KINETIC RESOLUTION OF PROPARGYLIC ALCOHOLS CATALYZED BY BENZOTETRAMISOLE

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SUPPORTING INFORMATION: Experimental procedures (7 pages), ^1H NMR and ^{13}C NMR spectra (24 pages).

EXPERIMENTAL PART.

1. GENERAL. All reagents were obtained commercially and used as received unless otherwise specified. Catalysts **2** and **3** were prepared as previously described. Substrate **9a** is commercially available from Sigma-Aldrich. All the other substrates are known compounds and have been prepared according to the literature procedures: **4a-d**,^{2c} **5**,¹¹ **6**,^{2c} **7**,¹² **8a**,^{9a} **8b,c**,¹³ **9b**.¹⁴

^1H NMR and ^{13}C NMR spectra were recorded on a Unity 300 or a Unity 500 MHz Varian spectrometer. The chemical shifts are reported as δ values (ppm) relative to TMS using residual CHCl_3 peak (7.26 ppm) as the reference. High-Resolution mass spectral analyses were performed at Washington University MS Center on a Kratos MS-50TA spectrometer using electron ionization (HR-EI) and fast atom bombardment (FAB) methods. Optical rotations were measured in dichloromethane at room temperature and 589 nm wavelength using a Perkin-Elmer 241 polarimeter.

2. KINETIC RESOLUTION EXPERIMENTS

Figure 1S. Catalysts and substrates used in this study

2.1. Optimization of reaction conditions

Procedure A: The first test. The procedure described earlier^{5c} was followed. Each of the stock catalyst solutions was prepared by dissolving 0.010 mmol of the respective catalyst [(*R*)-CI-PIQ **2** or (*R*)-BTM **3**] and 66 mg (0.38 mmol) of *N,N*-diisopropylethylamine in CDCl₃ in a 1.00 mL volumetric test tube and bringing the volume to the mark. Two one dram vials were each charged with 37 mg (0.25 mmol) of 4-phenyl-3-butyn-2-ol, 0.50 mL of the stock solution of the catalyst and 100 mg of dry granular Na₂SO₄, cooled to 0° C and treated with 24 μL (0.19 mmol) of propionic anhydride. The temperature was maintained at 0° C. The reaction was monitored by ¹H NMR and stopped by pouring the contents into a vial with MeOH upon reaching conversion about 50%. The workup and HPLC analysis followed the standard procedure.⁵ The results are shown in Table 1S.

Procedure B: Base-free conditions. Procedure A was followed except that no base was added.

Procedure C: The use of isobutyric anhydride. Procedure B was followed except propionic anhydride was replaced with isobutyric anhydride.

Procedure D: Variation of the solvent. Procedure B was followed except CDCl₃ was replaced with THF and *tert*-amyl alcohol, respectively.

Table 1S. Optimization of reaction conditions

entry	catalyst	anhydride	base	solvent	time, h	#	ee _E %	ee _A %	C _{HPLC} %	s	C _{AVG} %	s _{AVG}
1	2	(EtCO) ₂ O	<i>i</i> -Pr ₂ NEt	CDCl ₃	1.0	1	74.8	83.6	52.8	17.9	52	19
						2	77.1	81.0	51.2	19.1		
2	3	(EtCO) ₂ O	<i>i</i> -Pr ₂ NEt	CDCl ₃	5.0	1	81.3	89.2	52.3	28.8	52	28
						2	80.4	89.1	52.6	27.3		
3	2	(EtCO) ₂ O	none	CDCl ₃	45.5	1	80.0	57.0	41.6	15.9	41	18
						2	83.3	56.7	40.5	19.4		
4	3	(EtCO) ₂ O	none	CDCl ₃	10.5	1	69.0	99.5	59.0	30.7	59	31
						2	68.5	99.6	59.3	30.6		
5	2	<i>i</i> -PrCO) ₂ O	none	CDCl ₃	92	1	74.4	39.3	34.6	10.0	34	10
						2	74.0	38.7	34.3	9.7		
6	3	<i>i</i> -PrCO) ₂ O	none	CDCl ₃	21.5	1	81.2	70.2	46.4	20.1	47	21
						2	81.8	71.8	46.7	21.3		

