Terminal Alkyne−Ethylene Cross-Metathesis: Reaction of 1-Substituted Propargyl Esters at Elevated Ethylene Pressure

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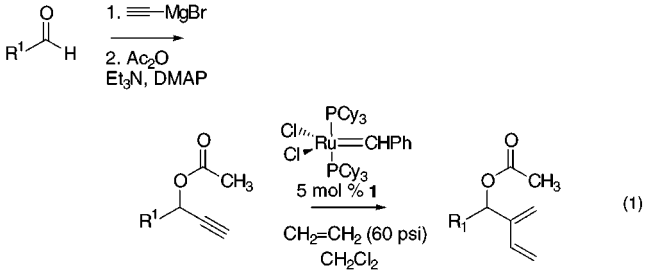
Substituted propargylic esters, resistant to complete ethylene cross-metathesis at ambient pressure, underwent cross-metathesis with ethylene at elevated pressure (4 atm) to give 2-substituted butadienes in good to excellent yields. Enantioenriched propargylic acetates, obtained through enzymatic kinetic resolution of secondary propargyl alcohols, similarly underwent ethylene metathesis with retention of stereochemistry at the chiral center.

In the context of synthetic studies directed toward the UCT4B[1] side chain, we required an enantioselective synthesis of enantiopure dienyl alcohols. Although there are several methods available to introduce the butadiene fragment, an enantioselective process that could be used with a variety of aldehydes was required. Existing methods for the direct introduction of the butadienyl fragment lack scope and further either lack enantioselection (homoallenyltrimethylsilane, $TiCl_4$;[2] homoallenyltributylstannane; and Lewis acid[3]) or require long reaction times at low temperature (diisopropylhomoallenylboronate, diethyl tartrate, −78 °C, 72 h).[4] The latter method was elegantly employed by Theodorakis in his synthesis of clerocidin.[5] For our studies, we required a practical multigram-scale reaction suitable for use with a variety of aromatic and aliphatic aldehydes. We report here an ethylene−alkyne metathesis (eq 1) that tolerates propargylic substitution and proves to be an efficient diene synthesis. The significance of higher ethylene pressure and the use of ethylene metathesis with enantiopure alkynes to prepare enantiomerically enriched 2-substituted butadienes are also reported.



(1)

Over the past few years, there has been tremendous application of metathesis to natural product synthesis and synthetic studies.[6] Notable attributes of the well-defined catalysts of Grubbs[7] and Schrock[8] include functional group tolerance, low catalyst loadings, alkene chemoselection, and commercial availability. These features have helped metathesis become a prominent synthetic method. Intramolecular examples of alkyne−alkene metathesis were documented by Katz and Sivavec[9] and the Grubbs group[10] to form carbocycles and fused carbobicyclic ring systems, respectively. It is significant to note that this catalytically efficient process is atom economical. Kinoshita, Mori, and co-workers developed the specific case of ethylene−alkyne metathesis,[11] which was used in natural product synthesis.[12] Blechert has explored the intermolecular reaction of terminal alkynes with excess α-olefins in an example of ene−yne cross-metathesis using the Grubbs benzylidene catalyst **1**.[13] In a recent publication, Mori has outlined the scope of ethylene−alkyne metathesis at 1 atm ethylene and provided one example of ethylene metathesis in an alkyl-substituted propargylic carbonate.[14] The dienes that result from ene−yne cross-metathesis (and a related Ru-catalyzed process[15]) are generally useful and have been employed in Diels−Alder reactions.[11,13,15]

Our preparation of racemic dienyl acetates is summarized in eq 1 (above). The diene fragment is introduced in three steps from aldehydes: addition of HC≡C−MgBr, protection of the alcohol, and ethylene−alkyne metathesis. The Grignard addition occurred in high yield (93% for PhCHO) and protection utilized standard conditions

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(13) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518.

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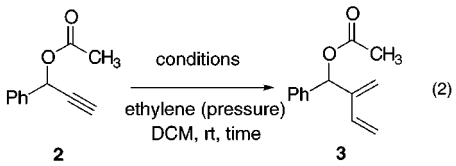
Table 1. Effect of Ethylene Pressure and Catalyst Loading



(2)

2 3

entry	conditions	isolated yield (%)
1	5 mol % **1** 1 atm (balloon), 29 h	38
2	5 mol % **1** 60 psi, 22 h	78
3	1 mol % **1** 60 psi, 22 h	44
4	1 mol % **1** 95 psi, 59 h	78

for acetylation (1.25 equiv of Ac_2O, 3 equiv of Et_3N, DMAP (cat.) in DCM, 99% for acetate **2**) to produce the metathesis substrates. Metathesis was conducted with Grubbs' catalyst **1** and ethylene pressure to provide the substituted dienes.

