Tetrahedron: *Asymmetry* 20 (2009) 2845–2853

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of 4,4′-biquinazoline alcohols as chiral catalysts in enantioselective alkynylation of aldehydes with phenyl acetylene

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ARTICLE INFO

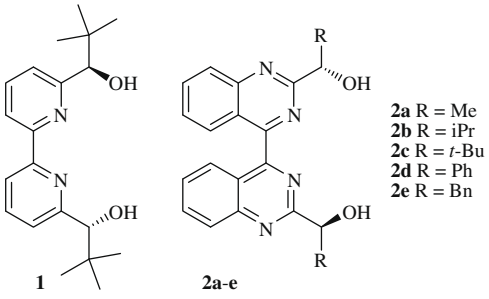
Article history:
Received 19 October 2009
Accepted 1 December 2009
Available online 8 January 2010

ABSTRACT

Optically active propargylic alcohols are important chiral-building blocks in asymmetric synthesis, while the asymmetric addition of a terminal alkyne to an aldehyde is one of the most important procedures to prepare these chiral-building blocks. In this work, a family of chiral 4,4′-biquinazoline alcohols has been conveniently prepared from the easily accessible (*S*)-2-acetoxycarboxylic acid chlorides by reaction sequences beginning with condensation and followed by key synthetic steps including chlorination, nickel(0)-mediated homocoupling, and deprotection in addition to being examined as potential ligands in the enantioselective addition of phenylacetylene to aldehydes. These chiral ligands can be combined with Ti(O*i*Pr)$_4$ and then used to catalyze the asymmetric addition of zinc acetylide, produced in situ by the reaction of phenylacetylene with diethylzinc, to aldehydes. The best enantiomeric excess obtained in this study was 75%.

1. Introduction

Chiral propargylic alcohols are useful and versatile building blocks in asymmetric synthesis as they are used in the preparation of a diverse range of molecules, including natural products, pharmaceuticals, and macromolecules.[1] For this reason, propargyl alcohols have been used as starting materials in many efficient syntheses. The two most common methods to prepare optically active propargylic alcohols include the asymmetric reduction of an ynone[2] and the asymmetric metal-catalyzed alkynylation of an aldehyde.[3] In recent years, great progress has been made in the asymmetric addition reactions of alkynylzinc to aldehydes to yield chiral propargylic alcohols with a high ee of up to 99%. Carreira et al. developed a method for the preparation of optically active propargylic alcohols based on the treatment of aldehydes with zinc acetylides in the presence of (+)-*N*-methylephedrine.[3f,4] Chan et al. have found that a combination of chiral BINOL and sulfonamide with Ti(O*i*Pr)$_4$ produces a highly enantioselective catalyst which catalyzes the addition of in situ-generated alkynylzinc to aromatic aldehydes.[5] Pu et al. developed a convenient process, utilizing the BINOL/Ti(O*i*Pr)$_4$/Et$_2$Zn system, to produce secondary propargylic alcohols with high enantioselectivities.[3i,l,6] Wang et al. found that complexes of sulfonamide alcohols and Ti(O*i*Pr)$_4$ also catalyze the highly enantioselective addition of phenylacetylene to both alkyl and aromatic aldehydes.[7] Other chiral ligands, including amino alcohols,[3n,8] oxazoline,[9] ferrocenyl-substituted aziridinylmethanols[3h,10] and amino acids[11] have also been reported to catalyze this asymmetric addition reaction. New structural motifs play important roles in determining enantioselectivities and reactivities for a given transformation. For example, bipyridine alcohol **1** has been explored as an effective scaffold for the asymmetric addition of diethylzinc to aldehydes.[12]



Prompted by these studies, we chose to make unknown chiral ligands that possess biquinazoline alcohol moiety. Herein, we report the synthesis of these novel chiral 4,4-biquinazoline 0alcohols **2a**–**e** from readily accessible enantiomerically pure (*S*)-2-acetoxycarboxylic acids **3a**–**e**[13–17] and their catalytic activities in the asymmetric addition of phenyl acetylene to aldehydes in the presence of Et$_2$Zn and Ti(O*i*Pr)$_4$. Furthermore metabolite chrysogine **5a**[18,19] derivatives **5b**,**c**,**d**, and **e** have been made available in enantiomerically pure forms.

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doi:10.1016/j.tetasy.2009.12.002

