Resolution of Carboxylic Acids Using Copper(I)-Promoted Removal of Propargylic Esters under Neutral Conditions

Partha Ghosh and Jeffrey Aubé*

Chemical Methodologies and Library Development Center, Delbert M. Shankel Structural Biology Center, 2034 Becker Drive, University of Kansas, Lawrence, Kansas 66047-3761, United States

Ⓢ *Supporting Information*

ABSTRACT: A method for the optical resolution of carboxylic acids is described. Condensation of racemic carboxylic acids with chiral terminal propargyl alcohols gave separable diastereomeric esters. Chromatographic separation followed by heating the individual diastereomers in methanol with catalytic copper(I) halide regenerated the carboxylic acids in good yields and in enantiomeric ratios of ≥94%. This method is particularly useful for the resolution of carboxylic acids that are incompatible with conventional ester hydrolysis.

Enantiomerically pure carboxylic acids are an important class of organic compounds. Even though great advances have been made in their asymmetric synthesis, in some cases resolution of the racemate may still be desired. The most common method of carboxylic acid resolution is still through crystallization of diastereomeric salts, although numerous other techniques exist.[1] We recently wished to resolve an isoquinoline-containing carboxylic acid intermediate used in the preparation of a series of potent and selective κ opioid receptor binders.[2] To accomplish this, we first attempted the low-tech approach of preparing a chiral ester from (R)-1-phenylethyl alcohol, separating the diastereomeric esters, and then regenerating the acid by basic hydrolysis (Scheme 1). Thus, the carboxylic acid shown could be converted into a pair of separable 2-phenylethyl esters, but upon saponification under basic conditions, an epimerized acid was obtained as the major product. In this Note, we present a simple means of resolving carboxylic acids that features the formation of a chiral propargylic ester from the acid substrate, separation by ordinary chromatography, and finally removal of the chiral ester under mild, neutral conditions.

An alternative to hydrolysis via acyl—oxygen bond cleavage is ester removal via alkyl—oxygen cleavage. However, such processes usually require strongly acidic or nucleophilic conditions except in cases where the alkyl carbocation that is generated is stabilized. One example of the latter is the copper-catalyzed amination of propargylic esters, in which the carboxylic acid is generally viewed as a byproduct.[3] In this case, the propargyl cation is stabilized by formation of a copper complex that reacts with the amine to form a propargyl amine (Scheme 2). These reaction conditions were neutral and therefore attractive for our purposes, but the literature procedure still required a stoichiometric amount of a weakly basic amine. Wishing to avoid potential complications arising from the presence of an added amine, we wondered if substituting an alcohol as the nucleophilic component would lead to an analogous reaction cleaving propargylic esters. Propargylic substitution of esters with alcohols is known, albeit under strongly Lewis acidic conditions (TiCl₄).[4]

Scheme 1
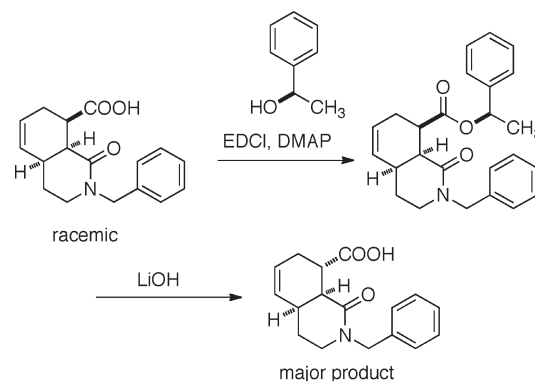
Scheme 2
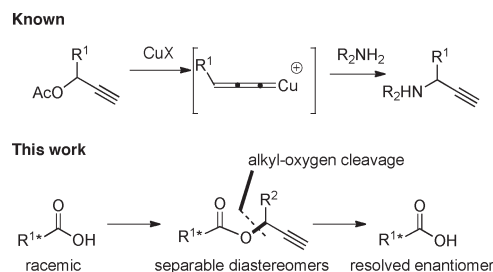
We first sought to identify conditions whereby the propargyl ester **1**, containing a potentially epimerizable axial ester bystander, could be converted to acid **2** in methanol (Table 1). Copper(I) chloride was found to be better than other copper(I) halides. The reaction time was significantly shorter for ester **1b** than **1a**. This is

Table 1. Optimization of Cu(I)-Promoted Propargylic Substitution
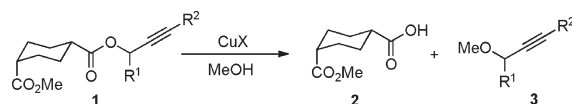
| entry	propargyl ester	CuX (10 mol %)	conditions	yield of 2 (%)
1	1a (R^1 = Ph, R^2 = H)	CuCl	rt, 16 h	74
2		CuCi	40 °C, 6 h	86
3		CuBr	40 °C, 12 h	64
4		CuI	40 °C, 12 h	<10
5[a]		[CuPPh$_3$]$_4$Cl$_4$	40 °C, 6 h	85
6[b]			40 °C, 6 h	0
7	1b (R^1 = o-OMePh, R^2 = H)	CuCl	40 °C, 2 h	82
8	1c (R^1 = Me, R^2 = H)	CuCl	40 °C, 12 h	23
9	1d (R^1 = Ph, R^2 = n-Bu)	CuCl	40 °C, 12 h	0

