Asymmetric 1,4-Addition of Organocuprates to Chiral α,β-Unsaturated N-Acyl-4-phenyl-2-oxazolidinones: A New Approach to the Synthesis of Chiral β-Branched Carboxylic Acids

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Introduction

The design of receptor-selective peptide and peptidomimetic ligands with highly potent and specific biological properties has become one of the primary goals of molecular biology and molecular pharmacology. Among the approaches that have been examined, the use of side chain modified amino acids have great potential because of the topographic constraints they can bring to design. We have been particularly interested in several biologically active phenylalanine and/or tyrosine-containing peptides in which the essential role of these amino acids for their bioactivity has been demonstrated. We have suggested[1-5] that the use of such side chain conformationally constrained analogues could provide valuable information and new insights about how these amino acids are involved in the binding of the peptide to the receptor and in signal transduction. The introduction of a β- and/or aromatic ring methyl group (e.g., the 2′ position) were considered suitable for this purpose, and thus asymmetric synthetic routes for the preparation of all isomers of each amino acid have had to be developed. We report here our results on the use of 4-phenyl-2-oxazolidinone (**2**, Figure 1) as a chiral auxiliary for stereoselective induction at the β position of butyric acid derivatives.

Results and Discussion

We have previously reported[6,7] the asymmetric synthesis of β-methylphenylalanine and β-methyltyrosine by modification of the chiral imide boron enolate approach, developed by Evans et al.[8,9] for highly stereoselective induction at the α-position. In this case, stereochemistry at the β-carbon was established by classical methods involving separation of diastereoisomers by fractional crystallization.

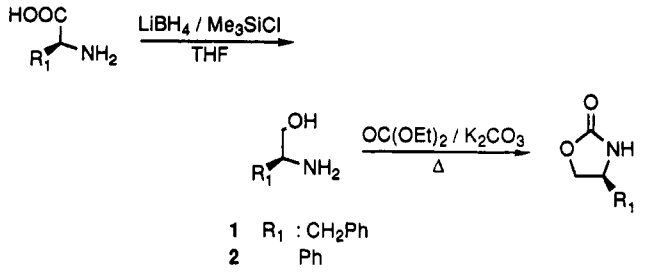

Figure 1.

The excellent results achieved with this methodology prompted us to test the use of 4-benzyl-2-oxazolidinone (**1**, Figure 1) for chiral induction of stereochemistry at the β position via a Michael-type addition,[10] with the aim of using this approach for the asymmetric synthesis of 3-phenylbutyric acid, 3-(4′-methoxyphenyl)butyric acid, and 3-(4′-methoxy-2′-methyl)butyric acid (intermediates for the preparation of the desired amino acid derivatives). Thus, 1,4-addition of organometallic reagents to 3-(α,β unsaturated)-acyl-2-oxazolidinone derivatives (Table I) was investigated in this particular case. For maximum yields and excellent asymmetric induction, the Grignard reagent/cuprous bromide system in THF/$(CH_3)_2S$ generally has proven to be one of the best in our hands. Thus, we decided to use similar conditions to examine the conjugate addition of the organometallic derivative of 4-bromoanisole to (3(2*E*),4*S*)-3-crotonyl-4-benzyl-2-oxazolidinone (Table II). The former was prepared from the respective Grignard reagent and cuprous bromide in THF/$(CH_3)_2S$, and the *N*-acyloxazolidinone was synthesized as previously reported.[11] The high-field proton NMR of the crude reaction showed no starting material (85% yield after chromatography), and two diastereoisomeric products were obtained which were characterized, after chromatographic separation, as (3(3*S*),4*S*)- and (3(3*R*),4*S*)-3-[3-(4′-methoxyphenyl)butanoyl]-4-benzyl-2-oxazolidinone. A ratio of 45:55 (Table II) was determined by integration of the protons at position 4 of the oxazolidinone ring, the highest value corresponding to the product from the addition of the reagent to the *re* face of the carbon atom of the double bond at β position.[12] This poor stereoselectivity was not improved with the addition of Lewis acids such as boron trifluoride. The longer distance between the reaction center and the chiral auxiliary and the possibility for the phenyl group to rotate around the C_4–C_{benzyl} bond could explain the less effective shielding of the benzyl group for asymmetric induction at the β-carbon relative to the α-carbon reported previously.

Melnyk et al.[13] have described the use of (4*R*,5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone as a chiral auxiliary for the synthesis of 3-phenylbutyric acid. In this case, a good enantiomeric excess was obtained, but the yield was low when phenylmagnesium bromide was used. Consid-

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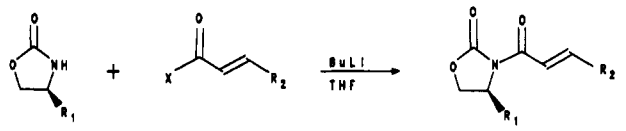
ering that the benzyl group at position four probably was mainly responsible for the asymmetric induction, and the oxazolidinone ring is very stable to the reaction conditions, we thought that 4-phenyl-2-oxazolidinone (**2**, Figure 1) might be a better alternative for asymmetric induction. Thus, the conjugate substrates **8–12** were synthesized by reaction of the lithiated oxizolidinone **2**[14] and either the corresponding acid chloride (**4–6**)[11] or the mixed pivalic acid anhydride derivative (**7**),[21] which was generated in situ (Table I). The organocopper derivatives were prepared from the Grignard reagents (prepared from magnesium and the desired phenylbromides[22] in THF) and transferring solutions of these reagents to the cuprous bromide solution in THF/$(CH_3)_2S$ at −40 °C via canula.