2. Results and discussion

Previous work has illustrated that enantiopure (*S*)-2-acetoxycarboxylic acid chloride and 2-aminobenzamide are useful building blocks that allow the preparation of enantiopure mold metabolite chrysogine **5a** in one step.[19] We envisaged that chlorination of the mold metabolite chrysogine derivatives **5a**–**e** with $POCl_3$ and subsequent nickel(0)-mediated homocoupling would produce the target compounds. The potential utility of this technique has been aptly illustrated in the literature by numerous examples in different fields of organic chemistry.[20–23] In this context, in order to reach the targeted compounds, we selected appropriate (*S*)-2-acetoxycarboxylic acid chlorides[14,15,24–26] and 2-aminobenzamide as key templates. Enantiomerically pure (*S*)-2-acetoxycarboxylic acids **3a**–**e** were converted into (*S*)-2-acetoxycarboxylic acid chlorides by treatment of $SOCl_2$, and reacted with 2-aminobenzamide to yield the corresponding amides **4a**–**e** (Scheme 1). The enantiomeric purities of amides **4a**–**e** were determined by a HLPC system equipped with a chiralyser, which gives the amides **4a**–**e** with enantiomeric purities in 99%, and prevent their original (*S*)-configuration with no partial rasemization; however we noticed that (*S*)-2-acetoxycarboxylic acids **3a**–**e** undergo gradual rasemization on standing at room temperature. The measured specific rotation of the known compound **4a** is in good agreement with the observed values.[19] Cyclization[27] of amides **4a**–**e** by NaOH to form **5a**–**e** was carried out in EtOH at room temperature. A solution of (*S*)-amide **4** in ethanol at 0 °C was treated with 10 M NaOH and stirred for 1 h at room temperature and neutralized with concentrated HCl at 0 °C. The reaction mixture was concentrated in vacuo (45 °C, 20 mbar) to a thick paste and diluted with water. The precipitate was filtered, washed with water, and air-dried. Crystallization from EtOH/H_2O afforded the corresponding (*S*)-quinazoline-4(3*H*)-one alcohols **5a**–**e** in yield of 75–95%. All spectroscopic data of the known compounds **5a** and **d**[20,28,29] are identical with those reported in the literature. The unknown compounds **5b**,**c** and **5e** were characterized by elemental analyses, IR and NMR spectra. Chiral HPLC analysis of **5a**–**e** shows that enantiomeric purities are around 99%. The observed enantiomeric purity of **5d** is higher than that (ee 80%) reported by Bergman.[19] The resulting quinazolinone alcohols **5a**–**e** were converted to the corresponding silyl ether **6a**–**e** with TBDMSCl.[30]

The chlorination[27] of the quinazolinone derivatives **6a**–**e** with phosphoryl chloride in the presence of *N*,*N*-diethyl aniline provided **7a**–**e** in excellent yields (Scheme 2). The chloroquinazolines **7a**–**e** were subjected to Ni(0)-mediated homocoupling[31] in DMF, to afford the desired products **8a**–**e** together with **6** and **9**. After purification of **8** on a silica gel column, deprotection[32] of **8a**–**e** with TBAF gave the desired biquinazoline alcohols **9a**–**e**. The structural assignments of the biquinazoline alcohols relied upon their ^1H NMR, ^{13}C NMR, and mass spectra. An X-ray diffraction analysis of **2c** confirmed the proposed structure (Fig. 1a). The absolute configuration of **2c** was determined to be (*S*) the basis of its source of chirality. The compound crystallizes in the orthorhombic space group C2221 (No: 20), with four molecules in the unit cell (Fig. 1b). In the structure, quinazoline fragments are almost planar (maximum deviation from mean plane for C7 is 0.029 Å) and rather rotated along the C8–C8a symmetry axis. O1–H···N1 and O1a–H···N1a are the strong intramolecular hydrogen bonds detected in the structure and stabilize the quinazoline planes with the substituted units (O1–H···N1 = 2.585(4) Å, O1–H···N1 = 120°).

The newly prepared biquiazoline ligands **2a**,**b**,**c,** and **e** were screened for the asymmetric alkynylation of benzaldehyde with phenylacetylene at 0 °C. Unfortunately, the ee of the benzyl derivative **2d** could not be accurately determined; thus **2d** was not tested in the asymmetric alkynylation reaction. Among them **2b** and **2e** provided promising results in terms of enantioselectivity as shown in Table 1 (entries 1–4). The conditions of the asymmetric alkynylation of benzaldehyde in the presence of chiral ligands **2b** and **e** were optimized (data not shown). We found that the reaction was influenced by the solvents. THF was found to be the best, while other solvents made the reaction sluggish and low enantioselectivities were obtained. Decreasing the reaction temperature from 0 °C to −10 °C led to slow conversions and low enantioselectivities. Increasing the amount of ligand from 10 to 20 mol % resulted in a low ee of 54%. Under the optimized reaction conditions, **2b** and **e** were employed as chiral catalysts for the asymmetric alkynylation of substituted arylaldehydes **10**,[10,33] and the results are summarized in Table 1. Depending on the structure of the ligand and aldehyde, the conversions vary from 0% to 67%. Most of the substituted arylaldehydes underwent the addition reaction with lower levels of enantioselectivity compared with the parent benzaldehyde. Comparison of the chloro-substituted aldehydes and the methoxy-substituted aldehydes show that electronic properties have an effect on the conversion and enantioselectivity of the addition.

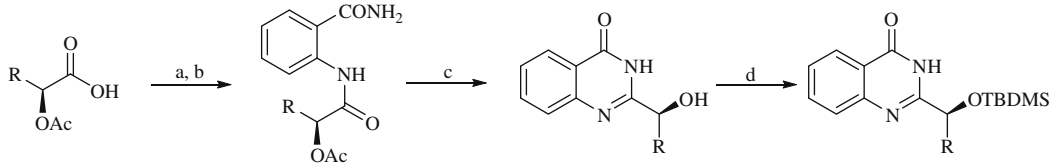
3. Conclusion

In conclusion, we have prepared (*S*)-biquinazoline alcohols **2** from readily accessible starting materials, and employed then as chiral catalysts in the asymmetric addition of phenylacetylene to various aldehydes. The ligands **2b** and **e** showed good enantioselectivities (up to 75% ee) in the asymmetric alkynylation of aldehydes.

