

HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 669 - 677. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 17th April, 2012, Accepted, 18th May, 2012, Published online, 25th May, 2012
DOI: 10.3987/COM-12-S(N)11

ENANTIOSELECTIVE MUKAIYAMA-ALDOL REACTION BETWEEN ENOL SILANES AND KETOMALONATE CATALYZED BY THE COPPER(II) COMPLEX OF TIPS-SUBSTITUTED BIS-OXAZOLINE†

Giovanni Desimoni,* Giuseppe Faita, Alessandro Livieri, and Laura Ponta

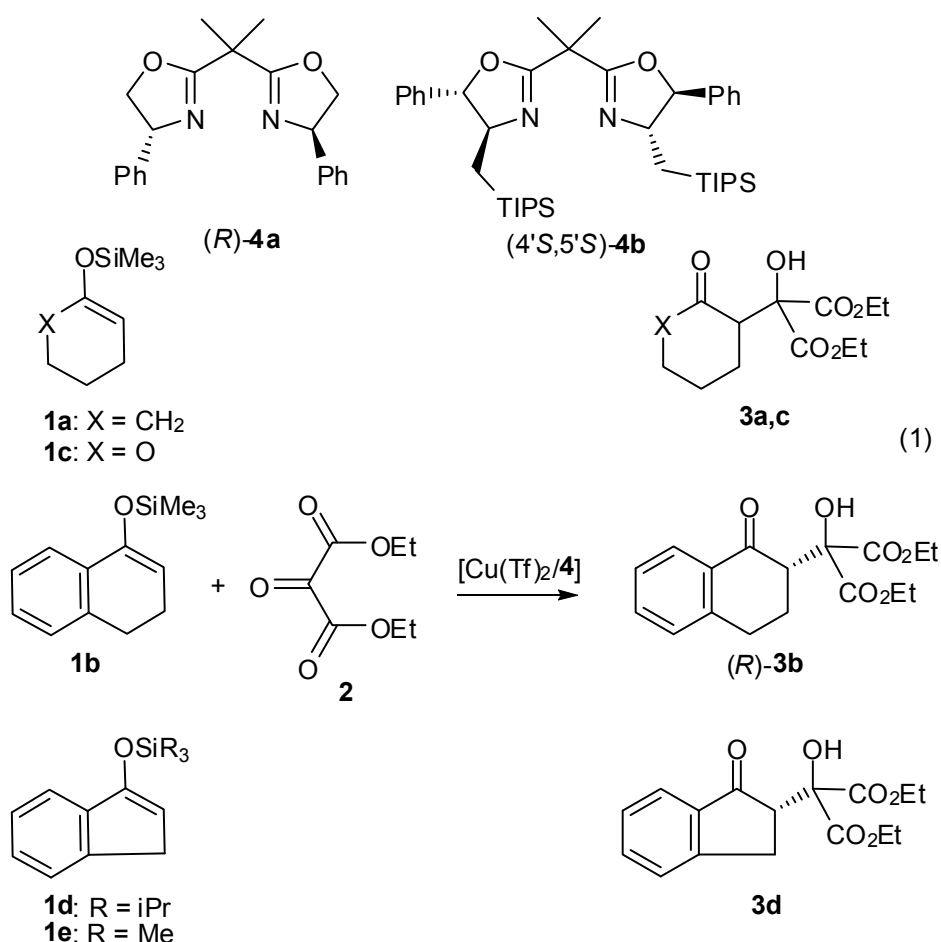
Department of Chemistry, University of Pavia, Viale Taramelli 10, 27100 Pavia, Italy. e-mail: desimoni@unipv.it

Abstract – The stable complex [(4'*S*,5'*S*)-**4b**/Cu(Tf)₂/H₂O] (**5**), obtained from TIPS-Box and Copper triflate, catalyzes enantioselectively the Mukaiyama-aldol reactions between two silyl enol ethers (**1a,b**) and diethyl ketomalonate (**2**). Yields are very good and the ee of (*R*)-**3b** is up to 94%. When the reaction was catalyzed by 4-Ph-Box complex [(4'*R*)-**4a**/Cu(Tf)₂], in which the configuration at the C-4 centre is opposite to that of **5**, the same enantiomer was obtained. The undistorted square pyramidal structure of complex **5**, determined by crystallographic structure, and the effect of water and molecular sieves on efficiency and selectivity of the catalyst, suggest some proposals to rationalize the resulting stereoselectivity.

