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Efficient asymmetric synthesis of 1-alk-2-yne-1,4-diols

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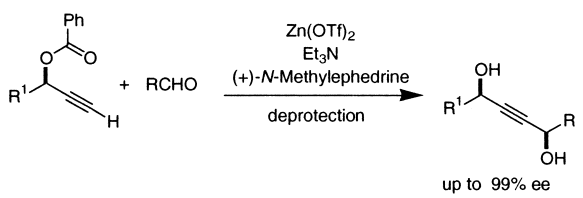
Abstract—We describe an expeditious process that provides ready access to symmetrical and unsymmetrical optically active bispropargylic 1,4-diols. The method employs the use of a recent method we have developed involving terminal acetylenes, $Zn(OTf)_2$, amine base, and *N*-methyl ephedrine. The 1,4-diol products should serve as useful building blocks for asymmetric synthesis.

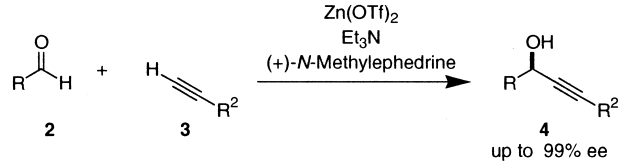
Access to versatile, optically active compounds that can be readily elaborated to value-added materials is one of the important objectives of research in asymmetric synthesis.[1] In this regard, optically active alcohols perform admirably as useful building blocks, not only because optically active alcohols are ubiquitous structural features in natural products and pharmaceuticals, but also as numerous methods are available for the interconversion of carbinols into other important functionality. There have been reports of methods aimed specifically at the preparation of 1,4-diols.[2] In some cases their generality and practicality have not been established. We have recently reported a convenient method for the preparation of propargylic alcohols.[3] The process involves in situ C-H activation of terminal acetylenes under mild conditions (Zn(II), amine base) to give a metal acetylide that participates in C=O and C=N addition reactions.[4–6] In the presence of an optically active amino alcohol such as *N*-methylephedrine, adducts are obtained in high selectivities and yields. More recently, we have documented modification of the process that permits the reaction to be carried out with substoichiometric quantities of Zn(II), amine base, and amino alcohol ligand. The fact that alkynes such as trimethylsilyl acetylene and 2-methyl-3-butyn-2-ol participate in the addition reaction leads to the question of whether a sequential acetylide addition process could provide access to optically active 1,4-diols. Herein, we describe the use of protected 1-butyn-3-ols in additions to aldehydes that afford optically active 1,4-diols (Scheme 1). As demonstrated herein, the method permits access to not only symmetrical but also non-symmetrical 1,4-diols.



Scheme 1.

We have previously documented an extensive series of aldehydes and terminal acetylenes that can be effectively coupled to give rise to propargylic alcohols in high selectivities (Scheme 2). We became interested in assaying whether the corresponding 1-propynyl-3-ol adducts would participate in equally selective additions. Additionally, in the context of these addition reactions of such substrates, an interesting question regarding the potential operation of the Horeau effect arises; if present, such a phenomena would provide additional benefits in leading to the isolation of chiral 1,4-diols of higher optical purity than would otherwise be expected from the stereoselectivity of the addition reaction.

The starting propargylic alcohols for the study were prepared as previously described.[3] We chose two key acetylenes with which to establish the feasibility of the process. For both cases, **5** and **9**, the optical purity of the starting materials was assayed at 96% ee by HPLC (Chiracel OD). Treatment of 1 equiv. of **5** with 1.1 equiv. cyclohexylcarboxaldehyde **6**, 1.1 equiv. $Zn(OTf)_2$, 1.2 equiv.



Scheme 2.

