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Tetrahedron: *Asymmetry* 17 (2006) 2738–2742

Zirconium–BINOLate-catalyzed, enantioselective aldol-Tishchenko reactions of aromatic ketone aldols

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Received 24 July 2006; accepted 16 October 2006

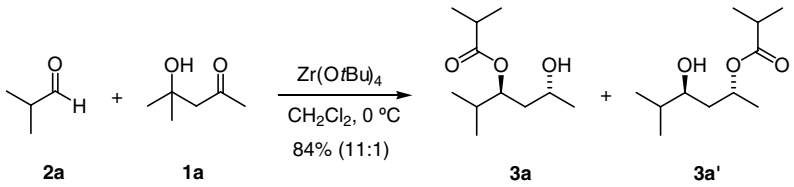
Abstract—3,3′-Substituted BINOL's have been identified as suitable chiral ligands for the zirconium-catalyzed aldol-Tishchenko reaction of aromatic ketone aldols with aliphatic aldehydes. 1,3-*anti*-Diol monoesters were obtained in excellent yields, complete *anti*-diastereocontrol, and enantioselectivities of up to 60% ee.

1. Introduction

The aldol-Tishchenko reaction has a long history in the direct, one-step synthesis of 1,3-dioxygenated compounds.[1] Much of the appeal of this transformation is based upon the domino-type pathway which does not require isolation or purification of the intermediate aldol product.[2] In recent years, a number of reports from different groups[3–9] have addressed the issue of relative and absolute stereocontrol in this reaction culminating in the first catalytic, enantioselective aldol-Tishchenko reaction of isobutyraldehyde and aromatic aldehydes reported by Morken et al.[10] Subsequently, Shibasaki et al.[11] established the first highly enantioselective aldol-Tishchenko reaction of alkyl aryl ketones and aromatic aldehydes catalyzed by a heterobimetallic complex. Mlynarski et al.[12] utilized chiral ytterbium catalysts for reactions of dialkyl ketones whereas Mahrwald et al.[13] employed Ti(O*t*Bu)$_4$/cinchona alkaloid-combinations for stoichiometric aldol-Tishchenko reactions. A distinct limitation in all of these processes is the necessity to employ aromatic aldehydes as coupling partners because aliphatic aldehydes compete with the ketones in the enolization event.

We[14] and Nevalainen et al.[15] have independently devised a conceptually different strategy. We found that ketone aldol adducts such as diacetone alcohol **1a** are excellent precursors for the in situ-generation of metal enolates through a retro-aldol process upon treatment with either Zr- or Al-based catalysts, respectively. When for example **1a** and isobutyraldehyde **2a** (2 equiv) were treated with Zr(O*t*Bu)$_4$ (10 mol %) in CH_2Cl_2 at 0 °C for 2 h, a 11:1-mixture of differentiated 1,3-*anti*-diol monoesters **3a**/**3a**′ was obtained in high yield (Scheme 1).[14]

Apparently, **3a**/**3a**′ were formed via an initial aldol reaction of the presumed acetone enolate followed by a highly *anti*-diastereoselective Tishchenko reduction of the result-



Scheme 1. The Zr-catalyzed aldol-Tishchenko reaction of ketone aldols.

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doi:10.1016/j.tetasy.2006.10.019

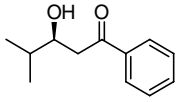
ing β-hydroxy ketone with a second equivalent of the aldehyde. The small amount of regioisomer **3a′** resulted from unselective Zr-catalyzed acyl migration. Subsequently, we reported the first catalytic, enantioselective aldol-Tishchenko reaction of ketone aldols which employed Zr–TADDOLate-complexes as chiral catalysts.[16]

In our preliminary experiments we could not achieve a satisfactory reaction with the catalyst $Zr(OtBu)_4$/(*R*)-BINOL in terms of yield and enantioselectivity which we attributed to the formation of oligomeric zirconium species with this rather small diol ligand. We speculated that substitution of the binaphthol backbone in the 3- and 3′-position, would lead to more reactive and possibly more enantioselective zirconium catalysts on the basis of the increased steric bulk in the backbone of the ligand. In this communication we show that 3,3′-substituted 2,2′-binaphthols with additional chelating groups are indeed selective chiral ligands for the zirconium-catalyzed aldol-Tishchenko reaction of aromatic ketone aldols.