Dicarbonyl derivatives are the suitable substrates to test the catalytic activity of a chiral complex between a cation acting as a Lewis acid and an optically active ligand. The carbonyl oxygen atoms in the reagent bind the cation in a bidentate fashion giving a rigid reacting intermediate suitable to promote the enantioselective reaction. Among the best catalysts, specific for these multi-use reactants, the C₂-symmetric copper(II) bis-(oxazoline) (Box) complexes can be mentioned.¹ These catalysts coordinate α- and β-dicarbonyl reagents (e.g. pyruvates and 3-alkenoyl-2-oxazolidinones) to form either five- or six-membered rings. These structures show a O-Cu-O fragment, which induce a face discrimination on the reactive site and give suitable informations to rationalize the resulting stereochemical outcome of the reaction.

† Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

Compared to the above reagents, diethyl ketomalonate has a specific structure with the schizophrenic capacity to behave as either an α - or a β -dicarbonyl reagent,² promoting with different chiral catalyst enantioselective hetero-Diels-Alder reactions,²⁻⁶ [2+2+2]-cycloadditions,⁷ and Mukaiyama-aldol reactions.^{8,9} Furthermore, aldol reaction¹⁰ and nitron-aldol reaction^{11,12} can be performed enantioselectively with organo-catalysts. Specifically, Mukaiyama-aldol reactions between silyl enol ethers (**1a,b**) and diethyl ketomalonate (**2**) to give **3a,b** [eq. 1], were at best catalyzed by [Box/Cu(OTf)₂] complexes. Highest yields and ees were obtained with the 4-phenyl-substituted Box (*4'R*)-**4a**.⁸ Silyl enol ether **1a** gave **3a** in 80% yield and 60% ee, **1b** gave (*R*)-**3b** in 91% yield and 86% ee.



The recently synthesized (*4'S,5'S*)-**4b** Box (TIPS-Box) gave a solid, stable Cu(Tf)₂ complex, whose crystal structure is reported in Figure 1.¹³ This was a valuable catalyst in Diels-Alder reaction between cyclopentadiene and β -dicarbonyl derivative such as 3-acryloyloxazolidin-2-one. This dienophile behaves as a bidentate reagent, and carbonyl groups substitute the triflate and the water molecule in the equatorial positions of the catalyst. An axial water molecule completed the penta-coordination of the reacting complex as shown in its X-rays crystal structure. This allowed to understand why **5** is suitable to favour

the downwards attack which induces the *Re* sense of the stereoinduction to the Diels-Alder adduct.¹³ Interestingly, the same *Re* induction, even with lower enantioselectivity (30%), is obtained with the [(4'*R*)-**4a**/Cu(Tf)₂] complex, in which the Box has the opposite configuration of the C-4 stereocenter in the oxazoline ring.^{1b,14}