For the conjugated additions (Table II), the reaction yields, determined after chromatography of the crude product, were between 80% and 90% in all cases. For characterization of the different products and the evaluation of the diastereoisomeric ratios, 500-MHz proton NMR was used.[12] The results are shown in Table II. The conditions used in this study were slightly modified depending on the substrate. Slow addition of the α,β unsaturated acyloxazolidinone to the organocopper reagent and moderately low temperatures (between −20 and −10 °C) were necessary to avoid polymerization problems when **9** was used.[23] In this particular case, the reactions proceeded extremely fast (a few min) and with high stereoselectivity (Table II, entries b–d). For **10–12**, the stereochemical excess was lower for all conditions studied (Table II, entries e–g). Though the reaction rates were lower, a gradient between −50 and 0 °C was used, since higher reaction temperatures led to a drop in the stereoselectivity of the process when **10** was used. The higher stereoselectivity induced by 4-phenyl-2-oxazolidinone chiral auxiliary as compared to that induced by 4-benzyl-2-oxazolidinone (entries a and c) supports our hypothesis about the suitability of this chiral auxiliary for the stereocontrol of carbon–carbon bond formation at a β acyl position. The fact that **9** afforded the best results indicates that interaction between the two aromatic groups could hinder complexation with the metal in **10–12**. On the other hand, the stereoselectivity dropped dramatically in the case of **10**, which could be related to a substituent effect in the aromatic ring.

The hydrolysis of the acyloxazolidinones[24] afforded the acids and the chiral auxiliary in 90%–95% yields. The already established absolute configurations of 3-phenylbutyric acid[25] and 3-(4-methoxyphenyl)-butyric acid[7] allowed us to directly determine the course of the reaction in most cases of this study (Table II; entries a–c). The results demonstrate a preferential attack at the double bond face opposite to the phenyl group of the oxazolidinone when the two carbonyls are considered to be complexed by a metal cation, and the acyl side chain is extended away from the chiral auxiliary as previously suggested.[26] As for the 3-(4′-methoxy-2′-methylphenyl)butanoic acids

Table I. Synthesis of *N*-Enoyloxazolidinones

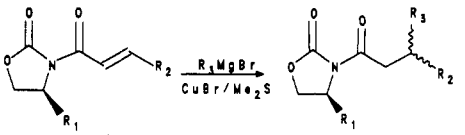


1,2 3-7 8-12

oxazolidinone		enoyl derivative		product	
R_1[a]	no.	R_2[b]	no.	no.	yield (%)
CH_2Ph	1	Me	3	8	85
Ph	2	Me	4	9	90
Ph	2	Ph	5	10	90
Ph	2	4-$OMeC_6H_4$–[c]	6	11	85
Ph	2	2-Me-4-$OMeC_6H_4$–[c]	7	12	82

[a] 1, benzyl; 2, phenyl. [b] 8–11 were obtained from the corresponding acyl chlorides **3–6** (X, Cl), and **12** was prepared from the mixed anhydride of pivalic acid (X, $-OCOCMe_3$). [c] (2*E*)-3-(4-methoxyphenyl)-2-propenoyl chloride (**6**) and (2*E*)-3-(4-methoxy-2-methylphenyl)-2-propenoic acid (the acid was used to afford **7**) were synthesized as previously reported.[27,28]

Table II. Stereoselectivity Induced by 4-Phenyl-2-oxazolidinone in the Addition Reactions Studied



	oxazolidinone			Grignard	product	
entry	R_1[a]	R_2[a]	no.	R_3	dr[b] (%)	yield (%)
a	Bn	Me	8	4-$OMeC_6H_4$–	10 (*R*)	85
b	Ph	Me	9	Ph	98 (*R*)	90
c	Ph	Me	9	4-$OMeC_6H_4$–	98 (*R*)	91
d	Ph	Me	9	2-Me-4-$OMeC_6H_3$–	98 (*R*)	31
e	Ph	Ph	10	Me	48 (*S*)	90
f	Ph	Ar	11	Me	84 (*S*)	86
g	Ph	Ar	12	Me	86 (*S*)	96

[a] See Table I. [b] Configuration at β carbon of the major product.