4. Experimental

4.1. General

Reagents and solvents were purchased from standard chemical suppliers and purified to match the reported physical and spectroscopic data. Melting points were determined with a Gallenkamp apparatus. Solvents were concentrated at reduced pressure (ca. 20 °C, 20 Torr). IR spectra were obtained on KBr pellets with a Perkin–Elmer apparatus. ^1H and ^{13}C NMR spectra were recorded on a



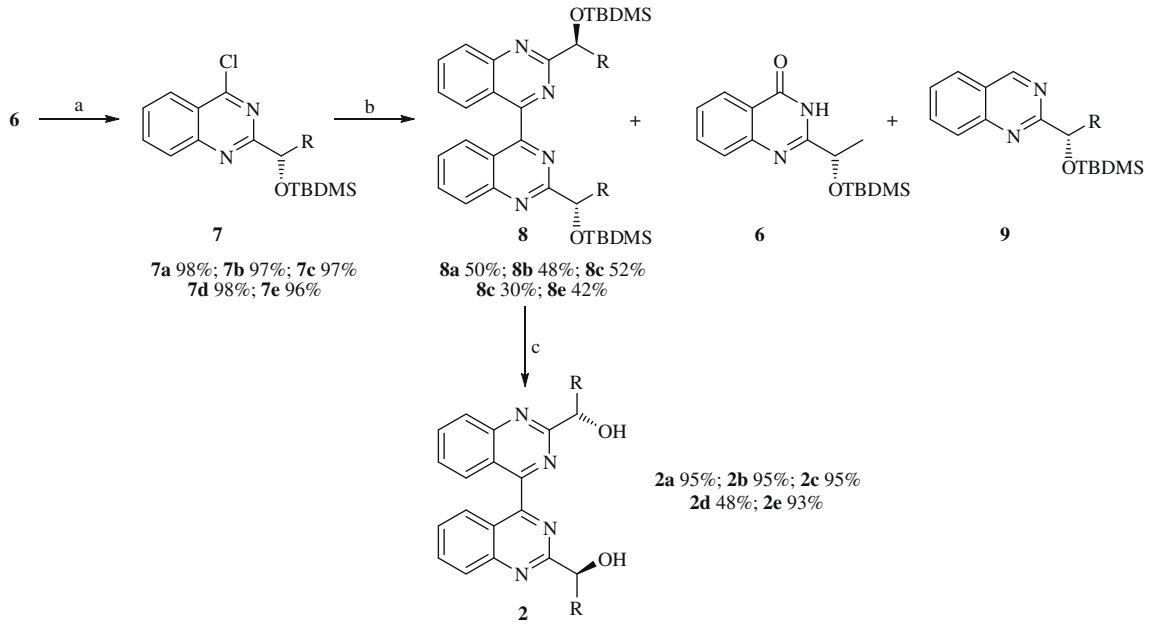
3
3a, R = Me; **3b**, R = *i*Pr
3c, R = *t*-Bu; **3d**, R = Ph
3e, R = Bn

4
4a 92%; **4b** 87%; **4c** 91%
4d 95%; **4e** 89%

5
5a 94%; **5b** 98%; **5c** 75%
5d 95%; **5e** 90%

6
6a 96%; **6b** 94%; **6c** 97%
6d 95%; **6e** 96%

Scheme 1. Synthesis of quinazolinones **6**. Reagents and conditions: (a) $SOCl_2$ (3.0 equiv); (b) anthranilamide (2.2 equiv), 5 °C, DCM; (c) 10 M NaOH (4 equiv), EtOH, rt, 1 h; (d) TBDMSCl (2.0 equiv), imidazole (2.5 equiv).



Scheme 2. Synthesis of the biquinazoline alcohols **2**. Reagents and conditions: (a) $POCl_3$ (1.2 equiv), $PhNEt_2$ (2.0 equiv); (b) PPh_3 (4.0 equiv), $NiCl_2{\cdot}6H_2O$ (1.0 equiv), Zn (1.5 equiv), DMF, 50 °C; Ratio of **8**:**6**:**9**; **8a**:**6a**:**9a** = 64:19:17; **8b**:**6b**:**9b** = 54:46:0; **8c**:**6c**:**9c** = 53:47:0; **8d**:**6d**:**9d** = 37:12:51; **8e**:**6e**:**9e** = 48:52:0; (c) Bu_4NF (2.5 equiv), THF, 20 °C.

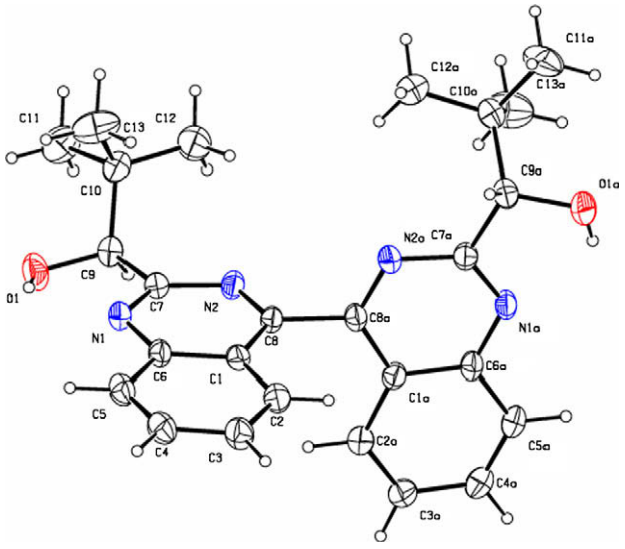


Figure 1a. X-ray crystal structure of biquinazoline **2c**. The asymmetric unit contains half of the molecule. Displacement ellipsoids are shown at the 40% probability level.

