Asymmetric addition of phenylzinc reagents to C-alkynyl nitrones. Enantiomeric enhancement by a product-like additive

doi: 10.1016/j.tetasy.2008.01.029

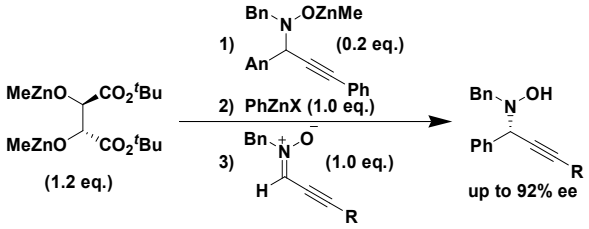
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Asymmetric Addition of Phenylzinc Reagents to *C*-Alkynyl Nitrones. Enantiomeric Enhancement by a Product-like Additive

Leave this area blank for abstract info.

Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* Katsuhiko Inomata*
Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192, Japan



Pergamon

TETRAHEDRON:
ASYMMETRY

Asymmetric Addition of Phenylzinc Reagents to *C*-Alkynyl Nitrones. Enantiomeric Enhancement by a Product-like Additive

Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192, Japan

(Received; E-mail: inomata@cacheibm.s.kanazawa-u.ac.jp)

Abstract—Asymmetric addition of diphenylzinc to *C*-alkynyl nitrones was achieved by utilizing di(*t*-butyl) (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding optically active (*S*)-*N*-(1-phenyl-3-substituted prop-2-ynyl)hydroxylamines. By the addition of a product-like additive, enantiomeric enhancement was observed. A mixed zinc reagent, PhZnMe, improved enantioselection affording the hydroxylamines up to 92% ee.

1. Introduction

Chiral amines are synthetically important target compounds, since they are found in natural products, pharmaceuticals, and other bioactive molecules.[1] For example, chiral benzylic amines are found in such biologically active compounds and their building blocks.[2] One of the most attractive approaches to the syntheses of benzylic amines is the enantioselective addition of phenylmetal reagents to imine derivatives.[3,4] Although various methods for the enantioselective synthesis of chiral benzylic amines are known including reduction and alkylation of aromatic imines, direct asymmetric addition of phenyl reagents to C=N bond is still one of the challenging problems especially in terms of availability of chiral auxiliaries. Very recently we have reported an enantioselective nucleophilic addition of alkynylzinc reagents to nitrones by utilizing a tartaric acid ester as a chiral auxiliary and unprecedented enantiomeric enhancement by a racemic product-like additive was realized.[5] Herein, we wish to describe an enantioselective addition of phenylzinc reagents to acyclic nitrones bearing an alkynyl substituent on the carbon utilizing the tartaric acid ester as a chiral auxiliary to produce *N*-(1-phenyl-3-substituted prop-2-ynyl)hydroxylamines. The enantiomeric enhancement by the addition of a product-like additive was again observed.

*Corresponding author. Tel.: +81-76-264-5700; fax: +81-76-264-5742; e-mail: inomata@cacheibm.s.kanazawa-u.ac.jp

2. Results and Discussion

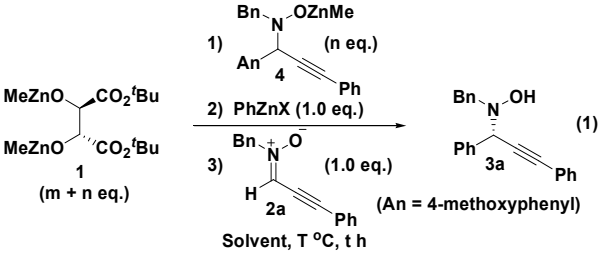


Table 1. Asymmetric addition of phenylzinc reagents to the nitrone **2a.**

Entry	m / eq.	n / eq	X	Solvent	T / °C	t / h	Yield / %	ee / %[a]
1	1.0	0	Ph	CH_2Cl_2	0	16	53	70
2	1.0	0	Ph	CH_2Cl_2	25	0.5	68	76
3	1.0	0	Ph	CH_2Cl_2	40	0.5	54	79
4	1.0	0.2	Ph	CH_2Cl_2	0	16	50	82
5	1.0	0.2	Ph	CH_2Cl_2	25	0.5	65	88
6	1.0	0.2	Ph	CH_2Cl_2	40	0.5	67	88
7	1.0	0.2	Ph	$CHCl_3$	25	0.5	72	88
8	1.0	0.2	Ph	Et_2O	25	0.5	67	82
9	1.0	0.2	Ph	Toluene	25	0.5	63	81
10	1.0	0.2	Ph	Benzene	25	0.5	60	80
11	0.2	0	Ph	$CHCl_3$	25	0.5	34	36
12	0.2	0.2	Ph	$CHCl_3$	25	0.5	63	56
13	1.0	0.2	Me[b]	CH_2Cl_2	25	1	75	91
14	1.0	0.2	Me[b]	$CHCl_3$	25	1	75	92