Higher ethylene pressures resulted in better chemical yields and shorter reaction times for complete conversion of alkynes. Initial studies were performed with αNpCH(OTBS)C≡CH using the standard literature conditions (1 atm of ethylene, 5 mol % of **1**). In this case, no conversion to the diene was apparent after 24 h. However, when ethylene pressure was increased to 60 psi, 12% conversion to diene occurred (GC analysis) after 16 h. With these contrasting data at different ethylene pressures, a less sterically bulky protecting group was sought for the substituted propargyl alcohol. Acyl groups were chosen for this purpose. Optimization studies were conducted with the acetyl group in the conversion of **2** to **3**, as summarized in eq 2 (Table 1). Metathesis conducted using literature conditions with 1 atm of ethylene at room temperature gave some conversion of **2** → **3** with a low chemical yield (entry 1). At 1 atm of ethylene, the conversion leveled off near 60% **3** after 40 h (analytical GLPC). Higher conversions were attained using slightly elevated ethylene pressure. In examples conducted at 50−60 psi, conversions were usually >95% (GC−MS) with isolated yields lower, possibly due to diene decomposition during isolation.[16] The effect of catalyst loading was also explored with **2** (entries 3 and 4). From the literature, typical catalyst loading is 5−10 mol %. It was found that low (1 mol %) loading gave inferior results after 22 h (entry 3); however, longer reaction time at 95 psi of ethylene produced an improved yield of **3** (44% to 78%), making 1 mol % loading feasible. This last result suggests that the catalyst is still viable after 22 h. It is speculated that higher ethylene pressure may also help avert catalyst decomposition pathways.[12a]

The rate of conversion of alkyne **2** to diene **3** at balloon ethylene pressure and at 60 psi of ethylene pressure illustrates the effect of higher pressure on conversion (Figure 1). Conversion to product was monitored over time (to 50 h) using a quantitative GLPC method. Each of the reactions was vigorously stirred in a 90 mL capacity vessel maintained at 15 °C using a thermostated

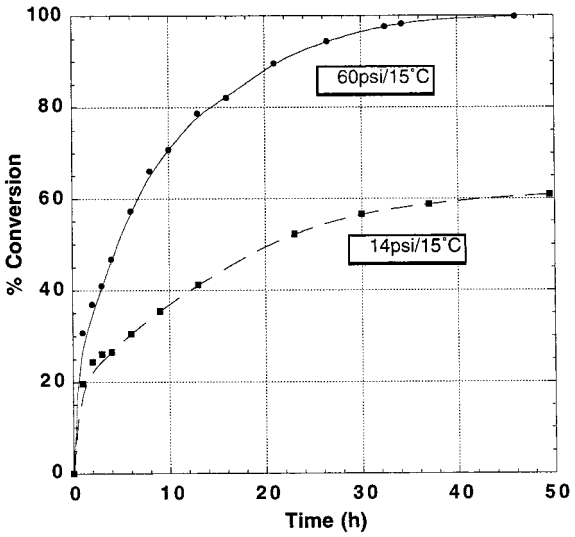


Figure 1. Conversion of **2** to **3** as a function of time.

circulating water bath. The initial concentration of alkyne was 0.2 M, similar to the reaction conditions presented in Table 2 below. Small variations in the rate were noted when aliquots were taken for analysis at frequent intervals. From these conversion data, it can be seen that balloon ethylene pressure is not sufficient to drive the metathesis to completion.[17] However, a modest increase in ethylene pressure can be used to overcome the rate and yield limitation, which may increase the alkyne substrate scope of the ethylene-alkyne metathesis.