Keywords: 1,4-diols; asymmetric synthesis; optically active compounds.
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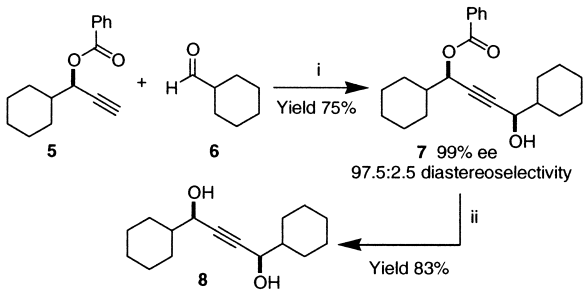
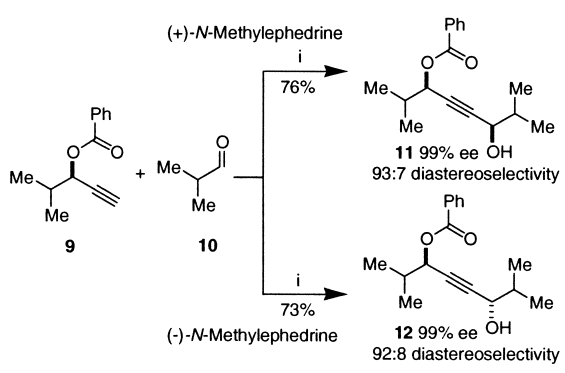


Scheme 3. (i) Alkyne (1 equiv.), $C_6H_{11}CHO$ (1.1 equiv.), $Zn(OTf)_2$ (1.1 equiv.), Et_3N (1.2 equiv.), (+)-*N*-methylephedrine (1.2 equiv.), toluene, 60°C, 5 h. (ii) KOH (1.5 equiv.), Et_2O, 23°C, 12 h.

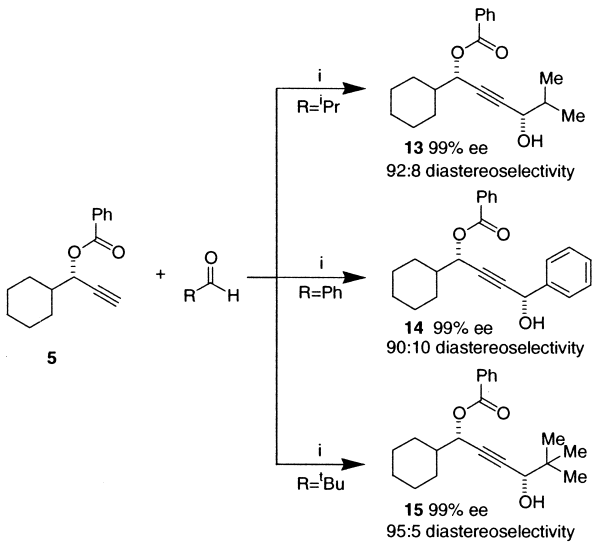
Et_3N, and 1.2 equiv. (+)-*N*-methylephedrine in toluene at 60°C afforded adduct **7** after 5 h. The extent of induction was analysed by HPLC chromatography employing a Chiralcel OD column. The adduct thus isolated in 75% yield displayed 97.5:2.5 diastereoselectivity and 99% ee. Although the addition reaction of acetylenes and aldehydes at 23°C have been documented to proceed in 99% ee, in our hands this level of induction is unprecedented at the elevated temperatures (60°C) reported herein. The observation of product formation in higher optical purity than that of the starting material employed (96% ee) is consistent with the operation of the Horeau effect. Adduct **7** could subsequently undergo deprotection (KOH, Et_2O, 23°C, 12 h) to furnish **8** in 83% yield (Scheme 3). A second useful example is illustrated with the reaction of isobutyraldehyde with **9**. Addition of **9** and isobutyraldehyde **10** affords adduct **11** in 76% yield, possessing 99% ee and 93:7 diastereoselectivity, as determined by HPLC analysis (Scheme 4). It is interesting to note that the extent of matching/mismatching between chiral acetylene and amino alcohol ligand employed is relatively miniscule. In this respect, when the addition reaction was carried out with enantiomeric *N*-methyl ephedrine, slightly lower selectivities are observed (93:7 for **11** vs 92:8 for **12**).

The addition reactions of 1-butynyl-3-ols are not limited to the preparation of C_2-symmetric 1,4-diols. Indeed, addition of *ent*-**5** to isobutyraldehyde, benzaldehyde, and pivaldehyde afford **13**–**15** in useful selectivities (Scheme 5).

