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Catalytic reductive carbon–carbon bond-forming reactions of alkynes

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Abstract—Enantioselective nickel/phosphine-catalyzed reductive coupling of alkynes and aldehydes provides rapid access to synthetically useful allylic alcohols with high enantiomeric excess. A related reaction involving epoxides is enantiospecific, transforming alkynes and chiral terminal epoxides into enantiomerically pure homoallylic alcohols containing a trisubstituted olefin of defined geometry. A gram-scale example of each of these processes is described.

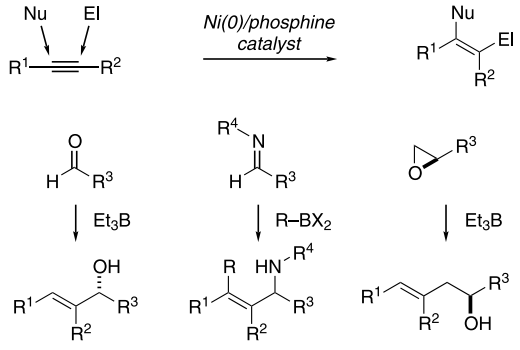
1. Introduction

Since Noyori and Nozaki first demonstrated that enantioselective carbon–carbon bond formation could be catalyzed by synthetic, low molecular weight, metal–ligand complexes,[1] the development of catalytic, highly enantioselective transformations of many types has been an active area of research. In contrast to other classes of catalytic reactions, such as enantioselective hydrogenation, epoxidation, and olefin isomerization, few catalytic asymmetric C–C bond forming processes have been implemented on an industrial scale.[2] Accordingly, new catalytic carbon–carbon bond-forming reactions that unite simple starting materials, provide useful chiral compounds, and are amenable to implementation on a large scale may be of significant practical impact.

As part of our program on catalytic multi-component coupling processes, we have developed several reactions in which an alkyne undergoes nickel-catalyzed *cis* addition of two groups that function as nucleophile and electrophile equivalents (Nu and El, Scheme 1).[3–5] These reactions have their origins in catalytic alkyne–alkyne oligomerizations first described by Reppe,[6] and in contrast to these pioneering investigations, a theme currently under investigation in several laboratories is the catalytic coupling of two different functional groups.[7] Our focus has been the use of an organoboron reagent (RBX_2) as the source of the Nu (H or R from RBX_2), and the Els that undergo coupling to date are aldehydes,[3] imines,[4] and epoxides,[5] affording chiral allylic alcohols, allylic amines, and homoallylic alcohols, respectively. Examples of aldehyde and epoxide variants that provide enantiomerically pure products on the gram scale are illustrated below.[8]

2. Enantioselective, catalytic reductive coupling of alkynes and aldehydes

Our interest in this area of catalytic multi-component reactions[9] was prompted by a structural motif found in many natural products possessing significant biological effects—chiral, (*E*)-trisubstituted allylic alcohols (Fig. 1).[10–13] Our aim was to develop a method that would allow for synthesis of this useful functional group pattern[14] from alkynes and aldehydes by way of catalytic, enantioselective and regioselective reductive cou-



Scheme 1.

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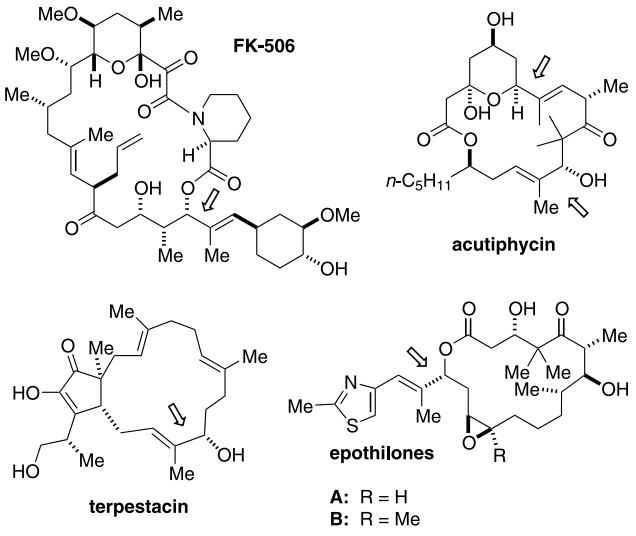


Figure 1. Natural products that contain (*E*)-trisubstituted allylic alcohols.