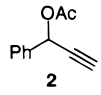
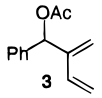
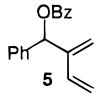
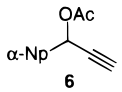
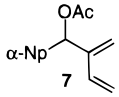
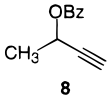
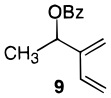
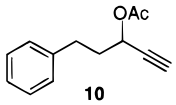
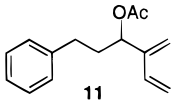
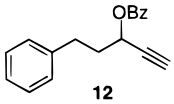
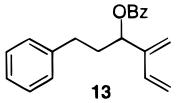
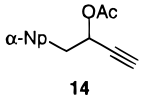
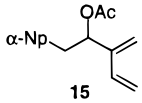
The higher solution concentration of ethylene at 60 psi can be used to explain the observed rate increase. The concentration of ethylene in CD_2Cl_2 was measured versus toluene concentration (internal standard) under balloon pressure and at 60 psi in a 5 mm NMR tube equipped with a Teflon valve. At balloon pressure, the ethylene concentration was found to be 32 mM. At 60 psi, the ethylene concentration was 690 mM, or ca. 20 times more concentrated than at atmospheric pressure. A similar difference in solution concentration of ethylene was found in $CDCl_3$.

The results of ethylene−alkyne metathesis with 1-acyloxy-1-substituted propynes are shown in Table 2. The reaction conditions of Table 2 employ 0.12 M alkyne in dichloromethane solvent and 5 mol % **1** held at 60 psi (4.1 atm) of ethylene in a pressure bottle for 22 h. Elevated temperatures were not explored due to the reported instability of active catalyst **16** (Scheme 1).[7] The reactions proved very clean, producing the diene and a trace of styrene as a byproduct. Dimers arising from the produced 1,3-dienes were not detected in the crude reactions as determined by GC−MS analysis. The products in Table 2 were isolated as colorless compounds after preparative layer or column chromatography, free of ruthenium catalyst byproducts. In contrast with literature examples,[11−13] substitution at the propargylic position was well-tolerated at elevated ethylene pressure. Entry 3 suggests that good yields are possible in hindered systems using the standard conditions of Table 2.

(16) For instance, storage of **11** at −20 °C for a period of 1 week resulted in discoloration and minor but detectable decomposition by ^{1}H NMR.

(17) The reaction conducted at 1 atm continued to convert to product **3** even after 50 h, but only reached 68% **3** after 95 h. The data taken after ca. 50 h are not considered reliable since evaporative loss of solvent became significant at 1 atm of pressure (balloon). Evaporative loss of solvent was not serious at higher pressures or shorter reaction times.

Table 2. Results of Ethylene−Alkyne Metathesis[a]

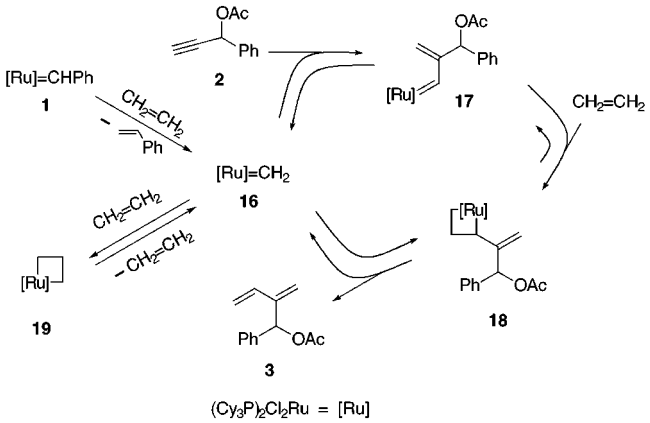
Entry	Substrate	Product	Isolated Yield
1	 **2**	 **3**	78%
2	 **4**	 **5**	80%
3	 **6**	 **7**	75%
4	 **8**	 **9**	92%
5	 **10**	 **11**	64%
6	 **12**	 **13**	57%
7	 **14**	 **15**	78%

[a] Conditions: 5 mol % **1**, ethylene (60 psi), DCM, rt, 22 h. The reaction conditions were optimized for the conversion of **2** to **3**.

The propargylic alcohol protecting group influenced the reaction. In the cases examined (Table 2), acyl protecting groups proved to be the best, with the acetate and benzoate giving similar results (cf. entries 1, 2 and entries 5, 6). Alkyl ethers were not investigated. With α-aryl substituents, the TBS protecting group was too bulky: αNpCH(OTBS)C≡CH was only 12% converted to the diene after 16 h at 60 psi of ethylene as determined by GC−MS analysis. The free alcohols αNpCH(OH)C≡CH and PhCH(OH)C≡CH underwent lower conversions and did not give synthetically useful yields under the normal conditions of Table 2.