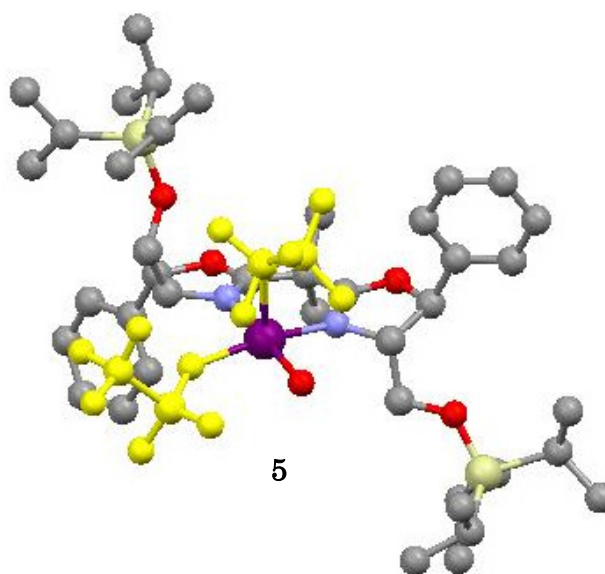


Figure 1. ORTEP view of the crystal structures of the [(4'*S*,5'*S*)-**4b**/Cu(OTf)₂] complex (**5**).¹³

The above results suggested to test the [(4'*S*,5'*S*)-**4b**/Cu(Tf)₂] complex (**5**) as catalyst for the Mukaiyama-aldol reactions between silyl enol ethers (**1a,b**) and diethyl ketomalonate (**2**).

The reaction with 1-TMSO-cyclohexene (**1a**) was performed in three different solvents using 5% mol **5** (Table, entries 1-3) at -70 °C, in the presence of 1 equiv. hexafluoroisopropanol (HFIP). The best result was obtained in diethyl ether (**3a**: yield 80%, ee 81%), and the enantioselectivity was slightly better than that obtained with [(4'*R*)-**4a**/Cu(Tf)₂] (Table 1, entry 4: ee 59%). The catalyst derived from (4'*R*)-**4a** induced the same sense of stereoinduction as **5**, derived from (4'*S*,5'*S*)-**4b**, did, giving the same *levo*-rotatory enantiomer of **3a**.

The results of three further experiments are reported in entries 5-7 of the Table. With 10% mol of (4'*S*,5'*S*)-**4b** and Cu(Tf)₂ the result is identical to that obtained with **5**, a clear proof that **5** is formed “in situ” from copper triflate and Box. Both yield and enantioselectivity of **3a** are unchanged when the reaction is performed in the presence of 10 equivalents water, whereas the catalytic efficiency of **5** is depressed when 3Å molecular sieves (MS) are added.

Table 1. Enantioselective Catalyzed Mukaiyama-Aldol Reaction between Silyl Enol Ethers (**1a-d**) and Diethyl Ketomalonate (**2**).^(a)