[a] 2.5 mol % of catalyst was used. [b] AcOH (3 equiv) was added.

probably due to better stabilization of the propargyl carbocation by the electron-rich aromatic ring. The necessity of cation stabilization by an aromatic group was evident by the poor yield obtained in the case of ester 1c, even after a long reaction time. In the case of propargyl ester 1d, with an internal alkyne, no reaction was observed under analogous conditions. Neither 1a nor 1b reacted when heated with 3 equiv of acetic acid in methanol at 40 °C, suggesting the need for Cu(I) promotion.

The requirement for a terminal alkyne is consistent with a mechanism similar to that shown in Scheme 2. The reaction took place at room temperature, however, with longer time and reduced yield relative to those carried out under reflux (cf. entries 1 and 2). The major side product was propargyl ether 3; in some cases, uncharacterized diyne-containing byproducts were also observed.[5] The proportion of diyne increased with decreasing yield of both 2 and 3 in the presence of air or oxygen. Thus, the reaction is air sensitive and proper degassing of the reaction with Ar was required. Significantly, no epimerization of the methyl ester to the more stable trans-1,4-cyclohexanedicarboxylic acid ester occurred under these reaction conditions.

Having determined suitable conditions for ester removal, we examined the use of the propargylic alcohols as resolution agents for a series of racemic carboxylic acids (5−9).[6] The acids were esterified with chiral propargyl alcohols 4a and 4b (Table 2).[6] Propargyl alcohol 4a is commercially available and propargyl alcohol 4b was obtained by reported methods.[7] The diastereomeric esters were separable by using column chromatography although in most cases more than one chromatographic operation was required to ensure good yield and dr values of >95:5. The chromatographic resolving ability may depend on the specific alcohol used. For example, the R$_f$ values of diastereomers 10a and 10b were 0.45 and 0.41 (1:3 ethyl acetate:hexane) compared to the R$_f$ values of 0.48 and 0.42 (1:4 ethyl acetate:hexane) for diastereomers 11a and 11b.[8] Some carboxylic acids did not easily afford separable diastereomers by this method, including ibuprofen and N-Boc-valine (not shown). No hydrolysis of the benzyl ester in compound 7 (entry 4) or carbamate in compound 5 (entry 1 and 2) was observed at the propargylic removal stage. Overall, highly conserved er values together with the absence of any detectable diastereomeric carboxylic acids (entries 5−7) exemplify the mildness of this method. The absolute configuration of the

Table 2. Resolution of Carboxylic Acids
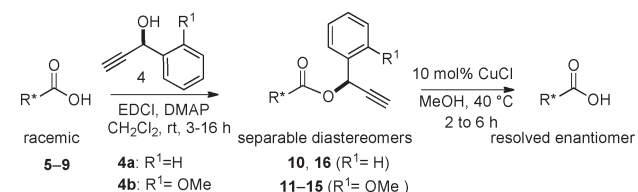
entry	racemic acid	alcohol	ester[a]	resolved enantiomers	% yield (% overall yield)[b]	er[c,d]
1	5	4a	10a	(S)-5	82 (33)	98:2
		4a	10b	(R)-5	84 (33)	98:2
2		4b	11a	(S)-5	81 (36)	96:4
		4b	11b	(R)-5	82 (34)	97:3
3	6	4a	12a	(R)-6	84 (37)	93:7
		4a	12b	(S)-6	84 (36)	94:6
4[e]	7	4a	13a	(S)-7	82 (34)	96:4
		4a	13b	(R)-7	82 (35)	94:6
5[f]	8	4a	14a	(1R, 2R)-8	85 (35)	94:6
		4a	14b	(1S, 2S)-8	82 (32)	94:6
6	9	4a	15a	(4aS, 8R, 8aS)-9	84 (35)	96:4
		4a	15b	(4aR, 8S, 8aR)-9	81 (32)	98:2
7	9	4b	16a	(4aS, 8R, 8aS)-9	79 (38)	98:2
		4b	16b	(4aR, 8S, 8aR)-9	82 (39)	98:2

carboxylic acids was determined by comparing reported optical rotation values of either the carboxylic acids or their derivatives,

except for the acid **9** where X-ray data[9] were used to determined the absolute stereochemistry.

In summary, we have developed a straightforward method for the resolution of carboxylic acids via diastereomeric propargylic esters under mild conditions. The method is particularly useful in chemical resolution of compounds having epimerizable centers or hydrolytically labile functional groups. Although it is not expected that the present method will supplant large-scale classical resolution methods using diastereoselective crystallization techniques, we have found it convenient for the expedient laboratory-scale separation of enantiomeric acids as it uses standard chromatography and does not require the identification of appropriate rescrystallization conditions.