Ethylene plays a dual role in ethylene−alkyne metathesis (Scheme 1). Ethylene is used to generate an active methylidene catalyst and is consumed stoichiometrically as a reactant. Exposure of the catalyst **1** to ethylene leads to the formation of the methylidene **16**.[7] In an intramolecular ene−yne metathesis that does not incorporate ethylene, Mori has suggested that 1 atm ethylene protects the catalyst **16** from a thermodynamic sink (e.g., **17**).[12a] In the present case, since **17** occurs in the catalytic cycle, it may be inferred that its conversion to ruthenacycle **18** is rate-limiting. Steric bulk at the propargylic position might further slow this step in the catalytic cycle. Higher ethylene pressure would be expected to have an accelerating effect due to increased concentration, as noted above. The equilibrium would

Scheme 1



likewise be shifted toward **18** due to mass action (**17** + excess $CH_2{=}CH_2 \rightarrow$ **18**). Even higher ethylene pressures (99.5% ethylene, 500 psi) did not further improve reaction rate or conversion (70% conversion after 14 h). It is conceivable that higher ethylene pressure results in an unproductive equilibrium ($CH_2{=}CH_2$ + **16** = **19**) that depletes the concentration of active catalyst **16** (Scheme 1). To achieve high conversions at reasonable (5 mol %) catalyst loadings, 50−60 psi of ethylene maintained in a pressure bottle proved sufficient and was experimentally convenient. For large-scale reactions, lower catalyst loading can be used in conjunction with longer reaction times, as noted in Table 1.

By coupling the present method with enantioselective synthesis, it is possible to obtain enantiomerically enriched dienyl acetates. The dienyl acetates were obtained by subjecting enantioenriched alkynyl acetates to ethylene metathesis (Scheme 2). Several chemical methods are available for preparing scalemic alkynols;[18] however, a simple kinetic resolution of readily available *rac*-**20** using cross-linked enzyme crystals (CLECs) of *Pseudomonas cepacia* (Altus) proved efficient and convenient. Alcohol **20** was resolved as shown in eq 3. From this reaction, the selectivity factor was calculated and the enantiomeric preference of the enzyme was verified by measuring the specific rotation of the products (*S*)-**20** and (*R*)-**2** (eq 3).[19] Higher enantiomeric excess of recovered alcohol *S*-**20** was obtained by running the resolution to higher conversion (see the Experimental Section). In a separate batch, (*S*)-**20** (>99% ee, 34% isolated yield from *rac*-**20**) was acetylated to give (*S*)-**2** (>99% ee, HPLC), which was subjected to ethylene metathesis at 60 psi to afford the diene (*S*)-**3** in 80% yield of >95% ee (eq 4). Due to minor (<1%, analytical GLPC) contamination by unreacted (*S*)-**2**, (*S*)-**3** was saponified and determined to have >95% ee by HPLC. The fact that the acetates **2** and **3** resist racemization by methylidene **16** attests to the mild Lewis acidic nature of the Grubbs-type catalysts.

In conclusion, it has been shown that α-substituted propargyl alcohol derivatives undergo efficient cross-

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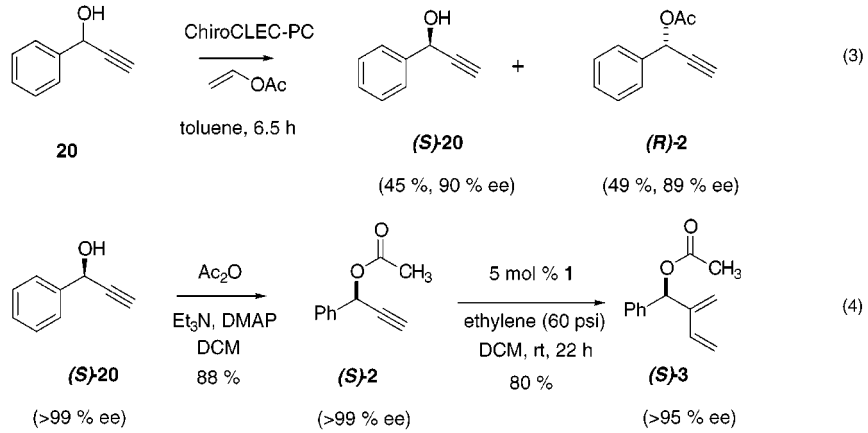
(19) Use of related lipases: (a) Viola, A.; Duddling, G. F.; Proverb, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 7390. (b) Kuenstler, T.; Schollmeyer, D.; Singer, H.; Steigerwald, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1645. (c) Glaenzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron* **1987**, *43*, 5791. (d) Waldinger, C.; Schneider, M.; Botta, M.; Corelli, F.; Summa, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1485. (e) Enantioselectivity model: Burgess, K. B.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.