(14) The synthesis of optically pure 4-phenyl-2-oxazolidinone, which has been used as a chiral auxiliary for the asymmetric 1,4-addition of allylsilanes to chiral α,β-unsaturated *N*-acylamides[15] and for the preparation of some β-lactam antibiotics,[16,17] was carried out from optically pure phenylglycine by treatment with BH_3–Me_2S and further cyclization of the reduced material with *N*-BuLi[16] and trichloromethyl chloroformate.[18] However, heating was required during the reduction of the amino acid in both cases. Giannis et al.[19] have described a convenient method by which the reduction of amino acids can be performed with borane, which is generated in situ from lithium borohydride and chlorotrimethylsilane in THF at rt (Figure 1). We have prepared (*S*)-phenylglycinol, using similar conditions, in a 85–90% yield after crystallization and without any detectable racemization.[20] The final product was synthesized in an 80% yield from the alcohol, following a procedure similar to that described for 4-benzyl-2-oxazolidinone.[6]

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(20) The optical purity of the *R* and *S* amino alcohols was determined by synthesizing their (*S*)-*N*-(*tert*-butoxycarbonyl)valyl derivatives and using a Vydac reversed-phase C_{18} HPLC column (water/acetonitrile/TFA (75:25:0.04); flow rate 1 mL/min; l = 220 nm) for analysis. Both analyses showed only one peak (*SS* isomer, 18.8 min; *SR* isomer 20.9 min).

(21) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525.

(22) Commercially available methylmagnesium bromide solution in THF was used.

(23) Experiments carried out at lower temperatures and faster addition rates of **9** to the organometallic reagent decreased the reaction yields because of the formation of a majority byproduct, which originally was attributed, after analysis of the ^1H NMR spectrum of the crude product, to the attack of the anion from the conjugate addition to another molecule of **9**.

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(Table II; entries d and g), the unambiguous determination of their absolute configurations remains to be established. However, if we assume that the stereochemistry of the reaction is the same in these cases as in the previous ones, and we further consider the additional steric hindrance that the *o*-methyl group in the aromatic ring can provide, it is quite likely that g corresponds to the 3(3*S*),4*R* isomer and d (Table II) corresponds to the 3(3*R*),4*R* isomer.

Further applications of 4-phenyl-2-oxazolidinone to the asymmetric synthesis of nonproteogenic amino acids are under investigation in our laboratories.

Experimental Section

All reagents, unless otherwise noted, were purchased from Aldrich Chemical Co. and were used without further purification, except for triethylamine (distilled from CaH_2 under Ar and stored over CaH_2), pivaloyl chloride (distilled under Ar), and crotonyl chloride (distilled under Ar). The synthesis of 8–12 and the Michael-like additions were performed under Ar. The reaction temperatures listed are the bath temperatures. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ at 250 MHz and at 62.9 MHz, respectively, at rt. Optical rotations were taken on a Autopol III polarimeter using a 1.0-dm cell. Column chromatography was performed on Aldrich silica gel 60, 230–400 mesh ASTM. Analytical TLC was performed on Aldrich precoated silica gel 60 F_{254} plates. Detection was done using either I_2, ninhydrin, or UV light. Solvents for chromatography were used without further purification. Anhydrous THF was distilled from Na/benzophenone ketyl under Argon in a recycling still.

(*S*)-Phenylglycinol. (*S*)-Phenylglycine was reduced as described in the literature[19] with some modifications. A solution of $LiBH_4$ in THF (2.0 M, 66.1 mL, 132 mmol, 2.00 equiv) was stirred at rt under Ar, while $(CH_3)_3SiCl$ (33.6 mL, 265 mmol, 4.00 equiv) was added. To the white suspension formed was added (*S*)-phenylglycine as a dry powder (10.0 g, 66.0 mmol, 1 equiv), at 0 °C, within 5 min. The mixture was stirred at this temperature for 1 h and at room temperature for 24 h. MeOH (50 mL) was added dropwise, and the volatiles were removed by rotatory evaporation. To the resulting mixture cooled to 0 °C was added carefully a solution of KOH in water (20%, 40 mL of water). Water (25 mL) and CH_2Cl_2 (20 mL) were added to the resulting pale yellow slurry and the organic phase separated. The aqueous solution was washed with CH_2Cl_2 (5 × 20 mL), and the organic layers were combined and dried over Na_2SO_4. The solvent was evaporated off and the resulting pale yellow crystalline residue recrystallized from EtOAc/hexanes, yielding 7.64 g (85%) of white crystals. Mp: 76.5–78.5 °C. Spectral data were equivalent to those reported by Aldrich: NMR 2(1), 1069B and FT-IR 1(1), 1272 C. MS: *m/e* (relative intensity) 137 (M, <1), 83 (100), 57 (55), 41 (51). $[\alpha]^{22}_D$: +32.1° (*c* 1.14, HCl 1 M). Anal. Calcd for $C_8H_{11}ON$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.93; H, 8.18; N, 10.17.