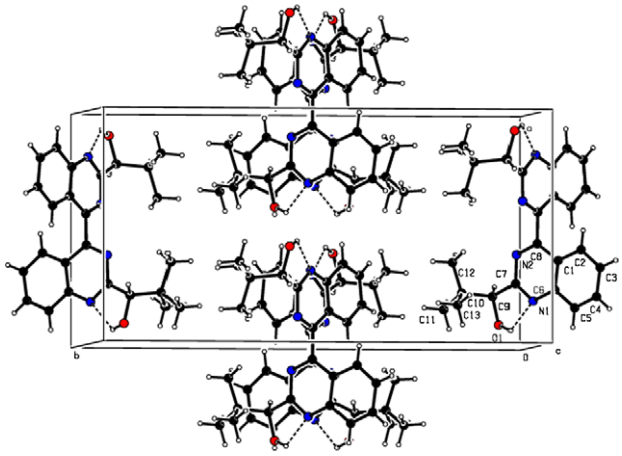


Figure 1b. Packing diagram of **2c** along the *a*-axis. Dashed lines indicate intramolecular hydrogen bonds.

Varian (200, 400) spectrometer in $CDCl_3$. Enantiomeric excesses were determined by HPLC analysis using a chiral column with eluent *n*-hexane–*i*-PrOH, and detection was performed at 254 nm. Optical rotations were measured with a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter in a 1 dm tube; Concentrations were given in g/100 mL. A polarimetric Chiralyser detector was used to assess the sign of configuration of the enantiomer formed. All column chromatography was performed on silica gel.

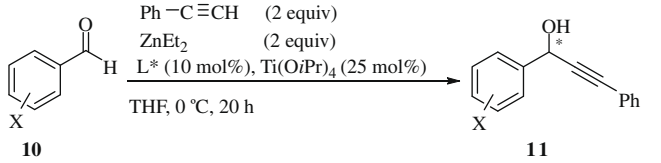
4.2. General procedure for the amide 4

At first, $SOCl_2$ (47.2 g, 0.4 mol) was added to (*S*)-2-acetoxycarboxylic acid **3** (0.1 mol) dropwise over 1 h at 0 °C. After the addition was complete, the reaction mixture was stirred for an additional 4 h at room temperature. Excess $SOCl_2$ was evaporated in vacuo to give corresponding acyl chloride. Without any further purification the acyl chloride was used in the next step. Then, to a pre cooled suspension of anthranilamide (29.9 g, 0.22 mol) in diethyl ether (150 mL) was added a solution of acyl chloride prepared as described above in diethylether (15 ml) over 1h. During vigorous stirring, a solution of acyl chloride prepared as described above in CH_2Cl_2 (15 mL) was added dropwise over 1 h. After the addition was complete, the mixture was stirred at room temperature overnight. The reaction mixture was washed with 2 M HCl (2 × 100 mL) and water (100 mL), the organic layer dried over Na_2SO_4, and the solvent removed under reduced pressure (20 mbar, 20 °C). Crystallization of crude mixture gave the corresponding amide **4**.

4.2.1. (*S*)-1-(2-Carbamoylphenylamino)-1-oxopropan-2-yl acetate 4a

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 92%; mp 131–133 °C; ^1H NMR (400 MHz, $CDCl_3$,

Table 1
Asymmetric alkynylation of aryldehydes with phenylacetylene in the presence of ligands **2a**,**b**,**c**, and **2e**



10 **11**

Entry	Aldehyde	Ligand	Convn[a] (%)	Yield[a] (%)	Ee[b] (%)
1	C_6H_5CHO	**2a**	nd	nd	*rac*
2	C_6H_5CHO	**2b**	67	64	(*S*) 75
3	C_6H_5CHO	**2c**	nd	nd	*rac*
4	C_6H_5CHO	**2e**	64	62	(*S*) 70
5	*o*-ClC_6H_4CHO	**2b**	63	69	(*S*) 73
6		**2e**	58	65	(*S*) 74
7	*o*-$MeOC_6H_4CHO$	**2b**	18	70	(*S*) 06
8		**2e**	0	—	—
9	*m*-ClC_6H_4CHO	**2b**	62	71	(*S*) 32
10		**2e**	60	86	(*S*) 38
11	*m*-$MeOC_6H_4CHO$	**2b**	15	65	(*S*) 60
12		**2e**	12	73	(*S*) 68
13	*p*-ClC_6H_4CHO	**2b**	46	65	(*S*) 08
14		**2e**	60	75	(*S*) 13
15	*p*-MeC_6H_4CHO	**2b**	60	90	(*S*) 58
16		**2e**	nd	nd	(*S*) 28

[a] The conversions and yields were assessed by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard.
[b] Determined by chiral HPLC analysis (Chiralcel OD-H); absolute configurations were determined by comparison of the order of the peaks observed from HPLC with the literature values. See Refs. 10 and 33.

ppm) δ 11.82 (br s, 1H), 8.64 (dd, J = 8.4, 0.8 Hz, 1H), 7.51 (dd, J = 7.9, 1.3 Hz, 1H), 7.48–7.45 (m, 1H), 7.11–7.07 (m, 1H) 6.34 (br s, 1H), 5.74 (br s, 1H), 5.31 (q, J = 6.9, Hz, 1H), 2.27 (s, 3H), 1.56 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 170.3, 169.9, 139.6, 133.5, 127.5, 123.3, 121.6, 119.2, 70.8, 21.2, 18.0; IR (KBr cm^{-1}) 3353, 3221, 1742, 1665, 1615, 1583, 1450, 1375, 1310, 1227, 1088, 1042. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.35; H, 5.65; N, 11.22; $[\alpha]_D^{20} = -102.3$ (*c* 1, EtOH)[19]; $[\alpha]_D^{20} = -103$ (*c* 1, EtOH); ee: 99%; retention time: 25.4 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 220 nm.