2. Results and discussion

As a model reaction we selected the reaction of acetophenone-based ketone aldol **4a** and isobutyraldehyde (**2a**) (3 equiv) in CH_2Cl_2 at 0 °C since this transformation constantly gave rise to very low enantioselectivity with the Zr–TADDOLates (Table 1).[16] Various 3,3′-substituted 2,2′-binaphthols **5a–g** which were easily available through cross-coupling chemistry according to the Snieckus protocol[17] were screened as chiral ligands together with Zr-$(OtBu)_4$ (10 mol % each) in CH_2Cl_2 which was found to be the solvent of choice.

As is evident from inspection of Table 1, all reactions proceeded in high yield and complete 1,3-*anti*-diastereocontrol as expected but furnished the product **6a** with varying enantioselectivities. The most promising levels of enantioselectivity were obtained with aromatic substituents in the 3- and 3′-positions of the BINOL backbone carrying a chelating *ortho*-methoxy group. Thus, when $Zr(OtBu)_4$ and 3,3′-di-*o*-anisyl-2-2′-binaphthol **5c**[18] (10 mol % each) were mixed in CH_2Cl_2 prior to the addition of **2a** (3 equiv) and **4a**, the aldol-Tishchenko product **6a** was formed in 90% yield and with 60% ee (Table 1, entry 3). In addition, no acyl migration occurred and **6a** was formed as a single regioisomer. The absolute configuration of **6a** was established through conversion into aldol product **7** via hydrolysis (KOH, MeOH) and chemoselective oxidation of the aryl carbinol with PDC[19] and comparison of the specific rotation value with the literature data.[20]



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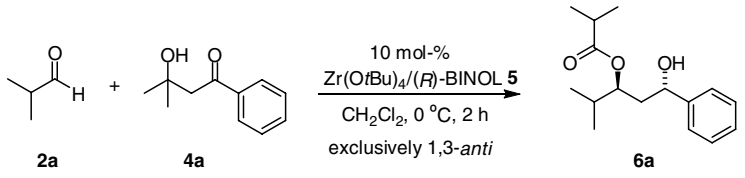
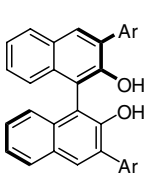
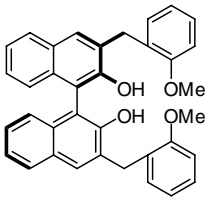
Additional alkyl and alkoxy substituents on the phenyl ring of the ligand did not alter the enantioselectivity significantly except for a bulky 3-substituent which presumably affected the coordination ability of the methoxy group (entry 5). Replacing the *ortho*-methoxy group with an ethyl group of similar steric size resulted in a complete loss of enantioselectivity (entry 6).When the *ortho*-methoxy

Table 1. The Zr–BINOLate-catalyzed aldol-Tishchenko reaction of ketone aldol **4a** and isobutyraldehyde **2a** with various (*R*)-BINOL-ligands **5a–g**





5a: Ar = Ph
5b: Ar = 4-*t*Bu-Ph
5c: Ar = 2-MeO-Ph
5d: Ar = 2,4-$(MeO)_2$-Ph
5e: Ar = 2-MeO-3,5-$(tBu)_2$-Ph
5f: Ar = 2-Et-Ph



5g

Entry	Ligand	Ar	ee[a] (%)	Yield[b] (%)
1	**5a**	Ph	11	89
2	**5b**	4-*t*Bu–Ph	26	88
3	**5c**	2-MeO–Ph	60	90
4	**5d**	2,4-$(MeO)_2$–Ph	57	75
5	**5e**	2-MeO–3,5-$(tBu)_2$–Ph	7	95
6	**5f**	2-Et–Ph	0	91
7	**5g**	CH_2–2-(MeO)–Ph	8	71