(4*S*)-4-Phenyl-2-oxazolidinone (2). The title compound was prepared according to a literature procedure[17] with modifications. A dry 25-mL, three-necked, round-bottomed flask equipped with a thermometer and an 8-in. Vigreux column with distillation head was charged with (*S*)-phenylglycinol (5.00 g, 36.4 mmol, 1 equiv), diethyl carbonate (8.80 mL, 76.4 mmol, 2.1 equiv), and K_2CO_3 (0.76 g, 5.47 mmol, 0.15 equiv). The flask was preheated to 130 °C and the suspension stirred vigorously. EtOH (7.5 mL) distilled within 1 h when the mixture was allowed to cool to rt. The crude product was dissolved in EtOAc (60 mL), the K_2CO_3 was filtered, the organic solution was washed with a saturated solution of $NaHCO_3$ (2 × 20 mL) and brine (20 mL) and dried over $MgSO_4$ and the volatiles were evaporated. The product was recrystallized from EtOAc/hexanes, yielding (two crops) 4.8 g of the desired material (80%). Mp: 128–130 °C (lit.[17] mp 131–132 °C). Spectral data were identical to those described in the literature.[17] $[\alpha]^{22}_D$: +58.0 (*c* 1.00, $CHCl_3$) [lit.[16] $[\alpha]^{22}_D$ + 49.5° (*c* 2.1, $CHCl_3$)]. Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.18; H, 5.50; N, 8.58.

General Method for the Synthesis of 9–11. These compounds were prepared using a procedure similar to the previously reported for 8.[11]

To a stirred, −78 °C precooled solution of (4*S*)-4-phenyl-2-oxazolidinone (0.98 g, 6.00 mmol, 1.00 equiv) in dry THF (30.0 mL) was added *n*-BuLi (1.6 M in hexanes; 3.80 mL, 6.00 mmol, 1.00 equiv) by syringe. The resulting solution was stirred at this temperature for 20 min, and the α,β unsaturated acyl chloride (6.60 mmol, 1.10 equiv) (**4**, 0.63 mL, by syringe; **5** and **6**, 1.10 g and 1.30 g, respectively, as solids) was added to the resulting slurry. The mixture was stirred at −78 °C for 30 min and at 0 °C for 2 h when a saturated solution of NH_4Cl (25 mL) was added. The resulting suspension was allowed to warm to rt and the volatiles were evaporated. EtOAc (25 mL) was added, and the organic layer separated and washed with a saturated solution of $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The organic solution was dried over $MgSO_4$, filtered, and evaporated and the resulting crude chromatographed (7:3 hexanes/EtOAc). The final product was obtained in 80–90% yield. An analytical sample was rechromatographed and recrystallized in hexanes/EtOAc for characterization in each case.

(4*S*)-4-Phenyl-3-(2(*E*)-butenoyl)-2-oxazolidinone (9). Yield: 1.25 g (90%). Mp: 77–79 °C. ^1H NMR (250 MHz, $CDCl_3$) δ TMS: 7.40–7.25 (m, 6 H), 7.15–6.90 (m, 1 H), 5.47 (dd, *J* = 3.9, 8.8 Hz; 1 H), 4.67 (dd, *J* = 8.8, 8.8 Hz; 1 H), 4.24 (dd, *J* = 3.9, 8.8 Hz; 1 H), 1.92 (d, *J* = 6.7 Hz; 3 H). ^{13}C NMR ($CDCl_3$) δ: 164.3, 153.6, 147.1, 139.0, 129.0, 128.5, 125.8, 121.6, 69.80, 57.57, 18.39. IR (KBr): 2990, 1785, 1690, 1640, 1340, 1190, 715 cm^{-1}. MS: *m/e* (relative intensity) 231 (M, 5), 69 (100). $[\alpha]^{22}_D$: +111.8° (*c* 1.08, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.50; H, 5.68; N, 6.05.

(4*S*)-4-Phenyl-3-(3-phenyl-2(*E*)-propenoyl)-2-oxazolidinone (10). Yield: 1.58 g (90%). Mp: 169–171 °C. ^1H NMR (250 MHz, $CDCl_3$) δ TMS: 7.94 (d, *J* = 15.7 Hz; 1 H), 7.78 (d, *J* = 15.7 Hz; 1 H), 7.61–7.57 (m, 2 H), 7.39–7.34 (m, 3 H), 5.55 (dd, *J* = 3.8, 8.7 Hz; 1 H), 4.73 (dd, *J* = 8.7, 8.7 Hz; 1 H), 4.31 (dd, *J* = 3.8, 8.7 Hz; 1 H). ^{13}C NMR ($CDCl_3$) δ: 164.6, 153.7, 146.5, 138.9, 134.3, 130.6, 129.0, 128.9, 128.7, 128.5, 125.8, 116.7, 69.84, 57.71. IR (KBr): 1775, 1680, 1625, 1330, 1210, 760, 710 cm^{-1}. MS: *m/e* (relative intensity) 293 (M, 11), 131 (100), 103 (61), 77 (52). $[\alpha]^{22}_D$: +3.4° (*c* 0.74, $CHCl_3$). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.67; H, 5.12; N, 4.80.

