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Scope and limitations of chiral bis(oxazoline) ligands in the copper-catalysed asymmetric cyclopropanation of trisubstituted alkenes

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Abstract—A series of derivatives of 3-methyl-2-buten-1-ol has been used to test the scope and limitations of the copper-catalysed asymmetric cyclopropanation of trisubstituted alkenes by ethyl diazoacetate in the presence of C_2-symmetric bis(oxazoline) ligands. In the best case, a *trans*/*cis* ratio of 91:9, with 92% ee for the major isomer, was obtained from the reaction of the *p*-methoxybenzoate derivative. The highest ee was 95%, for the *trans* isomer of a 80:20 diastereomer mixture (acetate derivative).

1. Introduction

In connection with an industrially related research project dealing with the synthesis of certain pyrethroids, we recently had occasion to study the asymmetric cyclopropanation of derivatives of 3-methyl-2-buten-1-ol. Upon consideration of methods which potentially could be amenable to large-scale synthesis, we decided to evaluate the copper-catalysed process[1] introduced independently by Pfaltz,[2a,b] Masamune[3] and Evans.[4] The method is based on C_2-symmetric semicorrin (Pfaltz) or bis(oxazoline) ligands (Masamune, Evans, Pfaltz) which form chiral copper complexes capable of mediating the asymmetric cyclopropanation of alkenes by diazo compounds, particularly ethyl diazoacetate. At the outset of our work, very few examples of the use of these catalytic systems for the cyclopropanation of *trisubstituted* olefins could be found in the literature,[5] and the present study was carried out partly in order to allow a comparison with the excellent catalysts developed in the pioneering work of Aratani.[6] In this paper, we wish to report our results involving a series of nine derivatives of 3-methyl-2-buten-1-ol and five chiral bis(oxazoline) ligands. The general reaction, substrates, ligands and copper species used in the present investigation are shown in Fig. 1. (Not

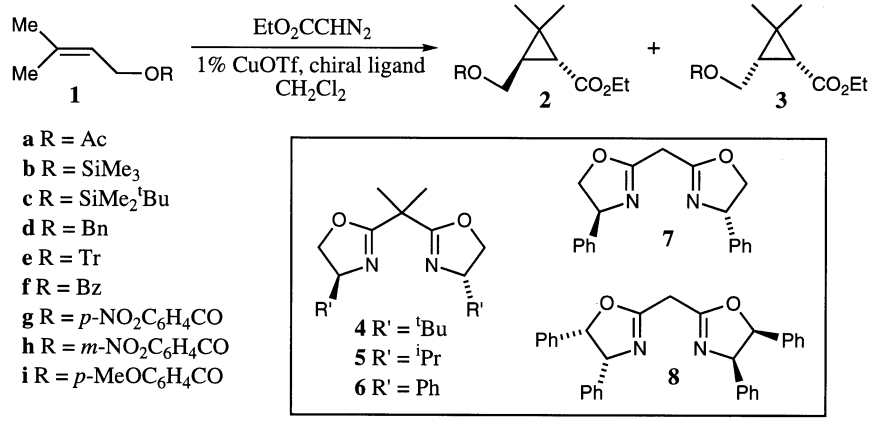

Figure 1. General reaction, substrates, ligands and copper species used in the present study.

Keywords: asymmetric synthesis; catalysis; copper and compounds; cyclopropanes.
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Table 1. Reaction conditions (2 equiv. alkene used; temp. in °C), yield (total yield), de and ee (determined by chiral GC) for cyclopropanation of **1a**

Entry	Ligand	Temperature	% Yield	*Trans*/*cis*	%ee (*trans*)	%ee (*cis*)
1	None	rt	61	57:43	Racemic	Racemic
2	**4**	rt	70	62:38	67	5
3	**4**	0	50	79:21	93	23
4	**4**	−6	50	80:20	95	47
5	**4**	−20	–	–	–	–
6	**5**	rt	89	43:57	73	0
7	**5**	0	80	39:61	78	0
8	**5**	−10	<5	41:59	80	0
9	**6**	0	47	49:51	69	3
10	**7**	rt	40	53:47	50	1
11	**7**	0	11	55:45	59	9
12	**8**	rt	<5	47:53	45	19
13	**8**	0	–	–	–	–

unexpectedly,[7] 3-methyl-2-buten-1-ol is itself not a good substrate for the cyclopropanation reaction, since it gives exclusively[8] the product of carbene insertion into the O–H bond.)

2. Results and discussion

All nine substrates were prepared in high yield from the parent alcohol by means of standard procedures. In all cases, the *trans*/*cis* ratio of the products from the cyclopropanation reaction was measured on the crude product (GC or ^{1}H NMR spectroscopy) and the enantioselectivity was also determined for the crude product mixture (chiral GC or chiral HPLC). In each case, a 'ligandless' cyclopropanation experiment was first performed to obtain racemic material which was used to determine the analytical conditions for baseline separation of diastereomers and enantiomers. This also allowed appraisal of any differences in 'inherent' diastereoselectivity of the various substrates. The acetate **1a** was chosen initially to screen the performance of the five chiral ligands, and the results are shown in Table 1.