[a] Determined by HPLC-analysis of the crude product on a Chiracel-OD-phase with hexane/*i*PrOH 97:3.
[b] Isolated yield of the purified material.

phenyl groups in the 3,3′-positions of the BINOL backbone were changed to *ortho*-methoxy benzyl groups, the enantioselectivity again dropped sharply suggesting a strict requirement for 7-membered chelates (entry 7). From these experiments it appears likely that intramolecular coordination of at least one of the *ortho*-methoxy groups to the Lewis acidic zirconium atom occurs with a beneficial effect on the enantioselectivity of the aldol-Tishchenko reaction. Pu et al.[21] and Jorgensen et al.[22] have observed similar phenomena in Et_2Zn-addition to aldehydes and Al–BINOLate catalyzed hetero Diels–Alder reactions, respectively.

The catalyst combination $Zr(OtBu)_4$/**5c** (10 mol %) was subsequently employed in aldol-Tishchenko reactions of various aromatic ketone aldols **4a–d** and aliphatic aldehydes (Table 2). The product 1,3-diol monoesters **6a–i** were generally obtained in good to excellent yields, complete 1,3-*anti*-diastereoselectivity and with enantiomeric excesses of up to 60% ee. As a general trend, α-branched aldehydes gave rise to more enantioselective reactions than straight-chain aldehydes, whereas variations within the ketone aldol component did not appear to have significant effects on the selectivity. The *anti*-diastereoselectivity of the Tishchenko step may best be explained through the model first put forth by Evans and Hoveyda in their samarium-catalyzed Tishchenko reduction.[23] Use of chiral ligand **5c** with different enantiopurities revealed a linear correlation between the ee of the product and that of the ligand suggesting a monomeric catalyst species.[24]

3. Conclusion

In conclusion, we have devised a novel chiral catalyst system for the enantioselective aldol-Tishchenko reaction between ketone aldols as enol equivalents and aliphatic aldehydes which comprise a 3,3′-substituted 2,2′-dihydroxy binaphthyl backbone with *ortho*-anisyl groups as chelating groups for the zirconium center. Current studies are directed at improving the enantioselectivity of the reaction.

4. Experimental

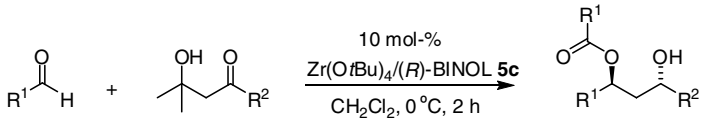
4.1. General

All reactions were performed in flame–dried glassware under a dry nitrogen atmosphere. The solvents used for the reactions were distilled from appropriate drying agents prior to use. Diethyl ether, petroleum ether, and pentane for chromatography were of technical grade and distilled from KOH before use. All reactions were followed by TLC on precoated silica gel SIL G/UV 254 plates (Machery, Nagel & Co.). Flash column chromatography was performed by using Merck silica gel 60 230–400 mesh. $Zr(OtBu)_4$ was purchased from Strem Chemical Co. as 99.99% PURATREM quality, packed in ampules. The ketone aldols were prepared according to literature procedure.[14] All other chemicals were used as received from commercial suppliers. ^1H and ^{13}C spectra were recorded with 200 MHz (Gemini 2000), 300 MHz (Mercury 300) or 400 MHz (Mercury 400) varian systems in $CDCl_3$ at 25 °C with TMS as internal standard. IR spectra were recorded with a Bruker avatar 360 FT-IR instrument. Mass spectra were measured with electron spray ionization (ESI) technique using an FT-ICR-MS Bruker Daltronics APEX II instrument or with a 70 eV EI Masscom MAT 8230 instrument. The enantiomeric excess (ee) was determined with a Jasco 2080 HPLC instrument with a CHIRALCEL OD column and hexane/isopropanol 97:3 as eluent. The optical rotations were measured using (Schmidt + Haensch) Polartronic-D digital polarimeter.