We have described a simple procedure for the preparation of alk-2-yne-1,4-diols that is convenient and operationally simple. The 1,4-diols that are isolated can serve as useful



Scheme 4. (i) Alkyne (1 equiv.), Me_2CHCHO (1.1 equiv.), $Zn(OTf)_2$ (1.1 equiv.), Et_3N (1.2 equiv.), toluene, 60°C, 5 h.



Scheme 5. (i) Alkyne (1 equiv.), $C_6H_{11}CHO$ (1.1 equiv.), $Zn(OTf)_2$ (1.1 equiv.), Et_3N (1.2 equiv.), (−)-*N*-methylephedrine (1.2 equiv.), toluene, 60°C, 3–6 h.

building blocks for the synthesis of value-added materials. Additional studies are in progress and results will be reported as they become available.

1. Experimental

1.1. General

All reactions were performed using oven dried glassware under an atmosphere of dry nitrogen. Toluene was distilled and dried before use. Reagents were purchased from Fluka or Aldrich chemical companies, and used without further purification except aldehydes which were distilled before use. Chromatographic purification of products was accomplished using forced flow chromatography on silica gel 60. NMR spectra were recorded on a Varian Mercury 300 operating at 300 and 75.5 MHz for ^1H and ^{13}C, respectively, and referenced to the internal solvent signals. IR spectra were recorded on a Perkin–Elmer Spectrum RX I FT-IR spectrometer as thin film unless otherwise noted. Optical rotations were measured on a JASCO DID-1000 digital polarimeter. Thin layer chromatography was performed using silica gel 60 F254 TLC plates and visualized either with ultraviolet light or stain with CAM-Stain. HPLC analysis were carried out on a Merck Hitachi D-7000 system. Combustion analysis were performed by the Mikroelementaranalytisches Laboratorium at the ETH, Zürich. Mass spectras were carried out by the Laboratorium für Massenspecktroskopie der ETH, Zürich.

1.2. Preparation of compounds 7 and 11–14: general procedure

A 50 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.1 mmol, 1.1 equiv.) and heated under vacuum using a heat gun for 5 min (+) or (−)-*N*-methyl ephedrine (216 mg, 1.2 mmol, 1.2 equiv.) was added and the flask was purged with nitrogen for 15 min. Toluene (3 mL) and triethylamine (0.17 mL, 1.2 mmol, 1.2 equiv.) were added. The resulting

mixture was vigorously stirred at 23°C for 2 h before the corresponding alkyne (1 equiv.) was added. After 15 min of stirring the aldehyde (1.1 equiv.) was added in one portion by syringe. The reaction was stirred and heated at 60°C for 5 h. The mixture was quenched with NH_4Cl(aq) and extracted with Et_2O or AcOEt (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using pentane/Et_2O (5:1 to 3:1).

1.2.1. (1*R*,4*R*)-Benzoic acid 4-hydroxy-1-isopropyl-5-methyl-2-hexynyl ester (11). Isolated in 76% yield and 99% ee and 86% de as determined by HPLC analysis (Chiracel OD, hexane/^{i}PrOH (99:1), 254 nm), t_r 17.6 (major), 22.6 (minor); colourless oil. $[\alpha]_D^{26}=+14.8°$ (c=0.56, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.4 (m, 3H), 5.5 (dd, J=5.6 and 1.6 Hz, 1H), 4.25–4.2 (m, 1H), 2.2 (d, J=5.3 Hz, 1H), 2.2–2.1 (m, 1H), 1.95–1.8 (m, 1H), 1.1 (dd, J=8.1 and 6.8 Hz, 6H), 1.0 (dd, J=6.6 and 5.9 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.6, 133.1, 130.0, 129.7, 128.4, 86.1, 81.7, 69.6, 67.8, 34.4, 32.6, 18.3, 18.2, 17.7, 17.4. FTIR (thin film) 3463, 3064, 2965, 2931, 2874, 1723, 1602, 1584, 1469, 1452, 1388, 1369, 1337, 1315, 1266, 1177, 1157, 1111, 1098, 1070, 1026, 977 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42%; H, 8.08%; found: C, 74.59%; H, 7.97%. MS (EI, 70 eV): m/z (%): 274 (M^+, 1), 122 (24), 109 (27), 105 (100), 77 (29).