[a]Enantiomer ratios were determined by HPLC analysis (Daicel Chiralcel OD-H).
[b]PhZnMe was prepared in situ from 0.5 eq. of Ph_2Zn and 0.5 eq. of Me_2Zn.

An asymmetric addition reaction of diphenylzinc to *N*-benzyl *C*-alkynyl nitrone **2a** was first examined (Table 1). To a solution of a 1.0 equivalent of bis(methylzinc) salt of di(*t*-butyl) (*R,R*)-tartrate **1**, prepared in situ from 1.0 equivalent of di(*t*-butyl) (*R,R*)-tartrate [(*R,R*)-DTBT] and 2.0 equivalents of dimethylzinc in CH_2Cl_2, diphenylzinc (X = Ph) and nitrone **2a** were successively added at 0 °C (eq. 1, m = 1.0, n = 0). After usual work up, the corresponding *N*-(propargylic)hydroxylamine **3a** was obtained in 53% yield with enantioselectivity of 70% ee (Entry 1). The addition predominantly occurred from *si*-face of the nitrone **2a**, and the sense of the enantiofacial differentiation was same as that in the previous our addition reaction of alkynylzinc reagents to *C*-(phenyl-substituted) nitrones.[5] When the reaction temperature was increased to 25 °C or 40 °C, the reaction proceeded smoothly to give the desired product **3a** with enantioselectivities of 76% ee and 79% ee, respectively (Entries 2 and 3). Previously, we observed the enantiomeric enhancement by a product-like additive in the addition of alkynylzinc reagents.[5] Thus, the effect of the addition of a product-like additive **4**, prepared in situ from 0.2 equivalent of racemic *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine and 0.2 equivalent of dimethylzinc, was also investigated in the present reaction at 0 °C, 25 °C and 40 °C, respectively (eq. 1, m = 1.0, n = 0.2).[5a] To our delight, the enantioselectivity was remarkably enhanced, respectively (Entries 4-6). When the reaction was carried out at 25 °C and 40 °C, **3a** was obtained with high enantioselectivity of 88% ee. The effect of the solvent was also investigated for further optimization at 25 °C. (Entries 5, 7-10). Although the enantioselectivity did not remarkably change depending on the solvent used, higher yield was resulted in $CHCl_3$. When 0.2 equivalent of **1** was used, enantioselectivity was not satisfactory (Enrty 11). However, enantiomeric enhancement was still observed by addition of the product-like additive **4** to give **3a** with improved enantioselectivity (Enrty 12). Finally it was found that utilization of a mixed zinc species PhZnMe, prepared in situ from Ph_2Zn and Me_2Zn,[6] achieved the highest enantioselectivity of 92% ee (Entry 14).

Asymmetric additions of phenylzinc reagents to several other nitrones **2** were performed (eq. 2) to furnish the corresponding *N*-(propargylic)hydroxylamines **3** with high enantioselectivities (Table 2). It was confirmed that the addition of the product-like additive **4** was effective to improve enantioselectivity as shown in the column of n = 0.2 in Table 2. Not only in the case of *C*-(aryl-substituted alkynyl) nitrones **2a-c**, but also in the case of *C*-(alkyl-substituted alkynyl) nitrone **2d**, the enantiomeric excess was remarkably enhanced in the presence of additive **4**. Furthermore, higher enantioselectivity was accomplished by the use of PhZnMe (Entries 2 and 8).

