Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1645–1649

TETRAHEDRON: *ASYMMETRY*

Copper(II)-catalyzed kinetic resolution of (±)-2-arylpropionic acids with chiral *N*-trimethylsilyloxazolidin-2-one

Shin-ichi Fukuzawa,* Yoshiaki Chino and Tetsuhiro Yokoyama

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

Received 10 June 2002; accepted 17 July 2002

Abstract—The reaction between (±)-2-arylpropanoyl chlorides **1** (2 equiv.) and enantiopure *N*-trimethylsilyloxazolidin-2-one **2** in the presence of a catalytic amount of $CuCl_2$ in hexane affords the corresponding *N*-acyloxazolidin-2-one in good chemical yields (97%) with up to 50% de.

1. Introduction

2-Arylpropionic acid derivatives are pharmaceutically important compounds with relatively simple structures for anti-inflammatory agents.[1] Ibuprofen and Naproxene are typical 2-arylpropionic acid pharmaceutical products currently on the market.[2] As 2-arylpropionic acids have one stereogenic center, they exist in two enantiomeric forms, in which one isomer exhibits a much higher biological activity than the other. Some synthetic methods to access these enantiomerically enriched 2-arylpropionic acids have been reported. For example, the asymmetric rearrangement of chiral aryl 2-bromoacetal and the asymmetric hydrogenation of 2-arylacrylic acids are practical synthetic methods. In a laboratory scale experiment, the stereoselective alkylation of a chiral *N*-acyloxazolidin-2-one followed by hydrolysis provides an effective method.[3]

In addition to the asymmetric synthetic approach, resolution of a racemic mixture of 2-arylpropionic acid is preparatively useful; esterification of the acid chloride with a chiral alcohol via the prochiral ketene[4] and enzymatic resolution by hydrolysis of the ester gives the single enantiomer in high enantiomeric purity.[5]

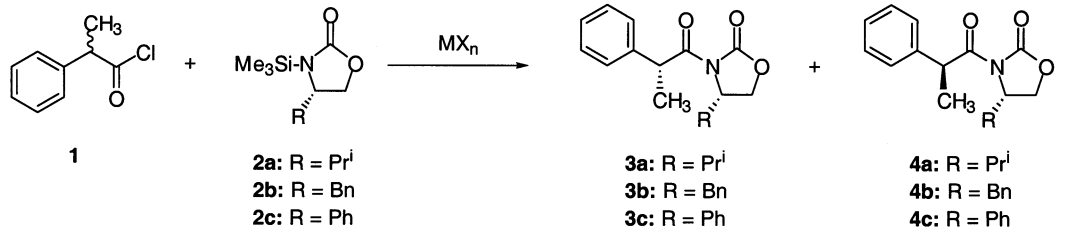
It has been reported that the kinetic resolution of (±)-2-acetoxy carboxylic acid chlorides with the lithium salt of a chiral oxazolidin-2-one auxiliary can afford the corresponding *N*-acyloxazolidin-2-one in good diastereoselectivity (up to 82% de).[6] However, no resolution took place in the reaction of (±)-2-phenylpropanoyl chloride with lithium (4*S*)-isopropyloxazolidin-2-one, and a near 1:1 mixture of diastereomers **3a** and **4a** was produced. After examining some acylation methods with a chiral oxazolidin-2-one,[7] we found that the reaction between (±)-2-phenylpropionyl chloride with enantiomerically pure *N*-trimethylsilyloxazolidin-2-one can give 3-acyloxazolidin-2-ones with moderate diastereoselectivities[8] and herein, we would like to report on the diastereoselective formation of *N*-(2-arylpropanoyl)oxazolidin-2-ones by metal salt-catalyzed acylation of chiral *N*-trimethylsilyloxazolidin-2-one with racemic 2-arylpropanoyl chlorides, in which kinetic resolution take place.

