The Absolute Configuration of the Products of the Enantioselective Rhodium(I)/BINAP-Catalyzed Enyne Cyclization

A. Stephen K. Hashmi,[a,*] Patrick Haufe,[a] Andreas Rivas Nass,[b] Jan W. Bats[c]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (+49)-711-685-4321, e-mail: hashmi@hashmi.de
[b] Umicore AG & Co. KG, Precious Metals Chemistry, Rodenbacher Chaussee 4, 63403 Hanau, Germany
[c] Institut für Organische Chemie und Chemische Biologie, Johann Wolfgang Goethe-Universität Frankfurt, Marie-Curie-Str. 11, 60439 Frankfurt, Germany

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Abstract: The absolute configuration of the product **7** obtained from a rhodium-catalyzed enyne cyclization of **6** with the (*R*)-BINAP ligand was determined by anomalous diffraction in the X-ray crystal structure analysis.

Keywords: alkenes; alkynes; asymmetric catalysis; cyclization; homogeneous catalysis; rhodium

Introduction

The intramolecular and transition metal-catalyzed version of the Alder-ene reaction,[1] the enyne cyclization, has become an important tool in organic synthesis. Since Trost et al.'s[2] initial work with palladium catalysts, many other groups have contributed and several other metals have proven to be catalytically active.[3] In these reactions from a planar sp^2-carbon in the starting material, a tetrahedral stereogenic center is generated in the product. Among several efforts for a catalytic enantioselective version of that reaction in the past years,[4,5] so far the most convincing synthetic results come from Zhang et al.'s recent work with rhodium(I) catalysts.[6,7,8]

Zhang et al. achieved excellent enantioselectivities and good to excellent yields.[6,7,8] But the absolute configuration of the newly formed stereogenic center remained unknown. Just recently Zhang et al. investigated the kinetic resolution of racemic substrates and were able to assign the *diastereoselectivity* and from that, in the case of starting materials with known configuration of the stereogenic center already present, also the absolute configuration of the products.[9]

At the same time, in continuation of our recent work,[10] we wanted to assign the absolute configuration of the products of an *enantioselective* reaction by a crystal structure analysis. The absence of additional stereogenic centers in the starting material would avoid possible matched/mismatched cases and allow a more direct assignment of the configuration in other products by correlation with the optical rotation or the CD spectra.

Results and Discussion

For the determination of the absolute configuration by anomalous diffraction a heavy atom is feasible. Thus we chose to use a brosyl-protected amine, the brosyl group should also facilitate crystallization.

Starting from propargylamine **1** and iodobenzene **2** the primary amine **3** was synthesized by a Sonogashira coupling.[11]

Protection with brosyl chloride led to the secondary sulfonamide **4**, of which an X-ray crystal structure analysis could be obtained (Figure 1).[12] The phenyl group labeled C10 through C15 is planar within the experimental uncertainty. The phenyl group labeled C1 through C6 shows a small deviation from planarity: atoms Br and S deviate by 0.18 and 0.13 Å, respectively, in the same direction from the plane of this phenyl group. The angle between the planes of the two phenyl groups is 76.6°. The molecule shows two intramolecular contacts: a possible $\pi\cdots\pi$ contact between the C1–C6 bond and atom C8 of the triple bond (C8···C1 3.41 Å and C8···C6 3.44 Å) and a C–H···π interaction between the C11–H11 bond and the C4–C5 bond (H11···C4 2.94 Å and H11···C5 2.73 Å). The molecules are connected by intermolecular N–H···O hydro-