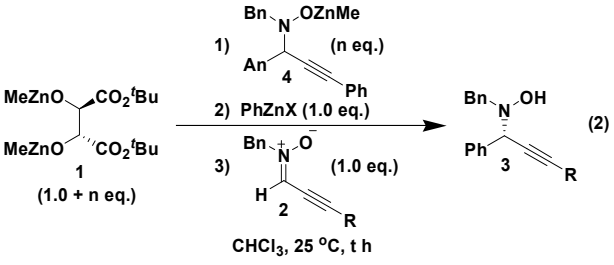
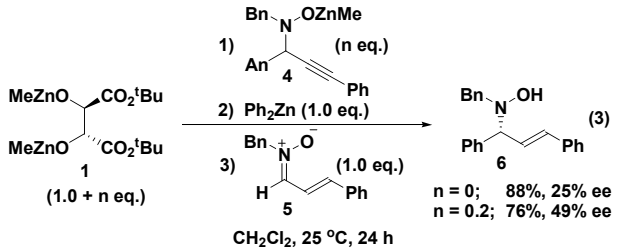


Table 2. Asymmetric additon of phenylzinc regents to nitrones **2** in the presence of a racemic product-like additive **4**

	2				n = 0.2		n = 0	
Entry	R		X	t / h	Yield / %	ee / %	Yield / %	ee / %
1	Ph	**a**	Ph	0.5	72	88[a]	70	64[a]
2			Me[c]	1	75	92[a]		
3	$^{p}CH_3C_6H_4$	**b**	Ph	1	75	87[a]	80	77[a]
4			Me[c]	1	66	87[a]		
5	$^{p}BrC_6H_4$	**c**	Ph	1	64	90[a]	68	53[a]
6			Me[c]	1	70	90[a]		
7	$^{n}C_6H_{13}$	**d**	Ph	1	67	82[b]	61	52[b]
8			Me[c]	1	67	87[b]		

[a]Enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OD-H).
[b]Enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OJ-H).
[c]PhZnMe was prepared in situ from 0.5 eq. of Ph_2Zn and 0.5 eq. of Me_2Zn.

It was now confirmed that enantiomeric enhancement occurrs in the preparation of **3** by both the phenylation of *C*-alkynyl nitrones and alkynylation of *C*-aromatic nitrones.[5] To scope such an intriguing enantiomeric enhancement,[7] asymmetric phenylation of a *C*-alkenyl nitrone **5** was next examined. The addition reaction was sluggish to afford the corresponding *N*-(allylic)hydroxylamine **6** with poor enantioselectivity, however, the enantioselectivity was also enhanced to 49% ee in the presence of the additive **4**.[8]



3. Conclusion

As described above, the asymmetric addition of phenylzinc reagents to *C*-alkynyl nitrones have been developed utilizing tartaric acid ester as a chiral auxiliary. By the addition of a product-like substrate, the high enantioselectivities were realized. Furthermore, the enantiomeric enhancement by the addition of *N*-(propargylic)hydroxylamine derivative **4** was also achieved in the case of *C*-alkenyl nitrone. Further investigation for the present peculiar enantiomeric enhancement by the product-like additive is now in progress in our laboratory.

4. Experimental

4.1 General

All of the melting points were determined by a micro melting apparatus (Yamagimoto-Seisakusho) and uncorrected. The ^{1}H NMR spectra were recorded on a JEOL Lambda 400 and a JEOL Lambda 300 spectrometers. The chemical shifts were determined in the δ-scale relative to tetramethylsilane (δ = 0) as an internal standard. The IR spectra were measured by JASCO FT/IR-230 spectrometer. The specific optical rotations were recorded on JASCO DIP-370 spectrometer. $CHCl_3$ was treated with Merck's aluminum oxide 90 active basic (0.063–0.200 mm, activity stage I, Art. 101076) and dried over MS 4A just before use. Et_2O was freshly distilled from sodium diphenylketyl. All other solvents were distilled and stored over drying agents. Flash column chromatography and thin-layer chromatography (TLC) were performed on Cica-Merck's silica gel 60 (No. 9385-5B) and Merck's silica gel 60 PF_{254} (Art. 107749), respectively.

4.2 Preparation of Aldehydes

Phenylpropynal was prepared according to the procedure described in reference 9. Other aldehydes were prepared in a similar manner.

Phenylpropynal:[9] An oil, IR (neat) 3297, 3061, 2856, 2189, 1660, 1489, 1444, 1388, 1261, 1174, 1027, 1002, 978, 758, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.36-7.40 (m, 2H), 7.44-7.49 (m, 1H), 7.52-7.64 (m, 2H), 9.47 (s, 1H, CHO); HRMS (FAB^+), Found: *m/z* 131.04970. Calcd for C_9H_7O: (M^+ + H), 131.05015.