7	2	(EtCO) ₂ O	none	THF	6.5	1	77.2	65.9	46.1	15.3	46	15
						2	77.6	65.7	45.8	15.6		
8	3	(EtCO) ₂ O	none	THF	24	1	-	-	-	-	NR	-
						2	-	-	-	-		
9	2	(EtCO) ₂ O	none	<i>t</i> -amyl alcohol	7.0	1	80.3	44.3	35.6	14.1	37	14
						2	78.1	48.0	38.1	13.0		
10	3	(EtCO) ₂ O	none	<i>t</i> -amyl alcohol	7.0	1	77.9	69.8	47.3	16.7	47	17
						2	77.8	70.2	47.4	16.6		

2.2. Variation of the substrates. Procedure B described above was followed in all cases, except that increased catalyst loadings (Table 2S, entries 5 and 8-12) and propionic anhydride concentrations (entry 5) were employed for slow-reacting substrates.

Table 5S. Kinetic resolution of propargylic alcohols

entry	substrate	catalyst loading	time, h	#	ee _E %	ee _A %	C _{HPLC} %	s	C _{AVG} %	s _{AVG}
1	4a	4 mol %	10.5	1	69.1	99.5	59.0	30.7	59	31
				2	68.5	99.6	59.3	30.6		
2	4b	4 mol %	10.5	1	75.4	95.8	56.0	27.1	56	27
				2	75.2	96.4	56.2	27.6		
3	4c	4 mol %	10.5	1	71.4	89.8	55.7	17.8	56	18
				2	71.3	90.6	56.0	18.2		
4	4d	4 mol %	10.5	1	69.7	53.0	43.2	9.4	53	43
				2	70.1	53.7	43.4	9.6		
5	5	10mol %	18	1	61.9	99.8	61.7	26.7	62	27
				2	63.0	99.8	61.3	27.5		
6	6	4 mol %	2.0	1	83.3	88.7	51.6	32.3	52	32
				2	82.3	89.7	52.1	31.1		
7	7	4 mol %	1.5	1	77.5	92.8	54.5	26.1	55	26
				2	77.7	93.1	54.5	26.7		
8	8a	10 mol %	25	1	76.7	54.5	41.5	13.0	42	13
				2	76.0	54.1	41.6	12.5		
9	8b	10 mol %	23	1	59.6	89.7	60.1	11.5	60	11
				2	58.4	87.6	60.0	10.4		
10	8c	10 mol %	19	1	59.7	55.4	48.1	6.8	48	7
				2	60.0	55.6	48.1	6.9		

11	9a	10 mol %	6.0	1	63.2	77.9	55.2	10.2	55	11
				2	67.0	80.9	54.7	12.3		
12	9b	10 mol %	2.5	1	49.7	63.2	56.0	5.5	57	5
				2	47.5	65.1	57.8	5.3		

4. HPLC analyses. HPLC analyses were performed on a Shimadzu LC system using UV detection at 254 or 204 nm. Most propargylic alcohols were separated on Chiralcel OD-H analytical chiral stationary phase column (4.6x250 mm, Chiral Technologies, Inc.) using hexane-isopropanol mixtures as mobile phase. Most esters of propargylic alcohols were hydrolyzed with methanolic NaOH to the alcohols, which were analyzed by HPLC. All exceptions are noted in the footnotes to Table 3S.

5. Absolute stereochemistry. The absolute configurations of the unreacted propargylic obtained by KR were assigned by comparison of the sign of optical rotation with the literature data or via the Mosher ester analysis¹⁵.