The first ligand tested was **4** (Table 1, entries 2–5). At room temperature, a total yield of 70% was obtained, with a *trans*/*cis* ratio of 62:38. The ee for the *trans* product was a modest 67%, while that for *cis* was only 5% (entry 2). Lowering the temperature (entries 3 and 4) also lowered the yield, but raised the diastereoselectivity to ca. 80:20, and at −6°C an excellent ee of 95% was obtained for the *trans* isomer, the ee of the *cis* product being also markedly increased. Further lowering of the temperature (entry 5) unfortunately served only to shut down the cyclopropanation reaction.

The less bulky ligand **5** was then tested, with some interesting results (entries 6–8). The chemical yields were now decidedly superior to those obtained with **4** but, much to our surprise, a *reversal* of diastereoselectivity was observed, and the ee for the *cis* component was essentially zero at the three temperatures tried. The ee of the *trans* isomer (which had the same absolute configuration as observed for entries 2–4) increased slightly as the temperature was lowered, reaching a maximum of ca. 80%. As in the previous runs, the chemical yield decreased rapidly with relatively modest decreases in temperature. Our results with **4** and **5** can be compared with those of Evans[4] who used the same two catalytic systems for cyclopropanation of styrene and obtained a clear preference for the *trans* isomer in both cases (73:27 for **4**, 69:31 for **5**). Upon going from mono- to trisubstituted alkenes, there is thus obviously a difference in the steric interactions between the substrate and the catalyst in the reaction step, which determines diastereoselectivity. Our results with the trisubstituted alkene can also be compared with those of Pfaltz,[2a] who used the analogous semicorrin ligands and concluded that for terminal olefins such as styrene, the diastereoselectivity of the reaction is determined mainly by the structure of the diazo component, and is much less dependent on steric variations in catalyst structure.

A single experiment was then performed using ligand **6** (entry 9) at 0°C. A slight preference for the *cis* isomer was observed, with very low ee for the major product. The ee for the *trans* isomer (69%) was also lower than that obtained by use of **4** and **5**, and since one of the goals of the project was to maximise yield and enantioselectivity for the *trans* product, this ligand was not investigated further.

We then turned to ligand **7** which lacks the geminal dimethyls of **4**–**6**, and should thus be more disposed toward enolisation, which in turn could have a deleterious effect on the cyclopropanation reaction. This was indeed the case, and both yield and enantioselectivity suffered (entries 10 and 11). Diastereoselectivity was also poor but, in contrast to the results with ligand **6**, the *trans* isomer was now the major product (compare entries 11 and 9).

Finally, we tested Masamune's ligand **8** (entries 12 and 13) which was reported to give good results[9] in the cyclopropanation of certain trisubstituted olefins with dicyclohexylmethyl diazoacetate. Again, we were surprised to find that the *cis* isomer was the major product, and the very low (or zero) chemical yield combined with poor levels of ee discouraged further investigation of this system. As expected, use of this ligand led to the opposite major enantiomer of the *trans* product, as compared to the other ligands used.

For the cyclopropanation of acetate **1a**, CuOTf–benzene complex was shown to be superior to $Cu(OTf)_2$/phenylhydrazine[10]

Table 2. Reaction conditions (2 equiv. alkene used; temp. in °C), yield (total yield), de (by ^{1}H NMR) and ee (by chiral GC) for cyclopropanation of **1b** and **1c**

Entry	Ligand	Temp.	% Yield	*Trans*/*cis*	%ee (*trans*)	%ee (*cis*)
1 (**1b**)	None	rt	32	53:47	Racemic	Racemic
2 (**1b**)	**4**	rt	44	65:35	76	n.d.
3 (**1b**)	**4**	0	33	76:24	87	n.d.
4 (**1b**)	**4**	−9	<5	86:14	87	n.d.
5 (**1b**)	**5**	0	73	50:50	74	n.d.
6 (**1b**)	**5**	−9	<5	65:35	80	n.d.
7 (**1b**)	**6**	0	52	64:36	66	n.d.
8 (**1c**)	None	rt	17	80:20	Racemic	Racemic
9 (**1c**)	**4**	0	<5	58:42	10	11

in terms of yield, ee and de, so the former source of copper(I) was used in all subsequent experiments.

The next substrates tested were the silyl ethers **1b** and **1c** (Table 2). In view of the results shown in Table 1, we decided to restrict ourselves to a screening of ligands **4**, **5** and **6**.

