclohexanol skeleton.[6c] Ligand **L4**, which is made from (+)-TADDOL and (1*S*,2*R*)-phenylcyclohexanol, was tested in this series. Indeed, this ligand had allowed us to obtain good results in the conjugate addition to cyclohexen-2-one[6] and better e.e.s were obtained with all of the three substrates (58% e.e. on **S1**, 56% e.e. on **S2** and 52% e.e. on **S3**). Following this result, we attempted to optimise the selectivity by changing the experimental conditions. Thus, in addition to toluene, dichloromethane, diethyl ether and THF were examined as solvents. However, lower or equal selectivities were observed for **S1** (CH_2Cl_2, 3% e.e.; Et_2O, 58% e.e.; THF, 41% e.e.; compared to 58% e.e. using toluene).

We also checked the selectivity obtained with **L4** using different dialkylzinc reagents. Thus, an e.e. of 50% was obtained in the conjugate addition of Bu_2Zn to **S1**, while an e.e. of 30% was obtained in the conjugate addition of Me_2Zn to **S2**; both reactions gave products in quantitative yield. When triethylaluminium was used instead of the dialkylzinc reagent no enantioselectivity was observed in reactions with any of the three substrates (Scheme 3).

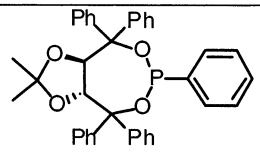
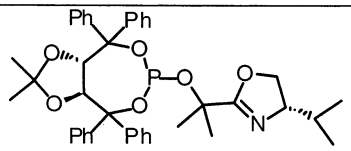
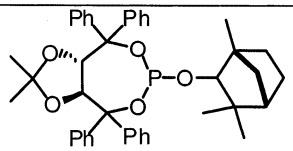
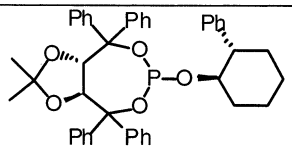
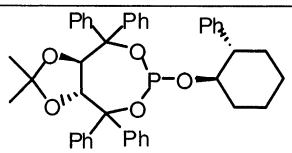
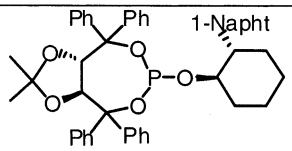
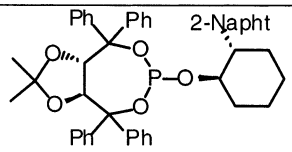
Scheme 3.

Ligand **L5**, which is a diastereoisomer of **L4**, was tested to check if there is a matched–mismatched effect. It can be seen that there is a slight effect on the reactions of **S1** and **S2**, with **L5** giving marginally lower e.e.s of 48 and 39%, respectively. However, the effect is much more pronounced in the reaction with **S3** (15% e.e. versus 52% e.e. with **L4**).

Replacing the phenyl substituent on the cyclohexanol with a 1-naphthyl group (ligand **L6**) resulted in decreased selectivity for the three substrates in comparison to the reactions in the presence of ligand **L4**, while replacing the phenyl group with the 2-naphthyl group allowed us to obtain the best enantioselectivities with all of the substrates. All three products were obtained in quantitative yield from these reactions. The adduct from the reaction of **S1** was obtained with 65% e.e., the same reaction with **S2** gave the adduct with 73% e.e. and the reaction of **S3** gave adduct with 64% e.e.

The second category of ligands examined were the binaphthol derived **L8**–**L10** (Table 2). The phosphorus ligand **L8**, which recently gave excellent results in conjugate addition reactions to acyclic enones,[6b] provided here moderate levels of asymmetric induction, rising from **S1** to **S3** (5, 15 and 27% e.e.). Other ligands of this class, Feringa's matched and mismatched ligands (**L9** and **L10**), were tested.[5c,d] Moderate selectivity was observed only on **S3** (45 and 31% e.e. with **L9** and **L10**, respectively). In addition, a slight mismatch effect was observed in reactions with ligand **L10**, which gave product with lower e.e. than **L9** on each of the substrates.