Table 3S. HPLC and optical rotation data

Substrate	HPLC conditions	Retention time (min)		Unreacted alcohol	
		(R)-ent	(S)-ent	Sign of rotation	Absolute Configuration
4a	15% IPA/hexane OD-H	6.76	12.30	(-)	S ^{9a}
4b	12% IPA/hexane OD-H	7.38	15.42	(-)	S ^{10e}
4c	10% IPA/hexane OD-H	6.64	10.83	(-)	S ^{10e}
4d	6% IPA/hexane OD-H	8.03	10.56	(-)	S ¹⁶
5	6% IPA/hexane OD-H	7.06	7.97	N/D	S ^a
6	2% IPA/hexane OD-H	17.91	19.31	(-)	S ^{2c}

7^b	0.5% IPA/hexane OD-H	15.40	16.60	N/D	S ^a
8a	1% IPA/hexane OD-H	18.05	20.30	(-)	S ^{9a}
8b	2% IPA/hexane OD-H	10.45	12.30	(-)	S ¹³
8c^c	6% IPA/hexane OD-H	10.05	11.87	(-)	S ¹³
9a	2% IPA/hexane OD-H	16.70	15.60	(-)	S ¹⁷
9b^d	2% IPA/hexane OD-H	16.70	15.60	(-)	S ^{10e,18}

^a) Absolute configuration was assigned by Mosher ester analysis¹⁵

^b) HPLC separation was achieved under the conditions shown using the propionate ester of **7** **8c** (obtained from the alcohol by treatment with (EtCO)₂O and DMAP).

^c) HPLC separation was achieved under the conditions shown using the phenylcarbamate of **8c** (obtained from the alcohol by treatment with PhNCO and DMAP).

^d) HPLC separation was achieved under the conditions shown using **9a** (obtained from **9b** and its propionate by treatment with NaOH/MeOH)

Spectral data for previously unreported compounds.

Propionate of 4a: ¹H NMR (300MHz,CDCl₃): δ 7.41-7.46 (m, 2H), 7.28-7.31 (m, 3H), 5.71(q, J=5.7Hz, 1H), 2.37 (q, J=5.1Hz, 2H), 1.57(d, J=3.6Hz, 3H), 1.17(t, J=8.1Hz, 3H); ¹³C NMR (75MHz, CDCl₃): δ 173.52, 132.08, 128.78, 128.45, 122.57, 87.81, 84.69, 60.82, 27.86, 21.75, 9.22; **IR (film, cm⁻¹)** 2987, 2940, 1742, 1177; **MS: HR-EI** calculated for C₁₃H₁₄O₂ m/z : 202.0994, found 202.0987.

Propionate of 4b: ¹H NMR (300MHz,CDCl₃): δ 7.43-7.46 (m, 2H), 7.26-7.31 (m, 3H), 5.78(q, J=5.7Hz, 1H), 2.39 (q, J=7.2Hz, 2H), 1.88 (quintet, J=6.6Hz, 2H), 1.18 (t, J=7.5Hz, 3H), 1.07 (t, J=7.5Hz, 3H); ¹³C NMR (75MHz, CDCl₃): δ 173.65, 132.11, 128.73, 128.45, 122.66, 86.78, 85.40, 65.66, 28.48, 27.87, 9.64, 9.28; **IR (film, cm⁻¹)** 2975, 2940, 1743, 1176; **MS: HR-EI** calculated for C₁₄H₁₆O₂ m/z : 216.1150, found 216.1142.

Propionate of 4c: ^1H NMR (300MHz, CDCl_3): δ 7.43-7.46 (m, 2H), 7.26-7.32 (m, 3H), 5.47 (d, $J=4.5\text{Hz}$, 1H), 2.40 (q, $J=6.3\text{Hz}$, 2H), 2.09 (sextet, $J=6.9\text{Hz}$, 1H), 1.18 (t, $J=7.5\text{Hz}$, 3H), 1.08 (d, $J=9.3\text{Hz}$, 3H), 1.06 (d, $J=9.6\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.65, 132.11, 128.70, 128.44, 122.75, 85.91, 85.72, 69.41, 32.92, 27.89, 18.51, 17.88, 9.36; **IR (film, cm^{-1})** 2968, 2940, 2875, 1742, 1177; **MS: HR-EI** calculated for $\text{C}_{15}\text{H}_{18}\text{O}_2$ m/z : 230.1307, found 230.1303.