Scheme 2



metathesis with ethylene at slightly elevated pressure to afford 2-substituted butadienes. Higher ethylene pressure proved crucial to obtain high conversions to diene products. Enantiomerically enriched alkynes undergo ethylene metathesis with retention of configuration at the propargylic/allylic center, making this method suitable for preparing enantiomerically enriched dienes. This method is currently being used to prepare the side chain of UCT4B.

Experimental Section

General Methods. Reactions were conducted under argon atmosphere unless otherwise noted. Dichloromethane (DCM) was distilled from CaH_2 immediately prior to use. Aldehydes were washed successively with Na_2CO_3, H_2O, and brine, dried ($MgSO_4$), and distilled. Ethynylmagnesium bromide (0.5 M in THF) was purchased from Aldrich. The Grubbs catalyst, bis-(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride, was purchased from Strem. Ethylene (CP grade, 99.5%, Matheson) was used from either a lecture bottle or a 13 kg capacity cylinder equipped with the appropriate regulator. ChiroCLEC PC (dry) was obtained from Altus Biologics. Reactions were conducted in oven-dried 90 mL capacity pressure tube equipped with a gas inlet, pressure gauge, and relief valve. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ at the indicated frequency. ^{1}H NMR spectra were referenced at 7.24 ppm on the residual $CHCl_3$ signal, and ^{13}C NMR were referenced at 77.0 ppm for $CDCl_3$. Optical rotations were measured using the sodium D line in a thermostated cell held at 23 °C. Enantiomeric excesses were determined by HPLC using conditions A (*R,R*-Whelk-O1 column, 2.5% IPA-hexanes, 1.0 mL/min, UV-254), conditions B (Chiracel OD column, 10% IPA-hex, 0.5 mL/min, UV-254), or by GC using a chiraldex-B capillary column (40−200 °C over 20 min, J & W Scientific, 0.25 mm × 30 m, 0.25 mm film thickness). Quantitative GLPC was obtained using a DB-wax capillary column (J & W Scientific, 0.25 mm × 30 m, 0.25 mm film thickness) calibrated with known standards.

General Procedure for Ethylene−Yne Metathesis: 2-(1-Acetoxy-1-phenylmethyl)-1,3-butadiene 3. Into an oven-dried pressure tube (90 mL capacity) equipped with magnetic stirbar was added 26 mg of bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (31.9 mmol, 5 mol %) under argon. A solution of 111 mg of 1-acetoxy-1-phenyl-2-propyne **2** (0.63 mmol) in 4.0 mL of DCM was added to the catalyst via syringe, and the vessel was pressurized to 60 psi of ethylene (CP grade, 99.5%) under rapid stirring. The pressure was released and the vessel subsequently flushed four times and then maintained at 60 psi of ethylene for 22 h. The pressure was released, and the solvent was removed in vacuo (rotary evaporator) to afford a dark brown oil that was purified by flash chromatography (4 in. column, elution with 1:10 ethyl acetate (EA)−hexane) to give **3** as a clear oil, 100 mg, 78% yield. Analytical TLC: R_f 0.44 (1:4 EA−hexanes).

2-(1-Acetoxy-1-(phenyl)methyl)-1,3-butadiene 3 (Entry 1). Obtained in 78% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.40−7.30 (m, 5H), 6.56 (s, 1H), 6.30 (dd, J = 17.7, 11.1 Hz, 1H), 5.35 (s, 1H), 5.34 (s, 1H), 5.23 (d, J = 17.7 Hz, 1H), 5.06 (d, J = 11.1 Hz, 1H) 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) d 169.8, 144.2, 138.3, 135.4, 128.4, 128.2, 127.6, 116.6, 115.7, 24.4, 21.1; High-resolution MS (EI$^+$) molecular ion calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0987, error 3.3 ppm; low-resolution FAB-MS 225.1 (M + Na).