***p*-Tolylpropynal:** An oil, IR (neat) 3295, 3033, 2922, 2856, 2185, 1657, 1605, 1508, 1448, 1408, 1385, 1266, 1180, 1020, 982, 817, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.39 (s, 3H, CH_3), 7.20 (d, *J* = 8.06 Hz, 2H), 7.49 (d, *J* = 8.06 Hz, 2H), 9.41 (s, 1H, CHO); HRMS (FAB^+), Found: *m/z* 145.06581. Calcd for $C_{10}H_9O$: (M^+ + H), 145.06535.

(4-Bromophenyl)propynal: Mp 95–97 °C (from hexane/AcOEt; unstable on storage); IR (KBr) 3283, 3087, 2922, 2890, 2191, 1654, 1581, 1475, 1392, 1264, 1067,

1009, 988, 822, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.46 (d, J = 8.61 Hz, 2H), 7.56 (d, J = 8.61 Hz, 2H), 9.41 (s, 1H, CHO); HRMS (FAB^+), Found: *m/z* 208.96006. Calcd for C_9H_6OBr: (M^+ + H), 208.96020.

Non-2-ynal: An oil, IR (neat) 2931, 2859, 2201, 1671, 1457, 1387, 1226, 1137, 824, 790, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.88 (t, J = 7.14 Hz, 3H, CH_3), 1.31 (m, 4H, $(CH_2)_2$), 1.39 (quin, J = 7.14 Hz, 2H, CH_2), 1.60 (quin, J = 7.14 Hz, 2H, CH_2), 2.41 (t, J = 7.14 Hz, 2H, C≡CCH_2), 9.17 (s, 1H, CHO); HRMS (FAB^+), Found: *m/z* 139.11263. Calcd for $C_9H_{15}O$: (M^+ + H), 139.11230.

4.3 Preparation of Nitrones

(*Z*)-1-Phenyl-*N*-(3-phenylprop-2-ynylidene)methanamine Oxide (2a): To a solution of phenylpropynal (262 mg, 2.0 mmol) in CH_2Cl_2 (3 ml) with MS 3A (342 mg) was added a CH_2Cl_2 (3 ml) solution of *N*-(benzyl)hydroxylamine (246 mg, 2.0 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C overnight. Then the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic extract was washed successively with water, brine, and dried over sodium sulfate. After evaporation of the solvent, the residue was separated by silica gel [treated with 10% (w/w) water in advance to deactivate] column chromatography (eluted with $CHCl_3$) to afford **2a** (170 mg) in 36% yield. The nitrone was so labile that it was partially decomposed during purification even by treatment with deactivated silica gel. An oil, IR (neat) 3062, 3030, 2923, 2215, 1654, 1578, 1541, 1495, 1451, 1238, 1178, 1072, 1027, 754, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.37 (s, 2H, CH_2Ph), 7.10 (s, 1H, ArHC=N), 7.29-7.39 (m, 6H), 7.47-7.55 (m, 4H); HRMS (FAB^+), Found: *m/z* 236.10799. Calcd for $C_{16}H_{14}NO$: (M^+ + H), 236.10754.

In a similar manner, nitrones **2b-2d** were prepared from the corresponding aldehydes and *N*-(benzyl)hydroxylamine.

(*Z*)-1-Phenyl-*N*-(3-*p*-tolylprop-2-ynylidene)methanamine Oxide (2b): An oil, IR (neat) 3029, 2921, 2188, 1655, 1606, 1541, 1507, 1454, 1240, 1178, 816, 753, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.39 (s, 3H, CH_3), 5.31 (s, 2H, CH_2Ph), 7.11 (s, 1H, ArHC=N), 7.20 (d, J = 8.01 Hz, 2H), 7.38 (d, J = 8.01 Hz, 2H), 7.30-7.38 (m, 3H), 7.53-7.40 (m, 2H); HRMS (FAB^+), Found: *m/z* 250.12306. Calcd for $C_{17}H_{16}NO$: (M^+ + H), 250.12319.