The TMS ether **1b** in conjunction with ligand **4** (Table 2, entries 2–4) gave de and ee values which were roughly comparable to those obtained with acetate **1a**, but chemical yields were lower. For ligands **5** and **6**, however, a distinct difference in the behaviour of **1a** and **1b** was apparent, as far as diastereoselectivity was concerned (compare entry 8 in Table 1 with entry 6 in Table 2; entry 9 in Table 1 with entry 7 in Table 2). The ee values for the *cis* product from **1b** could not be determined accurately, due to decomposition on the chiral GC column. The good chemical yield for the reaction with ligand **5** is noteworthy (entry 5) but no diastereoselectivity was observed in that case. Bis(oxazoline) **4** again gave the highest enantioselectivity for the *trans* isomer, and this ligand was thus chosen for the reaction with the bulkier TBDMS ether **1c**, but with very disappointing results (Table 2, entry 9). For the TBDMS substrate, the ligandless reaction actually gave a significantly higher diastereoselectivity than the reaction run in the presence of **4** (compare entries 8 and 9 in Table 2). We then decided to concentrate exclusively on ligand **4** and results of cyclopropanation of the remaining substrates **1d**–**1i** are gathered in Table 3.

Benzyl ether **1d** was found to be a good substrate (Table 3, entry 3), giving satisfactory chemical yield (74%), relatively high diastereoselectivity (88:12 in favour of the desired *trans* isomer) and good ee (93% for *trans*). The diastereoselectivity is perhaps the most interesting feature, since literature precedence[1] suggests that such high levels of diastereoselection are usually difficult to attain by use of the sterically relatively unhindered ethyl diazoacetate.

The more sterically demanding trityl ether **1e** was then tested (Table 3, entry 5) but gave lower yield and poorer enantioselectivity for the *trans* isomer. The ee of the minor diastereomer was not determined. As for the TBDMS ether, the bulky protecting group in **1e** led to a high de in the ligandless reaction, but in contrast to the results with **1c**, the de remained essentially unchanged when **1e** was cyclopropanated in the presence of the chiral ligand (compare entries 4 and 5).

The last class of derivatives we studied were esters **1f**–**1i** (entries 6–13). The benzoate **1f** (entry 7) gave a satisfactory 82% yield, combined with a diastereomer ratio of 82:18 in favour of the *trans* isomer, which had 92% ee. The enantiomers of the *cis* product did not separate on chiral HPLC.

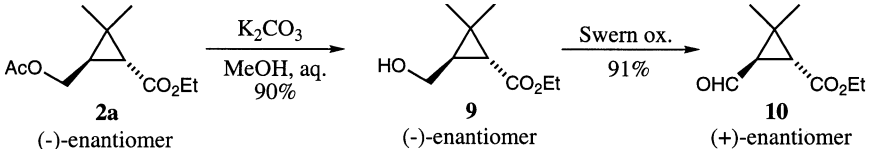
The remaining three substrates **1g**–**1i** were chosen to examine possible electronic effects of substituents on the aromatic ring of the ester. As shown in entries 9 and 11, the two nitro-substituted esters were very poor substrates for the catalyst, particularly in the presence of the chiral ligand, and the major products of the reaction were diethyl maleate and diethyl fumarate (vide supra). In sharp contrast, the *p*-methoxy benzoate **1i** (entry 13) gave very satisfactory results: 61% yield, and a diastereomer ratio of 91:9 in favour of the *trans* isomer, which showed 92% ee. The ee of the *cis* product was only 12%. The diastereoselectivity is remarkable, and this is one of the very best results obtained for intermolecular cyclopropanation with a copper-bis(oxazoline) ligand and ethyl diazoacetate.

3. Mechanistic considerations

We have not performed rigorous chemical correlations to determine the absolute configuration of the major diastereomers/enantiomers obtained, but transformation of the major product from the cyclopropanation of acetate **1a** (Table 1, entry 4) to the (+)-enantiomer of the aldehyde-ethyl ester **10** is shown in Scheme 1. By analogy with the

Table 3. Reaction conditions (2 equiv. alkene used for **1d**, 1 equiv. for **1e**–**1i**; temp. in °C), yield (total yield), de (by ^{1}H NMR) and ee (by chiral HPLC, except for **1e** (chiral GC after cleavage of trityl group)) for cyclopropanation of **1d**–**1i**

Entry	Ligand	Temperature	% Yield	*trans*/*cis*	%ee (*trans*)	%ee (*cis*)
1 (**1d**)	None	rt	51	55:45	Racemic	Racemic
2 (**1d**)	**4**	rt	55	86:14	91	n.d.
3 (**1d**)	**4**	0	74	88:12	93	n.d.
4 (**1e**)	None	rt	36	83:17	Racemic	Racemic
5 (**1e**)	**4**	0	46	82:18	87	n.d.
6 (**1f**)	None	rt	78	50:50	Racemic	Racemic
7 (**1f**)	**4**	0	82	82:18	92	n.d.
8 (**1g**)	None	rt	20	51:49	Racemic	Racemic
9 (**1g**)	**4**	0	2	75:25	90	46
10 (**1h**)	None	rt	26	51:49	Racemic	Racemic
11 (**1h**)	**4**	0	–	–	–	–
12 (**1i**)	None	rt	78	58:49	Racemic	Racemic
13 (**1i**)	**4**	0	61	1:9	92	12



2a (-)-enantiomer **9** (-)-enantiomer **10** (+)-enantiomer

Scheme 1. Correlation of (−)-**2a** with (+)-**10**.

known (+)-enantiomer of the aldehyde-*methyl* ester[11] we assign the (*R*,*R*) configuration to our major product.