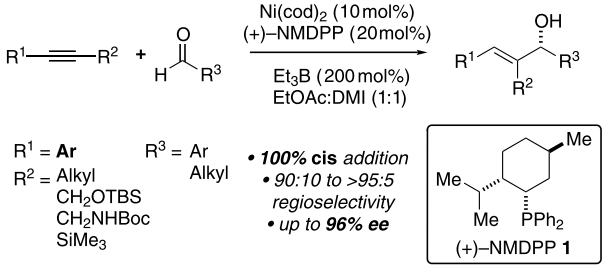
pling of alkynes and aldehydes. Development of catalytic, diastereoselective methods (i.e. for chiral alkynes and/or chiral aldehydes) were also high priorities, as they would be useful fragment coupling operations in target-oriented synthesis.

Nickel-catalyzed coupling of alkynes and aldehydes was first reported by Tsuda and Saegusa,[15] who proposed that formation of the conjugated enone products occurred by way of hydroacylation. Later, Montgomery reported a nickel-catalyzed, intramolecular alkyne/aldehyde coupling method that also effected an overall reduction, affording racemic allylic alcohols.[16,17] In the absence of a phosphine additive, transfer of an alkyl substituent from the organozinc reagent occurred, giving overall alkylative coupling. By analogy to related early transition metal complexes first studied by Buchwald,[18] Montgomery proposed an oxametallacyclopentene intermediate in the catalytic cycle.[19]

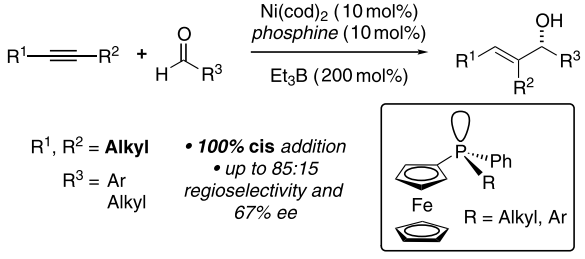
However, intermolecular reductive coupling was not possible with Montgomery's method, nor was any catalyst-controlled, enantioselective variant of this transformation available at that time. We found that use of a catalyst derived from $Ni(cod)_2$ and Bu_3P, in conjunction with Et_3B as the stoichiometric reductant, provided a solution to the first part of this problem, the first catalytic process for intermolecular alkyne/aldehyde reductive coupling.[3a,20] Exclusive *cis* addition to the alkyne was observed in every case, and alkynes of the general form aryl–C≡C–alkyl, R–C≡C–H, and R–C≡C–$SiMe_3$ displayed very high regioselectivity, favoring C–C bond formation adjacent to the alkyl, hydrogen, or trimethylsilyl substituent, respectively.

More recently, we described two catalytic asymmetric variants of this process differing in two respects that appear to be linked, the natures of the alkyne and the chiral phosphine ligand. Internal acetylenes having one aromatic substituent are coupled most effectively using (neomenthyl)diphenylphosphine (NMDPP, **1**, Scheme 2)[3c] while dialkylacetylenes undergo asymmetric reductive coupling most efficiently when *P*-stereogenic ferrocenylphosphines are used (Scheme 3).[3b] First prepared from menthol by Morrison in 1971[21] and commercially available as its dextrorotatory antipode,[22] NMDPP had been of only limited utility in asymmetric catalysis.[23] Nevertheless, catalysts derived from this chiral monophosphine[24] generally afford allylic alcohols derived from aryl–C≡C–alkyl alkynes and branched aldehydes in greater than 90% ee in reductive coupling reactions.

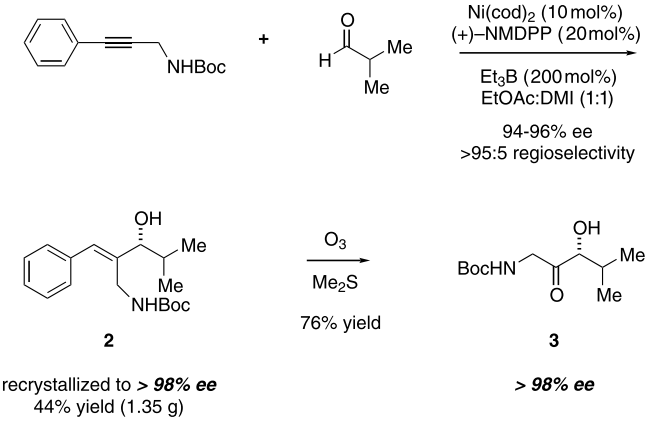
Highly enantioselective catalytic alkyne/aldehyde reductive coupling can be performed on a gram scale. Illustrated by the particular case shown in Scheme 4 is the tolerance of propargyl substitution on the alkyne and of protected nitrogen functional groups. Allylic alcohol **2** is isolated in 52–60% yield in 94–96% ee, and can be recrystallized to >98% ee in 44% overall yield (1.35 g). Previously we have shown that enantiomeric purity is



Scheme 2.