(*Z*)-1-Phenyl-*N*-[3-(4-bromophenyl)prop-2-ynylidene]methanamine Oxide (2c): Mp 90–91 °C (from hexane/AcOEt), IR (KBr) 3060, 3029, 2922, 2186, 1640, 1584, 1536, 1485, 1452, 1395, 1355, 1290, 1241, 1173, 1071, 1008, 952, 824, 771, 736, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.31 (s, 2H, CH_2Ph), 6.19 (s, 1H, ArHC=N), 7.32-7.41 (m, 4H), 7.50-7.54 (m, 5H); HRMS (FAB^+), Found: *m/z* 314.01786. Calcd for $C_{16}H_{13}NOBr$: (M^+ + H), 314.01805.

(*Z*)-1-Phenyl-*N*-(non-2-ynylidene)methanamine Oxide (2d): An oil, IR (neat) 3030, 2928, 2857, 2232, 1654, 1496, 1455, 1353, 1078, 1028, 754, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.89 (t, J = 7.14 Hz, 3H, CH_3), 1.35 (m, 4H, $(CH_2)_2$), 1.43 (quin, J = 7.14 Hz, 2H, CH_2), 1.59 (quin, J = 7.14 Hz, 2H, CH_2), 2.50 (t, J = 7.14 Hz, 2H, C≡CCH_2), 5.21 (s, 2H, CH_2Ph), 6.89 (s, 1H, ArHC=N), 7.30-7.39 (m, 3H), 7.40-7.56 (m, 2H); HRMS (FAB^+), Found: *m/z* 244.16954. Calcd for $C_{16}H_{22}NO$: (M^+ + H), 244.17014.

(*Z*)-1-Phenyl-*N*-[(*E*)-3-phenylallylidene]methanamine Oxide (5): To a solution of cinnamaldehyde (925 mg, 7.0 mmol) in CH_2Cl_2 (4.5 ml) was added a CH_2Cl_2 (4.5 ml) solution of *N*-(benzyl)hydroxylamine (865 mg, 7.0 mmol) at 25 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C overnight. Then the solvent was removed in vacuo and the residue was recrystallized from hexane/AcOEt to give the nitrone **5** (1.229 g) in 74% yield. Mp 124–125 °C (from hexane/AcOEt); IR (KBr) 3051, 1545, 1494, 1457, 1424, 1347, 1319, 1291, 1199, 1177, 1122, 1072, 1026, 961, 941, 915, 861, 821, 764, 747, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.96 (s, 2H, CH_2Ph), 6.94 (d, J = 16.34 Hz, 1H), 7.21 (d, J = 9.76 Hz, 1H), 7.28-7.36 (m, 3H), 7.38–7.50 (m, 8H). Found: C, 81.00; H, 6.37; N, 5.90%. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%.

4.4 Preparation of *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine: To a toluene (9 ml) solution of phenyl acetylene (337 mg, 3.3 mmol) was added dimethylzinc (3.3 ml of 1.0 M solution in hexane, 3.3 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 30 min. To the solution, a toluene (9 ml) solution of *N*-(4-methoxybenzylidene)-1-phenylmethanamine oxide (732 mg, 3.0 mmol) was added. The resulting solution was stirred at 0 ºC for 14 h and quenched by addition of a saturated aq. $NaHCO_3$ solution. After filtration of the precipitate, the filtrate was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed under reduced pressure. The residue was separated by TLC on SiO_2 to isolate the corresponding hydroxylamine (hexane/AcOEt = 3/1) in 97% yield (1.00 g). Mp 116–117 °C (from hexane/AcOEt), IR (KBr) 3235, 2924, 1608, 1509, 1489, 1456, 1333, 1303, 1246, 1172, 1077, 1033, 801, 753, 699, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.81 (s, 3H, OCH_3), 3.97 (d, J = 13.06 Hz, 1H, CH_2Ph), 4.06 (d, J = 13.06 Hz, 1H, CH_2Ph), 4.90 (s, 1H, OH), 4.97 (s, 1H, ArCHNBn), 6.91 (d, J = 8.61 Hz, 2H) 7.28-7.41 (m, 8H), 7.54-7.58 (m, 4H); HRMS (FAB^+), Found: *m/z* 344.1650. Calcd for $C_{23}H_{22}NO$: (M^+ + H), 344.1652.