4.2.2. (*S*)-1-(2-Carbamoylphenylamino)-3-methyl-1-oxobutan-2-yl acetate 4b

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 87%; mp 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.73 (br s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 7.54–7.53 (m, 1H), 7.52–7.41 (m, 1H), 7.07–7.03 (m, 1H), 5.13 (d, J = 4.3 Hz, 1H), 2.40–2.32 (m, 1H), 2.27 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6,9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 170.8, 169.1, 139.4, 133.4, 127.7, 123.4, 121.6, 119.2, 76.9, 30.9, 21.1, 19.1, 17.1; IR (KBr cm^{-1}) 3355, 2963, 2924, 2873, 1731, 1615, 1454, 1306, 1029; Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.16; H, 6.54; N, 10.08; $[\alpha]_D^{20} = -120$ (*c* 1, EtOH); ee: 99%; retention time: 20.1 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 220 nm.

4.2.3. (*S*)-1-(2-Carbamoylphenylamino)-3,3-dimethyl-1-oxobutan-2-yl acetate 4c

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 91%; mp 66–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.59 (br s, 1H), 8.63 (d, J = 8.4 Hz, 1H), 7.55–7.53 (m, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 4.89 (s, 1H), 2.27 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.8, 170.8, 168.1, 139.3, 133.4, 127.8, 123.4, 121.7, 119.2, 81.8, 34.5, 33.5, 26.5, 21.1; IR (KBr cm^{-1}) 3355, 3218, 2966, 2873, 1746, 1667, 1614, 1583, 1450, 1374, 1307, 1240, 1057; Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.23; H, 7.02; N, 9.57; $[\alpha]_D^{20} = -136$ (*c* 1, EtOH); ee: 99%; retention time: 21.9 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 220 nm.

4.2.4. (*S*)-2-(2-Carbamoylphenylamino)-2-oxo-1-phenylethyl acetate 4d

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 95%; mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 12.08 (br s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 7.56–7.44 (m, 4H), 7.40–7.32 (m, 3H), 7.08–7.04 (m, 1H), 6.16 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 169.9, 167.7, 139.8, 135,6, 133.6, 129.1, 128.9, 127.6, 127.5, 123.4, 121.7, 119.0, 76.2, 21.1; IR (KBr cm^{-1}) 3355, 3176, 3131, 3025, 2919, 1686, 1605, 1450, 1261, 1059; Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.09; H, 5.07; N, 8.84; $[\alpha]_D^{20} = +60$ (*c* 1, EtOH); ee: 99%; retention time: 31.8 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 220 nm.

4.2.5. (*S*)-1-(2-Carbamoylphenylamino)-1-oxo-3-phenylpropan-2-yl acetate 4e

Colorless oil. Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.75 (br s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 7.53–7.42 (m, 2H), 7.29–7.18 (m, 5H), 7.06 (ddd, J = 8.1, 7.5, 0.9 Hz, 1H), 5.47 (dd, J = 8.7, 3.9 Hz, 1H), 3.35 (dd, A part of AB system, J = 14.3, 3.9 Hz, 1H), 3.14 (dd, B part of AB system, J = 14.3, 8.7 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 170.3, 168.7, 139.3, 136.4, 133.4, 129.6, 128.6, 127.6, 127.1, 123.5, 121.6, 119.3, 74.9, 38.3, 21.0; IR (KBr cm^{-1}) 3434, 351, 3226, 1741, 1664, 1616, 1583, 1523, 1451, 1382, 1306, 1223, 1063; MS (FAB) *m*/*z* 327 (MH^+); HRMS (FAB); calcd for $C_{18}H_{19}N_2O_4$ [MH^+] 327.1345; found: 327.1342 $[\alpha]_D^{20} = -105$ (*c* 2.35, EtOH); ee: 99%; retention time: 36.8 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 220 nm.

4.3. General procedure for the preparation of quinazolinone 5

To a solution of (*S*)-amide **4** (50 mmol) in 60 mL of ethanol at 0 °C was added freshly prepared 10 M NaOH (10 g, 250 mmol) dropwise over 25 min. The mixture was then stirred for 1 h at room temperature and re-cooled to 0 °C and neutralized with concentrated HCl. The mixture was concentrated in vacuo (45 °C, 20 mbar) to a thick paste and diluted with water (150 mL). The precipitate was filtered, washed with a copious amount of water, and air-dried. Crystallization from EtOH/H_2O afforded quinazolinone **5**.

