Synthesis C. Chen et al. Special Topic

Copper-Catalyzed Asymmetric Hydroamination of Styrenes with ^{piv}ZPhos as Ligand

Chengsheng Chen
Ling Wu
Yuwen Wang
Linglin Wu*
Yongda Zhang*

Department of Chemical Development, Boehringer I ngelheim Pharmaceuticals, Inc., 900 Ridgebury Road/ P.O. Box 368, Ridgefield, CT 06877-0368, USA
yongda.zhang@boehringer-ingelheim.com
linglin.wu@boehringer-ingelheim.com

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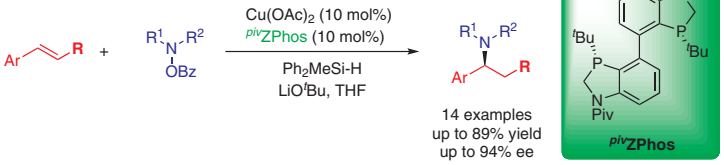

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Abstract A copper-catalyzed hydroamination of styrenes using ^{piv}ZPhos as ligand is reported. Enantioselectivities up to 94% are achieved under optimized conditions with aryl and heteroaryl styrenes. A variety of electrophilic *O*-benzoylhydroxylamines are well tolerated.

Key words hydroamination, asymmetric catalysis, copper catalysis, styrene, phosphine ligand

Efficient syntheses of chiral amines with synthetically useful enantiopurity are highly desirable due to the presence of chiral amines in numerous pharmaceutically active compounds and agrochemicals. Asymmetric hydroamination, which proceeds through addition of N–H bond of a suitable amine (primary or secondary) across an alkene double bond, represents the most straightforward and atom-economic approach to construct the target enantioenriched chiral amine. In the past decade, a great progress has been achieved in the field of asymmetric hydroamination employing late transition metal catalysis.[1] Nonetheless, some limitations and challenges remain with this 'traditional' hydroamination. For example, high selectivities and reactivities could only be realized in the intramolecular hydroamination. Moreover, addition of amine to unactivated internal alkenes remains a challenge for synthetic chemists. In 2013, a different and 'umpolung' approach to hydroamination was reported by Buchwald[2] and Miura[3] groups independently in the presence of chiral phosphine/copper catalyst with hydrosilane and *O*-benzoylhydroxylamine as the sources for hydrogen and nitrogen, respectively. High enantioselectivities were observed in the sequential hydrocupration and electrophilic amination of a series of styrenes and β-substituted styrenes.[4] Later on, these and other groups extended this hydroamination methodology to a variety of different alkenes.[5] Recently a breakthrough was achieved by the Buchwald group where unactivated internal olefins containing two minimally differentiated aliphatic substituents were effectively functionalized with excellent enantioselectivities via a mild and general copper-catalyzed hydroamination.[6]

In the past decade, our group has developed a series of P-chiral bis- and monophosphorus ligands based on 2,3-dihydrobenzo[*d*][1,3]oxaphosphole motif.[7] This type of ligands have shown high reactivities and exceptional selectivities in numerous asymmetric transformations including recent examples of asymmetric hydrogenation,[8] asymmetric hydroformylation,[9] asymmetric Suzuki–Miyaura coupling,[10] asymmetric addition of arylboroxines to ketones,[11] and asymmetric dearomatization,[12] *etc*. As part of our ongoing research program, we have reported the synthesis of new modular dihydrobenzoazaphosphole ligands by replacing the oxygen in 2,3-dihydrobenzo[*d*][1,3]oxaphosphole motif with a nitrogen.[13] This modification improves the tunability of electronic and steric properties of ligands by adjustment of the nitrogen substituting groups. Indeed, the ^{piv}ZPhos shows superior reactivity and enantioselectivity to its *O*-counterpart in the copper-catalyzed asymmetric hydrogenation of 2-substituted ketones[14] and aminoboration of alkenes.[15] Considering that ^{piv}ZPhos gives excellent enantioselectivities in the aminoboration of alkenes, we were interested in the application of ^{piv}ZPhos to hydromination of alkenes. Here we report the copper-catalyzed asymmetric hydroamination of alkenes with good reactivities and enantioselectivities using ^{piv}ZPhos as a ligand.