■ EXPERIMENTAL SECTION

General Procedure for Esterification and Separation: (S)-1-tert-Butyl 2-((R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl) Pyrrolidine-1,2-dicarboxylate (11a) and (R)-1-tert-Butyl 2-((R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl) Pyrrolidine-1,2-dicarboxylate (11b). To a solution of **5** (215 mg, 1.0 mmol), EDCl (286 mg, 1.50 mmol), and DMAP (6 mg, 0.05 mmol) in 5 mL of CH_2Cl_2 was added propargyl alcohol **4b** (162 mg, 1.0 mmol) at room temperature. The reaction was stirred for 3 h at room temperature. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed with water (5 mL), then the organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent and chromatography (10% EtOAc in hexane) gave **11a** (158 mg, 44%) as a white solid and **11b** (152 mg, 42%) as a colorless oil. **11a**: white solid (158 mg, 44%); mp 52−54°C; R_f 0.32 (1:4 EtOAc:hexanes); $[\alpha]_D$ −80.8 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$; 2.7:1 mixture of rotamers (minor rotamer in brackets)) δ 7.65 (1H, d, J = 7.5 Hz), 7.36−7.28 (1H, m), 7.02−6.95 (1H, m), 6.88 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 2.0 Hz), [4.36 (0.27H, dd, J = 2.5, 8.4 Hz)], 4.27 (0.73H, dd, J = 3.6, 8.6 Hz), [3.83 (0.8H, s)], 3.82 (2.2H, s), 3.54−3.30 (2H, m), 2.58 (0.7H, d, J = 2.3 Hz), [2.55 (0.3H, d, J = 2.0 Hz)], 2.28−1.72 (4H, m), [1.45 (2.4H, s)], 1.37 (6.6H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.6, [171.3], [156.7], 156.5, [154.2], 153.8, 130.5, [130.3], 128.9, [128.4], [124.4], 124.2, 120.6, [120.4], [110.7], 110.6, 80.1, 79.9, [79.5], 74.9, [74.6], 60.6, 59.0, [58.7], [55.5], 55.4, [46.4], 46.2, 30.7, [29.5], [28.4], 28.1 (3), [24.1], 23.3; IR (thin film) 3285, 2976, 1748, 1694, 1393 cm^{-1}; HRMS (ESI) m/z calcd for C$_{20}$H$_{26}$NO$_5$ ([M + H]$^+$) 360.1811, found 360.1821. **11b**: colorless oil (152 mg, 42%); R_f 0.27 (1:4 EtOAc:hexanes); $[\alpha]_D$ −19.0 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$; 3:1 mixture of rotamers (minor rotamer in brackets)) δ 7.67 (0.75H, dd, J = 1.5, 7.6 Hz), [7.62 (0.25H, d, J = 6.7 Hz)], 7.38−7.27 (1H, m), 7.03−6.83 (2H, m), 6.81 (1H, d, J = 2.1 Hz), [4.38 (0.25H, dd, J = 2.8, 8.6 Hz)], 4.25 (0.75H, dd, J = 3.3, 8.7 Hz), 3.82 (3H, s), 3.65−3.28 (2H, m), 2.60 (0.75H, d, J = 2.2 Hz), [2.57 (0.25H, d, J = 2.2 Hz)], 2.22−1.78 (4H, m), [1.40 (2.25H, s)], 1.39 (6.75H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.7, [171.3], 156.7, 153.9, 130.6, [130.3], 128.7, [128.3], [124.8], 124.2, 120.7, [120.6], 110.7, 80.1, 80.0, [79.6], 75.1, [74.9], 60.7, 59.0, [58.9], 55.5, [55.4], [46.5], 46.3, 30.7, [29.8], [28.4], 28.2 (3), [24.1], 23.5; IR (thin film) 3288, 2124, 1748, 1693, 1392 cm^{-1}; HRMS (ESI) m/z calcd for C$_{20}$H$_{26}$NO$_5$ ([M + H]$^+$) 360.1811, found 360.1817.

cis-1-Methyl 4-(1-phenylprop-2-yn-1-yl) cyclohexane-1,4-dicarboxylate (1a): colorless oil (574 mg, 96%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55−7.33 (5H, m), 6.46 (1H, d, J = 2.3 Hz), 3.66 (3H, s), 2.64 (1H, d, J = 2.3 Hz), 2.58−2.48 (2H, m), 1.98−1.82 (4H, m), 1.75−1.60 (4H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.3, 173.7, 136.6, 129.0, 128.7 (2), 127.5 (2), 80.3, 74.5, 65.1, 51.6, 40.6, 40.5, 25.9 (3), 25.8; IR (thin film) 3285, 2865, 2124, 1728, 1452 cm^{-1}; HRMS (ESI) m/z calcd for C$_{18}$H$_{21}$O$_4$ ([M + H]$^+$) 301.1440, found 301.1438.