| n | Silyl enol ether | Catalyst (mol %) | Solvent | Additive | 3 yield % | 3 ee% (<i>conf.</i>) |
|-------------------|------------------|--|---------------------------------|-------------------------------------|------------------|-------------------------------|
| 1 | 1a | 5 (5) | Toluene | - | 73 | 37 |
| 2 | 1a | 5 (5) | CH ₂ Cl ₂ | - | 77 | 78 |
| 3 | 1a | 5 (5) | Et ₂ O | - | 80 | 81 |
| 4 ^(b) | 1a | (4' <i>R</i>)- 4a /Cu(Tf) ₂ (10) | Et ₂ O | - | 74 | 59 |
| 5 | 1a | (4' <i>S</i> ,5' <i>S</i>)- 4b /Cu(Tf) ₂ (10) | Et ₂ O | - | 78 | 79 |
| 6 | 1a | 5 (5) | Et ₂ O | MS | 15 | racem. ^(c) |
| 7 | 1a | 5 (5) | Et ₂ O | 2μL H ₂ O ^(d) | 76 | 78 |
| 8 | 1b | 5 (5) | Hexane | - | 28 | 60 (<i>R</i>) |
| 9 | 1b | 5 (5) | Hexane | 2μL H ₂ O ^(d) | 27 | 56 (<i>R</i>) |
| 10 | 1b | 5 (5) | Hexane | MS | 14 | racem. |
| 11 | 1b | 5 (5) | Toluene | - | 62 | 62 (<i>R</i>) |
| 12 | 1b | 5 (5) | Toluene | 2μL H ₂ O ^(d) | 28 | 66 (<i>R</i>) |
| 13 | 1b | 5 (5) | Toluene | MS | 14 | racem. |
| 14 | 1b | 5 (5) | CH ₂ Cl ₂ | - | 69 | 55 (<i>R</i>) |
| 15 | 1b | 5 (5) | CH ₂ Cl ₂ | 2μL H ₂ O ^(d) | 38 | 50 (<i>R</i>) |
| 16 | 1b | 5 (5) | CH ₂ Cl ₂ | MS | 3 | racem. |
| 17 | 1b | 5 (5) | Et ₂ O | - | 89 | 94 (<i>R</i>) |
| 18 ^(e) | 1b | (4' <i>R</i>)- 4a /Cu(Tf) ₂ (10) | Et ₂ O | - | 90 | 87 (<i>R</i>) |
| 19 | 1b | 5 (5) | Et ₂ O | 2μL H ₂ O ^(d) | 87 | 94 (<i>R</i>) |
| 20 | 1b | 5 (5) | Et ₂ O | 5μL H ₂ O ^(f) | 11 | racem. |
| 21 | 1b | 5 (5) | Et ₂ O | MS | 14 | 69 (<i>R</i>) |
| 22 | 1c | 5 (5) | Et ₂ O | - | 94 | racem. |
| 23 | 1c | (4' <i>R</i>)- 4a /Cu(Tf) ₂ (10) | Et ₂ O | - | 90 | racem. |
| 24 | 1d | 5 (5) | Et ₂ O | - | 43 | 34 |
| 25 | 1d | (4' <i>R</i>)- 4a /Cu(Tf) ₂ (10) | Et ₂ O | - | 38 | 26 |
| 26 ^(g) | 1e | (4' <i>R</i>)- 4a /Cu(Tf) ₂ (10) | Et ₂ O | - | 82 | 58 |

^(a)All reactions performed at -70 °C in the presence of 1 mol HFIP. ^(b)This result is nearly identical to that reported for the reaction between **1a** and **2** with the same catalyst and solvent at -78 °C (ee 60%) [ref. 8]. ^(c)Racem. is racemate. ^(d)10 Equiv water. ^(e)This result is nearly identical to that reported in the literature for the reaction between **1b** and **2** with the same catalyst and solvent at -78 °C (ee 86%) [ref. 8]. ^(f)25 Equiv water. ^(g) Data taken from reference (8).

Then, the reaction with 1-TMSO-1,2-dihydronaphthalene (**1b**) was tested in details. The catalytic efficiency of **5** in hexane, toluene, and dichloromethane (Table, entries 8-16) is similar with or without 10 equiv. water, but the efficiency is entirely lost with MS as additive. The best result is obtained with diethyl ether as the solvent (Table, entry 17; **3b**: yield 89%, ee 94%). Again, the presence of MS has a strongly negative effect (Table, entry 21). The amount of water added is crucial: 10 equiv. do not alter the efficiency of **5**, but 25 equiv. water suppress the catalytic effect (Table, entries 19 and 20).

The same reaction was performed with [(4'*R*)-**4a**/Cu(Tf)₂] and the enantioselectivity is similar to that induced by **5** (Table, entry 18 vs. 17: ee 87% vs. 94%) and both catalysts gave the same enantiomer (*R*)-**3b**.

The Mukaiyama-aldol reactions of (5,6-dihydro-4*H*-pyran-2-yloxy)trimethyl silane (**1c**) and (1*H*-inden-3-yloxy)triisopropyl silane (**1d**) with **2** were tested to explore the flexibility of **5** vs [(4'*R*)-**4a**/Cu(Tf)₂].

The reactions between **1c** and **2** (Table 1, entries 22 and 23) gives very good yields, but **3c** is obtained as a racemate with both catalysts. Given the analogies between **1a** and **1c** (entries 3, 4 vs. 23, 24), a possible interference of the oxygen atom of the latter in the face attack step to the reacting intermediate [(**2**)/(**4**)/Cu(II)] cannot be ruled out.