Propionate of 4d: ^1H NMR (300MHz, CDCl_3): δ 7.43-7.46 (m, 2H), 7.29-7.31 (m, 3H), 5.37 (s, 1H), 2.41 (q, $J=7.5\text{Hz}$, 2H), 1.19 (t, $J=9.0\text{Hz}$, 3H), 1.08 (s, 9H); ^{13}C NMR (75MHz, CDCl_3): 173.68, 132.10, 128.65, 128.43, 122.83, 85.94, 85.75, 72.26, 35.71, 27.90, 25.90, 9.36; **IR (film, cm^{-1})** 2971, 2871, 1740, 1172; **MS: HR-EI** calculated for $\text{C}_{16}\text{H}_{20}\text{O}_2$ m/z : 244.1463, found 244.1458.

Propionate of 5: ^1H NMR (300MHz, CDCl_3): δ 6.13 (broad m, 1H), 5.59 (q, $J=6.6\text{Hz}$, 1H), 2.31 (q, $J=7.5\text{Hz}$, 2H), 2.15-2.04 (broad m, 4H), 1.70-1.51 (broad m, 4H), 1.48 (d, $J=5.1\text{Hz}$, 3H), 1.14 (t, $J=7.2\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.51, 136.03, 120.12, 86.49, 85.07, 60.93, 29.22, 27.85, 25.81, 22.42, 21.89, 21.63, 9.19; **IR (film, cm^{-1})** 2959, 2936, 1742, 1185, 1164; **MS: HR-EI** calculated for $\text{C}_{13}\text{H}_{18}\text{O}_2$ m/z : 206.1307, found 207.1310.

Propionate of 6: ^1H NMR (300MHz, CDCl_3): δ 5.45 (q, $J=6.6$, 1H), 2.35 (t, $J=7.8\text{Hz}$, 2H), 2.25 (t, $J=7.2\text{Hz}$, 2H), 1.51-1.35 (m, 4H), 1.46 (d, $J=9.9\text{Hz}$, 3H), 1.11 (t, $J=7.5\text{Hz}$, 3H), 0.88 (t, $J=7.2\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.29, 82.18, 73.78, 69.90, 64.49, 60.51; **IR (film, cm^{-1})** 2937, 2873, 1745, 1173; **MS: HR-EI** calculated for $\text{C}_{13}\text{H}_{18}\text{O}_2$ m/z : 206.1307, found 207.1343.

Propionate of 7: ^1H NMR (300MHz, CDCl_3): δ 5.52 (q, $J=6.6\text{Hz}$, 1H), 2.33 (q, $J=7.5\text{Hz}$, 2H), 2.31 (s, 3H), 1.50 (d, $J=6.9\text{Hz}$, 3H), 1.12 (t, $J=7.5\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 184.02, 173.22, 89.14, 83.64, 59.50, 32.69, 27.58, 20.60, 9.05; **IR (film, cm^{-1})** 2989, 2943, 1746, 1684, 1360, 1226, 1171; **MS: HR-FAB** calculated for $\text{C}_9\text{H}_{12}\text{O}_3$ ($\text{M}+\text{Li}^+$) m/z : 175.0946, found 175.0937.