4.2. General procedure for the catalytic, enantioselective aldol-Tishchenko reaction

$Zr(OtBu)_4$, (40 μL, 0.10 mmol) and the respective (*R*)-BINOL ligand **5** (0.10 mmol)[17,18] were dissolved in 4 mL of dry dichloromethane in a flame-dried round bottom flask at room temperature, stirred for 45 min and cooled to 0 °C. Ketone aldol **4** (1.00 mmol) and the aldehyde (3.00 mmol) were added and the reaction mixture was stir-

Table 2. The Zr–BINOLate **5c**-catalyzed aldol-Tishchenko reaction of ketone aldols **4a–d** and aldehydes **2**



2 **4a-d** **6a-i**

Entry	Ketone aldol	R^1	R^2	Product	ee[a,b] (%)	Yield[c] (%)
1	**4a**	*i*-Pr	Ph	**6a**	60	90
2	**4a**	*c*-Hex	Ph	**6b**	54	87
3	**4a**	*n*-Hex	Ph	**6c**	41	82
4	**4a**	*i*-Bu	Ph	**6d**	42	89
5	**4b**	*i*-Pr	4-Me–Ph	**6e**	50	50
6	**4b**	*c*-Hex	4-Me–Ph	**6f**	56	81
7	**4c**	*c*-Hex	4-MeO–Ph	**6g**	60	71
8	**4d**	2-Et–Pr	3-Me–Ph	**6h**	49	68
9	**4d**	*c*-Hex	3-Me–Ph	**6i**	53	85

[a] Determined by HPLC-analysis of the crude product on a Chiracel-OD-phase.
[b] Absolute configuration of products was assigned by analogy to **6a** assuming a unified reaction mechanism.
[c] Isolated yield of purified material.

red at 0 °C for 2 h. The reaction was quenched with 0.5 M HCl (4 mL). The layers were separated and the aqueous layer was extracted with ether (5 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using ether/pentane.

4.3. (1*S*,3*S*)-1-Hydroxy-4-methyl-1-phenylpentan-3-yl isobutyrate 6a

Yield: 90% of colorless oil; 60% ee (HPLC); $[\alpha]_D^{20} = -5.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.40$–7.25 (m, 5H, Ar–H), 5.05 (dt, $J = 8.0$, 5.5 Hz, 1H, C*H*OCOR), 4.54 (dd, $J = 7.5$, 5.5 Hz, 1H, C*H*OH), 3.30 (br s, 1H, OH), 2.65 (sept, $J = 7.0$ Hz, 1H, OCOC*H*$(CH_3)_2$), 1.98–1.75 (m, 3H, CH_2, C*H*$(CH_3)_2$), 1.23 (d, $J = 7.0$ Hz, 6H, CH(*CH*$_3)_2$), 0.94 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$), 0.93 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 178.5$, 144.0, 128.4, 127.3, 125.5, 75.36, 69.82, 42.14, 34.39, 32.16, 19.23, 19.18, 18.72, 17.50; IR (film): $\nu = 3489$, 3063, 3029, 2968, 2877, 1731, 1470, 1389, 1269, 1201, 1162, 1052, 758, 701 cm^{-1}; MS (DCI/NH_3): $m/z = 810$ (1) ([3M+NH_4^+]), 546 (20) [2M+NH_4^+], 282 (50) [M+NH_4^+], 247 (100) [M^+−OH]. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.68; H, 8.92.

4.4. (1*S*,3*S*)-1-Cyclohexyl-3-hydroxy-3-phenylpropyl cyclohexanecarboxylate 6b

Yield: 87% of colorless oil; 54% ee (HPLC); $[\alpha]_D^{20} = -17.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.21 (m, 5H, Ar–H), 5.04 (m, 1H, C*H*OCOR), 4.50 (ddd, $J = 7.6$, 6.0, 4.0 Hz, 1H, C*H*OH), 3.40 (d, $J = 6.0$ Hz, 1H, OH), 2.42–2.35 (m, 1H, OCOC*H*R), 1.98–0.98 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.4$, 144.1, 128.3, 127.2, 125.4, 74.75, 69.80, 43.82, 43.58, 42.26, 29.31, 27.82, 26.96, 25.79, 25.52; IR (film): $\nu = 3429$, 3028, 2927, 1727, 1708, 1603, 1449, 1384, 1278, 1195, 1172, 1091, 931, 894, 754 cm^{-1}; MS (ESI + Na-formate): $m/z = 739$ (100) [2M+$Na]^+$), 381 (8) [M+Na^+]. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.74; H, 9.29.