4.3.1. (*S*)-2-(1-Hydroxyethyl)quinazolin-4(3*H*)-one 5a

Crystallization from a mixture of EtOAc–H_2O gave colorless needles. Yield: 94%; mp 187–189 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm) δ 11.81 (br s, 1H), 8.08 (dd, J = 8.0, 1.1 Hz, 1H), 7.79–7.75 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48–7.44 (m, 1H), 5.65 (br s, 1H), 4.56 (q, J = 6.6 Hz, 1H), 1.41 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm) δ 164.7, 159.8, 150.7, 136.7, 129.2, 128.7, 128.4, 123.1, 69.5, 24.4; IR (KBr cm^{-1}) 3467, 3362, 3187, 3070, 2929, 1673, 1612, 1295, 1236, 1160. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.34; H, 5.39; N, 14.67; $[\alpha]_D^{20} = -39.8$ (*c* 2.5, EtOH)[19]; $[\alpha]_D^{20} = -41$ (*c* 2.5, EtOH); ee: 99%; retention time: 9.6 min, Chiralcel OD-H, *n*-hexane–*i*PrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.3.2. (*S*)-2-(1-Hydroxy-2,2-dimethylpropyl)quinazolin-4(3*H*)-one 5b

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 98%; mp 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$,

ppm) δ 10.86 (br s, 1H), 8.27 (ddd, J = 8.1, 1.5, 0.5 Hz, 1H), 7.77 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.68 (ddd, J = 8.4, 1.2, 0.5 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 4.62–4.59 (m, 1H), 3.83 (d, J = 5.5 Hz, 1H), 2.35 (d sept., J = 6.9, 3.9 Hz, 1H), 1.14 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.7, 156.9, 147.7, 135.1, 127.4, 127.0, 126.7, 121.2, 75.6, 33.8, 19.4, 15.8; IR (KBr cm^{-1}) 3467, 3362, 3187, 3070, 2929, 1673, 1612, 1295, 1236, 1160; Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.71; H, 6.46; N, 12.85; $[\alpha]_D^{20} = -46$ (c 1, EtOH); ee: 99%; retention time: 8.7 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.3.3. (*S*)-2-(1-Hydroxy-2,2-dimethylpropyl)quinazolin-4(3*H*)-one 5c

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 75%; mp 153.5–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.55 (br s, 1H), 8.26 (d, J = 7.9 Hz, 1H), 7.77–7.73 (m, 1H), 7.68–7.66 (m, 1H), 7.49–7.45 (m, 1H), 4.41 (s, 1H), 4.10 (br s, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.5, 155.9, 148.5, 134.9, 127.5, 127.0, 126.6, 121.3, 79.0, 36.7, 26.1; IR (KBr cm^{-1}) 3354, 3207, 3083, 2958, 2872, 1673, 1611, 1567, 1470, 1366, 1328, 1292, 1252, 1136, 1076, 1020. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.04; H, 7.13; N, 12.07; $[\alpha]_D^{20} = -33$ (c 1, EtOH); retention time: 12.8 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 0.6 mL/min, 254 nm.

4.3.4. (*S*)-2-[Hydroxy(phenyl)methyl]quinazolin-4(3*H*)-one 5d

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 95%; mp 188–190 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm) δ 12.03 (br s, 1H), 8.09–8.06 (m, 1H), 7.76–7.72 (m, 1H), 7.64–7.62 (m, 1H), 7.58–7.56 (m, 2H), 7.46–7.42 (m, 1H), 7.34–7.31 (m, 2H), 7.23–7.21 (m, 1H), 5.60 (s, 1H), 3.40, (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm) δ 162.4, 159.2, 148.9, 141.6, 135.1, 128.9, 128.4, 127.5, 127.3, 127.1, 126.5, 121.8, 73.9; IR (KBr cm^{-1}) 3354, 3215, 1739, 1666, 1614, 1521, 1451, 1385, 1306, 1222, 1044. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.32; H, 4.84; N, 11.00; $[\alpha]_D^{20} = +66$ (c 1, EtOH); ee: 99%; retention time: 12.9 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.3.5. (*S*)-2-(1-Hydroxy-2-phenylethyl)quinazolin-4(3*H*)-one 5e

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 90%; mp 230–231 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm) δ 11.97 (br s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.77 (td, J = 8.2, 1.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.47 (td, J = 8.2, 1.1 Hz, 1H), 7.24–7.14 (m, 5H), 5.77 (m, 1H), 4.63 (m, 1H), 3.16 (dd, A part of AB system, J = 13.6, 5.0 Hz, 1H), 2.99 (dd, B part of AB system, J = 13.6, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm) δ 162.2, 159.3, 149.1, 138.7, 135.1, 130.1, 128.7, 128.5, 127.7, 127.1, 126.8, 126.5, 121.9, 73.0, 41.8; IR (KBr cm^{-1}) 3137, 3025, 2918, 1944, 1667, 1605, 1496, 1448, 1128, 1059. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.33; N, 10.66; $[\alpha]_D^{20} = -1$ (c 1, AcOH); ee: 99%; retention time: 14.8 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.4. General procedure for the preparation of 6

To a solution of quinazolinone **5** (30 mmol) in 15 mL of DMF were added *tert*-butylchlorodimethylsilane (60 mmol) and imidazole (75 mmol) at room temperature. After completion of the reaction, the reaction was quenched with water (20 mL). The mixture was extracted with hexanes (3 × 100 mL) and the organic layer washed with plenty of water, dried over Na_2SO_4, and the solvent removed under reduced pressure (30 °C, 20 mbar). The crude mixture was chromatographed on a silica gel column by eluting with hexane–ethyl acetate (97:03) to afford **6** in a yield of 95–97%.