Scheme 3.



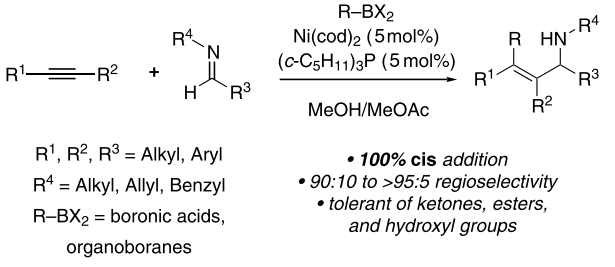
Scheme 4.

conserved upon ozonolysis of **2**,[3c] affording an (aminomethyl)hydroxyketone **3** whose α-amino-α′-hydroxy pattern is found in molecules targeted against trypanosomes, parasites that cause African sleeping sickness upon transmission from tsetse flies,[25] and in aerothionin natural products with anti-tuberculosis activity.[26] Common methods of α-hydroxy ketone synthesis via asymmetric catalysis involve dihydroxylation or epoxidation of ketone enolate derivatives.[27] The reductive coupling/ozonolysis approach obviates a regioselective ketone enolization that would be required (and difficult) for cases represented by **3** and is therefore complementary.[28]

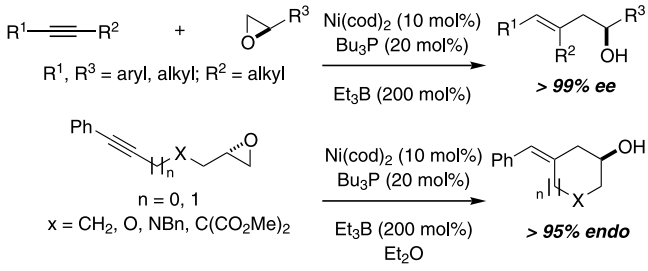
3. Nickel-catalyzed reductive coupling of alkynes and epoxides

In all of the nickel-catalyzed multi-component coupling transformations reported prior to 2003, a carbon–carbon bond was formed between two π-electron systems, one of which contained a carbonyl group (e.g. alkyne/aldehyde,[3,16,20] alkyne/conjugated enone,[7b] 1,3-diene/aldehyde[29]). Earlier this year we reported the first examples involving a nitrogen-based electrophile (imine), which also was the first utilization of boronic acids in this family of reactions (Scheme 5).[4]

More recently, we described the first member of this family that deviated from the π–π-coupling requirement (Scheme 6), wherein the π-system of one molecule (alkyne) combines with a functional group that has no multiple bonds (epoxide).[5] Affording synthetically useful, enantiomerically pure homoallylic alcohols, this process is effective for both cyclizations and intermolecular couplings. Very high regioselectivity is observed in nearly every example in both variants, and intramolecular cases proceed with complete *endo* selectivity, which is generally disfavored in intramolecular epoxide-opening reactions in the absence of a significant electronic bias.[30–32] This process may involve a nickella(II)oxetane intermediate, and thus appears to be mechanistically distinct from the other nickel-catalyzed multi-component coupling reactions that we and others have reported.

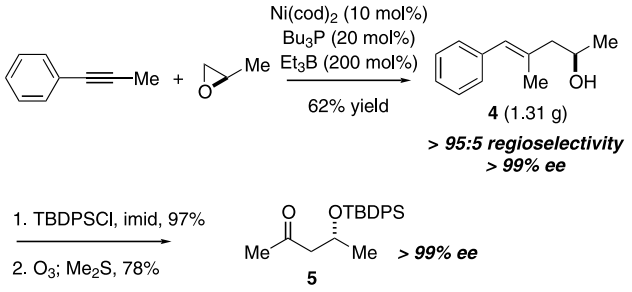


Scheme 5.