4.5. (1*S*,3*R*)-1-Hydroxy-1-phenylnonan-3-yl heptanoate 6c

Yield: 82% of colorless oil; 41% ee (HPLC); $[\alpha]_D^{20} = -3.0$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.25$–7.40 (m, 5H, Ar–H), 5.26–5.17 (m, 1H, C*H*OCOR), 4.59 (dd, $J = 8.8$, 4.5 Hz, 1H, C*H*OH), 3.36 (br s, 1H, OH), 2.36 (t, $J = 7.5$ Hz, 2H, OCOCH_2–), 1.92–1.85 (m, 2H, CH_2CHOH), 1.18–1.11 (m, 18H, CH_2 of *n*-heptyl), 0.98–0.79 (m, 6H, CH_3 of *n*-heptyl); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.1$, 143.8, 128.3, 127.3, 125.5, 71.53, 69.82, 44.90, 34.79, 34.53, 31.65, 31.42, 28.97, 28.82, 25.32, 25.07, 22.48, 22.45, 14.00; IR (film): $\nu = 3455$, 3063, 3030, 2930, 2859, 1732, 1455, 1379, 1174, 1060, 758, 700 cm^{-1}; MS (DCI/NH_3): $m/z = 714$ (48) [2M+NH_4^+], 366 (69) [M+NH_4^+], 331 (100) [M^+−OH]. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.48; H, 10.14.

4.6. (1*S*,3*R*)-1-Hydroxy-5-methyl-1-phenylhexan-3-yl 3-methylbutanoate 6d

Yield: 89% of colorless oil; 42% ee (HPLC); $[\alpha]_D^{20} = -4.5$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.25 (m, 5H, Ar–H), 5.34–5.24 (m, 1H, C*H*OCOR), 4.59 (ddd, $J = 9.0$, 5.0, 4.0 Hz, 1H, C*H*OH), 3.38 (d, $J = 4.0$ Hz, 1H, OH), 2.24 (dd, $J = 7.8$, 2.5 Hz, 2H, OCOCH_2CH-$(CH_3)_2$), 2.20–2.14 (m, 1H, OCOCH$_2$C*H*$(CH_3)_2$), 1.89–1.83 (m, 2H, CH_2), 1.72–1.61 (m, 2H, CH_2CH$(CH_3)_2$), 1.34–1.28 (m, 1H, CH_2C*H*$(CH_3)_2$), 1.00 (d, $J = 6.5$ Hz, 6H, CH(*CH*$_3)_2$), 0.93 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$), 0.90 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.5$, 144.0, 128.5, 127.4, 125.6, 70.14, 70.13, 45.69, 44.05, 43.60, 25.79, 24.69, 23.36, 22.57, 21.94; IR (film): $\nu = 3063$, 2958, 2871, 1731, 1711, 1603, 1494, 1466, 1431, 1385, 1369, 1295, 1256, 1194, 1140, 1093, 933, 757, 700, 627 cm^{-1}; MS (EI): $m/z = 292$ (2) [M^+] 209 (37) [M^+−$2C_3H_7$], 107 (75) [$PhCO^+$], 85 (25) [$C_5H_8O^+$], 58 (50) [$C_3H_5O^+$], 43 (100) [$C_3H_7^+$]. Anal. Calcd for. $C_{19}H_{26}O_3$: C, 73.93; H, 9.65. Found: C, 73.61; H, 9.85.