1.2.2. (1*R*,4*S*)-Benzoic acid 4-hydroxy-1-isopropyl-5-methyl-2-hexynyl ester (12). Isolated in 73% yield and 99% ee and 84% de as determined by HPLC analysis (Chiracel OD, hexane/^{i}PrOH (99:1), 254 nm), t_r 17.9 (minor), 22.4 (major); colourless oil. $[\alpha]_D^{26}=+26.7°$ (c=0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.4 (m, 3H), 5.5 (dd, J=5.6 and 1.6 Hz, 1H), 4.25–4.2 (m, 1H), 2.2 (d, J=5.3 Hz, 1H), 2.2–2.1 (m, 1H), 1.95–1.8 (m, 1H), 1.1 (dd, J=9.0 and 6.8 Hz, 6H), 1.0 (dd, J=6.5 and 6.2 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.6, 133.1, 130.0, 129.7, 128.4, 86.0, 81.6, 69.6, 67.8, 34.4, 32.6, 18.3, 18.1, 17.8, 17.4.

1.2.3. (1*R*,4*R*)-Benzoic acid 4-hydroxy-1,4-dicyclohexyl-2-butynyl ester (7). Isolated in 75% yield and 99% ee and 90% de as determined by HPLC analysis (Chiracel OD, hexane/^{i}PrOH (99:1), 254 nm), t_r 22.9 (major), 28.9 (minor), 30.4 (minor); colourless oil. $[\alpha]_D^{27}=+16.6°$ (c=0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.4 (m, 3H), 5.5 (dd, J=5.9 and 1.5 Hz, 1H), 4.2 (dd, J=5.9 and 1.5 Hz, 1H), 2.0–1.5 (m, 13H), 1.4–1.05 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 133.1, 130.1, 129.8, 128.4, 86.5, 82.0, 68.9, 67.1, 44.0, 42.0, 28.7, 28.6, 28.3, 28.0, 26.4, 26.3, 25.9, 25.85, 25.8, 25.7. FTIR (thin film) 3470, 3064, 2927, 2853, 1723, 1602, 1585, 1451, 1376, 1344, 1316, 1265, 1178, 1108, 1069, 1026, 972 cm^{-1}. Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93%; H, 8.53%; found: C, 77.68%; H, 8.56%. MS (EI, 70 eV): m/z (%): 354 (M^+, 1), 214 (13), 150 (12), 149 (16), 122 (54), 105 (100), 91 (22), 83 (28), 81 (21), 79 (19), 77 (47), 55 (31).

1.2.4. (1*S*,4*S*)-Benzoic acid 1-cyclohexyl-4-hydroxy-4-isopropyl-2-butynyl ester (13). Isolated in 72% yield and 99% ee and 84% de as determined by HPLC analysis (Chiracel OD, hexane/^{i}PrOH (99:1), 254 nm), t_r 19.9 (major), 22.1 (minor); colourless oil. $[\alpha]_D^{26}=-6.9°$ (c=0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.4 (m, 3H), 5.5 (dd, J=5.6 and 1.6 Hz, 1H), 4.2 (dd, J=5.6 and 1.6 Hz, 1H), 2.2 (s broad, 1H, OH), 2.0–1.6 (m, 13H), 1.3–1.1 (m, 10H), 1.0–0.95 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 133.1, 130.1, 129.8, 128.4, 86.2, 81.9, 68.9, 67.8, 42.0, 34.4, 28.6, 28.3, 26.3, 25.8, 25.7, 18.2, 17.5. FTIR (thin film) 3468, 2930, 2855, 1723, 1602, 1584, 1451, 1378, 1345, 1316, 1266, 1177, 1155, 1109, 1069, 1026, 972 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40%; H, 8.33%; found: C, 76.57%; H, 8.43%. MS (EI, 70 eV): m/z (%): 314 (M^+, 1), 149 (19), 122 (22), 105 (100), 77 (24).