Scheme 6.

As shown in the example below, the utility and ease of implementation of catalytic alkyne/epoxide coupling on gram scale is a direct result of the availability of terminal epoxides in >99% ee (Scheme 7).[33] Using only commercially available reagents and catalysts, this procedure is an alternative to enantioselective addition of allylmetal reagents to aldehydes,[34] and product ee is not dependent upon the scale of the reaction. Products corresponding to an asymmetric acetone-acetaldehyde aldol addition reaction are obtained upon further elaboration of **4**, affording in >99% ee β-silyloxyketones such as **5**, which has been used in natural product synthesis.[35]



Scheme 7.

4. Conclusion

Enantioselective nickel/phosphine-catalyzed reductive coupling of alkynes and aldehydes provides rapid access to synthetically useful allylic alcohols with high enantiomeric excess. The related reaction involving epoxides is enantiospecific, transforming alkynes and enantiomerically pure terminal epoxides into enantiomerically pure homoallylic alcohols containing a trisubstituted olefin of defined geometry. We are continuing to develop these and related transformations, such as a highly enantioselective three-component coupling of organoboron reagents, alkynes, and imines.[4] We are also using these methods in target-oriented synthesis as fragment coupling operations in which the alkyne and/or electrophile are chiral and the stereochemical outcome of a newly installed stereogenic center may be influenced by as many as three chiral molecules.

5. Experimental

5.1. General information

All reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Bis(cyclooctadi-

enyl)nickel(0), tetrakis(triphenylphosphine) palladium(0), and copper iodide (98%) were purchased from Strem Chemicals, Inc. Triethylborane (98%), tributylphosphine (97%), propylene oxide (99%), and iodobenzene were purchased from Aldrich Chemical Co. 1-Phenyl-1-propyne and isobutyraldehyde were purchased from Alfa Aesar and the latter was distilled prior to use. (*S*)-(+)-Neomenthyldiphenylphosphine (NMDPP) was prepared as previously reported.[22] Methylene chloride, pyrrolidine, and 1,3-dimethylimidazolidinone (DMI) were distilled over calcium hydride; tetrahydrofuran was distilled from a blue solution of sodium benzophenone ketyl; ethyl acetate was distilled over magnesium sulfate under argon atmosphere.

Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 aluminum plates precoated with a fluorescent indicator or EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh).[36] ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$), unless otherwise noted, on a Bruker Avance 400 or Varian Inova 500 MHz. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm). Infrared (IR) spectra were recorded on a Perkin–Elmer 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OJ column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm. Low temperatures were maintained using a Thermo Neslab CC-65 cryocool immersion cooler equipped with Cryotrol temperature controller; rt = ambient temperature.

5.2. (3-Phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester

Tetrakis(triphenylphosphine) palladium(0) (508 mg, 0.44 mmol) and copper iodide (42 mg, 0.22 mmol) were added to a 100 mL oven-dried, single-necked flask. *N*-*t*-Butoxycarbonylprop-2-ynylamine[37] (3.41 g, 22.00 mmol) dissolved in pyrrolidine (40 mL) was then added, followed by iodobenzene (2.47 mL, 22.00 mmol). The reaction mixture was heated to 40°C for 16 h, then cooled and concentrated under reduced pressure. To the resulting oil was added saturated aqueous NH_4Cl (40 mL), and the mixture was extracted with diethyl ether (3×50 mL), dried and concentrated. The resulting oil was purified by flash chromatography on silica gel (5–17% EtOAc/hexanes) to give a yellow solid. Recrystallization from 20% EtOAc/hexanes provided analytically pure (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester as white needles (3.18 g, 63% yield). $R_f = 0.50$ (17% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H); 7.33–7.29 (m, 3H); 4.80 (bs, 1H); 4.17 (d, $J = 4.5$ Hz, 2H); 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.9, 128.5, 128.5, 122.9, 85.5, 83.3, 80.2, 31.4, 28.6; IR (film): 3338, 2978, 2932, 1699, 1599, 1519, 1491, 1456, 1392, 1367, 1276, 1250, 1170; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{17}NO_2$, 254.116; found 254.115; mp: 94–95°C.