4.4.1. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)ethyl)quinazolin-4(3*H*)-one 6a

Crystallization from hexane gave colorless needles. Yield: 96%; mp 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.52 (br s, 1H, NH), 8.28 (dd, J = 8.2, 1.5 Hz, 1H), 7.75 (ddd, J = 8.2, 7.2, 1.5 Hz, 1H), 7.67–7.61 (m, 1H), 7.49–7.41 (m, 1H), 4.85 (q, J = 6.6 Hz, 1H), 1.54 (d, J = 6.6 Hz, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.6, 158.2, 149.1, 134.8, 127.3, 126.8, 126.7, 121.6, 69.4, 26.0, 24.1, 18.3, −4.4, −4.8; IR (KBr cm^{-1}) 3378, 3187, 3137, 3082, 2929, 2857, 1676, 1610, 1469, 1334, 1253, 1121, 1097; Anal. Calcd for $C_{16}H_{24}N_2O_2Si$; C, 63.12; H, 7.95; N, 9.20. Found: C, 63.18; H, 7.80; N, 9.27; $[\alpha]_D^{20} = -86$ (c 1, EtOH); ee: 99%; retention time: 6.1 min, Chiralcel OD-H, n-hexane–iPrOH, 99:01, flow rate of 1 mL/min, 254 nm.

4.4.2. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl)quinazolin-4(3*H*)-one 6b

Colorless oil. Yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.45 (br s, 1H), 8.30 (dd, J = 8.0, 1.2 Hz, 1H), 7.77 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.48 (ddd, J = 8.0, 7.0, 0.8 Hz, 1H), 4.51 (d, J = 4.6 Hz, 1H), 2.15 (d sept., J = 6.9, 4.6 Hz, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.96 (s, 9H), 0.95 (d, J = 6.9 Hz, 3H), 0.16 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.4, 157.0, 148.9, 134.8, 127.4, 126.8), 121.6, 77.6, 35.1, 26.0, 19.1, 18.3, 17.1, −2.7, −4.8; IR (KBr cm^{-1}) 3383, 3182, 3075, 2958, 2924, 2857, 1675, 1612, 1468, 1334, 1253, 1087; MS (FAB) m/z 333 (MH^+); HRMS (FAB) calcd for $C_{18}H_{28}N_2O_2Si$ [MH^+] 333.1998, found 333.1990; $[\alpha]_D^{20} = -88$ (c 1.0, EtOH); ee: 99%; retention time: 4.1 min, Chiralcel OD-H, n-hexane–iPrOH, 95:05, flow rate of 1 mL/min, 254 nm.

4.4.3. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpropyl)-quinazolin-4(3*H*)-one 6c

Colorless oil. Yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.21 (br s, 1H), 8.28 (ddd, J = 8.1, 1.5, 0.5 Hz, 1H), 7.75 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.68 (ddd, J = 8.4, 1.2, 0.5 Hz, 1H), 7.47 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 4.33 (s, 1H), 0.99 (s, 9H), 0.94 (s, 9H), 0.13 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.3, 155.8, 148.5, 134.9, 127.6, 127.0, 126.8, 121.7, 80.6, 36.9, 26.3, 26.0, 18.3, −4.9, −5.0; IR (KBr cm^{-1}) 3385, 3193, 3081, 2927, 2711, 1671, 1608, 1466, 1333, 1254, 1084, 1033; MS (FAB) m/z 347 (MH^+); HRMS (FAB) calcd for $C_{19}H_{31}N_2O_2Si$ [MH^+] 347.2125, found 347.2131; $[\alpha]_D^{20} = -111$ (c 4.0, EtOH); ee: 99%; retention time: 5.7 min, Chiralcel OD-H, n-hexane, flow rate of 1 mL/min, 254 nm.

4.4.4. (*S*)-2-((*tert*-Butyldimethylsilyloxy)(phenyl)methyl)quinazolin-4(3*H*)-one 6d

Crystallization from hexane gave colorless needles. Yield: 95%; mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.64 (br s, 1H), 8.26–8.23 (m, 1H), 7.75–7.66 (m, 2H), 7.56–7.54 (m, 2H), 7.46–7.42 (m, 1H), 7.36–7.26 (m, 3H), 5.75 (s, 1H), 0.95 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.8, 156.5, 149.0, 140.0, 134.8, 128.9, 128.7, 127.6, 127.0, 126.8, 126.0, 121.8, 75.1, 26.0, 18.5, −4.6, −4.9; IR (KBr cm^{-1}) 3354, 3215, 1739, 1666, 1614, 1521, 1451, 1385, 1306, 1222, 1044; Anal. Calcd for $C_{21}H_{26}N_2O_2Si$: C, 68.81; H, 7.15; N, 7.64. Found: C, 68.87; H, 7.18; N, 7.70; $[\alpha]_D^{20} = +7.0$ (c 1.0, EtOH); ee: 99%; retention time: 5.9 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 254 nm.

4.4.5. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-2-phenylethyl)quinazolin-4(3*H*)-one 6e

Crystallization from ethanol gave colorless needles. Yield: 96%; mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.38 (br s, 1H), 8.2

(dd, J = 7.96, 1.1 Hz, 1H), 7.82–7.73 (m, 1H), 7.70 (ddd, J = 8.2, 1.1, 0.5 Hz, 1H), 7.48 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.30–7.13 (m, 5H), 4.89 (dd, J = 8.2, 3.5 Hz, 1H), 3.20 (dd, A part of AB system, J = 13.5, 3.5 Hz, 1H), 2.99 (dd, B part of AB system, J = 13.5, 8.1 Hz, 1H), 0.85 (s, 9H), −0.14 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.4, 157.0, 148.9, 136.4, 134.8, 130.2, 128.5, 127.4, 127.2, 126.9, 121.7, 74.2, 44.1, 25.9, 18.3, −5.1, −5.3; IR (KBr cm^{-1}) 3461, 2927, 2850, 1736, 1681, 1608, 1492, 1464, 1334, 1258, 1093; Anal. Calcd for $C_{22}H_{28}N_2O_2Si$: C, 69.43, H, 7.42, N, 7.36. Found: C, 69.41, H, 7.64; N, 7.41; $[\alpha]_D^{20} = -45$ (c 1, EtOH); ee: 99%; retention time: 3.8 min, Chiralcel OD-H, n-hexane–iPrOH, 98:02, flow rate of 1 mL/min, 254 nm.