(4*S*)-4-Phenyl-3-[3-(4-methoxyphenyl)-2(*E*)-propenoyl]-2-oxazolidinone (11). Yield: 1.65 g (85%). Mp: 162–164 °C. ^1H NMR ($CDCl_3$) δ TMS: 7.83 (d, *J* = 15.7 Hz; 1 H), 7.73 (d, *J* = 15.7 Hz; 1 H), 7.54 (d, *J* = 8.8 Hz; 2 H), 7.40–7.30 (m, 5 H), 6.89 (d, *J* = 8.8 Hz; 2 H), 5.55 (dd, *J* = 3.9, 8.8 Hz; 1 H), 4.70 (dd, *J* = 8.8, 8.8 Hz; 1 H), 4.27 (dd, *J* = 3.9, 8.8 Hz; 1 H), 3.81 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ: 164.8, 161.7, 153.8, 146.3, 139.2, 130.3, 129.0, 128.5, 127.1, 125.8, 114.2, 69.80, 57.71, 55.24. IR (KBr): 2960, 1775, 1680, 1605, 1515, 1290, 1230, 1215, 1180 cm^{-1}. MS: *m/e* (relative intensity) 323 (M, 34), 161 (100), 31 (60). $[\alpha]^{22}_D$: −41° (*c* = 1.05, $CHCl_3$). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.62; H, 5.30; N, 4.36.

(4*S*)-4-Phenyl-3-[3-(4′-methoxy-2′-methylphenyl)-2(*E*)-propenoyl-2-oxazolidinone (12). This compound was prepared by the method of Evans et al.[21] with modifications. To a −78 °C precooled solution of (2*E*)-3-(4′-methoxy-2′-methylphenyl)-2-propenoic acid[25] (6.03 g, 31.4 mmol, 1.27 equiv) in dry THF (140 mL) were added triethylamine (4.80 mL, 24.8 mmol, 1 equiv) and pivaloyl chloride (4.10 mL, 33.3 mmol, 1.34 equiv) via syringe. The resulting mixture was stirred for 15 min at this temperature and for 45 min at 0 °C when it was transferred via cannula to a suspension of the lithiated oxazolidinone at −78 °C prepared from (4*S*)-4-phenyl-2-oxazolidinone (4.60 g, 28.2 mmol, 1.14 equiv) and *n*-BuLi (1.6 M in hexanes, 17.6 mL, 28.2 mmol, 1.14 equiv) in dry THF (120 mL). After 15 min the slurry was warmed to rt for 90 min when a saturated solution of $NaHCO_3$ (60 mL) was added. Volatiles were evaporated, and water (50 mL) was added. Following workup, the resulting crude product was chromatographed (7:3 hexanes/EtOAc). Yield: 7.78 g of **12** (82%). Mp: 136.0–137.0 °C. ^1H NMR (250 MHz, $CDCl_3$) δ TMS: 8.03 (d, *J* = 15.5 Hz; 1 H), 7.76 (d, *J* = 15.5 Hz; 1 H), 7.67 (d, *J* = 8.6 Hz; 1 H), 7.41–7.31 (m, 5 H), 6.76–6.69 (m, 2 H), 5.53 (dd, *J* = 4.0, 8.8 Hz; 1 H), 4.70 (t, *J* = 8.8 Hz; 1 H), 4.27 (dd, *J* = 4.0, 8.8 Hz;

1 H), 3.79 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ: 165.0, 161.3, 153.8, 143.7, 140.4, 139.2, 129.1, 128.7, 128.5, 125.8, 115.8, 114.8, 112.0, 69.82, 57.80, 55.19, 20.03. MS: *m/e* (relative intensity) 338 (M + 1, 100), 163 (36). $[\alpha]^{22}_D$ −20.0° (*c* 1.10, $CHCl_3$). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.22; H, 5.60; N, 4.19.

General Procedure for the Preparation of the Organocopper Reagents. To a suspension of magnesium turnings (0.34 g, 14.0 mmol, 3.10 equiv) in dry THF (6 mL) was added the bromophenyl derivative (13.5 mmol, 3.00 equiv) dropwise. The mixture was stirred for 1 h either at rt (R_3, Table II: phenyl or 4-methoxyphenyl) or reflux (R_3, Table II: 4-methoxy-2-methylphenyl, a little bit of iodine was needed). The resulting dark solution was cooled to 0 °C and transferred via cannula to a solution of CuBr–$(CH_3)_2S$ complex (1.37 g, 6.75 mmol, 1.50 equiv) in dry THF (16 mL) and $(CH_3)_2S$ (8 mL) at −40 °C. In the case of MeMgBr, a commercial solution (3.0 M in ethyl ether, 4.5 mL, 13.5 mmol, 3.00 equiv) was added by syringe to the CuBr solution. The resulting yellow-green mixture was stirred for 10 min and used for the conjugate addition at the given temperature.