5.3. (*E*)-(1-Benzylidene-2-hydroxy-3-methyl-butyl)-carbamic acid *tert*-butyl ester 2

In a glovebox, $Ni(cod)_2$ (280 mg, 1.00 mmol), and (+)-NMDPP (648 mg, 2.00 mmol) were placed into a 100 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (10 mL), and Et_3B (2.90 mL, 20.00 mmol) were added sequentially via syringe. The resulting solution was stirred at rt for 10 min and then placed in a precooled bath at −25°C. The solution was stirred at this temperature for 15 min, and then a solution of (3-phenyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester (2.31 g, 10.00 mmol) in DMI (10 mL) was added dropwise via syringe. Isobutyraldehyde (1.80 mL, 20.00 mmol) was then added dropwise over 8 h via syringe pump. The reaction was stirred at −25°C for an additional 36 h, at which point saturated aqueous NH_4Cl (20 mL) and 1 M HCl (5 mL) were added. The organic layer was then extracted with ethyl acetate (3×50 mL), dried and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (2–5% EtOAc/hexanes) to afford a 3:1 mixture of desired allylic alcohol **2** (94% ee) and isobutyraldehyde aldol dimer. Recrystallization of this solid from 17% EtOAc/hexanes provided **2** as a white solid (1.35 g, 44% yield, >98% ee). The supernatant was concentrated and further purified by flash chromatography on silica gel to yield an additional 0.24 g of **2** (52% overall yield). $R_f = 0.17$ (17% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2H), 7.28–7.23 (m, 3H); 6.62 (s, 1H); 4.86 (bs, 1H); 4.02 (dd, $J = 15.0$, 7.0 Hz, 1H); 3.91–3.85 (m, 2H); 1.92 (sept, $J = 7.5$ Hz, 1H); 1.43 (s, 9H); 1.06 (d, $J = 7.0$ Hz, 3H); 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 140.0, 136.8, 130.9, 128.8, 128.7, 127.4, 82.7, 79.9, 37.9, 32.5, 28.6, 20.0, 18.8; IR (film): 3287, 3082, 2952, 1670, 1559, 1265, 1183; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{27}NO_3$, 328.188; found 328.187; HPLC analysis (Chiralcel OD, 2% *i*PrOH/hexanes): t_R [(*R*)-**2**] = 21.7 min; t_R [(*S*)-**2**] = 27.1 min; $[\alpha]_D^{20} = -3.0$ (c 1.0, $CHCl_3$); mp: 140–141°C.

5.4. (3-Hydroxy-4-methyl-2-oxo-pentyl)-carbamic acid *tert*-butyl ester 3

Alcohol **2** (179 mg, 0.59 mmol) was dissolved in 17% MeOH/CH_2Cl_2 (5 mL), and the solution was cooled to

−78°C. Ozone was bubbled through the cooled solution until a blue color was obtained (~5 min). Argon was then bubbled through for 10 min, and dimethylsulfide (0.22 mL, 3.00 mmol) was added. The reaction was allowed to warm to room temperature and to stir overnight. Removal of solvent and purification by flash chromatography on silica gel (17% EtOAc/hexanes) provided the desired α-hydroxy ketone **3** as a clear oil (103 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (bs, 1H); 4.23–4.05 (m, 3H); 3.06 (bs, 1H); 2.14 (m, 1H); 1.46 (s, 9H); 1.12 (d, J=7.0 Hz, 3H); 0.79 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 155.8, 80.4, 79.9, 47.6, 32.0, 31.8, 28.5, 22.8, 19.8, 15.2, 14.4 (spectrum showed a mixture of rotomers); IR (film): 3426, 2975, 2934, 2876, 1695, 1510, 1393, 1368, 1252, 1168, 1020; HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{11}H_{24}NO_4$, 254.136; found 254.136; HPLC analysis of the corresponding benzoate **3a** (Chiralcel OJ, 5% *i*PrOH/hexanes, 0.3 mL/min): t_R [(*R*)-**3a**]=55.3 min; t_R [(*S*)-**3a**]=61.6 min; $[\alpha]_D^{20}=-112.5$ (*c* 1.0, $CHCl_3$).