The reactions between **1d** and **2** (Table, entries 24 and 25) give low yields, and the ees of **3d** are disappointing with both catalysts. A comparison between the results of **1d** and its trimethylsilyl analogue **1e** (Table, entry 25 vs. 26), suggests that the triisopropylsilyl group has a negative effect not only on the reaction yield, but also on the stereoselectivity.

Which comments can be made on the above results?

The [(4'*S*,5'*S*)-**4b**/Cu(Tf)₂] complex (**5**) is a good enantioselective catalyst not only for Diels-Alder and nitrene 1,3-dipolar cycloadditions, but also for the Mukaiyama-aldol reaction of some silyl enol ethers with ketomalonate. If the catalyst is **5**, which can be the structure of the reacting intermediate with **2**, and the attack to it of **1b** to give (*R*)-**3b** occurs up-or-down-wards?

A reaction that gives one single stereocentre is not the ideal model to solve this question. Nevertheless two data allow advancing some considerations. Firstly, two complexes, [(4'*S*,5'*S*)-**4b**/Cu(Tf)₂] (*i.e.* **5**) and [(4'*R*)-**4a**/Cu(Tf)₂], with opposite configuration at the C-4 stereocentre, give the same enantiomerically enriched product (*R*)-**3b**. And it is known that [(4'*R*)-**4a**/Cu(Tf)₂] gives reacting complexes with α - or a β -dicarbonyl reagents that undergo a bottom-down attack.¹⁵ Furthermore, [(4'*S*,5'*S*)-**4b**/Cu(Tf)₂] needs some water (that crystallized in **5** or somewhat more) to behave as an efficient catalyst (Table, entries 17, 19-21).

If the reacting intermediate formed between **5** and **2** has the same penta-coordination shown by the reacting intermediate formed between **5** and acryloyl-1,3-oxazolidin-2-one, with an axial water molecule,

then its position becomes crucial to prevent an upward attack of **1b**. If the addition of MS to the reaction mixture changes the penta-coordinated structure into a nearly square-planar one, a good enantioselective catalyst becomes a chiral useless complex.

EXPERIMENTAL

General. ^1H NMR spectra were recorded on a Brüker (300 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane: δ_{H} 0.00). Data are presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded a Brüker (75 MHz) spectrometer. Chemical shifts are reported relative to internal standard (CDCl_3 ; δ 77.0). IR spectra were registered on a Perkin-Elmer RX I spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm). Separation and purification of the products were carried out by column chromatography using Merck silica gel 60 (230-400 mesh). Analytical HPLC was performed on Water instrument using Daicel columns (0.46 cm x 25 cm), detection was performed at the λ value reported below for each single product. Solvents were dried according to standard procedures. Powdered molecular sieves 3 Å was Aldrich reagent heated under vacuum at 300 °C for 5 hours and kept in sealed vials in a dryer. Copper triflate, silyl enol ethers (**1a-c**), diethyl ketomalonate (**2**) and Box (4'*R*)-**4a** were Aldrich ACS reagents. Box (4'*S*,5'*S*)-**4b** and its $\text{Cu}(\text{Tf})_2$ complex were prepared in accordance to the literature method.¹³ (1*H*-Inden-3-yloxy)triisopropylsilane (**1d**) was prepared following the literature method.¹⁶

General procedure for the enantioselective Mukaiyama-aldol reaction between **1a-c** and **2** (Table).