Michael-like Additions. The procedure was slightly different depending on the substrate used. For **8** and **9**: a solution of the α,β-unsaturated acyloxazolidinone (4.50 mmol, 1.00 equiv) in dry THF (8 mL) was added dropwise to the organocopper solution at −15 °C, within a period of 1 h, and the resulting mixture was stirred for 10 min. For **12**: The substrate was added to the organocopper solution at 0 °C over 10 min and the mixture was stirred at this temperature for 1 h. For **10** and **11**: The substrate was added to the organocuprate at −10 °C, and the resulting slurries were allowed to warm slowly to rt (2 h). The reactions were quenched with saturated aqueous of NH_4Cl (10 mL), and the organic solvent was evaporated. Water (10 mL) and EtOAc (30 mL) were added, and the resulting suspension was filtered over glass wool. The aqueous layer was separated, and the organic solution was washed with 10% aqueous NH_4OH (2 × 30 mL), water (30 mL), and brine (30 mL) and dried over $MgSO_4$. The solvent was evaporated off, and the diastereoisomeric mixture was separated by column chromatography (7:3 hexanes/EtOAc) of the resulting crude material in 80–95% yields. Analytical samples were rechromatographed and recrystallized for characterization of the different diastereoisomers.

(3(3*R*),4*S*)-4-Benzyl-3-[3-(4′-methoxyphenyl)butanoyl]-2-oxazolidinone. Yield: 0.67 g (43%). Mp 107–108 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.31–7.19 (m, 3 H), 7.22 (d, *J* = 8.7 Hz; 2 H), 7.07–7.03 (m, 2 H), 6.85 (d, *J* = 8.7 Hz; 2 H), 4.66–4.57 (m, 1 H), 4.16–4.05 (m, 2 H), 3.75 (s, 3 H), 3.48–3.34 (m, 2 H), 3.11–2.99 (m, 2 H), 2.61 (dd, *J* = 9.2, 13.4 Hz; 1 H), 1.33 (d, *J* = 7.2 Hz; 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.6, 157.9, 153.1, 137.6, 134.9, 129.2, 128.6, 127.8, 127.0, 113.6, 65.72, 54.98, 54.71, 43.19, 37.37, 34.99, 21.99. IR (KBr): 2940, 1780, 1700, 1510, 1390, 1360, 1240, 1210 cm^{-1}. MS: *m/e* (relative intensity) 353 (M, 11), 135 (100). $[\alpha]^{22}_D$ +38.7° (*c* 1.16, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.32; H, 6.58; N, 3.95.

(3(3*S*),4*S*)-4-Benzyl-3-[3-(4′-methoxyphenyl)butanoyl]-2-oxazolidinone. Yield: 0.54 g (34%). Mp: 109–110 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.34–7.15 (m, 7 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 4.58–4.50 (m, 1 H), 4.10–3.98 (m, 2 H), 3.75 (s, 3 H), 3.44–3.08 (m, 4 H), 2.69 (dd, *J* = 9.7, 13.3 Hz; 1 H), 1.33 (d, *J* = 6.7 Hz; 3 H). ^{13}C NMR ($CDCl_3$) δ: 158.0, 146.9, 137.7, 135.3, 129.4, 128.9, 127.9, 127.3, 121.8, 113.8, 66.04, 55.21, 55.13, 43.48, 37.81, 35.25, 22.40. IR (KBr): 2960, 1785, 1770, 1700, 1515, 1365, 1245, 1200 cm^{-1}. MS: *m/e* (relative intensity) 353 (M, 19), 148 (63), 135 (100), 91 (58), 31 (55). $[\alpha]^{22}_D$: +77.3° (*c* 1.11, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.28; H, 6.54; N, 4.00.

(3(3*R*),4*S*)-4-Phenyl-3-(3-phenylbutanoyl)-2-oxazolidinone. Yield: 1.25 g (90%). Mp: 114–116 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.29–7.10 (m, 8 H), 7.07–7.03 (m, 2 H), 5.36 (dd, *J* = 4.0, 8.8 Hz; 1 H), 4.58 (dd, *J* = 8.8, 13.3 Hz; 1 H), 4.13 (dd, *J* = 4.0, 8.8 Hz; 1 H), 3.47 (dd, *J* = 6.5, 15.6 Hz; 1 H), 3.39–3.24 (m, 1 H), 3.03 (dd, *J* = 7.7, 15.6 Hz; 1 H), 1.24 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 153.5, 145.3, 138.6, 128.9, 128.3, 126.7, 126.1, 125.4, 69.63, 57.28, 42.93, 35.76, 21.58. IR (KBr): 2960, 1770, 1760, 1710, 1385, 1315, 1220, 1210, 700 cm^{-1}. MS: *m/e* (relative intensity) 309 (M, 12), 118 (100), 105 (94), 91 (51), 77 (73). $[\alpha]^{22}_D$: +40° (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.65; H, 6.18; N, 4.50.