2-(1-Benzoyloxy-1-(phenyl)methyl)-1,3-butadiene 5 (Entry 2). Obtained in 80% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.11−7.30 (m, 8H), 8.09 (m, 2H), 6.81 (s, 1H), 6.36 (dd, J = 17.7, 11.1 Hz, 1H), 5.43 (s, 1H), 5.39 (s, 1H), 5.31 (d, J = 17.7 Hz, 1H), 5.10 (d, J = 11.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.4, 144.3, 138.4, 135.4, 133.1, 130.1, 129.7, 128.5, 128.4, 128.2, 127.5, 116.9, 115.9, 75.1; high-resolution MS (EI$^+$) molecular ion calcd for $C_{18}H_{16}O_2$ 264.1150, found 264.1133, error 6.6 ppm; low-resolution FAB-MS (NBA/NaI) 287.4 (M + Na).

2-(1-Acetoxy-1-(α-naphthyl)methyl)-1,3-butadiene 7 (Entry 3). Obtained in 75% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.04 (d, J = 7.8 Hz, 1H), 7.91−7.83 (m, 2H), 7.60−7.38 (m, 4H), 6.44 (dd, J = 18.0, 11.4 Hz, 1H), 5.44 (br s, 1H), 5.25 (br s, 1H), 5.19 (d, J = 18.0 Hz, 1H), 5.09 (d, J = 11.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.05, 144.14, 135.94, 133.84, 133.67, 131.14, 129.15, 128.84, 126.59, 125.79, 125.58, 125.22, 123.22, 117.90, 114.44, 70.58, 21.06; high-resolution MS (EI$^+$) molecular ion calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1170, error 8 ppm; low-resolution FAB-MS (NBA/NaI) 275.4 (M + Na), 193.3 (M − 59).

2-(1-Benzoyloxy-1-methyl)-1,3-butadiene 9 (Entry 4). Obtained in 92% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.08 (br d, J = 6.9 Hz, 1H), 7.56 (m, 2H), 7.44 (m, 2H), 6.38 (dd, J = 18.0, 11.1 Hz, 1H), 5.86 (q, J = 6.6 Hz, 1H), 5.41 (d, J = 18.0 Hz, 1H), 5.34 (br s, 1H), 5.20 (br s, 1H), 5.17 (d, J = 11.1 Hz, 1H), 1.58 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.68, 146.49, 135.73, 132.9, 130.48, 129.59, 128.34, 114.87, 114.74, 70.0, 20.29; high-resolution MS (EI$^+$) molecular ion calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0984, error 5 ppm.

2-(1-Acetoxy-3-(phenyl)propyl)-1,3-butadiene 11 (Entry 5). Obtained in 64% yield after 22 h at 60 psi of ethylene. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.27 (m, 2H), 7.17 (m, 3H), 6.30 (dd, J = 18.0, 11.5 Hz, 1H), 5.50 (t, J = 6.5 Hz, 1H), 5.25 (d, J = 17.5 Hz, 1H), 5.19 (br s, 1H), 5.17 (br s, 1H), 5.09 (d, J = 11.0 Hz, 1H), 2.65 (m, 2H), 2.06 (s, 3H), 2.03 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) d 170.1, 145.1, 135.5, 128.4, 128.3, 125.9, 115.2, 114.7, 72.6, 35.6,31.8, 21.0; low-resolution FAB-MS (NBA/NaI) molecular ion calcd for $C_{15}H_{18}O_2Na$ 253.3, found 253.3 (M + Na).

2-(1-Benzoyloxy-3-(phenyl)propyl)-1,3-butadiene 13 (Entry 6). Obtained in 57% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.07 (br d, J = 7.5 Hz, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 7.26 (m, 2H), 7.18 (m, 3H), 6.36

(dd, J = 17.5, 11.0 Hz, 1H), 5.76 (dd, J = 7.0, 5.5 Hz, 1H), 5.33 (d, J = 18.0 Hz, 1H), 5.28 (br s, 1H), 5.20 (br s, 1H), 5.13 (d, J = 11.5 Hz, 1H), 2.75 (m, 2H), 2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 165.6, 145.1, 141.2, 135.5, 132.9, 130.3, 129.5, 128.4, 128.3, 125.9, 115.4, 114.8, 73.3, 35.8, 31.8; low-resolution FAB-MS (NBA/NaI) calcd for $C_{20}H_{20}O_2Na$ 315.1, found 315.1 (M + Na).