Diethyl ketomalonate (**2**) (52 mg, 0.30 mmol, 1.0 equiv.), catalyst **5** (16.5 mg, 0.015 mmol, 0.05 equiv.) [or alternatively the suitable Box **4** (0.03 mmol, 0.1 equiv.) and copper triflate (10.8 mg, 0.03 mmol, 0.1 equiv.), the amounts of MS (about 40 mg) or water when required, were added to the suitable solvent (0.3 ml) at ambient temperature in a rubber septum sealed vial, and the mixture was stirred 1 h and then cooled at -70 °C. Hexafluoroisopropanol (50 mg = 32 μL , 0.3 mmol, 1.0 equiv.) and the suitable silyl enol ether **1** (0.45 mmol, 1.5 equiv.) were then added with a microsyringe and stirring was continued for about 48 h. The reaction was decomposed in water, extracted with CH_2Cl_2 , dried, and the residue was column chromatographed. The eluant was cyclohexane/EtOAc [80:20] for **3a**, cyclohexane/EtOAc [85:15] for **3b**, cyclohexane/EtOAc [70:30] for **3c**, and cyclohexane/EtOAc [85:15] for **3d**, checking the fractions by thin layer chromatography on Merck Kieselgel 60 F₂₅₄ plates with visualization by ultraviolet or iodine vapours. The separated products **3a-d** were submitted to HPLC analysis under the conditions reported below for each single product.

Diethyl 2-hydroxy-2-(2-oxocyclohexyl)malonate (3a). Colourless oil; $[\alpha]_{\text{D}}$ -0.79 (*c* 2.16, CHCl_3) for 81% ee; IR (film): 3500 cm^{-1} (OH), 1737 cm^{-1} broad (C=O); ^1H NMR (300MHz, CDCl_3) δ 1.27 (t, *J* = 7.3

Hz, 3H, CH₃), 1.30 (t, $J = 7.5$ Hz, 3H, CH₃), 1.64-2.11 (m, 6H, 3CH₂), 2.35 (m, 1H, CHH), 2.43 (m, 1H, CHH), 3.93 (s, 1H, OH), 3.53 (dd, $J = 12.1$ Hz, 5.2 Hz, 1H, H-1), 4.27 (q, $J = 7.3$ Hz, 2H, OCH₂), 4.30 (m, 2H, OCH₂); ¹³C NMR (75MHz, CDCl₃) δ 13.4, 13.5, 24.2, 26.5, 27.2, 41.46, 54.9, 62.2, 63.0, 78.6, 168.7, 169.5, 208.7. These spectra are identical to those reported in the literature.¹⁷ The enantiomeric excess of **3a** was determined to be 81% by HPLC with Chiralcel OJ column (hexane/*i*-PrOH = 98 : 2, flow rate 1.0 mL/min, $\lambda = 220$ nm): t_R (major) = 27.4 min; t_R (minor) = 31.9 min.

(R)-Diethyl 2-hydroxy-2-[1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl]malonate (3b). Colourless oil; $[\alpha]_D -1.33$ (c 0.6, CHCl₃) for 94% ee; IR (film): 3490 cm⁻¹ (OH), 1736, and 1687 (C=O); ¹H NMR (300MHz, CDCl₃) δ 1.31 (t, $J = 7.2$ Hz, 3H, CH₃), 1.34 (t, $J = 7.2$ Hz, 3H, CH₃), 2.15 (m, 1H, CHH), 2.28 (ddd, $J = 17.4$ Hz, 12.9 Hz, 4.5 Hz, 1H, CHH), 3.03 (dt, $J = 16.2$ Hz, 3.3 Hz, 1H, CHH), 3.16 (ddd, $J = 17.4$ Hz, 12.7 Hz, 4.5 Hz, 1H, CHH), 3.79 (dd, $J = 13.5$ Hz, 4.5 Hz, 1H, H-2), 4.06 (s, 1H, OH), 4.32 (q, $J = 7.2$ Hz, 2H, OCH₂), 4.37 (q, $J = 7.2$ Hz, 2H, OCH₂), 7.26 (d, $J = 7.2$ Hz, 1H, H-5), 7.31 (t, $J = 7.4$ Hz, 1H, H-7), 7.42 (t, $J = 7.4$ Hz, 1H, H-6), 8.02 (d, $J = 7.2$ Hz, 1H, H-8); ¹³C NMR (75MHz, CDCl₃) δ 13.4, 13.6, 24.0, 28.6, 52.9, 62.2, 62.5, 79.3, 126.2, 127.1, 128.2, 131.6, 133.3, 143.4, 168.9, 170.0, 195.2. The enantiomeric excess of **3b** was determined to be 94% by HPLC with Chiralcel OJ column (hexane/*i*-PrOH = 98 : 2, flow rate 1.0 mL/min, $\lambda = 245$ nm): t_R (major) = 34.5 min for (*R*)-enantiomer; t_R (minor) = 39.8 min for (*S*)-enantiomer.