This assignment is also in line with a prediction made on the basis of the transition state model introduced by Pfaltz[1,2a] to rationalise the stereochemical outcome of cyclopropanation reactions involving the closely related semicorrin ligands. From inspection of models of the four plausible combinations for the approach of the substrate to the presumed copper-carbenoid complex, the transition state shown in Fig. 2 appears to be that in which steric interactions (ligand–carbenoid; ligand–substrate; carbenoid–substrate) are minimised.

We have recently addressed[12] the mechanism of the bis-(oxazoline)/copper-catalysed cyclopropanation of styrene by a combination of isotopic labeling, Hammett-type kinetic studies, and high-level computational methods, and the results are in good agreement with those predicted by the Pfaltz model. Extension of mechanistic and computational studies to more heavily substituted alkenes such as those used in the present study is currently under way.

4. Conclusions

In this study, we have investigated the scope and limitations of the intermolecular copper-catalysed asymmetric cyclopropanation of some trisubstituted olefins. Of the five chiral bis(oxazoline) ligands tested, the Evans[13] ligand **4** was found to be best in terms of diastereo- and enantioselectivity. In contrast to previous results for mono-substituted olefins, both diastereo- and enantioselectivity were found to be markedly dependent on the steric properties of the ligands employed. A remarkably high diastereomeric ratio (91:9) was found for one of the substrates, and this is one of the highest values yet observed for this type of cyclopropanation reaction involving ethyl diazoacetate. In addition, synthetically useful levels of enantioselectivity (up to 95% ee) could be obtained.

The major goal of this study was to explore the limits of 'state of the art' catalytic asymmetric cyclopropanation, and our results underline that we still have a considerable way to go before truly general and practical procedures are at hand.

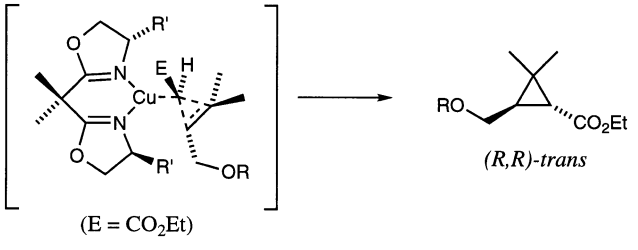


Figure 2. Proposed transition state leading to the (*R*,*R*)-*trans* isomer, **2**.

5. Experimental

5.1. General methods

All reactions involving air-sensitive reagents were performed under N_2 using syringe-septum cap techniques. All glassware was flame-dried under vacuum prior to use. Flash column chromatography was performed using silica gel (Merck, 40–63 mesh). TLC was performed using Merck silica gel 60 F_{254} aluminium sheets. Spots were visualised under UV light (254 nm) and by an ethanolic 20% phosphomolybdic acid solution/heat. ^{1}H NMR (200 MHz) and ^{13}C (50 MHz) spectra were recorded for $CDCl_3$ solutions on a Bruker AC-200 instrument with tetramethylsilane as internal standard. Optical rotations were measured at ca. 20°C on a Perkin Elmer 241 polarimeter ($c=g/100$ mL). IR spectra were recorded for neat samples on a Perkin Elmer 1600 series FTIR instrument, and only the strongest/structurally most important peaks are listed (ν_{max} cm^{-1}). Diastereomeric ratios were measured either by GC or by ^{1}H NMR. Enantiomeric purities were determined by GC analysis (Hewlett Packard 5890 series II using a Chrompack Chiralsil-Dex column) or by HPLC analysis (Varian 9065 polychrom system using a Chiralcel OD-H or Chiralcel OJ column). Microanalyses were provided by the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria.

5.2. Materials

All solvents, reagents and ligands were obtained from Fluka or Aldrich and used without further purification except CH_2Cl_2, which was distilled from CaH_2 under N_2. Ligand **5** was synthesised from L-valinol by adaptation of a recent procedure[13] for **4**. Copper(I) trifluoromethanesulfonate benzene complex was prepared as previously described[14] and stored under N_2.

5.3. General procedure for asymmetric cyclopropanation

To a solution of CuOTf–benzene complex (10 mg, 0.040 mmol) in CH_2Cl_2 (2 mL) was added a solution of a chiral bis(oxazoline) ligand (0.045 mmol) in CH_2Cl_2 (1 mL). After 1 h at room temperature, the resulting solution was cooled to the desired temperature. The alkene (8 mmol) was added followed by addition of a solution of ethyl diazoacetate (4 mmol) in CH_2Cl_2 (4 mL) over a period of 10 h via syringe pump. When addition was complete, the mixture was stirred until all ethyl diazoacetate had reacted according to TLC (usually <1 h). The CH_2Cl_2 was removed

at reduced pressure and the crude product was taken up in the minimum amount of ethyl acetate/hexane (1:1) and filtered through a short plug of silica gel before a sample was collected for determination of enantiomeric and diastereomeric excess. For every cyclopropanation reaction, the formation of varying amounts of diethyl fumarate and diethyl maleate was observed.