Propionate of 8a: ^1H NMR (300MHz, CDCl_3): δ 5.45 (q, $J=2.4\text{Hz}$, 1H), 2.33 (q, $J=7.5\text{Hz}$, 2H), 2.19 (t, $J=7.2\text{Hz}$, 2H), 1.56-1.35 (m, 4H), 1.42 (d, $J=6.2\text{Hz}$, 3H), 1.12 (t, $J=7.8\text{Hz}$, 3H), 0.88 (t, $J=7.2\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.56, 85.59, 78.91, 60.82, 30.75, 27.85, 22.07, 22.02, 18.53, 13.72, 9.18; **IR (film, cm^{-1})** 2936, 1742, 1185, 1164; **MS: HR-EI** calculated for $\text{C}_{11}\text{H}_{18}\text{O}_2$ m/z : 182.1307, found 182.1314.

Propionate of 8b: ^1H NMR (300MHz, CDCl_3): δ 5.46 (q, $J=5.1\text{Hz}$, 1H), 2.35 (m, 1H), 2.31 (q, $J=7.2\text{Hz}$, 2H), 1.80-1.60 (m, 4H), 1.54-1.20 (m, 6H), 1.43 (d, $J=6.6\text{Hz}$, 3H), 1.12 (t, $J=7.5\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.55, 89.57, 78.93, 60.85, 32.66, 29.13, 27.90, 26.05, 24.97, 22.14, 9.21; **IR (film, cm^{-1})** 2932, 1742, 1165; **MS: HR-EI** calculated for $\text{C}_{13}\text{H}_{20}\text{O}_2$ m/z : 208.1463, found 208.1487.

Propionate of 8c: ^1H NMR (300MHz, CDCl_3): δ 5.46 (q, $J=6.6\text{Hz}$, 1H), 2.31 (q, $J=7.5\text{Hz}$, 2H), 1.41 (d, $J=6.6\text{Hz}$, 3H), 1.19 (s, 9H), 1.12 (t, $J=7.5\text{Hz}$, 3H); ^{13}C NMR (75MHz, CDCl_3): δ 173.51, 93.63, 77.39, 60.76, 31.04, 27.91, 27.46, 22.15, 9.21; **IR (film, cm^{-1})** 2971, 2869, 1743, 1181; **MS: HR-EI** calculated for $\text{C}_{11}\text{H}_{18}\text{O}_2$ m/z : 182.1307, found 182.1291.

Phenylcarbamate of 8c: ^1H NMR (300MHz, CDCl_3): δ 7.28-7.40 (m, 4H), 7.06 (t, $J=6.6\text{Hz}$, 1H), 6.68 (broad s, 1H), 5.53 (q, $J=6.6\text{Hz}$, 1H), 1.51 (d, $J=6.6\text{Hz}$, 3H), 1.23 (s, 9H); ^{13}C NMR (75MHz, CDCl_3): δ 152.66, 138.05, 129.20, 123.60, 118.88, 94.11, 77.31, 62.04, 31.04, 27.48, 22.49; **IR (film, cm^{-1})** 3320, 2970, 1703, 1600, 1542, 1226, 1051; **MS: HR-EI** calculated for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ m/z : 245.1416, found 245.1423.

Propionate of 9b: ^1H NMR (300MHz, CDCl_3): δ 5.37 (t, $J=5.1\text{Hz}$, 1H), 1.78-1.65 (m, 2H), 1.50-1.12 (m, 4H), 1.12 (t, $J=7.2\text{Hz}$, 3H), 0.87 (t, $J=6.0\text{Hz}$, 3H), 0.14 (s, 9H); ^{13}C NMR (75MHz, CDCl_3): δ 173.42, 103.23, 90.19, 90.19, 64.37, 34.97, 31.39, 27.81, 24.78, 22.60, 14.06, 9.20; **IR (film, cm^{-1})** 2958, 2863, 1745, 1250, 1176, 844; **MS: HR-EI** calculated for $\text{C}_{13}\text{H}_{24}\text{O}_2\text{Si}$ m/z : 254.1702, found 254.1699.

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Propionate of 4b

Propionate of 4c

Propionate of 4d

Propionate of 5

Propionate of 6

Propionate of 8a

Propionate of 8a

Propionate of 8b

Propionate of 8c

Propionate of 8c

Phenylcarbamate of 8c