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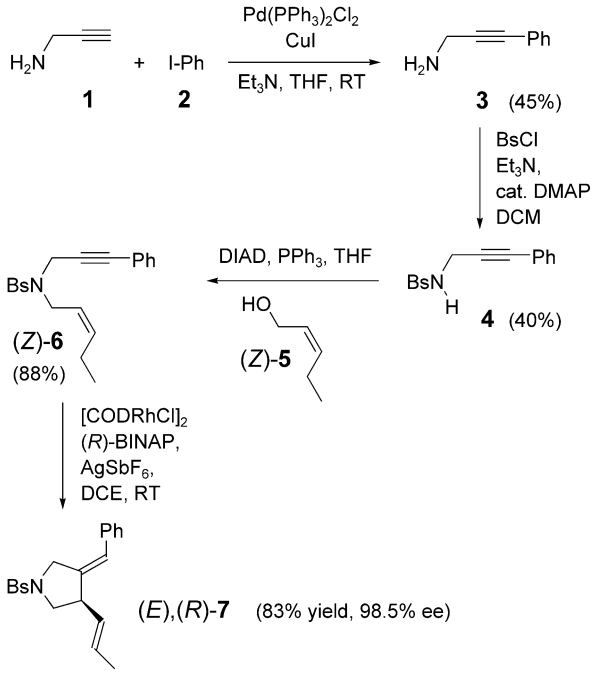

Scheme 1.

gen bonds [N···O1 (at x-1, y, z): 2.994 (2) Å] to chains running in the crystallographic *a* direction, which also corresponds to the long dimension of the crystal. The chains may also be stabilized by π···π interactions between phenyl C atoms [C3···C6 (at x − 1, y, z) 3.39 Å and C14···C11 (at x − 1, y, z) 3.33 Å]. Neighboring chains are connected by a weak intermolecular C–H···N, C–H···O and C–H···Br interactions.

Then a Mitsunobu reaction with (*Z*)-2-penten-1-ol (*Z*)-**5** furnished (*Z*)-**6**. The vicinal coupling of the two vinylic protons of 10.8 Hz nicely reflects the (*Z*)-configuration of the double bond. In addition, a crystal structure analysis confirmed that structure (Figure 2).[12] Both phenyl groups are planar within the experimental uncertainty. The angle between the planes of the two phenyl groups is 49.2°. The N atom is non-planar: the sum of the three valence angles about N is 349.9°. The molecule shows a number of intramolecular contacts: H6···O1 2.50 Å, H7A···O1 2.48 Å, H16B···O2 2.41 Å, H7B···C17 2.71 Å, H16A···C8 2.66 Å and H11···C5 2.98 Å. The molecules form centrosymmetric dimers connected by intermolecular C–H···Br contacts with H···Br distances of 2.89 Å. The dimers are connected by two intermolecular C–H···O contacts and two intermolecular C(phenyl)–H···π(phenyl) interactions to layers parallel to the 0 0 1 plane. Neighboring layers are connected only by a very weak intermolecular C–H···O interaction.

The Rh(I)/(*R*)-BINAP-catalyzed isomerization afforded (*E*),(*R*)-**7** with an ee of 98.5%. The optical rotation of the sample was $[\alpha]_D^{20}$: − 81.8° (*c* 0.5 g/100 mL $CHCl_3$). We again succeeded in obtaining single crystals of (*E*),(*R*)-**7** (Figure 3).[12] The five-membered ring has an envelope conformation: atom C10 deviates 0.62 Å from the plane through N/C7/C8/C9 in the direction of the C11/C12/C13 side chain. The C9–C11 bond is in a pseudo-equatorial position with respect to the five-membered ring. The phenyl group attached to C14 is almost coplanar with the C8–C14 double bond: the angle between the planes of the phenyl ring and the double bond system is 4.5°. This coplanarity results in a rather short intramolecular distance of 2.50 Å between C7 and H20. Consequently the C7–C8–C14 angle is almost 5° larger than the corresponding C9–C8–C14 angle. The plane of the C11–C12 double bond lies almost perpendicular to the C8–C9–C10 plane. There is a short intramolecular C–H···π interaction between the C14–H14 bond and the C11–C12 double bond with a H14···C11 contact distance of only 2.62 Å. The molecules form stacks in the crystallographic *a* direction, which corresponds to the needle axis of the crystal. The molecules in the stacks are connected by two intermolecular C–H···O interactions with H···O distances of 2.60 Å and 2.65 Å and an intermolecular C–H···π(phenyl) interaction with an H···Cg distance of 2.68 Å (Cg is the centroid of the phenyl ring labeled C15 through C20). Neighboring stacks are connected by an additional intermolecular C–H···O interaction and two weak intermolecular C–H···Br interactions.