We initiated our studies by adapting Miura's conditions with 10 mol% of CuCl and ligand, PMHS (polymethylhydrosiloxane) as hydride source and LiO*t*Bu as base in THF (Table 1, entry 1).[3] Although the yield in the reaction between styrene (**1a**) and *O*-benzoyldibenzylhydroxylamine (**2a**) was low (22%) the initial trial gave promising enantioselectivity

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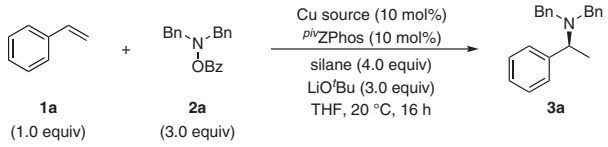
Table 1 Reaction Condition Optimization for the Asymmetric Hydroamination of Styrene (**1a**) with *O*-Benzoyldibenzylhydroxylamine (**2a**)[a]



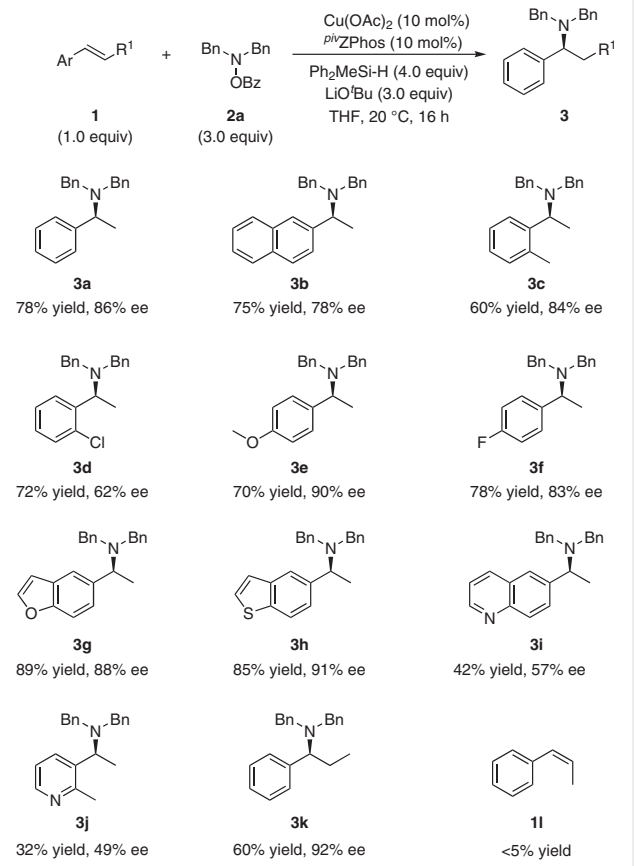
1a (1.0 equiv) + **2a** (3.0 equiv) → **3a**

Entry	Cu source	Silane	Yield (%)	ee
1	CuCl	PMHS	22	84
2[b]	CuCl	PMHS	15	80
3	CuCl	DMMS	<10	–
4	CuCl	Ph_3SiH	47	86
5	CuCl	$PhSiH_3$	<5	–
6	CuCl	Ph_2MeSiH	74	86
7	CuOAc	Ph_2MeSiH	16	56
8	CuOTf	Ph_2MeSiH	54	52
9	$CuCl_2$	Ph_2MeSiH	48	80
10	**$Cu(OAc)_2$**	**Ph_2MeSiH**	**78**	**86**
11[c]	$Cu(OAc)_2$	Ph_2MeSiH	32	74
12[d]	$Cu(OAc)_2$	Ph_2MeSiH	42	82
13[e]	$Cu(OAc)_2$	Ph_2MeSiH	76	82
14[f]	$Cu(OAc)_2$	Ph_2MeSiH	45	52

[a] Absolute configuration was determined by comparing specific rotation with literature.[2]
[b] Ligand: *O*-BABIPhos.
[c] Base: NaO*t*Bu.
[d] Solvent: toluene.
[e] Catalyst: 5 mol%.
[f] 10 mol% of PPh_3 was added.

(84% ee) for the product **3a**. Switching the ligand to its oxygen analogue *O*-BABIPhos led to lower yield and ee (entry 2). The hydride source had a profound effect on the reactivity and enantioselectivity. While DMMS (dimethoxymethylsilane) and $PhSiH_3$ gave little product, Ph_3SiH delivered the product **3a** in moderate yield and high enantiomeric excess (entries 3–5). The optimal silane turned out to be Ph_2MeSiH, which gave the product **3a** in 74% yield and 86% ee (entry 6). An additional screen of copper source revealed that $Cu(OAc)_2$ (entry 10) gave higher yield and enantiomeric excess than those of CuCl (entry 6), CuOAc (entry 7), CuOTf (entry 8), or $CuCl_2$(entry 9). Changing other reaction parameters such as base (NaO*t*Bu, entry 11) or solvent (toluene, entry 12) proved to be detrimental to both reactivity and enantioselectivity. Reduction of the catalyst loading resulted in lower yield and enantiomeric excess of the product **3a** (entry 13). Lipshutz[16] and Buchwald[4a] groups found that addition of secondary ligand PPh_3 is beneficial to the reactivity of the reaction. However, in our catalytic system, introduction of a secondary ligand such as PPh_3 led to lower reactivity and enantioselectivity (entry 14)