2. Results and discussion

We first examined the reaction of (±)-2-phenylpropanoyl chloride **1** (2 equiv. to **2**) with (4*S*)-isopropyl-3-(trimethylsilyl)oxazolidin-2-one **2a** in refluxing toluene for 16 h (Scheme 1). The *N*-acyloxazolidin-2-one was obtained in 41% yield (based on **2**) as a mixture of diastereomers in the ratio of **3a**:**4a** = 54:46 (8% de). Although the addition of a catalytic amount of $CuCl_2$ (10 mol%) to the reaction increased the yield of product up to 98%, the selectivity for **3a** was still low (12% de). The stereochemistry was determined by the comparing the ^{1}H NMR spectrum of the products with that of an authentic sample prepared by methylation of

* Corresponding author. Fax: 81338171895; e-mail: fukuzawa@chem.chuo-u.ac.jp

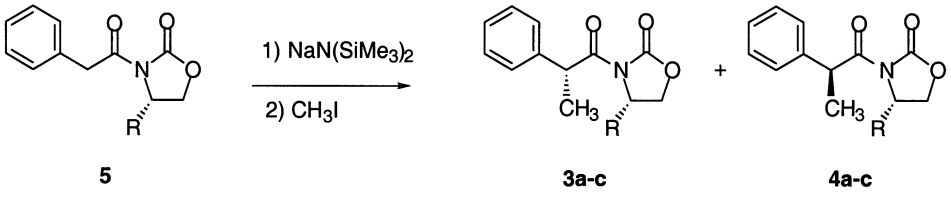
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00409-3



Scheme 1.

(4*S*)-3-phenylacetyl-4-(isopropyl)oxazolidin-2-one **5**, where the major isomer was **4a** (Scheme 2). When the catalytic reaction was carried out in refluxing benzene and hexane, the diastereoselectivities improved to 24 and 40% de, respectively, retaining the high yield. We could finally optimize the selectivity to 42–44% de by performing the reaction under mild conditions, i.e. **3a** was obtained as the major isomer when the reaction was completed in hexane at 40°C or refluxing pentane over 16 h. However, the reaction hardly proceeded if the reaction time was shortened to 4 h. Higher selectivity could be achieved at room temperature but the yield was not satisfactory even with an extended reaction time (72 h). Tetrahydrofuran and diethyl ether were not suitable solvents as they gave lower yields with lower selectivities, and complex product mixtures. The reaction could be carried out in supercritical carbon dioxide ($scCO_2$, 50°C, 15 MPa),[9] which is a non-toxic and safe medium, but the yield (38%) and the selectivity (32% de) were poor.[10] These results are summarized in Table 1.

Table 2 shows the results of completing the reaction in the presence of several different metal salts. The acylation reaction was very slow in the absence of a catalyst in hexane at 40°C. Copper(I) compounds catalyzed the reaction with moderate yields and with almost the same selectivity (40% de) as reactions completed with $CuCl_2$ (entries 6–9). It is of note that CuCN and $(CuOTf)_2{\cdot}C_6H_6$ also catalyzed the reaction. Iron(II) and iron(III) compounds also afforded the product with low yields and selectivities (entries 10 and 11), and catalysis with a palladium complex (entry 12) was poor. Lewis acids, such as Et_2AlCl and $In(OTf)_3$ catalyze the coupling reaction, but they tend to give lower diastereoselectivities (entries 13–15). $Cu(OTf)_2$ may act as a Lewis acid catalyst either in hexane or $scCO_2$ but produced a lower yield and lower selectivity (entries 4 and 5).



Scheme 2.