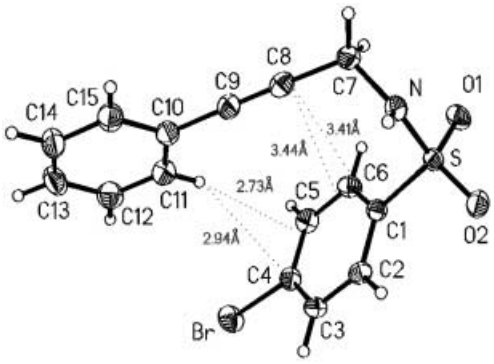

Figure 1. Crystal structure of **4**.

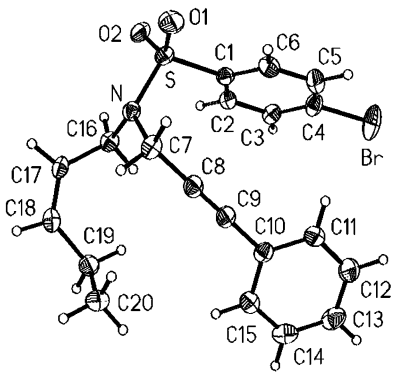

Figure 2. Crystal structure of (*Z*)-**6**.

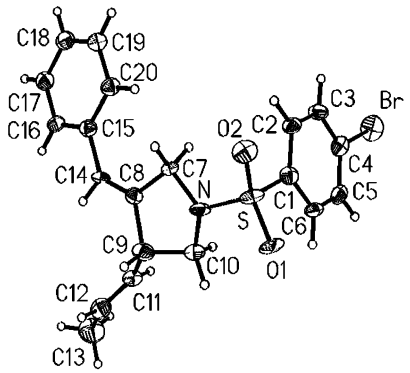

Figure 3. Crystal structure of (*E*),(*R*)-**7**.

Although the large number of very weak reflections in the data set resulted in rather large R values, the absolute configuration of the structure was derived from the value of the Flack x parameter [x = 0.07(3)] to be (*R*) as shown in Figure 3. It also nicely confirmed the (*E*)-configuration of the new stereogenic double bond which was deduced from the vicinal H-H coupling constant of 15.1 Hz in analogy to our earlier work.[10]

The CD-spectrum of (*E*),(*R*)-**7** shows a maximum at 252 nm and a minimum at 230 nm (see supplementary material).

Conclusion

The configuration of the enantioselective reaction forming a new stereogenic center in the product from an achiral substrate investigated here is in complete accord with Zhang's results of the diastereoselective kinetic resolution forming a second stereogenic center in the product from a substrate already possessing a stereogenic center. The (*R*)-BINAP-ligand on rhodium (I) induces the (*R*)-configuration of that new center. The CD data measured should help to assign the configuration in other related products.

Experimental Section

3-Phenyl-2-propynylamine (3)

In a Schlenk flask containing propargylamine (**1**; 328 mg, 5.95 mmol) in absolute THF at room temperature were added $Pd(PPh_3)_2Cl_2$ (83.7 mg, 119 μmol, 2 mol %), CuI (45.4 mg, 238 μmol, 4 mol %) and Et_3N (1.66 mL, 1.21 g, 12.0 mmol) with stirring. Then iodobenzene (**2**; 1.00 mL, 1.82 g, 8.92 mmol) was injected. After 16 hours the solvent was removed and the product was purified by column chromatography (petroleum ether:ethyl acetate:MeOH; 1:1:1) to afford **3**; yield: 351 mg (2.68 mmol, 45%). The ^{1}H NMR spectrum was in accordance with the literature data.[13] R_f (petrol ether:ethyl acetate:MeOH; 1:1:1) = 0.26; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.60 (br s, 2H), 3.67 (s, 2H), 7.29 – 7.31 (m, 3H), 7.39 – 7.43 (m, 2H).