cis-1-(1-(2-Methoxyphenyl)prop-2-yn-1-yl) 4-methylcyclohexane-1,4-dicarboxylate (1b): colorless oil (296 mg, 90%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (1H, dd, J = 1.7, 7.6 Hz), 7.33 (1H, dt, J = 1.7, 7.6 Hz), 6.98 (1H, dt, J = 0.9, 7.5 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.78 (1H, d, J = 2.2 Hz), 3.81 (3H, s), 3.65 (3H, s), 2.59 (1H, d, J = 2.3 Hz), 2.55−2.38 (2H, m), 2.0−1.55 (8H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.4, 173.5, 156.7, 130.4, 128.7, 124.5, 120.5, 110.7, 80.3, 74.8, 60.2, 55.5, 51.6, 40.8, 40.4, 26.0, 25.9 (2), 25.8; IR (thin film) 3282, 2949, 1728, 1493, 1029 cm^{-1}; HRMS (ESI) m/z calcd for C$_{19}$H$_{23}$O$_5$ ([M + H]$^+$) 331.1545, found 331.1528.

cis-1-But-3-yn-2-yl 4-methyl cyclohexane-1,4-dicarboxylate (1c): colorless oil (110 mg, 92%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.45 (1H, dq, J = 2.1, 6.7 Hz), 3.68 (3H, s), 2.53−2.45 (2H, m), 2.45 (1H, d, J = 2.2 Hz), 1.98−1.85 (4H, m), 1.74−1.62 (4H, m), 1.49 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.2, 173.6, 82.1, 72.7, 59.7, 51.5, 40.5, 40.4, 25.9 (3), 25.8, 21.1; IR (thin film) 3273, 2867, 1728, 1451, 1031 cm^{-1}; HRMS (ESI) m/z calcd for C$_{13}$H$_{19}$O$_4$ ([M + H]$^+$) 239.1283, found 239.1278.

cis-1-Methyl 4-(1-phenylhept-2-yn-1-yl) cyclohexane-1,4-dicarboxylate (1d): colorless oil (172 mg, 96%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62−7.32 (5H, m), 6.47 (1H, t, J = 2.0 Hz), 3.66 (3H, s), 5.53−2.42 (2H, m), 2.26 (2H, t, J = 7.0 Hz), 1.98−1.35 (12H, m), 0.90 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.3, 173.8, 137.8, 128.5 (3), 127.5 (2), 88.2, 76.7, 65.8, 51.5, 40.6 (2), 30.4, 25.9, 25.8 (3), 21.9, 18.5, 13.5; IR (thin film) 2864, 2235, 1730, 1452, 1135 cm^{-1}; HRMS (ESI) m/z calcd for C$_{22}$H$_{29}$O$_4$ ([M + H]$^+$) 357.2066, found 357.2061.

(S)-1-tert-Butyl 2-((R)-1-Phenylprop-2-yn-1-yl) Pyrrolidine-1,2-dicarboxylate (10a) and (R)-1-tert-Butyl 2-((R)-1-Phenylprop-2-yn-1-yl) Pyrrolidine-1,2-dicarboxylate (10b). Isomers were separated via three successive column chromatography steps using 10% EtOAc in hexane to give **10a** (136 mg, 41%) and **10b** (128 mg, 39%), both as colorless oils. **10a**: TLC (R_f 0.45, 1:4 EtOAc:hexanes); $[\alpha]_D$ +60.7 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$; 2:1 mixture of rotamers (minor rotamer in brackets)) δ 7.55−7.46 (2H, m), 7.44−7.32 (3H, m), [6.50 (0.34H, d, J = 1.9 Hz)], 6.48 (0.66H, d, J = 2.1 Hz), [4.39 (0.34H, dd, J = 3.2, 8.7 Hz)], 4.27 (0.66H, dd, J = 3.4, 8.7 Hz), 3.60−3.25 (2H, m), 2.65 (1H, d, J = 2.0 Hz), 2.22−2.10 (1H, m), 1.98−1.72 (3H, m), [1.41 (3H, s)], 1.35 (6H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.9, [171.5], [154.2], 153.7, [136.3], 136.1, 129.1, [128.8], 128.7 (2), [128.5], 127.5 (2), [127.4], 80.0, 79.9, [79.7], [75.7], 75.6, 65.6, 59.0, [58.9], [46.4], 46.3, 30.7, [29.7], [28.3], 28.2 (3), [24.2], 23.5; IR (thin film) 3288, 2976, 1748, 1694, 1393 cm^{-1}; HRMS (ESI) m/z calcd for C$_{19}$H$_{24}$NO$_4$ ([M + H]$^+$) 330.1705, found 330.1705. **10b**: R_f 0.41 (1:4 EtOAc:hexanes); $[\alpha]_D$ −46.3 (c 1.0, CHCl$_3$) ;^{1}H NMR (400 MHz, CDCl$_3$; 2.3:1 mixture of rotamers by ^{1}H NMR, minor rotamer in brackets)) δ 7.57−7.48 (2H, m), 7.43−7.32 (3H, m), 6.47 (0.7H, d, J = 2.2 Hz), [6.46 (0.3H, d, J = 2.0 Hz)], [4.37 (0.3H, dd, J = 3.4, 8.7 Hz)], 4.25 (0.7H, dd, J = 3.8, 8.7 Hz), 3.58−3.47 (1H, m), 3.46−3.33 (1H, m), 2.65 (0.7H, d, J = 2.3 Hz), [2.63 (0.3H, d, J = 2.2 Hz)], 2.28−2.12 (1H, m), 2.06−1.79 (3H, m), [1.46 (2.7H, s)], 1.30 (6.3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.9, [171.7], [154.4], 153.7, 136.2, [136.0], 129.2, [128.9], 128.7 (2), [128.6], 127.8 (2), [127.5], 80.0, 79.9, [79.8], 75.8, [75.5], 65.8, [65.7], 59.0, [58.7], [46.5], 46.3, 30.7, [29.6], [28.4], 28.2 (3), [24.2], 23.5; IR (thin film) 3290, 2881, 1750, 1694, 1393 cm^{-1}; HRMS (ESI) m/z calcd for C$_{19}$H$_{24}$NO$_4$ ([M + H]$^+$) 330.1705, found 330.1706.