Table 1. $CuCl_2$-catalyzed reaction of (±)-2-phenylpropanoyl acid chloride **1** with (4*S*)-isopropyl-3-(trimethylsilyl)oxazolidine-2-one **2a**[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	**3a**:**4a**[c]
1[d]	Toluene	110	16	41	54:46
2	Toluene	110	16	98	56:44
3	Benzene	80	16	93	62:38
4	Hexane	69	16	99	69:31
5	Hexane	40	16	97	71:29
6	Hexane	40	4	0	–
7	Hexane	25	72	49	75:25
8	Pentane	35	16	99	72:28
9	Et_2O	35	16	35	68:32
10	THF	67	16	41	47:53
11	CH_2Cl_2	40	16	71	56:44
12[e]	$scCO_2$	50	16	38	66:34

[a] **1** (2.0 mmol), **2a** (1.0 mmol), $CuCl_2$ (0.1 mmol), solvent (5.0 mL).
[b] GC yield based on **2a**.
[c] Determined by GC (HP-5ms).
[d] Without $CuCl_2$.
[e] 10 mL, 15 MPa.

Table 2. Metal salt catalysts in the reactions of **1** with **2a** in hexane[a]

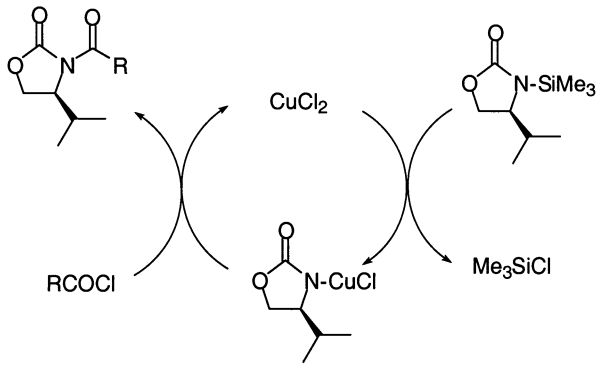
Entry	MX_n	Yield (%)[b]	**3a**:**4a**[c]
1	None	0	–
2	$CuCl_2$	97	71:29
3	$CuBr_2$	39	67:33
4	$Cu(OTf)_2$	63	67:33
5[d]	$Cu(OTf)_2$	49	48:52
6	CuCl	61	73:27
7	$CuBr{\cdot}Me_2S$	62	74:26
8	CuCN	62	72:28
9	$(CuOTf)_2C_6H_6$	76	63:37
10	$FeCl_3$	32	67:33
11	$FeCl_2$	52	68:32
12	$PdCl_2/PPh_3$	0	–
13[e]	Et_2AlCl	59	54:46
14	$InCl_3$	Trace	–
15	$In(OTf)_3$	45	53:47

[a] **1** (2.0 mmol), **2a** (1.0 mmol), hexane (5.0 mL), catalyst (0.1 mmol); 40°C, 16 h.
[b] GC yield based on **2a**.
[c] Determined by GC (HP-5ms).
[d] 50°C, 15 MPa in $scCO_2$.
[e] Room temperature, 40 h in CH_2Cl_2.

The reaction of **1** with other chiral *N*-silyloxazolidin-2-one derivatives, **2b** and **2c**, in the presence of $CuCl_2$ gave the corresponding acyloxazolidin-2-one as a mixture of diastereomers in moderate to good yields with similar selectivities with **2a**; **3b**:**4b** = 67:33, 61% yield; **3c**:**4d** = 70:30, 62% yield.

We applied this method to the resolution of (±)-ibuprofen: the $CuCl_2$-catalyzed reaction of the acid chloride of (±)-ibuprofen **6** with **2a** was carried out under the optimized conditions described above. The (4*S*,3*R*) isomer of *N*-acyloxazolidin-2-one **7a** was obtained as the major product in 79% yield with de of 41% (Scheme 3).[3]

$CuCl_2$ was found to be a poor catalyst for Friedel–Crafts acylation of toluene with (±)-2-phenylpropanoyl chloride (completed at 110°C for 16 h), while $In(OTf)_3$ catalyzed the acylation well, a result which shows that $CuCl_2$ does not behave as a Lewis acid, indicating it may activate the Si–N bond of the *N*-silyloxazolidin-2-one rather than the acyl chloride. A metal exchange experiment between a lithiated oxazolidin-2-one (R = *i*-Pr) and $CuCl_2$ improved the diastereoselectivity of the reaction to form acyloxazolidin-2-one **3a** from 50:50 to 60:40. Thus, the $CuCl_2$-catalyzed reaction may involve Si–Cu metal exchange, which gives Cu-oxazolidin-2-one as a likely intermediate species (Scheme 4).