4-Bromo-*N*-(3-phenyl-2-propynyl)-benzenesulfonamide (4)

To a stirred solution of **3** (351 mg, 2.68 mmol), Et_3N (560 μL) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP; 3.10 mg, 26.8 μmol) in dichloromethane (DCM; 10 mL) at 0 °C 4-bromobenzenesulfonyl chloride (754 mg, 2.95 mmol) was added in portions. The reaction mixture was stirred at 0 °C for 15 minutes and then at room temperature overnight. Water (5 mL) was added, the phases were separated and the aqueous phase was extracted with two portions of DCM (3 mL each). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The resulting solid was recrystallized from petroleum ether/DCM to furnish pale yellow needles of **4**; yield: 374 mg (1.07 mmol, 40%); R_f (petroleum ether:ethyl acetate; 10:1) = 0.29; mp 125 – 127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.05 (d, *J* = 6.2 Hz, 2H), 4.68 (t, *J* = 6.2 Hz, 1H), 7.04 (m, 2H), 7.22 (m, 3H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 34.2 (t), 83.2 (s), 85.5 (s), 122.1 (s), 128.4 (s), 128.7 (d, 2C), 129.1 (d), 129.4 (d, 2C), 131.9 (d, 2C), 132.8 (d, 2C), 139.5 (s); IR (neat): ν = 3280, 1573, 1430, 1390, 1169, 1089, 1054, 823, 756 cm^{-1}; MS [EI (+), 70 eV]: *m/z* (%) = 351 (3) [MH^+], 202 (10), 130 (100) [M^+ – brosyl], 146 (23), 103 (16); anal. calcd. for $C_{15}H_{12}BrNO_2S$ (350.2): C 51.44, H 3.45, N 4.00; found: C 51.10, H 3.61, N 3.95.

(*Z*)-4-Bromo-*N*-(2-pentenyl)-*N*-(3-phenyl-2-propynyl)benzenesulfonamide (6)

In analogy to a literature procedure[14] for comparable substrates, at 0 °C **4** (202 mg, 577 μmol), PPh_3 (212 mg, 808 μmol) and (*Z*)-2-penten-1-ol (**5**; 80.0 μL, 65.0 mg, 750 μmol) were dissolved in THF (10.0 mL). Then diisopropyl azodicarboxylate (DIAD; 160 μL) was added dropwise, the solution was allowed to warm to room temperature and then stirred overnight. The solvent was removed under vacuum, ethyl acetate (10 mL) was added and after washing with saturated NaCl solution the organic phase was dried over Na_2SO_4. Column chromatography (petroleum ether:DCM; 5:1) afforded **6** as a white solid; yield: 211 mg (505 μmol, 88%); R_f (petroleum ether:ethyl acetate, 12:1) = 0.26; mp 63 – 65 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 7.5 Hz, 3H), 2.04 (qdd, *J* = 7.5 Hz, 7.5 Hz, 1.6 Hz, 2H), 3.86 (d, *J* = 7.5 Hz, 2H), 4.23 (s, 2H), 5.27 (dtt, *J* = 10.8 Hz, 7.5 Hz, 1.6 Hz, 1H), 5.63 (dtt, *J* = 10.8 Hz, 7.5 Hz, 1.6 Hz, 1H), 6.95 – 7.00 (m, 2H), 7.17 – 7.22 (m, 3H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.2 (q), 20.7 (t), 36.5 (t), 43.2 (t), 81.5 (s), 85.8 (s), 121.9 (d), 122.3 (d), 127.8 (s), 128.4 (d, 2C), 128.6 (d), 129.4 (d, 2C), 131.4 (d, 2C), 132.2 (d, 2C), 138.0 (s), 138.4 (d); IR (neat): ν = 2932, 1574, 1490, 1471, 1443, 1389, 1352, 1274, 1165, 1091, 1010, 900, 823 cm^{-1}; MS [EI (+), 70 eV]: *m/z* (%) = 417 (1)[M^+ – H], 198 (48) [M^+ – brosyl], 143 (18), 115 (100), 91 (15); anal. calcd. for $C_{20}H_{20}BrNO_2S$ (418.4): C 57.42, H 4.82, N 3.35; found: C 57.23, H 4.88, N 3.29.