(3(3*S*),4*S*)-4-Phenyl-3-(3-phenylbutanoyl)-2-oxazolidinone. Yield: 0.88 g (63%). Mp: 146–148 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.37–7.10 (m, 10 H), 5.24 (dd, *J* = 3.5, 8.8 Hz; 1 H), 4.47 (dd, *J* = 8.8, 8.8 Hz; 1 H), 4.15 (dd, *J* = 3.5, 8.8 Hz; 1 H), 3.39–3.24 (m, 2 H), 3.12 (dd, *J* = 5.0, 14.9 Hz; 1 H), 1.24 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.1, 145.5, 139.0, 129.0, 128.5, 128.3, 126.9, 126.2, 125.8, 69.74, 57.36, 43.13, 35.71, 22.12. IR (KBr): 2950, 1765, 1700, 1380, 1370, 1230, 1200, 700 cm^{-1}. MS: *m/e* (relative intensity) 309 (M, 6), 118 (99), 105 (100). $[\alpha]^{22}_D$: +91.9° (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.69; H, 6.20; N, 4.51.

(3(3*R*),4*S*)-4-Phenyl-3-[3-(4′-methoxyphenyl)butanoyl]-2-oxazolidinone. Yield: 1.38 g (91%). Mp: 85.5–86.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.28–7.24 (m, 3 H), 7.12 (d, *J* = 8.7 Hz; 2 H), 7.09–7.02 (m, 2 H), 6.78 (d, *J* = 8.7 Hz; 2 H), 5.36 (dd, *J* = 3.9, 8.8 Hz; 1 H), 4.59 (dd, *J* = 8.8, 8.8 Hz; 1 H), 4.14 (dd, *J* = 3.9, 8.8 Hz; 1 H), 3.77 (s, 3 H), 3.47 (dd, *J* = 6.9, 15.5 Hz; 1 H), 3.27 (m, 1 H), 2.97 (dd, *J* = 7.6, 15.5 Hz; 1 H), 1.22 (d, *J* = 6.9, 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.3, 157.8, 153.4, 138.7, 137.3, 128.8, 128.2, 127.7, 125.4, 113.6, 69.60, 57.25, 54.99, 43.08, 35.08, 21.76. IR (KBr): 2960, 1785, 1700, 1515, 1380, 1245, 1205 cm^{-1}. MS: *m/e* (relative intensity) 339 (M, 13), 148 (50), 135 (100). $[\alpha]^{22}_D$: +23.8° (*c* 0.92, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.85; H, 6.24; N, 4.10.

(3(3*S*),4*S*)-4-Phenyl-3-[3-(4′-methoxyphenyl)butanoyl]-2-oxazolidinone. Yield: 1.18 g (77%). Mp: 87.0–88.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.37–7.21 (m, 5 H), 7.12 (d, *J* = 8.7 Hz; 2 H), 6.79 (d, *J* = 8.7 Hz; 2 H), 5.27 (dd, *J* = 3.5, 8.7 Hz; 1 H), 4.51 (dd, *J* = 8.7, 8.7 Hz; 1 H), 4.18 (dd, *J* = 3.5, 8.7 Hz; 1 H), 3.75 (s, 3 H), 3.39–3.22 (m, 2 H), 3.10 (dd, *J* = 4.8, 14.6 Hz; 1 H), 1.22 (d, *J* = 6.7 Hz; 3 H). ^{13}C ($CDCl_3$) δ: 171.3, 158.0, 139.0, 137.6, 129.0, 128.5, 127.8, 125.8, 113.7, 69.77, 57.41, 55.09, 43.39, 35.01, 22.30. IR (KBr): 2980, 1790, 1715, 1520, 1330, 1250, 1235 cm^{-1}. MS: *m/e* (relative intensity) 339 (M, 25), 148 (92), 135 (100), 91 (59), 77 (64). $[\alpha]^{22}_D$: +97.4° (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.67; H, 6.29; N, 4.11.

(3(*R*),4*S*)-4-Phenyl-3-[3-(4′-methoxy-2′-methylphenyl)-butanoyl]-2-oxazolidinone. Yield: 0.50 g (31%). Mp: 94.5–96.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ TMS: 7.36–7.22 (m, 5 H), 7.12 (d, *J* = 2.8 Hz, 1 H), 6.69 (dd, *J* = 8.5, 2.8 Hz; 1 H), 6.66 (d, *J* = 2.8 Hz, 1 H), 5.31 (dd, *J* = 8.6, 3.6 Hz; 1 H), 4.56 (dd, *J* = 8.6, 8.6 Hz; 1 H), 4.20 (dd, *J* = 8.6, 3.6 Hz; 1 H), 3.78 (s, 3 H), 3.55–3.49 (m, 1 H), 3.38 (dd, *J* = 16.7, 7.6 Hz; 1 H), 3.14 (dd, *J* = 16.7, 7.1 Hz; 1 H), 2.31 (s, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.4, 157.3, 153.9, 138.9, 136.7, 136.0, 129.0, 128.5, 126.1, 125.7, 115.7, 111.2, 69.70, 57.42, 55.01, 42.43, 30.00, 21.80, 19.59. IR (KBr): 2970, 1780, 1700, 1500, 1380, 1300, 1190, 760, 710 cm^{-1}. MS: *m/e* (relative intensity) 354 (M + 1, 100), 149 (69). $[\alpha]^{22}_D$: +76.9° (*c* 1.09 $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.40; H, 6.53; N, 3.97.