Table 1. Results of conjugate addition of diethylzinc onto **S1**–**S3** using TADDOL ligands

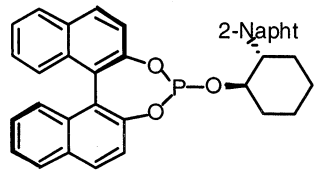
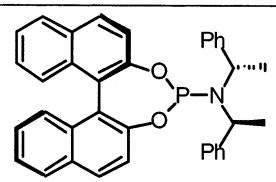
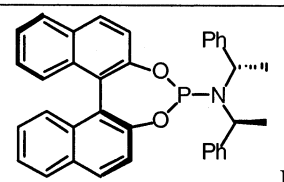
	S1 Yield %[a], **ee%**, Conf. Abs.	**S2** Yield %[a], **ee%**, Conf. Abs.	**S3** Yield %[a], **ee%**, Conf. Abs.
 **L1**	100, **20,** R	55, **8,** S	100, **15,** S
 **L2**	100, **19,** S	62, **6,** R	100, **22,** S
 **L3**	100, **10,** R	100, **30,** S	100, **10,** R
 **L4**	100 (87), **58,** R 100 (86), **50,** R [b]	100 (91), **56,** S 100 (82), **30,** S [c]	100 (93), **52,** R
 **L5**	100, **48**, R	93, **39,** S	100, **15,** S
 **L6**	100, **30**, R	100, **40,** S	100, **13,** R
 **L7**	100 (89), **65,** R	100 (93), **73,** S	100 (89) , **64,** R

a) Isolated yield in parentheses.
b) Conjugate addition of Bu_2Zn
c) Conjugate addition of Me_2Zn

The third category of ligands examined were the commercially available phosphines (Table 3). The results with these ligands are in agreement with our previous results with enones; (*S*)-BINAP (**L11**) has no influence on the enantioselectivity of the reaction. On the other hand, the use of (+)-NORPHOS in toluene (**L12**) gave moderate asymmetric induction on **S1** (35% e.e.) and **S3** (33% e.e.) but was lower (20% e.e.) in the reaction of **S2**.

Better e.e.s were obtained using dichloromethane as solvent in the reaction of **S1** (38% e.e.) and **S3** (42% e.e.), but the e.e. decreased to 10% in the reaction of **S2**. ($\alpha R,S$)-PPFA (**L13**), PPh_2-Fc-$Pyrazo_{t\text{-}Bu}$ (**L14**) and PPh_2-Fc-Sbu (**L15**) were tested as *P*,*N*-ferrocenylphosphine ligands. First, PPFA (**L13**) gave moderate selectivity in the reaction of **S1** (33% e.e.) and **S3** (28% e.e.), but improved selectivity was seen in the reaction of **S2** (adduct e.e. = 45%). Dichloromethane was again found

Table 2. Results of conjugate addition of diethylzinc using binaphthol ligands

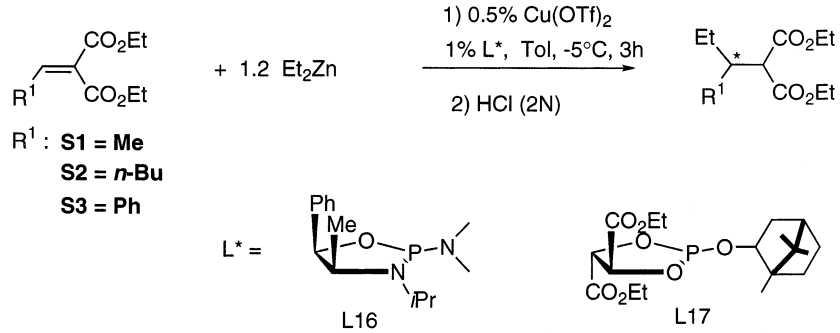
	S1	S2	S3
	Yield %[a], **ee%**, Conf. Abs.	Yield %[a], **ee%**, Conf. Abs.	Yield %[a], **ee%**, Conf. Abs.
 **L8**	100, **5,** S	89, **15%** R	100, **27%** S
 **L9**	100, **12%** S	100, **26%** R	100 (90), **45%** S
 **L10**	100, **5%** R	100, **22%** S	100, **31%** R

a) Isolated yield in parentheses.

to be a better solvent than toluene in reactions using ferrocenyl ligands. Thus, **L14**, which bears a bulky pyrazole group, and **L15**, which includes a benzothioether attached to the PPFA, were tested on the pentylidene malonate (**S2**). Ligand **L14** gave a slight improvement in e.e. over PPFA but a lower yield (75% yield, 53% e.e.). Ligand **L15** (which is in fact a tridentate ligand) also gave better enantioselectivity than PPFA but this time the conversion was quantitative and the product had an e.e. of 57%.