Diethyl 2-(tetrahydro-2-oxo-2H-pyran-3-yl)-2-hydroxymalonate (3c). The product isolated from entry 22 in the Table as colourless oil has: IR (film): 3483 cm⁻¹ (OH), 1736 cm⁻¹ (C=O); ¹H NMR (300MHz, CDCl₃) δ 1.30 (t, $J = 7.1$ Hz, 3H, CH₃), 1.95-2.10 (m, 4H, CH₂), 3.65 (dd, $J = 11.0$ Hz, 7.5 Hz, 1H, CH), 4.2 (bs, 1H, OH), 4.27 (q, $J = 7.1$ Hz, 2H, OCH₂), 4.32 (q, $J = 7.1$ Hz, 2H, OCH₂), 4.73 (m, 2H, OCH₂); ¹³C NMR (75MHz, CDCl₃) δ 13.8, 13.9, 20.1, 22.1, 45.7, 62.7, 63.2, 68.9, 79.6, 168.4, 169.4, 170.5. Anal. Calcd for C₁₂H₁₈O₇: C, 52.55; H, 6.62. Found: C, 52.73; H, 6.48. The above sample of **3c** was determined to be a racemate by HPLC with Chiralcel OJ column (hexane/*i*-PrOH = 90 : 10, flow rate 1.0 mL/min, $\lambda = 230$ nm): $t_R = 25.3$ min and 28.9 min.

Diethyl 2-(2,3-dihydro-1-oxo-1H-inden-2-yl)-2-hydroxymalonate (3d). The product isolated from entry 24 in the Table as a white solid (white crystals mp 77 °C from EtOH, lit¹⁸ mp 79-80 °C) has: $[\alpha]_D -5.12$ (c 0.87, CHCl₃) for 34% ee; IR (nujol): 3474 cm⁻¹ (OH), 1751 cm⁻¹ (C=O) and 1710 cm⁻¹ (C=O); ¹H NMR (300MHz, CDCl₃) δ 1.33 (t, $J = 7.1$ Hz, 3H, CH₃), 1.38 (t, $J = 7.1$ Hz, 3H, CH₃), 3.21 (dd, $J = 17.2$ Hz, 4.9 Hz, 1H, CHH), 3.45 (dd, $J = 17.2$ Hz, 8.2 Hz, 1H, CHH), 3.76 (dd, $J = 8.2$ Hz, 4.9 Hz, 1H, CH), 4.07 (s, 1H, OH), 4.30 (dq, $J = 10.8$ Hz, 7.1 Hz, 1H, OCHH), 4.34 (dq, $J = 10.8$ Hz, 7.1 Hz, 1H, OCHH), 4.44 (m, 2H, OCH₂), 7.38 (t, $J = 7.7$ Hz, 1H, H6 ind.), 7.49 (d, $J = 7.7$ Hz, 1H, H4 ind.), 7.62 (t, $J = 7.7$ Hz, 1H, H5 ind.), 7.74 (d, $J = 7.7$ Hz, 1H, H7 ind.). ¹³C NMR (75MHz, CDCl₃) δ 13.8, 13.9, 29.1, 51.3, 62.5, 63.2, 79.1,

123.8, 126.4, 127.4, 135.1, 136.3, 153.8, 168.9, 170.1, 203.7. Anal. Calcd for C₁₆H₁₈O₆: C, 62.74; H, 5.92. Found: C, 62.88; H, 6.02. The enantiomeric excess of **3d** was determined to be 34% by HPLC with Chiralcel OJ column (hexane/*i*-PrOH = 95 : 5, flow rate 1.0 mL/min, λ = 254 nm): t_R (minor) = 27.4 min; t_R (major) = 35.8 min.