1.2.5. (1*S*,4*S*)-Benzoic acid 1-cyclohexyl-4-hydroxy-4-phenyl-2-butynyl ester (14). Isolated in 41% yield and 99% ee and 80% de as determined by ^{19}F NMR of the corresponding Mosher ester; colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.25 (m, 8H), 5.6–5.5 (m, 2H), 2.6–2.5 (m, 1H), 2.0–1.6 (m, 7H), 1.4–1.1 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 140.3, 133.2, 130.0, 129.8, 128.6, 128.4, 128.35, 126.7, 85.9, 83.3, 68.9, 64.6, 42.0, 28.6, 28.4, 26.2, 25.8, 25.7. FTIR (thin film) 3437, 3064, 3033, 2930, 2855, 1722, 1602, 1584, 1493, 1451, 1377, 1343, 1316, 1264, 1177, 1108, 1069, 1026, 971 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28%; H, 6.94%; found: C, 79.01%; H, 6.96%. MS (EI, 70 eV): m/z (%): 346 (M^+-2, 1), 128 (22), 122 (42), 106 (24), 105 (100), 77 (37).

1.2.6. (1*S*,4*S*)-Benzoic acid 4-*tert*-butyl-1-cyclohexyl-4-hydroxy-2-butynyl ester (15). Isolated in 77% yield and 99% ee and 90% de as determined by HPLC analysis (Chiracel OD, hexane/^{i}PrOH (99:1), 254 nm), t_r 15.7 (major), 17.0 (minor), 18.3 (minor); colourless oil. $[\alpha]_D^{25}=-21.0°$ (c=0.86, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1–8.0 (m, 2H), 7.6–7.4 (m, 3H), 5.5 (dd, J=5.9 and 1.5 Hz, 1H), 4.05–4.0 (m, 1H), 2.6–2.5 (m, 1H), 2.1–1.6 (m, 7H), 1.4–1.1 (m, 5H), 1.0 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.6, 133.1, 130.1, 129.8, 128.4, 86.2, 82.0, 71.2, 69.0, 42.0, 35.9, 28.7, 28.3, 26.3, 25.8, 25.7, 25.4. FTIR (thin film) 3481, 3064, 2931, 2856, 1722, 1602, 1585, 1479, 1452, 1364, 1316, 1267, 1177, 1109, 1069, 1026, 1009, 972 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79%; H, 8.59%; found: C, 76.85%; H, 8.58%. MS (EI, 70 eV): m/z (%): 328 (M^+, 1), 188 (13), 150 (38), 149 (27), 122 (34), 105 (100), 77 (30).

1.3. Preparation of 8

To a solution of the corresponding benzoate **7** (1 equiv.) in Et_2O was added finely powdered KOH (1.5 equiv.) and the mixture was stirred at room temperature until consumption of the starting material (usually overnight). The mixture was quenched with NH_4Cl(aq) and extracted with Et_2O or AcOEt (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purfied by column chromatography on silica gel using pentane/Et_2O (3:1 to 1:1).

1.3.1. (*R*,*R*)-1,4-Dicyclohexyl-2-butyn-1,4-diol (8). Isolated

in 83% yield as a white solid, mp 126–128°C. $[\alpha]_D^{26}=-5.6°$ (c=0.84, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD) δ 4.9 (s, 2H), 4.1 (d, J=5.9 Hz, 2H), 1.95–1.6 (m, 10H), 1.55–1.45 (m, 2H), 1.35–1.0 (m, 10H). ^{13}C NMR (75.5 MHz, CD_3OD) δ 86.3, 67.8, 45.8, 30.0, 29.4, 27.7, 27.2, 27.1. FTIR (KBr) 3350, 2929, 2904, 2848, 1454, 1373, 1351, 1320, 1232, 1189, 1139, 1024, 891 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75%; H, 10.47%; found: C, 76.55%; H, 10.43%. MS (EI, 70 eV): m/z (%): 249 (M^+-1, 1), 94 (23), 91 (21), 83 (98), 81 (30), 79 (24), 70 (24), 68 (37), 67 (20), 55 (100), 41 (38).

Acknowledgements

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