(*E*),(*R*)-3-Benzylidene-1-(4-bromobenzenesulfonyl)-4-(1-propenyl)pyrrolidine [(*E*),(*R*)-7]

In a Schlenk tube compound **6** (83.7 mg, 200 μmol) in dichloroethane (2.0 mL) was degassed. Then $[CODRhCl]_2$ (4.9 mg, 10 μmol) and (*R*)-BINAP (12.5 mg, 20 μmol) were added. The solution was stirred for a minute, then a few milligrams of $AgSbF_6$ were added. The reaction was monitored by TLC, finally column chromatography (petroleum ether:DCM; 1:1) gave (*E*),(*R*)-**7** as a colorless solid; yield: 69.5 mg (166 μmol, 83%). Crystallization from diethyl ether provided a single crystal for a crystal structure analysis. The ee was 98.5% as determined by analytical HPLC on a Chiralpak AS 10μ column, isocratic hexane:15% ethanol as the eluent and comparison with a racemic sample obtained by the same procedure using *rac*-BINAP as the ligand [column 250 × 4.6 mm; flow 1.0 mL/min, temperature 25 °C, *c* 1 mg/mL hexane:ethanol = 1:1, elution times: 7.11 min for the (+)-enantiomer and 8.10 min for the (−)-enantiomer]. R_f (petroleum ether:DCM; 1:1) = 0.31; mp 129 – 131 °C; IR (neat): ν = 3333, 2961, 2866, 1574, 1466, 1447, 1386, 1343, 1164, 1088, 1052, 1005, 963, 814, 739, 688, 616, 574 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.65 (dd, *J* = 6.5 Hz, 1.6 Hz, 3H), 2.72 (dd with similar coupling constants, thus t, *J* = 9.1 Hz, 9.1 Hz, 1H), 3.32 – 3.34 (m, 1H), 3.55 (dd, *J* = 9.1 Hz, 7.7 Hz, 1H), 3.90 (ddd with two similar coupling constants, thus dt, *J* = 14.9 Hz, 2.5 Hz, 2.5 Hz, 1H), 4.25 (ddd, *J* = 14.9 Hz, 2.5 Hz, 1.5 Hz, 1H), 5.12 (ddq, *J* = 15.1 Hz, 8.2 Hz, 1.6 Hz, 1H), 5.55 (dqd, *J* = 15.1 Hz, 6.5 Hz, 0.8 Hz, 1H), 6.13 (dd, *J* = 4.8 Hz, 2.5 Hz, 1H), 7.05 – 7.07 (m, 2H), 7.16 – 7.19 (m, 1H), 7.26 – 7.29 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4 (q), 48.7 (d), 51.0 (t), 52.8 (t), 124.5 (d), 127.6 (d), 128.3 (s), 128.5 (d, 2C), 128.8 (d), 129.0 (d, 2C), 129.6 (d, 2C), 130.3 (d), 132.8 (d, 2C), 135.5 (s), 136.7 (s), 139.6 (s); MS [EI (+), 70 eV]: *m/z* (%) = 419 (28) [M^+ + H], 328 (89), 221 (8) [brosyl$^+$], 198 (59) [M^+ – brosyl], 197 (64) [M^+ – brosyl – H], 155 (40), 115 (32), 104 (66), 91 (100); anal. calcd. for $C_{20}H_{20}BrNO_2S$ (418.4): C 57.42, H 4.82, N 3.35; found: C 57.35, H 4.87, N 3.33; $[\alpha]_D^{20}$: − 81.8 ° (*c* 0.5 g/100 mL, $CHCl_3$). CD data in the supplementary material.

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[12] CCDC-226041 (**4**) and CCDC-226042 [(*E*)-(*R*)-**7**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk). Due to interesting polymorphism the crystal structure of **6** will be published separately: J. W. Bats, P. Haufe, A. S. K. Hashmi, *Acta Cryst. Sect. C* **2004**, to be published.
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