The products were purified by flash chromatography, and all cyclopropanation products were obtained pure as colourless oils. Reaction temperatures, isolated total yields, diastereoselectivities, and enantioselectivities are given in Tables 1–3. Since we were primarily interested in the *trans* isomers of the cyclopropanes, only these which were obtained in good yield and relatively high de/ee have been fully characterised; the *cis* isomers have in most cases been characterised by ^{1}H and ^{13}C NMR spectroscopy only.

5.3.1. (−)-*trans*-Ethyl 3-acetoxymethyl-2,2-dimethylcyclopropanecarboxylate, 2a. ^{1}H NMR: δ 4.18 (dd, J=12, 7 Hz, 1H), 4.13 (m, 2H), 4.00 (dd, J=12, 8 Hz, 1H), 2.07 (s, 3H), 1.73 (ddd, J=8, 7, 5.5 Hz, 1H), 1.43 (d, J=5.5 Hz, 1H), 1.27 (s, 3H), 1.26 (t, J=7 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR: δ 171.5, 170.9, 63.5, 60.3, 31.7, 30.2, 26.8, 21.1, 20.8, 20.4, 14.2; IR: 1740, 1726, 1442, 1368, 1239, 1178, 1032; $[\alpha]_D$=−28 (c=1.15; CH_2Cl_2, ee=95%); TLC: R_f=0.65 (EtOAc/hexane 1:4). FAB-HRMS $(M+H)^+$: Calcd for $C_{11}H_{18}O_4$ 215.1283. Found 215.1297.

Data for *cis* isomer **3a**: ^{1}H NMR: δ 4.50 (dd, J=12, 7 Hz, 1H), 4.39 (dd, J=12, 8 Hz, 1H), 4.11 (m, 2H), 2.06 (s, 3H), 1.60 (d, J=9 Hz, 1H), 1.44 (ddd, J=9, 8, 7 Hz, 1H), 1.27 (s, 3H), 1.25 (t, J=7 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR: δ 171.1, 60.5, 60.1, 30.3, 28.8, 28.6, 21.0, 14.2, 14.1; TLC: R_f=0.68 (EtOAc/hexane 1:4).

5.3.2. (−)-*trans*-Ethyl 3-[(trimethylsilyl)oxymethyl]-2,2-dimethylcyclopropanedicarboxylate, 2b. ^{1}H NMR: δ 4.12 (m, 2H), 3.74 (dd, J=11, 6 Hz, 1H), 3.53 (dd, J=11, 8 Hz, 1H), 1.66 (ddd, J=8, 6, 5.5 Hz, 1H), 1.33 (d, J=5 Hz, 1H), 1.26 (t, J=7 Hz, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.10 (s, 9H); ^{13}C NMR: δ 172.1, 61.5, 60.1, 34.2, 31.3, 27.0, 21.0, 20.6, 14.2, −0.4; IR: 1727, 1445, 1378, 1250, 1173, 1079; $[\alpha]_D$=−15.8 (c=0.89, CH_2Cl_2, ee=76%); TLC: R_f=0.27 (EtOAc/hexane 1:19).

Data for *cis* isomer **3b**: ^{1}H NMR: δ 4.08 (m, 2H), 3.91 (dd, J=6.5, 2.5 Hz, 2H), 1.52 (d, J=9 Hz, 1H), 1.40 (ddd, J=9, 6.5 2.5 Hz, 1H), 1.25 (s, 3H), 1.25 (t, J=7 Hz, 3H), 1.18 (s, 3H), 0.10 (s, 9H); ^{13}C NMR: δ 171.4, 59.7, 57.7, 34.5, 28.7, 28.4, 25.0, 14.2, 13.9, −0.1; TLC: R_f=0.32 (EtOAc/hexane 1:19).

Compounds **2b** and **3b** decomposed partly upon purification and no satisfactory microanalyses or HRMS data were obtained.

5.3.3. *trans*-Ethyl 3-[(*tert*-butyldimethylsilyl)oxymethyl]-2,2-dimethylcyclopropanecarboxylate, 2c. ^{1}H NMR: δ 4.12 (m, 2H), 3.77 (dd, J=11, 6 Hz, 1H), 3.55 (dd, J=11, 8 Hz, 1H), 1.63 (ddd, J=9, 6, 5 Hz, 1H), 1.35 (d, J=5 Hz, 1H), 1.24 (t, J=7 Hz, 3H), 1.22 (s, 3H), 1.18 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0,05 (s, 3H); ^{13}C NMR: δ 172.3, 61.9, 60.0, 34.5, 31.2, 27.0, 25.7, 21.0, 20.7, 14.2, 14.0, −5.2; IR: 1727, 1463, 1378, 1256, 1174, 1088; TLC: R_f=0.50 (EtOAc/hexane 1:19).