4.5 Asymmetric Phenylation

Representative Procedure for Asymmetric Phenylation of *N*-Benzyl *C*-Alkynyl Nitrone 2a (Table 2, Entry 2): To

a $CHCl_3$ (3 ml) solution of (*R*,*R*)-DTBT (157 mg, 0.6 mmol) was added dimethylzinc (1.55 ml of 1.0 M solution in hexane, 1.55 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 10 min. To the solution, a $CHCl_3$ (3 ml) solution of racemic *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine (34 mg, 0.1 mmol) was added. After stirring for 10 min, diphenylzinc (1.95 ml of 0.128 M solution in toluene, 0.25 mmol) was added to the solution. The reaction mixture was warmed to 25 ºC and stirred for 1 h, then a $CHCl_3$ (3 ml) solution of the nitrone **2a** (117 mg, 0.5 mmol) was added. The resulting solution was stirred at 25 ºC for 1 h and quenched by addition of a saturated aq. NH_4Cl solution. After filtration of the precipitate, the filtrate was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed under reduced pressure. The residue was separated by TLC on SiO_2 to isolate **3a** (hexane/AcOEt = 3/1) in 75% yield (117 mg).

(*S*)-*N*-Benzyl-*N*-(1,3-diphenylprop-2-ynyl)hydroxylamine (3a):[10] Mp 133–134 °C (from EtOH); $[\alpha]_D^{25}$ –42 (c 1.23, EtOH, 92% ee); IR (KBr) 3239, 3029, 2905, 1597, 1488, 1452, 1331, 1298, 1179, 1070, 1026, 1003, 988, 916, 826, 812, 757, 729, 690 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.89 (d, *J* = 12.69 Hz, 1H, CH_2Ph), 3.99 (d, *J* = 12.69 Hz, 1H, CH_2Ph), 4.87 (s, 1H, ArCHNBn), 5.69 (s, 1H, OH), 7.28-7.37 (m, 10H), 7.59-7.61 (m, 5H). Found: C, 84.31; H, 6.15; N, 4.43%. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47%. The enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/^{i}PrOH = 45/1, detected at 254 nm).

(*S*)-*N*-Benzyl-*N*-(1-phenyl-3-*p*-tolylprop-2-ynyl) hydroxylamine (3b): Mp 135–136 °C (from EtOH); $[\alpha]_D^{25}$ –45 (c 1.23, EtOH, 87% ee); IR (KBr) 3236, 3028, 2918, 1600, 1542, 1508, 1495, 1453, 1353, 1289, 1075, 1029, 1020, 985, 913, 861, 815, 757, 738, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.37 (s, 3H, CH_3), 3.99 (s, 2H, CH_2Ph), 4.93 (s, 1H, ArCHNBn), 5.25 (s, 1H, OH), 6.87-7.86 (m, 14H). Found: C, 84.09; H, 6.50; N, 4.34%. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28%. The enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/^{i}PrOH = 60/1, detected at 254 nm).

(*S*)-*N*-Benzyl-*N*-[3-(4-bromophenyl)-1-phenylprop-2-ynyl]hydroxylamine (3c): Mp 166-167 °C (from EtOH); $[\alpha]_D^{25}$ –69 (c 0.50, EtOH, 90% ee); IR (KBr) 3339, 3063, 3030, 2971, 2894, 1602, 1485, 1453, 1393, 1297, 1272, 1070, 1049, 1011, 880, 824, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.98 (d, *J* = 13.17 Hz, 1H, CH_2Ph), 4.06 (d, *J* = 13.17 Hz, 1H, CH_2Ph), 4.98 (s, 1H, ArCHNBn), 5.05 (s, 1H, OH), 7.28-7.49 (m, 12H), 7.57-7.63 (m, 2H). Found: C, 67.51; H, 4.70; N, 3.52%. Calcd for $C_{22}H_{18}NOBr$: C, 67.35; H, 4.60; N, 3.57%. The enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/^{i}PrOH = 45/1, detected at 254 nm).