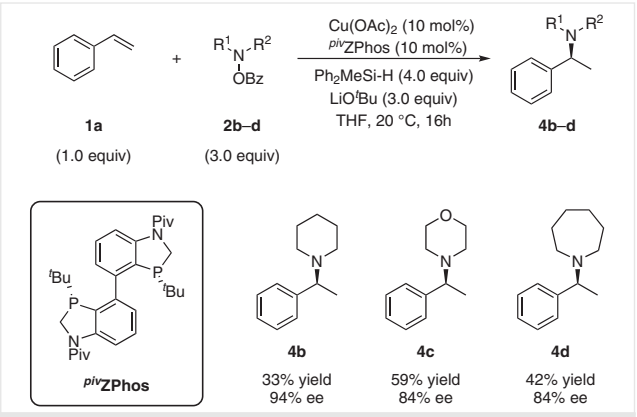
Based on the optimization studies, we set out to evaluate the alkene scope with *O*-benzoyldibenzylhydroxylamine (Scheme 1). 2-Vinylnaphthalene (**1b**) delivered the product **3b** in 75% yield and 78% ee. Sterically hindered styrenes such as **1c** were well tolerated and the product was isolated in moderate yield and good ee (**3c**). When the styrene bearing an electron-withdrawing group at the *ortho*-position was used, the selectivity decreased to moderate level (62% ee) in 72% yield (**3d**). Reactions of substrates with electron-donating (**3e**) or electron-withdrawing (**3f**) groups at *para*-position proceeded smoothly delivering the amines in high yields and enantioselectivities. Vinyl-substituted heteroarenes are challenging substrates and very limited examples were reported by the Buchwald group using 1,2-benzisoxazole as electrophilic amine source.[17] We found that nitrogen-containing substrates proved to be poor starting materials for the hydroamination and only low to moderate reactivities and enantioselectivities were observed (**3i**, **3j**). To our delight, our catalytic system was able to accommodate oxygen- and sulfur-bearing substrates including 5-vinylbenzofuran(**3g**) and 5-vinylbenzo[*b*]thiophene (**3h**). For *trans*-β-methylstyrene, chiral amine **3k** was prepared in moderate yield and with excellent enantioselectiv-



Scheme 1 Substrate scope of alkenes for the hydroamination

ity (92% ee). As expected, *cis*-isomer **1l** showed little activity, which is consistent with our previous observations in the aminoboration.[15]

Our catalytic system was also applicable to cyclic amine coupling partners (Scheme 2). The cyclic amine products containing piperidine (**4b**), morpholine (**4c**), and azepane (**4d**) were prepared in moderate yields (33–59%) and with good to excellent enantioselectivities (84–94% ee).



Scheme 2 Substrate scope of cyclic *O*-benzoylhydroxylamine for the hydroamination

In summary, we have demonstrated the application of ^{piv}ZPhos as a versatile ligand in copper-catalyzed asymmetric hydroamination of styrenes, delivering the resulting chiral amines with up to 89% yields and 94% enantioselectivities. Styrenes with a variety of substitution groups and heterocyclic styrenes are suitable substrates. A series of electrophilic *O*-benzoylhydroxylamines are well tolerated. Further studies on application of the same catalytic system to other asymmetric transformations are currently underway.

Copper-Catalyzed Hydroamination of Styrenes; General Procedure

To a sealed tube was added $Cu(OAc)_2$ (7 mg, 10 mol%), ^{piv}ZPhos (22 mg, 10 mol%), LiO*t*Bu (96 mg, 3.0 equiv), and anhyd THF (2.0 mL). The tube was evacuated and refilled with argon and stirred for 15 min. A solution of the respective styrene (0.40 mmol, 1 equiv) and *O*-benzoylhydroxlyamine (1.20 mmol, 3.0 equiv) in anhyd THF (2.0 mL) was added to the tube followed by the addition of silane Ph_2MeSiH (317 mg, 1.60 mmol, 4 equiv). The reaction mixture was stirred at 20 °C for 16 h before being quenched with H_2O (20 mL). The mixture was extracted with EtOAc (2 × 20 mL) and dried (anhyd Na_2SO_4). After filtration and concentration, the product was purified by silica gel column chromatography.