(R)-1-(2-(R)-Methoxyphenyl)prop-2-yn-1-yl 2-(3-Benzoylphenyl)propanoate (12a) and (S)-1-(2-(R)-Methoxyphenyl)prop-2-yn-1-yl 2-(3-Benzoylphenyl)propanoate (12b). Purification by three successive column chromatography steps (10% EtOAc in hexane) gave **12a** (176 mg, 44%) and **12b** (171 mg, 43%) as colorless oils. **12a**: Rf 0.37 (1:4 EtOAc:hexanes); $[\alpha]_D$ −27.8 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66−7.18 (11H, m), 6.83 (1H, dt, J = 0.9, 7.5 Hz), 6.70 (1H, dd, J = 0.6, 7.6 Hz), 6.68 (1H, d, J = 2.2 Hz), 3.75 (1H, q, J = 7.2 Hz), 3.53 (3H, s), 2.53

(1H, d, J = 2.3 Hz), 1.48 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.4, 172.6, 156.7, 140.5, 137.8, 137.4, 132.5, 131.6, 130.4, 130.0 (2), 129.5, 128.8, 128.5, 128.4, 128.3 (2), 124.2, 120.4, 110.5, 79.9, 75.1, 60.9, 55.3, 45.2, 18.2; IR (thin film) 3286, 2939, 2125, 1736, 1655 cm^{-1}; HRMS (ESI) m/z calcd for C$_{26}$H$_{23}$O$_4$ ([M + H]$^+$) 399.1596, found 399.1590. **12b:** R_f 0.33 (1:4 EtOAc:hexanes); [α]$_D$ −17.2 (c 0.7, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75−7.24 (11H, m), 6.90 (1H, dt, J = 0.7, 7.6 Hz), 6.80 (1H, d, J = 8.3 Hz), 7.72 (1H, d, J = 2.2 Hz), 3.76 (1H, q, J = 7.2 Hz), 3.70 (3H, s), 2.44 (1H, d, J = 2.2 Hz), 1.46 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.5, 172.7, 156.7, 140.4, 137.8, 137.5, 132.5, 131.6, 130.5, 130.1 (2), 129.4, 128.9, 128.7, 128.5, 128.3 (2), 124.3, 120.6, 110.7, 79.8, 75.0, 60.8, 55.5, 45.2, 18.5; IR (thin film) 3288, 2250, 1736, 1655, 1493 cm^{-1}; HRMS (ESI) m/z calcd for C$_{26}$H$_{23}$O$_4$ ([M + H]$^+$) 399.1596, found 399.1587.

(S)-2-(((R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl)oxy)-2-oxo-1-phenylethyl Benzoate (13a) and (R)-2-(((R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl)oxy)-2-oxo-1-phenylethyl Benzoate (13b). Purification by three successive column chromatography steps (10% EtOAc in hexane) gave **13a** (168 mg, 42%) and **13b** (172 mg, 43%) as colorless oils. **13a:** R_f 0.41 (1:4 EtOAc:hexanes); [α]$_D$ +7.8 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (2H, d, J = 7.6 Hz), 7.56−7.24 (10H, m), 6.89 (1H, t, J = 7.5 Hz), 6.81 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 2.2 Hz), 6.15 (1H, s), 3.72 (3H, s), 2.44 (1H, d, J = 2.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.4, 165.6, 156.9, 133.8, 133.4, 130.7, 130.0 (2), 129.4, 129.2, 128.8, 128.7 (2), 128.4 (2), 127.9 (2), 123.7, 120.4, 110.7, 79.1, 75.4, 74.6, 61.7, 55.5; IR (thin film) 3286, 2128, 1758, 1723, 1493 cm^{-1}; HRMS (ESI) m/z calcd for C$_{25}$H$_{21}$O$_5$ ([M + H]$^+$) 401.1389, found 401.1381. **13b:** R_f 0.37 (1:4 EtOAc:hexanes); [α]$_D$ −55.0 (c 0.9, CHCl$_3$); ^{1}H NMR (400 MHz, CDCH$_3$, δ 8.04 (2H, dd, J = 1.2, 8.2 Hz), 7.52−7.15 (10H, m), 6.78 (1H, dt, J = 0.8, 7.6 Hz), 6.72 (1H, d, J = 2.2 Hz), 6.64 (1H, d, J = 8.3 Hz), 6.13 (1H, m), 3.40 (3H, s), 2.59 (1H, d, J = 2.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.5, 165.7, 156.7, 133.9, 133.4, 130.5, 130.0 (2), 129.3, 129.1, 128.6 (2), 128.4 (3), 127.8 (2), 123.7, 120.3, 110.3, 79.2, 75.9, 74.7, 61.9, 55.1; IR (thin film) 1760, 1725, 1494, 1110 cm^{-1}; HRMS (ESI) m/z calcd for C$_{25}$H$_{21}$O$_5$ ([M + H]$^+$) 401.1389, found 401.1376.