5.5. (+)-(4*E*)-4-Methyl-5-phenylpent-4-en-2-ol 4

To $Ni(cod)_2$ (325 mg, 1.18 mmol) at rt were added PBu_3 (600 mL, 2.41 mmol), Et_3B (700 mL, 4.76 mmol), (*R*)-propylene oxide[33] (1.70 mL, 24.26 mmol), and 1-phenyl-1-propyne (1.50 mL, 11.98 mmol). Additional Et_3B (2.80 mL, 19.34 mmol) was added via syringe pump over 4 h. The brownish solution was stirred at rt for 24 h. EtOAc (25 mL) was added and the resulting solution was quenched with 2 M aqueous NaOH (10 mL) and 30% aqueous H_2O_2 (3 mL). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–20% EtOAc/hexanes) to afford the title compound (1.31 g, 62% yield) as a colorless liquid: R_f=0.24 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 6.39 (s, 1H), 4.09–4.01 (m, 1H), 2.36–2.34 (m, 2H), 2.20 (s, 1H), 1.95 (s, 3H), 1.31 (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.5, 128.7, 127.94, 127.91, 126.1, 65.3, 50.6, 22.8, 17.8; IR (film) 3374, 3081, 3056, 3023, 2966, 2926, 1946, 1884, 1806, 1721, 1650, 1599, 1490, 1445, 1374, 1314, 1269, 1118, 1073, 1022, 940, 918, 815, 744, 699 cm^{-1}; HRMS–EI (m/z): [M]$^+$ calcd for $C_{12}H_{16}O$, 176.1196; found 176.1202. HPLC analysis (Chiralcel OD: 0.5% *i*PrOH/hexanes): t_R [(*S*)-**4**]=39.7 min, t_R [(*R*)-**4**]=42.4 min. $[\alpha]_D^{20}=+1.9$ (*c* 1.9, EtOH) [lit.:[35] $[\alpha]_D=+3$ (*c* 1, EtOH)].

5.6. (+)-[(1*E*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylpent-1-enyl]benzene

To a stirred solution of **4** (0.20 g, 1.13 mmol) in dry DMF (1 mL) and THF (4 mL) at rt, was added imidazole (0.23 g, 3.38 mmol) and *tert*-butyldiphenylsilyl chloride (0.35 mL, 1.34 mmol). The reaction mixture was stirred 16 h, and the resulting solution was diluted with ether and aqueous NH_4Cl and extracted. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100% hexanes) to afford the title compound (455 mg, 97% yield) as a colorless liquid: R_f=0.75 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.46–7.28 (m, 11H), 7.21–7.17 (m, 3H), 6.25 (s, 1H), 4.13–4.01 (m, 1H), 2.40 (dd, J=13.8, 5.8 Hz, 1H), 2.24 (dd, J=13.0, 6.8 Hz, 1H), 1.64 (d, J=1.2 Hz, 3H), 1.13 (d, J=6.1 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 136.0, 135.9, 134.6, 134.3, 129.49, 129.45, 128.7, 127.9, 127.48, 127.43, 125.8, 68.2, 51.1, 27.0, 23.2, 19.2, 18.0; IR (film) 3071, 3024, 2964, 2931, 2894, 2857, 1959, 1889, 1824, 1651, 1599, 1589, 1488, 1472, 1462, 1446, 1427, 1390, 1376, 1361, 1111, 1084, 1027, 997, 910, 822, 739, 700, 613 cm^{-1}; HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{28}H_{34}OSiNa$, 437.2271; found 437.2269; $[\alpha]_D^{20}=+36.9$ (*c* 2.1, $CHCl_3$).

5.7. (−)-(4*R*)-(*tert*-Butyldiphenylsilyloxy)pentan-2-one 5

Ozone was bubbled 5 min into a stirred solution of (+)-[(1*E*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)-2-methylpent-1-enyl]benzene (86 mg, 0.21 mmol) in dry CH_2Cl_2 (4 mL) at −78°C. Dimethylsulfide (0.7 mL) was then added, and the solution was allowed to warm to rt. The resulting solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (0–5% Et_2O/hexanes) to afford the title compound[35] (53 mg, 78% yield) as a colorless liquid: R_f=0.50 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 5H), 7.47–7.38 (m, 8H), 4.37–4.28 (m, 1H), 2.66 (dd, J=15.2, 5.9 Hz, 1H), 2.24 (dd, J=15.2, 6.3 Hz, 1H), 2.08 (s, 3H), 1.11 (d, J=6.1 Hz, 3H), 1.05 (s, 9H); $[\alpha]_D^{20}=-5.0$ (*c* 0.40, $CHCl_3$) [lit.[35] >97% ee: $[\alpha]_D^{20}=-3.2$ (*c* 0.53, $CHCl_3$)].

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