(3(*S*),4*S*)-4-Phenyl-3-[3-(4′-methoxy-2′-methylphenyl)-butanoyl]-2-oxazolidinone. Yield: 1.56 g (86%). Mp 103–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ TMS: 7.29–7.26 (m, 3 H), 7.18 (d, *J* = 8.5 Hz; 1 H), 7.06–7.03 (m, 2 H), 6.73 (dd, *J* = 8.5, 2.8 Hz; 1 H), 6.62 (d, *J* = 2.8 Hz; 1 H), 5.40 (dd, *J* = 8.8, 4.0 Hz, 1 H), 4.64 (dd, *J* = 8.8, 8.8 Hz; 1 H), 4.19 (dd, *J* = 8.8, 4.0 Hz; 1 H), 3.78 (s, 3 H), 3.54 (m, 2 H), 3.12–3.01 (m, 1 H), 2.20 (s, 3 H), 1.19 (d, *J* = 6.3 Hz; 3 H). ^{13}C NMR ($CDCl_3$) δ: 171.7, 157.4, 153.6, 138.6, 136.6, 135.8, 128.9, 128.3, 126.4, 125.4, 115.8, 111.2, 69.70, 57.41, 55.00, 42.12, 30.53, 21.70, 19.49. IR (KBr): 2830, 1780, 1700, 1500, 1380, 1340, 1250, 1200 cm^{-1}. MS: *m/e* (relative intensity) 354 (M + 1, 100), 149 (81). $[\alpha]^{22}_D$: +33.2° (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.64; H, 6.52; N, 3.94.

Hydrolysis of the Acyloxazolidinones. The products from entries b–d in Table II were hydrolyzed as follows.[24] A solution of the acyloxazolidinone (4 mmol, 1 equiv), THF (18.0 mL), and water (4.50 mL) was stirred and cooled to −5 °C, and H_2O_2 (30%, 1.76 mL, 4.00 equiv) was added carefully by syringe. To the resulting slurry was added dropwise a solution of LiOH in water

(0.8 M, 8.00 mL, 1.60 equiv) within a period of 45 min (the temperature was always kept below 0 °C). The resulting mixture was stirred at 0 °C for 2 h, and then a solution of Na_2SO_3 was added (1.3 M, 12.2 mL, 4.00 equiv). The organic solvent was evaporated (25–30 °C), and the aqueous suspension was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL). The organic solution was dried over $MgSO_4$, filtered, and evaporated to yield 0.59–0.62 g of chiral auxiliary (90–95%). The aqueous solution was acidified with 6 N HCl (5 mL) to pH 1–2 and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated. The desired acids were recovered in 90–95% yields.

(*R*)-3-Phenylbutanoic Acid. Yield: 0.59 g (90%), oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.20–7.34 (m, 5 H), 3.27 (m, 1 H), 2.62 (m, 2 H), 1.31 (d, 3 H). ^{13}C NMR ($CDCl_3$) δ: 179.3, 145.9, 129.1, 127.2, 127.0, 43.1, 36.6, 22.4. IR (KBr): 3400, 2980, 2940, 1715, 765, 700 cm^{-1}. MS: *m/e* (relative intensity): 164 (M, 12), 105 (100), 77 (22). $[\alpha]^{22}_D$: −54.2° (*c* 1.12, benzene). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.09; H, 7.37.

(*R*)-3-(4-Methoxyphenyl)butanoic Acid. Yield: 0.69 g (90%), oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.15 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 3.79 (s, 3 H), 3.31–3.16 (m, 1 H), 2.69–2.50 (m, 2 H), 1.30 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ: 178.9, 158.1, 137.5, 127.6, 113.9, 55.18, 42.89, 42.83, 35.31, 21.98. IR (KBr): 3000, 1700, 1510, 1200, 710, 660 cm^{-1}. MS: *m/e* (relative intensity): 195 (M − 1, 14), 135 (100). $[\alpha]^{22}_D$: −55.5° (*c* 1.00, benzene). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.94; H, 7.28.

(*R*)-3-(4′-Methoxy-2′-methylphenyl)butanoic Acid. Yield: 0.82 g, oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ TMS: 7.09 (d, *J* = 8.2 Hz; 1 H), 6.74–6.70 (m, 2 H), 3.77 (s, 3 H), 3.50 (m, 1 H), 2.63 (dd, *J* = 15.6, 6.9 Hz; 1 H), 2.54 (m, 1 H), 2.34 (s, 3 H), 1.25 (d, *J* = 6.9 Hz; 3 H). ^{13}C NMR ($CDCl_3$) δ: 179.1, 157.5, 136.6, 135.8, 125.9, 115.9, 111.3, 55.10, 42.11, 30.53, 21.50, 19.60. IR (KBr): 3000, 1700, 1510, 1200, 710, 660 cm^{-1}. MS: *m/e* (relative intensity): 208.2 (M, 100), 190.2 (42), 149.1 (79). $[\alpha]^{22}_D$: +31.7 (*c* 1.30, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.77.

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