Scheme 4.

Treatment of a 1:1 mixture of diastereomers **3a** and **4a** with $CuCl_2$ at 40°C in hexane for 16 h did not change the isomer ratio, showing that stereoisomerization via enolization between these compounds did not occur in the reaction system.

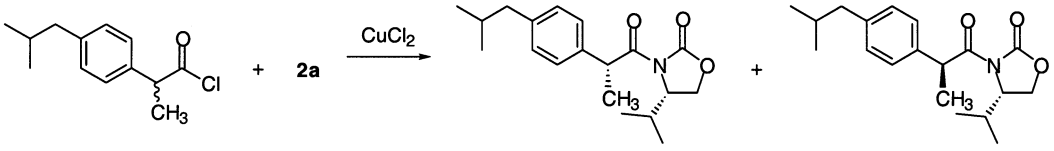
3. Conclusion

By careful consideration of the reaction conditions and the catalyst it has been shown that kinetic resolution between the *N*-trimethylsilyloxazolidin-2-one and racemic 2-arylpropionic acid chlorides is possible. Currently, the method affords good chemical yields but moderate selectivities.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR (300 MHz) spectrometer as solutions in $CDCl_3$. The chemical shifts are reported in δ units downfield from the internal reference, Me_4Si. IR spectra were obtained using a JASCO Herschel FT/IR-230A spectrometer. The HPLC analyses were carried out on a Hitachi L-7100 apparatus equipped with a UV detector using Daicel Chiralcel OB, OJ and OD columns (0.46 mm, 25 cm) eluting with 2-propanol/*n*-hexane (10/90–1/99). The GC/MS analyses were carried out on a Hewlett–Packard 5980/5972 instrument equipped with a capillary column (HP-5ms) (0.25 mm, 30 m) (helium as carrier gas). The optical rotations were determined by a JASCO DIP-370 apparatus. The elemental analyses were carried out using a Yanaco CHN CORDER MT-5. Column chromatography was performed on a Yamazen YFLC-254 and a Michael



6 **7a** **8a**

Scheme 3.

Miller column equipped with a UV detector using Merck Silica Gel 60. Preparative TLC was conducted using a 20×20 cm glass sheet coated with a 2 mm thick layer of Merck Kieselgel 60 PF_{254}.

Hexane, pentane, benzene, and toluene were distilled from calcium hydride and stored over 4 Å molecular sieves. (4*S*)-Isopropyl, (4*S*)-phenyl-, and (4*S*)-benzyl-3-(trimethylsilyl)oxazolidin-2-one were prepared from the corresponding commercial chiral oxazolidin-2-ones by the reported method.[7] (±)-2-Phenylpropanoyl chloride was prepared by the reaction of (±)-phenylpropionic acid with oxalyl chloride and purified by distillation under reduced pressure. All anhydrous metal salts were commercially available and used without further purification.

4.2. (4*S*)-Isopropyl-3-(trimethylsilyl)oxazolidin-2-one, 2a

$[\alpha]_D^{25}=+28.5$ (*c* 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.33 (s, 9H, $Si(CH_3)_3$), 0.89 (d, 3H, $J=6.8$ Hz, $CHCH_3$), 0.91 (d, 3H, $J=6.8$ Hz, $CHCH_3$), 1.93 (m, 1H, $CHMe_2$), 3.68 (m, 1H, NCH), 4.15 (m, 2H, OCH_2); ^{13}C NMR ($CDCl_3$): δ −1.06 ($Si(CH_3)_3$), 13.7 (CH_3), 18.0 (CH_3), 31.9 ($CHMe_2$), 60.5 (NC), 64.5 (OCH_2), 161.5 (C=O); IR (KBr): 1671 (C=O) cm^{-1}. Anal. calcd for $C_9H_{19}NO_2Si$: C, 53.69; H, 9.51; N, 6.96. Found: C, 53.25; H, 9.74; N, 6.69%.