ACKNOWLEDGEMENTS

This work was supported by the Ministero dell'Università e della Ricerca (MIUR) (PRIN 2008), and by the University of Pavia.

REFERENCES AND NOTES

1. (a) G. Desimoni, G. Faita, and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561; (b) G. Desimoni, G. Faita, and K. A. Jørgensen, Update 1: *Chem. Rev.*, 2011, **111**, PR284.
2. S. Yao, M. Roberson, F. Reichel, R. C. Hazell, and K. A. Jørgensen, *J. Org. Chem.*, 1999, **64**, 6677.
3. M. Quimpère and K. Jankowski, *J. Chem. Soc., Chem. Commun.*, 1987, 676.
4. C. Bolm and O. Simić, *J. Am. Chem. Soc.*, 2001, **123**, 3830.
5. C. Bolm, M. Verrucci, O. Simić, P. G. Cozzi, G. Raabe, and H. Okamura, *Chem. Commun.*, 2003, 2826.
6. C. Bolm, M. Verrucci, O. Simić, and C. P. R. Hackenberger, *Adv. Synth. Catal.*, 2005, **347**, 1696.
7. K. Tanaka, Y. Otake, H. Sagae, K. Noguchi, and M. Hirano, *Angew. Chem. Int. Ed.*, 2008, **47**, 1312.
8. F. Reichel, X. Fang, S. Yao, M. Ricci, and K. A. Jørgensen, *Chem. Commun.*, 1999, 1505.
9. (a) M. Frings, I. Atodiresei, J. Runsink, G. Raabe, and C. Bolm, *Chem. Eur. J.*, 2009, **15**, 1566; (b) M. Frings, I. Atodiresei, Y. Wang, J. Runsink, G. Raabe, and C. Bolm, *Chem. Eur. J.*, 2010, **16**, 4577.
10. A. Bøgevig, N. Kumaraguruban, and K. A. Jørgensen, *Chem. Commun.*, 2002, 620.
11. A. Bøgevig, K. Gothelf, and K. A. Jørgensen, *Chem. Eur. J.*, 2002, **8**, 5652.
12. A. Bøgevig, T. B. Poulsen, W. Zhuang, and K. A. Jørgensen, *Synlett*, 2003, 1915.
13. G. Desimoni, G. Faita, M. Toscanini, and M. Boiocchi, *Chem. Eur. J.*, 2009, **15**, 9674.
14. D. A. Evans, S. J. Miller, T. Lectka, and P. Von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559.
15. D. A. Evans, J. S. Johnson, and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635.
16. J.-F. Zhao, B.-H. Tan, and T.-P. Loh, *Chem. Sci.*, 2011, **2**, 349.
17. A. Armstrong, T. J. Critchley, M.-E. Gourdel-Martin, R. D. Kelsey, and A. A. Mortlock, *J. Chem. Soc., Perkin Trans. I*, 2002, 1344.

18. Product **3d** has been prepared as a racemate from L. Costantino, G. Rastelli, K. Vescovini, G. Cignarella, P. Vianello, A. Del Corso, L. Cappiello, U. Mura, and D. Barlocco, *J. Med. Chem.*, 1996, **39**, 4396, as an enantiomerically enriched product as described in the ref. (8), and it is also commercially available, but the IR, the ^1H and ^{13}C NMR spectra, and the $[\alpha]_{\text{D}}$ value have been never reported.