(1R,2R)-(R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl-2-benzoyl-cyclohexanecarboxylate (14a) and (1S,2S)-(R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl-2-benzoylcyclohexanecarboxylate (14b). Purification by three successive column chromatography steps (10% EtOAc in hexane) gave **14a** (154 mg, 41%) and **14b** (141 mg, 38%) as colorless oils. **14a:** R_f 0.41 (1:4 EtOAc:hexanes); [α]$_D$ −15.2 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02−7.95 (2H, m), 7.62−7.41 (4H, m), 7.32 (1H, dt, J = 1.7, 8.2 Hz), 6.95 (1H, dt, J = 0.8, 7.6 Hz), 6.86 (1H, d, J = 8.3 Hz), 6.68 (1H, d, J = 2.2 Hz), 3.79 (3H, s), 3.70−3.60 (1H, m), 3.02−2.92 (1H, m), 2.51 (1H, d, J = 2.2 Hz), 2.34−1.20 (8H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.8, 173.9, 156.8, 136.4, 132.8, 130.3, 128.5 (3), 128.4 (2), 124.3, 120.4, 110.7, 80.2, 74.5, 60.4, 55.5, 46.7, 44.3, 29.9, 28.9, 25.6, 25.5; IR (thin film) 3285, 1732, 1679, 1493, 1167 cm^{-1}; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$O$_4$ ([M + H]$^+$) 377.1753, found 377.1747. **14b:** R_f 0.35 (1:4 EtOAc:hexanes); [α]$_D$ −30.5 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90−7.85 (2H, m), 7.57 (1H, dd, J = 1.7, 7.6 Hz), 7.55−7.23 (4H, m), 6.90 (1H, dt, J = 0.9, 7.6 Hz), 6.71 (1H, d, J = 8.2 Hz), 6.68 (1H, d, J = 2.2 Hz), 3.67 (3H, s), 3.63−3.55 (1H, m), 3.03−2.94 (1H, m), 2.54 (1H, d, J = 2.3 Hz), 2.22−1.15 (8H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.6, 173.6, 156.6, 136.3, 132.7, 130.2, 128.5 (2), 128.4, 128.3 (2), 124.5, 120.4, 110.4, 80.0, 74.9, 60.4, 55.3, 46.7, 44.4, 29.9, 29.0, 25.6, 25.5; IR (thin film) 3285, 1732, 1678 cm^{-1}; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$O$_4$ ([M + H]$^+$) 377.1753, found 377.1739.

(4aS,8R,8aS)-(R)-1-Phenylprop-2-yn-1-yl-2-benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylate (15a) and (4aR,8S,8aR)-(R)-1-(2-Methoxyphenyl)prop-2-yn-1-yl-2-benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylate (15b). Purification by three successive column chromatography steps (20% EtOAc in hexane) gave **15a** (181 mg, 42%) as a colorless oil

and **15b** (168 mg, 39%) as a white solid. **15a:** R_f 0.34 (1:3 EtOAc:hexanes); [α]$_D$ −20.5 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (1H, dd, J = 1.7, 7.6 Hz), 7.36−7.10 (6H, m), 6.99 (1H, td, J = 0.9, 7.6 Hz), 6.88 (1H, d, J = 0.7 Hz), 6.87 (1H, d, J = 2.2 Hz), 5.86−5.80 (1H, m), 5.51 (1H, d, J = 10.0 Hz), 4.53 (1H, d, J = 14.7), 4.42 (1H, d, J = 14.7 Hz), 3.81 (3H, s), 3.39−3.34 (1H, m), 3.05−2.98 (2H, m), 2.85−2.76 (1H, m), 2.74−2.64 (1H, m), 2.57 (1H, d, J = 2.3 Hz), 2.51−2.29 (2H, m), 2.01−1.89 (1H, m), 1.83−1.72 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.4, 168.9, 156.7, 137.4, 130.0, 129.1, 128.5, 128.4 (2), 127.9 (2), 127.7, 127.1, 125.3, 120.4, 110.8, 81.1, 74.0, 60.3, 55.6, 49.9, 43.8, 42.6, 41.4, 34.7, 27.3, 23.7; IR (thin film) 3285, 1737, 1635, 1493, 1251 cm^{-1}; HRMS (ESI) m/z calcd for C$_{27}$H$_{28}$NO$_4$ ([M + H]$^+$) 430.2018, found 430.2011. **15b:** R_f 0.31 (1:3 EtOAc:hexanes); mp 149−151 °C; [α]$_D$ −30.6 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (1H, dd, J = 1.7, 7.6 Hz), 7.36−7.14 (6H, m), 6.99 (1H, dt, J = 0.9, 7.5 Hz), 6.91 (1H, d, J = 2.2 Hz), 6.89 (1H, d, J = 8.2 Hz), 5.84−5.80 (1H, m), 5.49 (1H, d, J = 10.0 Hz), 4.79 (1H, d, J = 14.7 Hz), 4.31 (1H, d, J = 14.7 Hz), 3.84 (3H, s), 3.47−3.42 (1H, m), 3.07−2.62 (4H, m), 2.58 (1H, d, J = 2.3 Hz), 2.50−1.65 (4H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.2, 169.0, 156.7, 137.3, 130.0, 129.0, 128.5, 128.4 (2), 127.9 (2), 127.8, 127.1, 125.6, 120.5, 110.8, 80.7, 74.2, 60.3, 55.7, 50.2, 43.9, 42.6, 41.3, 34.3, 27.3, 23.8; IR (thin film) 3285, 1736, 1634, 1492, 1250 cm^{-1}; HRMS (ESI) m/z calcd for C$_{27}$H$_{28}$NO$_4$ ([M + H]$^+$) 430.2018, found 430.2005.