4.3. (4*S*)-Benzyl-3-(trimethylsilyl)oxazolidin-2-one, 2b

$[\alpha]_D^{25}=+35.9$ (*c* 1.02, $CHCl_3$);[11] ^1H NMR ($CDCl_3$, 300 MHz): δ 0.31 (s, 9H, $Si(CH_3)_3$), 2.62 (dd, 1H, $J=8.7$, 13.6 Hz, $CHCH_2$), 2.89 (dd, $J=3.9$, 13.6 Hz, 1H, $CHCH_2$), 3.86 (dq, $J=4.4$, 8.7, 1H, NC*H*), 3.98 (d, 2H, $J=4.4$ MHz, OCH_2), 7.16 (m, 5H, Ph); ^{13}C NMR: δ −0.7 ($SiCH_3$), 41.4 (CH_2), 57.1 (CN), 67.6 (CO), 126.7, 128.6, 128.7, 135.7, 160.9 (C=O). Anal. calcd for $C_{13}H_{19}NO_2Si$: C, 62.61; H, 7.68; N, 5.62. Found: C, 62.31; H, 8.01; N, 5.56%.

4.4. (4*S*)-Phenyl-3-(trimethylsilyl)oxazolidin-2-one, 2c

$[\alpha]_D^{25}=+68.1$ (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.15 (s, 9H, $Si(CH_3)_3$), 4.05 (dd, 1H, $J=3.41$, 8.30 Hz, NCH), 4.61 (dd, 1H, $J=8.3$, 8.3 Hz, OCH_2), 4.81 (dd, 1H, $J=3.4$, 8.3 Hz, OCH_2), 7.31 (m, 5H, Ph); ^{13}C NMR: δ −1.33 ($SiCH_3$), 59.7 (NC), 71.9 (OCH_2), 125.7, 128.6, 128.7, 141.9, 161.3 (C=O). Anal. calcd for $C_{12}H_{17}NO_2Si$: C, 61.24; H, 7.28; N, 5.95. Found: C, 61.22; H, 7.31; N, 5.88%.