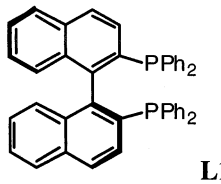
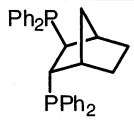
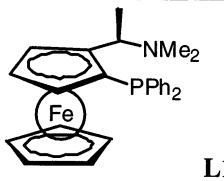
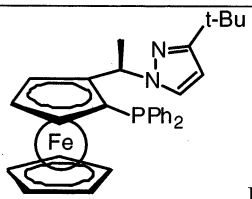
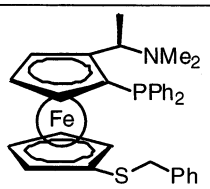
Finally, the oxazaphospholidine ligand (**L16**), which gave excellent results in the stoichiometric conjugate addition to cyclohexen-2-one,[4] and the diethyl tartrate ligand (**L17**), which gave good results on benzalacetone,[17] were tested (Scheme 4): quantitative yield and moderate asymmetric inductions on the three substrates were obtained with **L16** (20% e.e., **S1**; 30% e.e., **S2**; 30% e.e., **S3**), whereas no asymmetric induction was observed with **L17** on **S1**.

It may be concluded that ligand **L7**, derived from TADDOL and arylcyclohexanol, was the most effective of the ligands studied, affording products with e.e.s in the range of 64–73%; these are the highest values reported to date for the conjugate addition of alkyl groups to achiral arylidene or alkylidene malonates. This ligand was also the best for conjugate additions to cyclic enones, having *s-trans* conformation. It was not, however, very efficient on acyclic enones (most of which adopt an *s-cis* conformation). Alkylidene malonates, having two identical functionalities, are ambiguous substrates, and their behaviour could not be anticipated. The results of the study we have presented

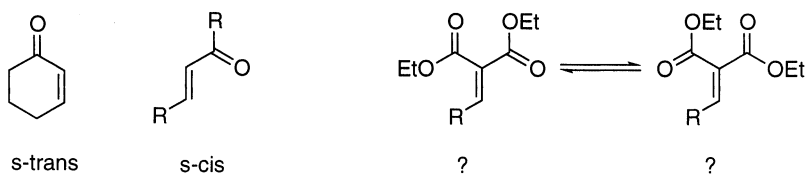


Scheme 4.

Table 3. Results of conjugate addition of diethylzinc using phosphine ligands

	S1	S2	S3
	Yield %[a], **ee%**, Conf. Abs.	Yield %[a], **ee%**, Conf. Abs.	Yield %[a], **ee%**, Conf. Abs.
 **L11**	100, **0**		
 **L12**	100, **35%** S[b] 100, **38%** S[c]	100, **20%** R[b] 100, **10%** R[c]	100, **33%** S[b] 100, **42%** S[c]
 **L13**	100, **33%** R[c]	100, 40% S[b] 100 (87), **45%** S[c]	100, **28%** R[b]
 **L14**		75 (63), **53%** S[c]	
 **L15**		100 (85), **57%** S[c]	

a) Isolated yield in parentheses.
b) reaction performed in toluene
c) reaction performed in dichloromethane



Scheme 5.

here indicate that they behave more closely to *s-trans* enones (Scheme 5).

3. Experimental

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on Bruker AC-400 (400 MHz) spectrometers. Chemical shifts are quoted in ppm relative to tetramethylsilane (0 ppm) and referenced to the solvent residual. For convenience, the following abbreviations are used; s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd-doublet of doublet etc. Coupling constants (J) are given in hertz (Hz). Optical rotations were measured using a Perkin–Elmer 241 polarimeter, in a cell of 1 dm path length. The concentration (c) is expressed in g/100 cm^3 (equiv-

alent to g/0.1 dm^3). Specific rotations denoted as $[\alpha]_D^T$, imply units of deg. dm^2 g^{-1} (T=temp (°C)).

3.1. General procedure for catalytic conjugate addition

To a solution of copper triflate (3.6 mg, 0.01 mmol) in dry toluene (2 mL) at room temperature under argon was added 2 equiv. of ligand (0.02 mmol). The solution was stirred at 25°C for 30 min and then cooled to −15°C. A solution of Et_2Zn (1N in hexane 2.4 mL) or Et_3Al (2.4 mL, 1N in hexane) was added dropwise at a rate such that the temperature did not rise above 0°C. After stirring for 5 min, the malonate (2 mmol) was added dropwise over 1 min. The reaction mixture was stirred at 0°C for 3 h before being quenched by HCl (2N). The product was extracted with Et_2O (10 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The e.e. of the product was determined by Chiral GC.