(*S*)-*N*,*N*-Dibenzyl-1-phenylethan-1-amine (3a)

Prepared according to the general procedure from styrene (42 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (94 mg, 78%) with 86% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 2.32, 3.09 min; $[\alpha]_D^{20}$ –47.0 (*c* 1.30, $CHCl_3$).

^{1}H NMR spectrum was identical with that reported.[3]

(*S*)-*N*,*N*-Dibenzyl-1-(naphthalen-2-yl)ethan-1-amine (3b)

Prepared according to the general procedure from 2-vinylnaphthalene (62 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (106 mg, 75%) with 78% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/IPA, 3 mL/min, 220 nm); t_R = 5.18, 6.55 min.

^{1}H NMR spectrum was identical with that reported.[2]

(*S*)-*N*,*N*-Dibenzyl-1-(*o*-tolyl)ethan-1-amine (3c)

Prepared according to the general procedure from 2-methylstyrene (47 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (76 mg, 60%) with 84% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/IPA, 3 mL/min, 220 nm); t_R = 2.37, 2.97 min.

^{1}H NMR spectrum was identical with that reported.[2]

(*S*)-*N*,*N*-Dibenzyl-1-(2-chlorophenyl)ethan-1-amine (3d)

Prepared according to the general procedure from 2-chlorostyrene (55 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (97 mg, 72%) with 62% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/IPA, 3 mL/min, 220 nm); t_R = 2.96, 3.51 min.

^{1}H NMR spectrum was identical with that reported.[2]

(*S*)-*N*,*N*-Dibenzyl-1-(4-methoxyphenyl)ethan-1-amine (3e)

Prepared according to the general procedure from 4-methoxystyrene (54 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (93 mg, 70%) with 90% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/IPA, 3 mL/min, 220 nm); t_R = 4.27, 5.18 min.

^{1}H NMR spectrum is identical to the one reported in literature.[2]

(*S*)-*N*,*N*-Dibenzyl-1-(4-fluorophenyl)ethan-1-amine (3f)

Prepared according to the general procedure from 4-fluorostyrene (49 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (100 mg, 78%) with 83% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 2.18, 3.63 min.

^{1}H NMR spectrum is identical to the one reported in literature.[2]

(*S*)-1-(Benzofuran-5-yl)-*N*,*N*-dibenzylethan-1-amine (3g)

Prepared according to the general procedure from 5-vinylbenzofuran (58 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (122 mg, 89%) with 88% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 4.11, 5.62 min; $[\alpha]_D^{20}$ –90.4 (*c* 0.20, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.2 Hz, 1 H), 7.57–7.56 (m, 1 H), 4.47 (d, *J* = 8.6 Hz, 1 H), 7.40–7.35 (m, 5 H), 7.32–7.28 (m, 4 H), 7.22–7.28 (m, 2 H), 6.76 (dd, *J* = 2.2, 0.9 Hz, 1 H), 4.02 (q, *J* = 6.8 Hz, 1 H), 3.62 (d, *J* = 13.8 Hz, 2 H), 3.48 (d, *J* = 13.8 Hz, 2 H), 1.48 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.0, 145.0, 140.5, 137.4, 128.7, 128.2, 126.7, 125.0, 120.0, 110.7, 106.7, 56.2, 53.6, 14.3.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{24}H_{24}NO$ [M + H]$^+$: 342.1852; found: 342.1853.

(*S*)-1-(Benzo[*b*]thiophen-5-yl)-*N*,*N*-dibenzylethan-1-amine (3h)

Prepared according to the general procedure from 5-vinylbenzo[*b*]thiophene (64 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). After column chromatography, impurity could be washed off by acid/base extraction. The product was isolated as a colorless oil (122 mg, 85%) with 91% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-3 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 5.50, 8.19 min; $[\alpha]_D^{20}$ –69.4 (*c* 1.30, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 4.2, 1.7 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 8.8 Hz, 1 H), 7.88 (dd, *J* = 8.8, *J* = 1.9 Hz, 1 H), 7.72 (s, 1 H), 7.40–7.37 (m, 5 H), 7.33–7.29 (m, 4 H), 7.24–7.20 (m, 2 H), 4.1 (q, *J* = 6.8 Hz, 1 H), 3.58 (d, *J* = 3.5 Hz, 4 H), 1.54 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.0, 147.7, 141.8, 140.1, 136.0, 130.9, 129.0, 128.7, 128.3, 126.9, 125.6, 121.0, 55.9, 53.6, 12.5.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{24}H_{24}NS$ [M + H]$^+$: 358.1624; found: 358.1623.