4.5. General procedure for the acylation of *N*-trimethyloxazolidin-2-one with (±)-2-arylpropionyl chloride

4.5.1. (4*S*,2′*R*)-4-Isopropyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 3a and (4*S*,2′*S*)-4-isopropyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 4a. In a 10 ml two-necked round-bottomed flask containing a magnetic stirring bar were charged anhydrous $CuCl_2$ (13.4 mg, 0.10 mmol), (4*S*)-4-isopropyl-3-trimethylsilyl-oxazolidin-2-one **2a** (216 mg, 1.0 mmol), and dry hexane (10.0 ml) under a slight pressure of nitrogen. (±)-2-Phenylpropanoyl chloride **1** (337 mg, 2.0 mmol) was added using a syringe through the septum with magnetic stirring at room temperature. The resulting mixture was stirred at 40°C for 16 h. The reaction was quenched with aqueous $NaHCO_3$ and the solution was then extracted with three 10 ml portions of ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4. GC/MS (HP-5ms) analysis revealed the presence of acylated product as a mixture of diastereomer in a ratio of 72:28 and a yield was determined using biphenyl as an internal standard. The solution was filtered and the solvent was removed on a rotary evaporator leaving a pale yellow residue, which was subjected to preparative TLC (hexane/ethyl acetate = 5/1 as eluent). Major isomer **3a**: colorless oil; $[\alpha]_D^{25}=+7.8$ (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.44 (d, 3H, $J=7.0$ Hz, CH_3), 0.79 (d, 3H, $J=7.0$ Hz, CH_3), 1.47 (d, 3H, $J=6.8$ Hz, CH_3), 2.15–2.25 (m, 1H, CH), 4.08 (dd, 1H, $J=3.3$, 9.0 Hz, CH_2O), 4.22 (dd, 1H, $J=9.01$, 9.01 Hz, CH_2O), 4.45–4.51 (m, 1H, CHN), 5.13 (q, 1H, $J=6.81$, 3H, C*H*Ph); ^{13}C NMR: δ 13.8 (CH_3), 17.6 (CH_3), 18.5 (CH_3), 27.7 ($CHCH_3$), 43.1 (*C*HPh), 57.9 (NCH), 62.7 (OCH_2), 127.0, 127.8, 128.2, 140.3, 153.3 (O-C=O), 174.3 (C=O). Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.43; N, 5.31%. Minor isomer **4a**: colorless oil; $[\alpha]_D^{25}=+100.6$ (*c* 1.11, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, 3H, $J=6.8$ Hz, CH_3), 0.91 (d, 3H, $J=7.04$ Hz, CH_3), 1.51 (d, 3H, $J=7.0$ Hz, CH_3), 2.37–2.48 (m, 1H, CH), 4.06 (dd, 1H, $J=9.0$, 9.0 Hz, CH_2O), 4.12 (dd, 1H, $J=3.0$, 9.0 Hz, CH_2O), 4.31–4.37 (m, 1H, CHN), 5.14 (q, 1H, $J=7.0$ Hz, CHPh), 7.2–7.35 (m, 5H, Ph); ^{13}C NMR: δ 14.5 (CH_3), 17.8 (CH_3), 19.5 (CH_3), 28.4 ($CHCH_3$), 42.9 (CHPh), 58.9 (NCH), 62.9 (OCH_2), 127.0, 128.0, 128.2, 128.4, 140.2, 153.4 (O-C=O), 174.4 (C=O).

4.5.2. (4*S*,2′*R*)-4-Benzyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 3b and (4*S*,2′*S*)-4-benzyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 4b. The title compounds were obtained as a mixture by the reaction of **1** with **2b**. Major isomer **3b**: colorless oil; $[\alpha]_D^{25}=+16.1$ (*c* 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.52 (d, 3H, $J=7.0$ Hz, CH_3), 2.58 (dd, 1H, $J=8.80$, 13.6 Hz, CH_2Ph), 3.09 (dd, 1H, $J=3.3$, 13.6 Hz, CH_2Ph), 4.07 (dd, 1H, $J=3.3$, 9.0 Hz, CH_2O), 4.18 (dd, 1H, $J=9.0$, 9.0 Hz, CH_2O), 4.74 (m, 1H, CHN), 5.11 (q, 1H, $J=6.95$ Hz, CH_3CH), 7.0–7.3 (m, 5H, Ph); ^{13}C NMR: δ 19.1 (CH_3), 37.3 (CH), 43.2 (CH_2Ph), 54.8 (CHN), 65.7 (CHO), 127.2, 128.2, 128.6, 128.8, 129.3, 134.8, 140.0, 152.8 (O-C=O), 174.4 (C=O). Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.76; H, 6.21; N, 4.52%. Minor isomer **4b**: white solid, mp 65–66°C; $[\alpha]_D^{25}=+107.1$ (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.53 (d, 3H, $J=7.0$ Hz, CH_3), 2.78 (dd, 1H, $J=9.7$, 13.2 Hz, CH_2Ph), 3.33 (dd, 1H, $J=3.11$, 13.19 Hz, CH_2Ph), 4.00 (dd, 1H, $J=9.0$, 9.0 Hz, CH_2O), 4.07 (dd, 1H, $J=2.4$, 9.0 Hz, one of CH_2O), 4.62 (m, 1H, CHN), 5.11 (q, 1H, $J=7.0$, 1H, CH_3CH); ^{13}C NMR: δ 19.4 (CH_3), 37.8 (CH), 43.0 (CH_2Ph), 55.7 (CHN), 65.8 (CHO), 127.2, 128.0, 128.5, 128.7, 129.0, 129.3, 135.2, 140.1, 152.8 (O-C=O), 174.5 (C=O).