3.2. 2-*sec*-Butyl-malonic acid diethyl ester

Conjugate addition of diethylzinc onto ethylidene malonate **S1** using the general procedure, followed by flash chromatography purification of the crude product (49/1 pentane:ether, R_f=0.4), afforded the title compound as a colourless oil.

Enantiomer separation: ChirasildexGTA, 25 m, 50 cm^3 s^{-1}, T: 75°C, 80 min, 1°C/min, 110°C. Rt (R)-(−)-enantiomer=70.0 min, rt (S)-(+)-enantiomer=72.00 min. Purification by flash chromatography on silica gel (98/2 pentane:ether, R_f=0.3) to afford a colourless oil (64% e.e. (R): $[\alpha]_D^{25}$=−3.5 (c=2.0 in $CHCl_3$)); δ_H (400 MHz; $CDCl_3$) 0.85 (t, J=7.6 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H), 1.2 (t, J=12.5 Hz, 6H), 1.25–1.4 (2m, 2H), 2.15 (m, 1H), 3.2 (d, J=8.6 Hz, 1H), 4.14 (q, J=7.3 Hz, 4H); δ_C (50 MHz; $CDCl_3$) 11.1, 13.9, 14.0, 16.3, 27.0, 34.8, 57.4, 60.9, 60.9, 168.7, 168.9.

3.3. 2-(1-Ethyl-pentyl)-malonic acid diethyl ester

Conjugate addition of diethylzinc onto pentylidene malonate[18] **S2** using the general procedure, followed by flash chromatography purification of the crude product (98/2 pentane:ether, R_f=0.4), afforded the title compound as a colourless oil.

Enantiomer separation: ChirasildexGTA, 25 m, 50 cm^3 s^{-1}, T: 80°C, 50 min, 1°C/min, 140°C. Rt (R)-(+)-enantiomer=87.65 min, rt (S)-(−)-enantiomer=88.27 min. Purification by flash chromatography (98/2 pentane: ether, R_f=0.3) to obtain a colourless oil (73% e.e. (S): $[\alpha]_D^{25}$=−1.5 (c=1.6 in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.87 (t, 6H, CH_3), 1.50–1.25 (m, CH_2), 1.27 (t, 6H, CH_3CH_2O), 2.07 (m, CH), 3.41 (d, CH), 4.18 (q, 4H, CH_2O); δ_C (100 MHz, $CDCl_3$) 2×10.6 (CH_3), 13.8 (CH_3CH_2O), 13.9 (CH_3CH_2O), 22.7, 23.4, 28.6, 29.9 (4×CH_2), 39.3 (CH), 55.1 (CH_2), 2×60.9 (CH_2O), 2×169 (CO).

3.4. Preparation of 2-(1-phenyl-propyl)-malonic acid diethyl ester

Conjugate addition of diethylzinc onto benzylidene malonate **S3** using the general procedure followed by purification by flash chromatography (98/2 pentane:ether, R_f=0.3) afforded the title compound as a colourless oil.

The separation on Chiral GC was measured on the monoester. δ_H (400 MHz, $CDCl_3$) 0.75 (t, J_{HH}=7.3 Hz, 3H, CH_3), 0.97 (t, J_{HH}=7.0 Hz, 3H, CH_3) 1.35 (t, J_{HH}=7.0 Hz, 3H, CH_3), 1.85–1.56 (2m, 2H, CH_2), 3.34 (dt, J_{HH}=3.5 Hz, J_{HH}=10.9 Hz, 1H, CHbenz), 3.70 (d, J_{HH}=11 Hz, 1H, CH), 3.91 (q, J_{HH}=6.5 Hz, 2H, CH_2O), 4.28 (q, J_{HH}=6.5 Hz, 2H, CH_2O), 7.30–7.22 (2m, 5H, Ph); δ_C (100 MHz, $CDCl_3$) 11.6 (CH_3), 13.6 (CH_3), 14.0 (CH_3), 27.0 (CH_2), 47.2 (CH), 58.6 (CH), 61.0 (CH_2O), 61.4 (CH_2O), 126.7, 128.2, 128.3, 140.6, 167.8 (CO), 168.5 (CO).