4.7. (1*S*,3*S*)-1-Hydroxy-4-methyl-1-*p*-tolylpentan-3-yl isobutyrate 6e

Yield: 50% of colorless oil; 50% ee (HPLC); $[\alpha]_D^{20} = -14.8$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.7$ Hz, 2H, Ar–H), 7.14 (d, $J = 7.0$ Hz, 2H, ArH), 5.05 (dt, $J = 9.3$, 5.3 Hz, 1H, C*H*OCOR), 4.50 (ddd, $J = 9.0$, 5.0, 3.0 Hz, 1H, C*H*OH), 3.21 (d, $J = 3.0$ Hz, 1H, OH), 2.68–2.59 (m, 1H, OCOC*H*$(CH_3)_2$), 2.34 (s, 3H, Ar–CH_3), 1.92–1.82 (m, 3H, CH_2, C*H*$(CH_3)_2$), 1.23 (d, $J = 7.0$ Hz, 6H, CH(*CH*$_3)_2$), 0.95 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$), 0.91 (d, $J = 7.0$ Hz, 3H, CH(*CH*$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.5$, 141.2, 137.0, 129.0, 125.6, 75.52, 69.82, 42.29, 34.50, 32.15, 21.22, 19.38, 18.87, 17.67; IR (film): $\nu = 3416$, 2966, 1730, 1613, 1513, 1429, 1385, 1264, 1198, 1089, 877, 815, 627 cm^{-1}; MS (ESI + Na-formate): $m/z = 579.4$ (100) [2M+$Na]^+$, 301.2 (9) [M+$Na]^+$. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.01; H, 8.87.

4.8. (1*S*,3*S*)-1-Cyclohexyl-3-hydroxy-3-*p*-tolylpropyl cyclohexanecarboxylate 6f

Yield: 81% of colorless oil; 56% ee (HPLC); $[\alpha]_D^{20} = -15.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.8$ Hz, 2H, Ar–H), 7.14 (d, $J = 7.6$ Hz, 2H, Ar–H), 5.06–5.02 (m, 1H, C*H*OCOR), 4.47 (dd, $J = 9.2$, 5.2 Hz, 1H, C*H*OH), 3.25 (br s, 1H, OH), 2.33 (s, 3H, Ar–CH_3), 2.42–2.36 (m, 1H, OCOC*H*R), 1.97–0.99 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.4$, 141.2, 136.9, 129.1, 125.6, 74.82, 69.74, 65.92, 43.63, 42.24, 42.09, 29.36, 29.33, 29.25, 28.17, 26.46, 26.1; IR (film): $\nu = 3435$, 2927, 2853, 1728, 1614, 1449, 1384, 1313, 1278, 1248, 1195, 1090, 941, 894, 814, 656 cm^{-1}; MS (EI): $m/z = 358$ (12) [M^+], 121 (30) [Ar–CH_3–CO^+], 43 (100) [$C_3H_7^+$]. Anal. Calcd for $C_{23}H_{34}O_3$: C, 76.82; H, 9.56. Found: C, 76.53; H, 9.27.

4.9. (1*S*,3*S*)-1-Cyclohexyl-3-hydroxy-3-(4-methoxyphenyl)-propyl cyclohexanecarboxylate 6g

Yield: 71% of colorless oil; 60% ee (HPLC); $[\alpha]_D^{20} = -9.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.24$ (dd, $J = 6.0$, 2.2 Hz, 2H, Ar–H), 6.86 (dd, $J = 6.8$, 1.8 Hz, 2H, Ar–H), 5.05–4.96 (m, 1H, C*H*OCOCy), 4.44 (dd, $J = 8.6$, 4.0 Hz, 1H, C*H*OH), 3.70 (s, 3H, OMe), 3.25 (s, 1H, OH), 2.42–2.29 (m, 1H, OCOC*H*R), 2.00–0.92 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.5$, 158.9, 136.4, 126.8, 113.8, 74.87, 69.50, 55.30, 43.66, 42.05, 29.39, 28.19, 26.48, 26.24, 26.03, 25.47; IR (film): $\nu = 3436$, 2928, 2853, 1726, 1612, 1586, 1512, 1449, 1384, 1312, 1247, 1172, 1133, 1036, 830 cm^{-1}; MS (ESI + Na^+-formate): $m/z = 1145$ (100) [3M+Na^+], 771 (100) [2M+ Na^+], 397 (8) [M+Na]$^+$. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.58; H, 8.92.