(4aS,8R,8aS)-1-((R)-Phenylprop-2-yn-1-yl)-2-benzyl-1-oxo-1,2,3,4,4a,7,8,8a octahydroisoquinoline-8-carboxylate (16a) and (4aR,8S,8aR)-1-((R)-Phenylprop-2-yn-1-yl)-2-benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylate (16b). Purification by three successive column chromatography steps (10% EtOAc in hexane) gave **16a** (190 mg, 48%) and **16b** (192 mg, 48%) as white foams. **16a:** R_f 0.58 (1:3 EtOAc:hexanes); [α]$_D$ −37.0 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70−7.60 (2H, m), 7.40−7.10 (8H, m), 6.63 (1H, d, J = 2.2 Hz), 5.90−5.83 (1H, m), 5.51 (1H, dd, J = 10.0, 1 Hz), 4.64 (1H, d, J = 14.7 Hz), 4.38 (1H, d, J = 14.7 Hz), 3.34 (1H, dd, J = 5.4, 3.3 Hz), 3.10−2.98 (2H, m), 2.85-2.76 (1H, m), 2.74−2.65 (1H, m), 2.69 (1H, d, J = 2.2 Hz), 2.46−2.38 (2H, m), 1.98−1.86 (1H, m), 1.84−1.74 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.6, 169.0, 137.3, 136.5, 129.1, 128.6, 128.5 (2), 128.4 (2), 127.9 (2), 127.8 (2), 127.6, 127.2, 80.5, 75.5, 65.0, 50.1, 43.8, 42.5, 41.1, 34.2, 27.3, 23.6; IR (thin film) 2122, 1737, 1630, 1356 cm^{-1}; HRMS (ESI) m/z calcd for C$_{26}$H$_{26}$NO$_3$ ([M + H]$^+$) 400.1913, found 400.1902. **16b:** R_f 0.52 (1:3 EtOAc:hexanes); [α]$_D$ −15.0 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70−7.60 (2H, m), 7.40−7.15 (8H, m), 6.62 (1H, d, J = 2.2 Hz), 5.85−5.78 (1H, m), 5.50 (1H, dd, J = 10.0, 1.6 Hz), 4.75 (1H, d, J = 14.7 Hz), 4.36 (1H, d, J = 14.7 Hz), 3.47 (1H, dd, J = 5.4, 3.2 Hz), 3.10−3.00 (2H, m), 2.85−2.60 (2H, m), 2.65 (1H, d, J = 2.2 Hz), 2.48−2.28 (2H, m), 2.05−1.95 (1H, m), 1.82−1.77 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.6, 169.1, 137.2, 137.0, 129.0, 128.7, 128.5 (2), 128.4 (2), 127.9 (2), 127.8, 127.7 (2), 127.2, 80.5, 75.3, 65.3, 50.3, 43.8, 42.8, 41.4, 34.3, 27.3, 23.6; IR (thin film) 2123, 1734, 1630, 1356 cm^{-1}; HRMS (ESI) m/z calcd for C$_{26}$H$_{26}$NO$_3$ ([M + H]$^+$) 400.1913, found 400.1908.

General Procedure for Removal of Propargylic Esters: N-Boc-D-Proline ((R)-5). To the propargyl ester **11b** (108 mg, 0.30 mmol) and CuCl (3 mg, 0.03 mmol) in a 10 mL flask was added 3.0 mL of MeOH (degassed with Ar). The reaction solution was degassed with Ar for 5 min and then heated for 2 h at 40 °C with constant stirring. The reaction was cooled, concentrated, and chromatographed with 20−100% EtOAc in hexane to give (R)-**5** (53 mg, 82% yield) as a white solid. The er (97:3) of (R)-**5** was determined by converting it into phenyl amide (EDCl, DMAP-mediated coupling with aniline in CH$_2$Cl$_2$) and then using analytical HPLC (Chiralcel OD-H, 0.5 mL/min, 10% i-PrOH/hexane).