4.5.3. (4*S*,2′*R*)-4-Phenyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 3c and (4*S*,2′*S*)-4-phenyl-3-(2′-phenylpropanoyl)oxazolidin-2-one, 4c. The title compounds were obtained as a mixture by the reaction of **1** with **2c**. Major isomer **3c**: pale yellow solid, mp 41–42°C; $[\alpha]_D^{25}=+7.4$ (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40 (d, 3H, $J=7.0$ Hz, CH_3), 4.09 (dd, 1H, $J=5.1$ Hz, 8.8 Hz, CH_2O), 4.65 (dd, 1H, $J=9.0$, 9.0 Hz, CH_2O), 5.11 (q, 1H, $J=7.0$ Hz, $CHCH_3$), 5.46 (dd, 1H, $J=5.1$, 9.2 Hz, CHN), 7.2–7.4 (m, 10H, Ph); ^{13}C NMR: δ 18.6 (CH_3), 43.8 (CH), 57.7 (NCH), 69.5 (OCH_2), 125.7, 127.2, 128.1, 128.4, 128.7, 129.2, 138.2, 139.7, 153.1 (O-C=O), 173.6 (C=O). Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.85; H, 5.85; N, 4.54%. Minor isomer **4c**: white solid, mp 141–142°C; $[\alpha]_D^{25}=+141.1$ (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40 (d, 3H, $J=7.0$ Hz, CH_3), 4.21 (dd, 1H, $J=3.1$ Hz, 8.7 Hz, CH_2O), 4.55 (dd, 1H, $J=8.6$, 8.6 Hz, CH_2O), 5.12 (q, 1H, $J=7.0$ Hz, $CHCH_3$), 5.34 (dd, 1H, $J=3.10$, 8.57 Hz, CHN), 7.2–7.4 (m, 10H, Ph); ^{13}C NMR: δ 19.3 (CH_3), 43.2 (CH), 58.1 (NCH), 69.7 (OCH_2), 125.8, 127.2, 128.2, 128.6, 128.7, 129.2, 139.3, 140.1, 153.1 (OC=O), 173.6 (C=O).

4.5.4. (4*S*,2′*R*)-4-Isopropyl-3-[2′-(4-isobutylphenyl)propanoyl]oxazolidin-2-one, 7a and (4*S*,2′*S*)-4-isopropyl-3-[2′-(4-isobutylphenyl)propanoyl]oxazolidin-2-one, 8a. The title compounds were obtained as a mixture by the reaction of (±)-2-(4-isobutylphenyl)propanoyl chloride **6** with **2a**. Major isomer **7a**: pale yellow oil; $[\alpha]_D^{25}=-30.8$ (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.40 (d, 3H, $J=6.8$ Hz, CH_3), 0.78 (d, 3H, $J=7.3$ Hz, CH_3), 0.86 (d, 3H, $J=6.6$ Hz, CH_3), 0.87 (d, 3H, $J=6.6$ Hz, CH_3), 1.46 (d, 3H, $J=7.0$ Hz, CH_3), 1.82 (sept., 1H, $J=6.8$ Hz, CH), 2.1–2.2 (m, 1H, CH), 2.42 (d, 2H, $J=7.0$ Hz, CH_2), 4.08 (dd, $J=3.5$, 9.0 Hz, CH_2O), 4.23 (dd, $J=9.0$, 9.0 Hz, 1H, CH_2O), 4.45–4.52 (m, 1H, CHN), 5.13 (q, 1H, $J=7.0$, 1H, CHAr), 7.06 (d, 2H, $J=8.1$ Hz, *o*-H), 7.26 (d, 2H, $J=8.1$ Hz, *m*-H); ^{13}C NMR: δ 13.8 (CH_3), 17.6 (CH_3), 18.3 (CH_3), 22.1 (CH_3), 27.7 (CH), 30.1 (CH), 42.7 (CH), 44.9 (CH_2), 57.8 (CHN), 62.7 (CHO), 127.7, 129.2, 131.5, 140.5, 153.4 (O-C=O), 174.6 (C=O). Anal. calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.55; H, 8.61; N, 4.27%. Minor isomer **8a**: pale yellow oil; $[\alpha]_D^{25}=+111.0$ (*c* 1.02, $CHCl_3$) (lit.[3] +131.0); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, 6H, $J=6.6$ Hz, $(CH_3)_2$), 0.91 (d, 3H, $J=6.8$ Hz, CH_3), 0.92 (d, 3H, $J=6.8$ Hz, CH_3), 1.50 (d, 3H, $J=7.0$ Hz, CH_3), 1.81 (sept., 1H, $J=6.8$ Hz, CH), 2.2.4–2.5 (m, 1H, CH), 2.42 (d, 2H, $J=7.0$ Hz, CH_2), 4.09–4.13 (m, 2H, CH_2O), 4.31–4.38 (m, 1H, CHN), 5.12 (q, 1H, $J=7.03$ Hz, CHAr), 7.07 (d, 2H, $J=8.1$ Hz, *o*-H), 7.24 (d, 2H, $J=8.1$ Hz, *m*-H); ^{13}C NMR: δ 14.6 (CH_3), 17.9 (CH_3), 19.6 (CH_3), 22.3 (CH_3), 28.4 (CH_3), 30.0 (CH), 42.5 (CH), 44.9 (CH_2), 58.9 (CHN), 62.9 (CHO), 127.7, 129.2, 137.4, 140.5, 153.5 (O-C=O), 174.8 (C=O).