Data for *cis* isomer **3c**: ^{1}H NMR: δ 4.08 (m, 2H), 3.96 (dd, J=11, 7 Hz, 1H), 3.90 (dd, J=11, 6.5 Hz, 1H), 1.52 (d, J=9 Hz, 1H), 1.40 (ddd, J=9, 7, 6.5 Hz, 1H), 1.25 (s, 3H), 1.25 (t, J=7 Hz, 3H), 1.18 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR: δ 171.4, 59.7, 58.2, 34.7, 28.7, 28.5, 25.8, 25.1, 18.1, 14.2, 14.0, −5.3; TLC: R_f=0.63 (EtOAc/hexane 1:19).

5.3.4. (−)-*trans*-Ethyl 3-benzyloxymethyl-2,2-dimethylcyclopropanecarboxylate, 2d. ^{1}H NMR: δ 7.35–7.25 (m, 5H), 4.50 (d, J=1 Hz, 2H), 4.11 (m, 2H) 3.61 (dd, J=11, 6 Hz, 1H), 3.38 (dd, J=11, 8.5 Hz, 1H), 1.75 (ddd, J=8.5, 6, 5 Hz, 1H), 1.36 (d, J=5 Hz, 1H), 1.25 (t, J=7 Hz, 3H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR: δ 172.0, 138.2, 128.3, 127.6, 72.5, 68.7, 60.2, 31.6, 31.4, 26.9, 21.1, 20.6, 14.2; IR: 1720, 1453, 1378, 1176, 1096; $[\alpha]_D$=−20 (c=0.95; CH_2Cl_2, ee=93%). TLC: R_f=0.40 (EtOAc/hexane 1:4). FAB-HRMS $(M+H)^+$: Calcd for $C_{16}H_{23}O_3$ 263.1647. Found 263.1637.

Data for *cis* isomer **3d**: ^{1}H NMR: δ 7.35–7.25 (m, 5H), 4.52 (d, J=1 Hz, 2H), 4.11 (m, 2H), 3.86 (dd, J=10.5, 5 Hz, 1H), 3.78 (dd, J=10.5, 4.5 Hz, 1H), 1.57 (d, J=9 Hz, 1H), 1.44 (ddd, J=9, 5, 5.5, 1H), 1.25 (s, 3H), 1.24 (t, J=7 Hz, 3H), 1,19 (s, 3H); ^{13}C NMR: δ 171.4, 138.6, 128.2, 127.6, 127.4, 72.8, 65.4, 59.9, 32.0, 28.6, 25.1, 14.2, 14.1; TLC: R_f=0.44 (EtOAc/hexane 1:4).

5.3.5. (+)-*trans*-Ethyl 3-trityloxymethyl-2,2-dimethylcyclopropanecarboxylate, 2e. ^{1}H NMR: δ 7.50–7.40 (m, 6H), 7.35–7.15 (m, 9H), 4,10 (m, 2H), 3.31 (dd, J=10, 6 Hz, 1H), 2.85 (dd, J=10, 8.5 Hz, 1H), 1.75 (ddd, J=8.5, 6, 5 Hz, 1H), 1.32 (d, J=5 Hz, 1H), 1,28 (t, J=7 Hz, 3H), 1,26 (s, 3H), 1.02 (s, 3H); ^{13}C NMR: δ 172.2, 144.1, 128.5, 127.6, 126.8, 86.3, 62.7, 60.1, 32.2, 31.3, 26.9, 21.1, 20.6, 14.2; IR: 1725, 1596, 1490, 1447, 1378, 1176, 1061; $[\alpha]_D$=+6.4 (c=0.93, CH_2Cl_2, ee=87%); R_f=0.35 (EtOAc/hexane 1:9). Anal. Calcd for $C_{28}H_{30}O_3$: C, 81.13; H, 7.29. Found: C, 80.99; H, 7.36.

Data for *cis* isomer **3e**: ^{1}H NMR: δ 7.50–7.40 (m, 6H), 7.35–7.15 (m, 9H), 3.98 (m, 2H), 3.43 (dd, J=7, 0.5 Hz, 2H), 1.50 (d, J=9 Hz, 1H), 1.37 (dt, J=9, 7 Hz, 1H), 1.18 (s, 3H), 1.17 (t, J=7 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR: δ 171.3, 144.4, 128.7, 127.6, 126.8, 86.3, 59.7, 59.1, 32.3, 28.8, 28.8, 25.0, 14.2, 14.2; R_f=0.42 (EtOAc/hexane 1:9).