(R)-Ketoprofen ((R)-6) and (S)-Ketoprofen ((S)-6). The er values of (R)- and (S)-**6** were determined by converting them into phenyl amides

(EDCl, DMAP-mediated coupling with aniline in CH_2Cl_2) and then using analytical HPLC (Chiralcel OD-H, 0.5 mL/min, 5% *i*-PrOH/hexane).

(*S*)-*O*-Benzoylmandelic Acid [(*S*)-7] and (*R*)-O-Benzoylmandelic Acid [(*R*)-7]. The er values of (*R*)- and (*S*)-7 were determined by converting them into phenyl amides (EDCl, DMAP-mediated coupling with aniline in CH_2Cl_2) and then using analytical HPLC (Chiralcel OD-H, 1.0 mL/min, 1% *i*-PrOH/hexane). (*R*)-7: $[\alpha]_D$ −47.1 (*c* 1.0, CHCl$_3$) [lit.[10] $[\alpha]_D$ −48.28 (*c* 1.0, CHCl$_3$)].

(1*R*,2*R*)-2-Benzoylcyclohexanecarboxylic Acid [(1*R*,2*R*)-8] and (1*S*,2*S*)-2-Benzoylcyclohexanecarboxylic Acid [(1*S*,2*S*)-8]. The er values of (1*R*,2*R*)-8 and (1*S*,2*S*)-8 were determined by first converting them into the methyl ester (EDCl, DMAP-mediated coupling with methanol in CH_2Cl_2) and then using analytical HPLC (Chiralcel OD-H, 0.5 mL/min, 5% *i*-PrOH/hexane). (1*R*,2*R*)-8: optical rotation for the methyl ester $[\alpha]_D$ +8.5 (*c* 0.8, hexane) [lit.[11] $[\alpha]_D$ +11.1 (*c* 1.9, isooctane)].

(4a*S*,8*R*,8a*S*)-2-Benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid ((4a*S*,8*R*,8a*S*)-9) and (4a*S*,8*R*,8a*S*)-2-Benzyl-1-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxylic Acid ((4a*S*,8*R*,8a*S*))-9. The er values of (4a*S*,8*R*,8a*S*)-9 and (4a*R*,8*S*,8a*R*)-9 were determined by first converting them into 4-chloro-3-trifluoromethylphenyl amides (EDCl, DMAP-mediated coupling with 4-chloro-3-trifluoromethyl aniline in CH_2Cl_2) and then using analytical HPLC (Chiralcel OD-H, 0.5 mL/min, 10% *i*-PrOH/hexane).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information.   Copies of ^1H and ^{13}C NMR spectra for new compounds and chiral HPLC data and X-ray data for the derivative of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: jaube@ku.edu.

■ ACKNOWLEDGMENT

■ REFERENCES

(1) Reviews: (a) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley−Interscience: New York, 1981. (b) Porter, W. H. *Pure Appl. Chem.* **1991**, *63*, 1119–1122. (c) Sekhon, B. S. *Int. J. PharmTech Res.* **2010**, *2*, 1584–1594.

(2) (a) Frankowski, K. J.; Hirt, E. E.; Zeng, Y.; Neuenswander, B.; Fowler, D.; Schoenen, F.; Aubé, J. *J. Comb. Chem.* **2007**, *9*, 1188–1192. (b) Frankowski, K. J.; Ghosh, P.; Setola, V.; Tran, T. B.; Roth, B. L.; Aubé, J. *ACS Med. Chem. Lett.* **2010**, *1*, 189–193.

(3) (a) Yamada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S. *J. Org. Chem.* **1994**, *59*, 2282–2284. (b) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777–3780.

(4) Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463–7468.

(5) For a review of the Glaser coupling of alkynes, see: Gribble, G. W. In *NameReactions for Homologation*, Part 1; Li, J. J., Part 1 Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; pp 236−257.

(6) Carboxylic acids **5**−**8** are commercially available and **9** is known (ref 2b).

(7) (a) Waldinger, C.; Schneider, M.; Botta, M.; Corelli, F.; Summa, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1485–1488. (b) Baldoli, C.; Buttero,

P. D.; Licandro, E.; Maiorana, S.; Papagni, A.; Torchio, M. *Tetrahedron Lett.* **1993**, *34*, 7943–7946.

(8) Authentic samples were prepared by reacting racemic 1-(2-methoxyphenyl)prop-2-yn-1-ol with L-Boc-proline, diastereomer separation, and hydrolysis with LiOH.

(9) Carboxylic acid (4a*S*,8*S*,8a*R*)-9 was converted to the analogous 4-bromo-2-(trifluoromethyl)aniline amide, which was subjected to anomalous X-ray diffraction to determine the absolute stereochemistry.

(10) Kumar, P. S.; Banerjee, A.; Baskaran, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 804–807.

(11) Hagishita, S.; Kuriyama, K. *J. Chem. Soc., Perkin. Trans. 2* **1974**, *6*, 686–696.