Acknowledgements

This work was financially supported by the Institute of Science and Engineering, Chuo University, Special Project Research 'Development of Green Chiral Technology'.

References

1. For a review, see: Stahly, G. P.; Starret, R. M. In *Chirality in Industry II*; Production Methods for Chiral Non-steroidal Anti-inflammatory Profen Drugs. Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds. Wiley: New York, 1997; Chapter 3 and references cited therein.
2. Villa, C. G. M. M.; Panossian, S. P. In *Chirality in Industry*; Naproxen: Industrial Asymmetric Synthesis. Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds. Wiley: New York, 1992; Chapter 15.
3. Fadel, A. *Synlett* **1992**, 48.
4. Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. *J. Am. Chem. Soc.* **1989**, *111*, 7650.
5. Enzymatic resolution of racemic 2-arylpropionic acid is an alternative method. See: (a) Kato, D.-i.; Mitsuda, S.; Ohta, H. *Org. Lett.* **2002**, *4*, 371; (b) Colton, I. J.; Ahmed, S. N.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 212; (c) Wu, S.-H.; Guo, Z.-W.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 1990.
6. (a) Bew, S. P.; Davies, S. G.; Fukuzawa, S. *Chirality* **2000**, *12*, 483–487; (b) Haigh, D.; Birrell, H. C.; Cantello, B. C. C.; Hindley, R. M.; Ramaswamy, A.; Rami, H. K.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1335.
7. Thom, C.; Kocienski, P. *Synthesis* **1992**, 582.
8. The base-catalyzed *N*-acylation with (±)-2-phenylpropionic acid or acid chloride resulted in a poor selectivity (5–10% de). See: (a) Prashad, M.; Kim, H.-Y.; Har, D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 9369; (b) Lee, J. Y.; Chung, Y. J.; Kim, B. H. *Synlett* **1994**, 197; (c) Ho, G.-J.; Mathre, D. *J. Org. Chem.* **1995**, *60*, 2271.
9. For reviews, see: (a) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475; (b) Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 917.
10. Fukuzawa, S.; Metoki, K.; Komuro, Y.; Funazukuri, T. *Synlett* **2002**, 134.
11. The literature reports that the sign of the specific rotations of the (*R*)-isomer is positive (+35, $CHCl_3$).[7] On the other hand, that its $[\alpha]_D$ was found to be about −35 by our measurement, which was repeated several times.