4.10. (1*S*,3*S*)-4-Ethyl-1-hydroxy-1-*m*-tolylhexan-3-yl 2-ethylbutanoate 6h

Yield: 68% of colorless oil; 49% ee (HPLC); $[\alpha]_D^{20} = -10.4$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$–7.06 (m, 4H, Ar–H), 5.30 (dt, $J = 10.5$, 2.7 Hz, 1H, C*H*OCOR), 4.50 (dt, $J = 10.5$, 3.2 Hz, 1H, C*H*OH), 3.30 (d, $J = 3.2$ Hz, 1H, OH), 2.35 (s, 3H, Ar–CH_3), 2.33–2.28 (m, 1H, OCOC*HR*), 1.99–0.89 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.7$, 144.1, 138.2, 128.4, 128.2, 126.2, 122.6, 77.57, 77.08, 76.63, 72.56, 69.98, 49.56, 45.41, 42.00, 25.20, 22.59, 22.32, 21.69, 12.24, 11.88; IR (film): $\nu = 3458$, 2968, 2934, 2877, 1712, 1597, 1489, 1469, 1387, 1370, 1341, 1268, 1200, 1161, 1090, 1014, 961, 855, 828, 558 cm^{-1}; MS (ESI + Na^+-formate): $m/z = 669$ (100) [2M+H^+], 464, 357 (2) [M+Na^+]. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.43, H, 10.33.

4.11. (1*S*,3*S*)-1-Cyclohexyl-3-hydroxy-3-*m*-tolylpropyl cyclohexanecarboxylate 6i

Yield: 85% of colorless oil; 53% ee (HPLC); $[\alpha]_D^{20} = -11.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$–7.05 (m, 4H, Ar–H), 5.00 (dt, $J = 13.5$, 3.5 Hz, 1H, C*H*OCOCy), 4.47 (dd, $J = 9.0$, 4.2 Hz, 1H, C*H*OH), 3.27 (s, 1H, OH), 2.37 (m, 1H, OCOC*HR*), 2.35 (s, 3H, Ar–CH_3), 1.99–1.00 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.4$, 144.1, 138.0, 128.3, 128.0, 126.3, 122.7, 74.83, 69.84, 43.64, 42.3, 42.29, 42.09, 29.3, 29.36, 29.34, 29.26, 28.18, 27.00, 26.45, 26.18, 26.12, 25.83, 25.57, 25.55, 21.52; IR (film): $\nu = 3443$, 3024, 2927, 2853, 1709, 1608, 1590, 1449, 1383, 1312, 1278, 1248, 1173, 1133, 1038, 972, 938, 910, 894, 784, 441 cm^{-1}; MS (ESI + Na^+-formate): $m/z = 1097$ (100) [3M+Na^+], 739 (55) [2M+Na^+], 381 (6) [M+Na^+]. Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.86. Found: C, 76.93, H, 10.09.

4.12. Determination of absolute configuration of aldol-Tishchenko product 6a

Aldol-Tishchenko product **6a** was hydrolyzed (KOH, MeOH) quantitatively to the corresponding 1,3-*anti* diol and subsequently oxidized with pyridinium dichromate[19] to yield aldol product **7** in 56% yield. The specific rotation of this material, $[\alpha]_D^{20} = -42.0$ (*c* 1.2, $CHCl_3$) for 60% ee, was in good correlation with the reported value for the enantiomer, $[\alpha]_D^{20} = +77.8$ (*c* 1, $CHCl_3$).[20] All other absolute configurations were assigned by analogy.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Schn 441/4-1) and the Fonds der Chemischen Industrie. We thank Wacker AG for a generous donation of TBDMSCl.

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