3.5. Preparation of 3-phenyl-pentanoic acid ethyl ester

The monoester was obtained by using Krapcho's method:[12] the corresponding malonic acid diethyl ester (2 mmol) was added to a solution of DMSO (2 mL), water (8 mmol) and LiCl (2.5 mmol). The mixture was warmed to 160°C for 15 h. The product was extracted with Et_2O and the ethereal extract washed with water. The organic layers were combined and dried ($MgSO_4$). The product was obtained in quantitative yield as a colourless oil (64% e.e. (R): $[\alpha]_D^{25}$ −13.7 (c=1.4 in $CHCl_3$)). E.e. was measured on a ChirasildexGTA, 25 m, 50 cm^3 s^{-1}, T: 70°C, 1°C/min, 95°C, 35 min. Rt (R)-(−)-enantiomer=52.48 min, rt (S)-(+)-enantiomer=53.37 min; δ_H (400 MHz, $CDCl_3$) 0.84 (t, J_{HH}=7.3 Hz, 3H, CH_3), 1.20 (t, J_{HH}=7.0 Hz, 3H, CH_3), 1.76–1.62 (2m, 2H, CH_2), 2.68 (dq, J_{HH}=8 Hz, J_{HH}=14.8 Hz, 2H), 3.04 (m, 1H, CH), 4.09 (q, J_{HH}=7.2 Hz, 2H, CH_2O), 7.25 (2m, 5H, Ph); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 14.0 (CH_3), 29.0 (CH_2), 41.4 (CH_2), 43.8 (CH), 60.1 (CH_2O), 126.3, 127.4, 128.2, 143.8, 172.4 (CO).

3.6. Preparation of 3-phenyl-pentanoic acid[19]

In a 5 mL flask equipped with a condenser was placed 3-phenyl-pentanoic acid ethyl ester (1 mmol). Potassium hydroxide (0.1 g) and ethanol (0.5 mL) were then added. The reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature and the ethanol was evaporated under reduced pressure. The residue was diluted with water (3 mL) and extracted with ethyl acetate (5 mL). The layers were separated and the aqueous phase was acidified to pH 2 (HCl) and extracted with ethyl acetate (2×10 mL). The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The product was isolated after chromatography on silica gel (95/5 pentane:ether, R_f=0.3) to afford a white solid in quantitative yield. E.e.=64% (R)-enantiomer; $[\alpha]_D^{25}$=−33 (c=5.2 in C_6H_6; lit.:[13] $[\alpha]_D^{25}$ −51.7 100% e.e. (R)-enan-

tiomer ($c=5.2$ in C_6H_6)); δ_H (400 MHz, $CDCl_3$) 0.79 (t, $J_{HH}=7.5$ Hz, 3H, CH_3), 1.74–1.61 (2m, 2H, CH_2), 2.65 (dq, $J_{HH}=8$ Hz, $J_{HH}=14.8$ Hz, 2H), 3.04 (m, 1H, CH), 7.25 (2m, 5H, Ph); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 29.0 (CH_2), 41.0 (CH_2), 43.4 (CH), 126.3, 127.4, 128.3, 143.5, 172.5 (CO).

3.7. 2-(1-Methyl-pentyl)-malonic acid diethyl ester

Conjugate addition of dibutylzinc onto **S1** or dimethylzinc onto **S2** using the general procedure gave the desired product. Purification by flash chromatography (98/2 pentane:ether, $R_f=0.3$) afforded a colourless oil. Enantiomer separation: ChirasildexGTA, 25 m, 50 $cm^3\ s^{-1}$, T: 75°C, 80 min, 1°C/min, 110°C. Rt (+)-enantiomer = 83.04 min, rt (−)-enantiomer = 83.17 min. Purification by flash chromatography (49/1 pentane:ether, $R_f=0.3$) afforded a colourless oil (50% e.e. (R): $[\alpha]_D^{25}=+6.1$ ($c=2.6$ in $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.80 (t, 3H, CH_3), 0.80 (t, 3H, CH_3), 1.36–1.07 (m, CH_2), 1.21 (t, 6H, CH_3CH_2O), 2.15 (m, CH), 3.16 (d, CH), 4.14 (q, 4H, CH_2OCH_3); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 14.1 (CH_3), 22.6, 29.0, 33.3, 34.0: (4×CH_2), 57.8 (CH), 2×60.9 (CH_2O), 168.8 (CO), 169 (CO).

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