5.3.6. (−)-*trans*-Ethyl 3-(benzoyloxymethyl)-2,2-dimethylcyclopropanecarboxylate, 2f. ^{1}H NMR: δ 8.10–8.00 (m, 2H), 7.62–7.38 (m, 3H), 4.48 (dd, J=12, 7 Hz, 1H), 4.23 (dd, J=12, 9 Hz, 1H), 4.14 (m, 2H), 1.88 (ddd, J=9, 7, 5 Hz, 1H), 1.53 (d, J=5 Hz, 1H), 1.27 (s, 3H), 1.26 (t, J=7 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR: δ 171.5, 166.3, 132.8, 129.5, 128.2, 64.0, 60.4, 31.8, 30.3, 26.9, 21.3, 20.4, 14.2; IR: 1720 (broad), 1451, 1271, 1177, 1111; $[\alpha]_D$=−22.1 (c=0.10, CH_2Cl_2, ee=92%); TLC: R_f=0.40 (EtOAc/hexane 1:9); Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.35; H, 7.37.

Data for *cis* isomer **3f**: ^{1}H NMR: δ 8.10–8.00 (m, 2H),

7.62–7.38 (m, 3H), 4.73 (ddd, *J*=22, 7, 1 Hz, 1H), 4.68 (ddd, *J*=22, 5.5, 2 Hz, 1H), 4.10 (m, 2H), 1.75–1.52 (m, 2H), 1.35 (s, 3H), 1.26 (t, *J*=7 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR: δ 171.0, 166.4, 132.7, 129.4, 128.1, 60.9, 60.0, 30.3, 28.9, 28.5, 28.5, 20.4, 14.2; TLC: R_f=0.47 (EtOAc/hexane 1:9).

5.3.7. *trans*-Ethyl 3-(4-nitrobenzoyloxymethyl)-2,2-dimethylcyclopropanecarboxylate, 2g. ^{1}H NMR: δ 8.35–8.15 (m, 4H), 4.53 (dd, *J*=12, 7 Hz, 1H), 4,32 (dd, *J*=12, 9 Hz, 1H), 4.14 (m, 2H), 1.90 (ddd, *J*=9, 7, 5 Hz, 1H), 1.58 (d, *J*=5 Hz, 1H), 1.30 (t, *J*=7 Hz, 3H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR: δ 171.2, 164.3, 135.3, 130.6, 129.6, 123.4, 65.0, 60.4, 31.8, 30.0, 26.8, 21.2, 20.3, 14.1; IR: 1720, 1713, 1609, 1529, 1442, 1338, 1275, 1177, 1103; TLC: R_f=0.53 (EtOAc/hexane 1:4).

Data for *cis* isomer **3g**: ^{1}H NMR: δ 8.35–8.15 (m, 4H), 4.80 (dd, *J*=22, 7 Hz, 1H), 4.75 (dd, *J*=22, 7, 1 Hz, 1H), 4.11 (q, *J*=7 Hz, 2H), 1.65 (d, *J*=9 Hz, 1H), 1.64 (ddd, *J*=9, 7, 7 Hz, 1H), 1.35 (s, 3H), 1.25 (t, *J*=7 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR: δ 170.9, 164.4, 135.6, 130.5, 123.3, 62.0, 60.0, 29.9, 28.9, 28.4, 28.4, 25.4, 14.1; TLC: R_f=0.62 (EtOAc/hexane 1:4).

5.3.8. *trans*-Ethyl 3-(3-nitrobenzoyloxymethyl)-2,2-dimethylcyclopropanecarboxylate, 2h. ^{1}H NMR: δ 8.85 (td, *J*=2, 1 Hz, 1H), 8.43 (ddd, *J*=8, 4, 1 Hz, 1H), 8.38 (ddd, *J*=8, 2, 1 Hz, 1H), 7.68 (td, *J*=8, 1 Hz, 1H), 4.53 (dd, *J*=12, 7 Hz, 1H), 4.33 (dd, *J*=12, 8 Hz, 1H), 4.16 (m, 2H), 1.92 (ddd, *J*=8, 7, 5 Hz, 1H), 1.59 (d, *J*=5 Hz, 1H), 1.30 (s, 6H), 1.28 (t, *J*=7 Hz, 3H); ^{13}C NMR: δ 171.3, 164.1, 146.0, 135.1, 131.7, 129.6, 127.2, 123.4, 65.0, 60.4, 31.8, 30.6, 26.8, 21.2, 20.3, 14.1.

Data for *cis* isomer **3h**: ^{1}H NMR: δ 8.85 (td, *J*=2, 1 Hz, 1H), 8.43 (ddd, *J*=8, 4, 1 Hz, 1H), 8.38 (ddd, *J*=8, 2, 1 Hz, 1H), 7.68 (td, *J*=8, 1 Hz, 1H), 4.81 (dd, *J*=18, 7 Hz, 1H), 4.77 (dd, *J*=18, 6, 1 Hz, 1H), 4.11 (m, 2H), 1.65 (d, *J*=9 Hz, 1H), 1.64 (ddd, *J*=9, 7, 6 Hz, 1H), 1.35 (s, 3H), 1.28 (t, *J*=7 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR: δ 170.9, 164.2, 146.0, 135.1, 129.6, 129.4, 127.1, 124.3, 61.9, 60.1, 30.0, 28.8, 28.4, 28.4, 25.5, 14.1.