(*S*)-*N*,*N*-Dibenzyl-1-(quinolin-6-yl)ethan-1-amine (3i)

Prepared according to the general procedure from 6-vinylquinoline (62 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (59 mg, 42%) with 57% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-4 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 4.69, 5.44 min; $[\alpha]_D^{20}$ +8.0 (*c* 0.30, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.15–8.12 (m, 1 H), 8.09 (d, *J* = 9.2 Hz, 1 H), 7.88 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.72 (br, 1 H), 7.39–7.29 (m, 9 H), 7.24–7.20 (m, 2 H), 4.10 (q, *J* = 6.9 Hz, 1 H), 3.58 (q, *J* = 3.60 Hz, 4 H), 1.54 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.0, 146.7, 140.8, 139.1, 135.0, 129.9, 128.0, 127.7, 127.2, 126.8, 125.9, 124.5, 120.0 54.8, 52.6, 28.7.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{25}H_{25}N_2$ [M + H]$^+$: 353.2012; found: 353.2013.

(*S*)-*N*,*N*-Dibenzyl-1-(2-methylpyridin-3-yl)ethan-1-amine (3j)

Prepared according to the general procedure **A** from 2-methyl-3-vinylpyridine (48 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (41 mg, 32%) with 49% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-4 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 2.29, 2.82 min; $[\alpha]_D^{20}$ +103.3 (*c* 0.50, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.73 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.29–7.21 (m, 10 H), 7.09 (dd, *J* = 7.8, 4.8 Hz, 1 H), 4.09 (q, *J* = 6.8 Hz, 1 H), 3.58 (q, *J* = 13.8 Hz, 4 H), 2.35 (s, 3 H), 1.40 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8, 147.1, 139.6, 137.1, 134.7, 129.0, 128.1, 126.9, 120.8, 54.2, 29.7, 22.2, 13.2.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{22}H_{25}N_2$ [M + H]$^+$: 317.2012; found: 317.2013.

(*S*)-*N*,*N*-Dibenzyl-1-phenylpropan-1-amine (3k)

Prepared according to the general procedure from *trans*-β-methylstyrene (47 mg, 0.40 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (380 mg, 1.20 mmol). The product was isolated as a colorless oil (78 mg, 60%) with 92% ee. Enantiomeric excess was determined by SFC with a Lux Cellulose-4 column (CO_2/MeOH, 3 mL/min, 220 nm); t_R = 1.81, 2.41 min.

^{1}H NMR spectrum was identical with that reported.[2]

(*S*)-1-(1-Phenylethyl)piperidine (4b)

Prepared according to the general procedure from styrene (42 mg, 0.40 mmol) and piperidin-1-yl benzoate (246 mg, 1.20 mmol). The product was isolated as a colorless oil (25 mg, 33%) with 94% ee. Enantiomeric excess was determined by chiral GC with a Supelco beta-DEX325 column (30 m × 0.25 mm × 0.25 µm), He 1.0 mL/min, 100 °C; t_R = 23.05, 23.32 min.

^{1}H NMR spectrum was identical with that reported.[3]

(*S*)-4-(1-Phenylethyl)morpholine (4c)

Prepared according to the general procedure from styrene (42 mg, 0.40 mmol) and morpholino benzoate (248 mg, 1.20 mmol). The product was isolated as a colorless oil (45 mg, 59%) with 84% ee. Enantiomeric excess was determined by chiral GC with a Supelco beta-DEX325 column (30 m × 0.25 mm × 0.25 µm), He 1.0 mL/min, 120 °C; t_R = 32.20, 32.72 min.

^{1}H NMR spectrum was identical with that reported.[3]

(*S*)-1-(1-Phenylethyl)azepane (4d)

Prepared according to the general procedure from styrene (42 mg, 0.40 mmol) and azepan-1-yl benzoate (263 mg, 1.20 mmol). The product was isolated as a colorless oil (34 mg, 42%) with 84% ee. Enantiomeric excess was determined by chiral GC with a Supelco beta-DEX325 column (30 m × 0.25 mm × 0.25 µm), He 1.0 mL/min, 100 °C; t_R = 31.85, 32.37 min.

^{1}H NMR spectrum was identical with that reported.[3]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707346.

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