(*S*)-*N*-Benzyl-*N*-(1-phenylnon-2-ynyl)hydroxylamine (3d): An oil, $[\alpha]_D^{25}$ –43 (c 1.14, EtOH, 87% ee); IR (neat) 3256, 3086, 3063, 3030, 2930, 2857, 2227, 1603, 1585, 1558, 1494, 1454, 1330, 1180, 1074, 1050, 879, 831, 813, 755, 735, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 6.69 Hz, 3H, CH_3), 1.23-1.35 (m, 4H, $(CH_2)_2$), 1.43-1.51 (m, 2H, CH_2), 1.58-1.74 (m, 2H, CH_2), 2.38 (t, *J* = 5.04 Hz, 2H, $C{\equiv}CCH_2$), 3.90 (d, *J* = 13.11 Hz, 1H, CH_2Ph), 4.00 (d, *J* = 13.11 Hz, 1H, CH_2Ph), 4.77 (s, 1H, ArCHNBn), 4.89 (s, 1H, OH), 7.14-7.39 (m, 8H), 7.52-7.58 (m, 2H); HRMS (FAB^+), Found: *m/z* 322.21737. Calcd for $C_{22}H_{28}NO$: (M^+ + H), 322.21709. The enantiomer ratio was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/EtOH = 75/1, detected at 254 nm).

Asymmetric Phenylation of (*Z*)-1-Phenyl-*N*-[(*E*)-3-phenylallylidene]methanamine Oxide (5) (Eq. 3): To a CH_2Cl_2 (1.8 ml) solution of (*R*,*R*)-DTBT (95 mg, 0.36 mmol) was added dimethylzinc (0.78 ml of 1.0 M solution in hexane, 0.78 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 10 min. To the solution, a CH_2Cl_2 (1.8 ml) solution of racemic *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine (21 mg, 0.06 mmol) was added. After stirring for 10 min, diphenylzinc (2.3 ml of 0.129 M solution in toluene, 0.30 mmol) was added to the solution. Then a CH_2Cl_2 (1.8 ml) solution of the nitrone **5** (72 mg, 0.30 mmol) was added. The resulting solution was stirred at 25 ºC for 24 h and quenched by addition of a saturated aq. $NaHCO_3$ solution. After filtration of the precipitate, the filtrate was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed under reduced pressure. The residue was separated by TLC on SiO_2 to isolate **6** (hexane/AcOEt = 10/1) in 76% yield (73 mg).

(*R*,*E*)-*N*-Benzyl-*N*-(1,3-diphenylallyl)hydroxylamine (6): An oil, $[\alpha]_D^{25}$ +7 (c 0.73, EtOH, 49% ee); IR (neat) 3529, 3082, 3059, 3027, 2923, 2850, 1599, 1494, 1452, 1246, 1072, 1028, 966, 744, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.81 (d, *J* = 13.42 Hz, 1H, CH_2Ph), 3.95 (d, *J* = 13.42 Hz, 1H, CH_2Ph), 4.44 (d, *J* = 8.04 Hz, 1H), 4.75 (s, 1H, OH), 6.54 (m, 1H), 6.65 (d, *J* = 11.20 Hz, 1H), 7.27-7.58 (m, 15H); HRMS (FAB^+), Found: *m/z* 316.16955. Calcd for $C_{22}H_{22}NO$: (M^+ + H), 316.17014. The enantiomeric ratio was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/^{i}PrOH = 20/1, detected at 254 nm).

Acknowledgements

The present work was financially supported in part by Grant-in-Aid for Scientific Research on Priority Areas from The Ministry of Education, Culture, Sports, Science and Technology (MEXT) and NOVARTIS Foundation (Japan) for the Promotion of Science.

References

1 (a) Bloch, R. *Chem. Rev*. **1998**, *98*, 1407. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069.

2 (a) Kuo, D.; Weidner, J.; Griffin, P.; Shah, S. K.; Knight, W. B. *Biochemistry* **1994**, *33*, 8347. (b) Finke, E. P.; Shah, S. K.; Fletcher, D. S.; Ashe, B. M.; Brause, K. A.; Chandler, G. O.; Dellea, P. S.; Hand, K. M.; Maycock, A. L.; Osinga, D. G.; Underwood, D. J.; Weston, H.; Davies, P.; Doherty, J. B. *J. Med. Chem.* **1995**, *38*, 2449. (c) Grell, W.; Hurnaus, R.; Griss, G.; Sauter, R.; Rupprecht, E.; Mark, M.; Luger, P.; Nar, H.; Wittneben, H.; Müller, P. *J. Med. Chem.* **1998**, *41,* 5219. (d) Bartholomeusz, G.; Talpaz, M.; Bornmann, W.; Kong, L.-Y.; Donato, N. J. *Cancer Res.* **2007**, *67*, 3912.

3 Recent examples of asymmetric phenylation: (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 3692. (c) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc*. **2004**, *126*, 8128. (d) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307. (e) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.