2-(1-Acetoxy-2-(α-naphthyl)ethyl)-1,3-butadiene 15 (Entry 10). Obtained in 78% yield after 22 h at 60 psi of ethylene: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.14 (br d, J = 9.0 Hz, 1H). 7.84 (br d, J = 8.0 Hz, 1H), 7.73 (br d, J = 8.0 Hz,1H), 7.53 (m, 1H), 7.47 (m, 1H), 7.37 (m, 1H), 7.31 (br d, J = 6.5 Hz, 1H), 6.36 (dd, J = 18.0, 11.0 Hz, 1H), 5.83 (dd, J = 8.0, 6.0 Hz, 1H), 5.44 (d, J = 18.0 Hz, 1H), 5.17 (br s, 1H), 5.15 (d, J = 11.0 Hz,1H), 5.13 (br s, 1H), 3.50 (AB q, J_{AB} = 14.0 Hz, J_{AX} = 8.3 Hz, 1H), 3.44 (AB q, J_{AB} = 14.0 Hz, J_{BX} = 5.9 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.0, 145.1, 135.5, 133.7, 133.5, 132.2, 128.7, 127.6, 127.4, 125.9, 125.5, 125.2, 123.8, 116.1, 115.1, 73.7, 37.5, 21.0; high-resolution MS (EI$^+$) molecular ion calcd for $C_{18}H_{18}O_2$ 266.1307, found 266.1281, error 3.2 ppm; low-resolution FAB-MS (NBA/NaI) 289.4 (M + Na), 207.3 (M − 59).

Determination of Absolute Configuration in Enzymatic Resolution of Alkynol 20. Into a 50 mL round-bottom flask equipped with a magnetic stirbar was placed 0.823 g of *rac*-**20** (6.23 mmol, 1.0 equiv) and 0.86 mL of vinyl acetate (9.35 mmoL, 1.5 equiv) in 20 mL of toluene containing 10 μL of H_2O. To the rapidly stirred solution was added 10 mg of ChiroCLEC PC (dry), and the reaction was monitored by HPLC (UV-254, *R,R*-Whelk-O 1 column, 6% IPA-hexanes, 1.0 mL/min), which showed about 49% conversion (uncorrected for molar extinction coefficient) after 6.5 h. The reaction was then filtered through a plug of glass wool, evaporated in vacuo (rotovap), and chromatographed on silica gel (6 in. column, gradient elution with hexane to 1:3 EA−hexane) to give 534 mg of (*R*)-**2** (3.07 mmol, 49% yield, 89.8% ee (HPLC), $[\alpha]_{589}$ = +4 (c = 3.05, $CHCl_3$)) and 368 mg of (*S*)-**20** (2.79 mmol, 45% yield, 90% ee (HPLC), $[\alpha]_{589}$ = +22 (c = 3.3, $CHCl_3$)). The enantioselectivity factor E = 58 based on 50% conversion.

Large-Scale Enzymatic Resolution of Alkynol 20. Into a 200 mL round-bottom flask equipped with magnetic stirbar was placed 5.5 g of *rac*-**20** (41.6 mmol, 1.0 equiv) and 5.75 mL of vinyl acetate (5.37 g, 62.5 mmol, 1.5 equiv) in 100 mL of toluene containing 30 μL of H_2O. To the rapidly stirred solution was added 30 mg of ChiroCLEC PC (dry), and the reaction was monitored by GLPC (Chiraldex-B), which showed about 60% conversion (uncorrected for response factor) after 25 h. The reaction was then filtered through a plug of glass wool, evaporated in vacuo (rotovap), and chromatographed on silica gel (12 in. column, gradient elution with hexane to 1:3 EA−hexane) to give 3.5 g of (*R*)-**2** [20.1 mmol, 48% yield, 83% ee (GC, chiraldex B), R_f 0.42 (1:4 ether−petroleum ether)] and 2.2 g of (*S*)-**20** [16.6 mmol, 40% yield, 97% ee (GC, Chiraldex-B), R_f 0.15 (1:4 ether−petroleum ether)].

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Supporting Information Available: Proton NMR for dienes **3**, **5**, **7**, **9**, **11**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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