5.3.9. *trans*-Ethyl 3-(4-methoxybenzoyloxymethyl)-2,2-dimethylcyclopropanecarboxylate, 2i. ^{1}H NMR: δ 7.99 (dt, *J*=9, 2 Hz, 2H), 6.93 (dt, *J*=9, 2 Hz, 2H), 4.46 (dd, *J*=12, 7 Hz, 1H), 4.20 (dd, *J*=12, 8 Hz, 1H), 4.14 (m, 2H), 3.87 (s, 3H), 1.87 (ddd, *J*=8, 7, 5 Hz, 1H), 1.52 (d, *J*=5 Hz, 1H), 1.27 (s, 3H), 1.26 (t, *J*=7 Hz, 3H), 1.25 (s, 3H); ^{13}C NMR: δ 171.6, 166.1, 163.3, 131.5, 122.5, 113.5, 63.7, 60.3, 55.3, 31.8, 30.4, 26.9, 21.2, 20.4, 14.2; IR: 1718 (broad), 1606, 1512, 1258, 1168, 1101, 1030; $[\alpha]_D$=−24.2 (*c*=1.23, CH_2Cl_2, ee=92%); TLC: R_f=0.35 (EtOAc/hexane 1:4); Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.65; H, 7.15.

Data for *cis* isomer **3i**: ^{1}H NMR: δ 7.99 (dt, *J*=9, 2 Hz, 2H), 6.91 (dt, *J*=9, 2 Hz, 2H), 4.70 (dd, *J*=22, 7 Hz, 1H), 4.65 (ddd, *J*=22, 6, 2 Hz, 1H), 4.11 (m, 2H), 3.86 (s, 3H), 1.62 (d, *J*=6 Hz, 1H), 1.60 (m, 1H), 1.34 (s, 3H), 1.25 (t, *J*=7 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR: δ 171.0, 166.2, 163.1, 131.4, 122.8, 113.4, 60.6, 60.0, 55.2, 30.4, 28.9, 28.5, 28.5, 25.3, 14.1; IR: 1718 (broad), 1606, 1511, 1257, 1168, 1101, 1031; TLC: R_f=0.39 (EtOAc/hexane 1:4).

Data for (−)-enantiomer of **9**: ^{1}H NMR: δ 4.11 (q, *J*=7 Hz, 2H), 3.73 (dd, *J*=12, 7 Hz, 1H), 3.60 (dd, *J*=12, 9 Hz, 1H), 1.70 (ddd, *J*=9, 7, 5 Hz, 1H), 1.40 (d, *J*=5 Hz, 1H), 1.27 (s, 3H), 1.26 (t, *J*=7 Hz, 3H), 1.25 (s, 3H); ^{13}C NMR: δ 172.1, 61.8, 60.3, 34.4, 31.5, 27.0, 21.0, 20.7, 14.3; IR: 3427, 1723, 1379, 1172, 1116, 1028; $[\alpha]_D$=−37.7 (*c*=0.73; CH_2Cl_2, e.e.=93%); TLC: R_f=0.15 (EtOAc/hexane 1:4). (The ^{1}H NMR and IR data are in accord with those in the literature[15] for the racemic material.)

Data for (+)-enantiomer of **10**: ^{1}H NMR: δ 9.58 (d, *J*=3 Hz, 1H), 4.11 (m, 2H), 2.50–2.40 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H), 1.27 (t, *J*=7 Hz, 3H). (These data are in accord with those in the literature[15] for the racemic material.) $[\alpha]_D$=+12 (*c*=0.2; acetone). For comparison, the corresponding methyl ester is reported[11] to have $[\alpha]_D$=+19.2 (*c*=1.84; acetone).

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References

1. For a recent review, see: Pfaltz, A. Comprehensive Asymmetric Catalysis II. In *Cyclopropanation and C–H Insertion with Cu*, Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp. 513–538.
2. (a) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, C. *Helv. Chim. Acta* **1988**, *71*, 1541. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
3. Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
4. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
5. For examples, see Ref. 1.
6. Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839 and references therein.
7. See: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. From Cyclopropanes to Ylides*, Wiley: New York, 1998; pp. 445–468.
8. Østergaard, N.; Tanner, D. Unpublished results.
9. Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
10. For a discussion of the use of Cu(I) and Cu(II) in catalytic asymmetric cyclopropanation, see Ref. 1, pp. 518–519.
11. Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1989**, *45*, 3039.
12. Rasmussen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O., submitted for publication.
13. Improved preparation of ligand **4**: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.
14. Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889.
15. Babler, J. H.; Tortorello, A. J. *J. Org. Chem.* **1976**, *41*, 885.