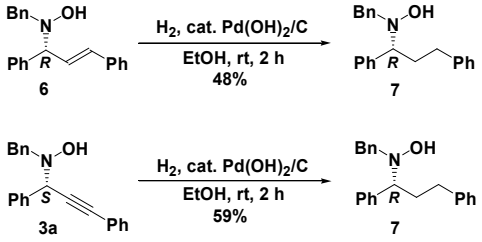
4 (a) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3284. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev*. **2006**, *35*, 454.

5 (a) Wei, W.-L.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Chem. Lett*. **2006**, *35*, 176. (b) Konishi, A.; Wei, W.-L.; Kobayashi, M.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Chem. Lett*. **2007**, *36*, 44.

6 It was reported that a mixed zinc reagent PhZnEt was prepared from Ph_2Zn and Et_2Zn in situ. The mixed zinc species was more effective for controlling the reactivity than Ph_2Zn. (a) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 1488. (b) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem*. **2004**, *69*, 2532. (c) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem*. **2004**, *69*, 3997. See also reference 3b.

7 Examples for asymmetric amplification by additives: (a) Faller, J. M.; Lavoie, A. R.; Parr, J. *Chem. Rev*. **2003**, *103*, 3345. (b) Mikami, K.; Yamanaka, M. *Chem. Rev*. **2003**, *103*, 3369. (c) Soai, K. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 673. (d) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660.

8 The absolute configuration of hydroxylamine **6** was confirmed to be *R* by chemical correlation. Namely, the double bond in **6** (38% ee) was reduced to give a saturated *N*-hydroxylamine **7**. Furthermore, (*S*)-**3a** (92% ee) was also reduced to **7**. Although the value of the specific rotation of **7** was too small to be compared, the major peaks in HPLC analyses (Chiralcel OD-H, hexane/EtOH = 4/1) were identical each other.

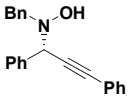


9 Journet, M.; Cai, D.-W.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett*. **1998**, *39*, 6427.

10 Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett*. **2000**, *2*, 2331.

Stereochemistry Abstract

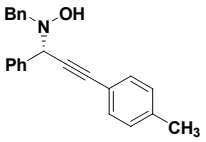
Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*



$C_{22}H_{19}NO$
(*S*)-*N*-benzyl-*N*-(1,3-diphenylprop-2-ynyl)hydroxylamine

Ee = 92%
$[\alpha]_D^{25}$ –42 (c 1.23, EtOH)
Source of chirality: (*R,R*)-DTBT
Absolute configuration: (*S*)

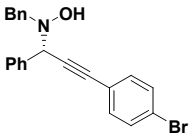
Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*



$C_{23}H_{21}NO$
(*S*)-*N*-benzyl-*N*-(1-phenyl-3-*p*-tolylprop-2-ynyl)hydroxylamine

Ee = 87%
$[\alpha]_D^{25}$ –45 (c 1.23, EtOH)
Source of chirality: (*R,R*)-DTBT
Absolute configuration: (*S*)

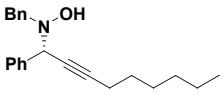
Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*



$C_{22}H_{18}NOBr$
(*S*)-*N*-benzyl-*N*-[3-(4-bromophenyl)-1-phenylprop-2-ynyl]hydroxylamine

Ee = 90%
$[\alpha]_D^{25}$ –69 (c 0.50, EtOH)
Source of chirality: (*R,R*)-DTBT
Absolute configuration: (*S*)

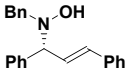
Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*



$C_{22}H_{27}NO$
(*S*)-*N*-benzyl-*N*-(1-phenylnon-2-ynyl)hydroxylamine

Ee = 87%
$[\alpha]_D^{25}$ –43 (c 1.14, EtOH)
Source of chirality: (*R,R*)-DTBT
Absolute configuration: (*S*)

Weilin Wei, Yoshihira Hamamoto, Yutaka Ukaji,* and Katsuhiko Inomata*



$C_{22}H_{21}NO$
(*R,E*)-*N*-benzyl-*N*-(1,3-diphenylallyl)hydroxylamine

Ee = 49%
$[\alpha]_D^{25}$ +7 (c 0.73, EtOH)
Source of chirality: (*R,R*)-DTBT
Absolute configuration: (*R*)