4.5. General procedure for the preparation of 7

To a solution of (*S*)-**6** (20 mmol) in dry benzene (50 mL) were added $PhNEt_2$ (40 mmol) followed by $POCl_3$ (24 mmol) at 0 °C. The reaction mixture was then refluxed for 3–4 h, cooled to room temperature, and diluted with EtOAc (150 mL). The mixture was washed successively with icy water (3 × 50 mL), 1 M HCl (2 × 50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, and evaporated under reduced pressure (20 °C, 15 mbar). Purification by column chromatography (silica gel, hexane–EtOAc, 98:02) gave 4-chloroquinazoline **7** in a yield of 96–98%.

4.5.1. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)ethyl)-4-chloroquinazoline 7a

Colorless oil. Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24 (dd, J = 8.4, 0.7 Hz, 1H), 8.06 (ddd, J = 8.4, 1.1, 0.7 Hz, 1H), 7.93 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 7.68 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 5.16 (q, J = 6.6, Hz, 1H), 1.63 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.9, 162.8, 151.5, 134.9, 128.9, 128.5, 125.9, 122.8, 72.6, 26.1, 23.7, 18.7, −4.3, −4.7; IR (KBr cm^{-1}) 2974, 2929, 1613, 1558, 1485, 1376, 1306, 1264, 1132, 1104, 1034; MS (FAB) m/z 323 (MH^+); HRMS (FAB) calcd for $C_{16}H_{24}ClN_2OSi$ [MH^+] 323.1346, found 323.1340; $[\alpha]_D^{20} = -83$ (c 1.0, CH_2Cl_2).

4.5.2. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl)-4-chloroquinazoline 7b

Colorless oil. Yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24 (ddd, J = 8.3, 1.4, 0.6 Hz, 1H), 8.05 (ddd, J = 8.5, 1.2, 0.6 Hz, 1H), 7.92 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.67 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 2.36–2.27 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.85 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.01 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.3, 162.6, 151.3, 134.8, 128.9, 128.5, 125.9, 122.7, 81.7, 34.6, 26.0, 19.5, 18.6, 18.2, −4.3, −4.7; IR (KBr cm^{-1}) 2952, 2851, 1613, 1567, 1482, 1339, 1306, 1251, 1191, 1127, 1110, 1065; MS (FAB) m/z 351 (MH^+); HRMS (FAB) calcd for $C_{18}H_{28}ClN_2OSi$ (MH^+) 351.1659, found 351.1652; $[\alpha]_D^{20} = -56$ (c 3, CH_2Cl_2).

4.5.3. (*S*)-2-(1-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpropyl)-4-chloroquinazoline 7c

Colorless oil. Yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (dd, J = 8.2, 1.4 Hz, 1H), 8.05 (dd, J = 8.4, 1.2 Hz, 1H), 7.92 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.68 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 4.68 (s, 1H), 1.00 (s, 9H), 0.88 (s, 9H), −0.02 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 161.6, 151.1, 134.6, 128.9, 128.5, 125.8, 122.6, 83.6, 37.0, 26.4, 26.0, 18.5, −4.5, −4.9; IR (KBr cm^{-1}) 2952, 2851, 1619, 1569, 1549, 1476, 1359, 1334, 1306, 1244, 1104; MS (FAB) m/z 365 (MH^+); HRMS (FAB) calcd for $C_{19}H_{30}ClN_2OSi$ (MH^+) 365.1816, found 365.1808; $[\alpha]_D^{20} = -50$ (c 0.6, CH_2Cl_2).

4.5.4. (*S*)-2-((*tert*-Butyldimethylsilyloxy)(phenyl)methyl)-4-chloroquinazoline 7d

Colorless oil. Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.20 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.90 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.69–7.62 (m, 3H), 7.34–7.22 (m, 3H), 6.13 (s, 1H), 0.94 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 163.0, 151.5, 142.1, 134.8, 129.0, 128.6, 128.3, 127.7, 126.7, 125.9, 122.8, 78.3, 26.1, 18.7, −4.4, −4.5; IR (KBr cm^{-1}) 2928, 2856, 1613, 1567, 1481, 1339, 1307, 1225, 1112, 1065; Anal. Calcd for $C_{21}H_{25}ClN_2OSi$: C, 65.52; H, 6.55; N, 7.28. Found: C, 65.14; H, 6.55; N, 7.30; $[\alpha]_D^{20} = -55$ (c 1, CH_2Cl_2).

4.5.5. (*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-2-phenylethyl)-4-chloroquinazoline 7e

Crystallization from hexane gave colorless needles. Yield: 96%; mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.98–7.91 (m, 1H), 7.74–7.64 (m, 1H), 7.39–7.16 (m, 5H), 5.13 (dd, J = 9.6, 3.7 Hz, 1H), 3.29 (dd, A part of AB system, J = 13.3, 3.7 Hz, 1H), 3.11 (dd, B part of AB system, J = 13.3, 9.6 Hz, 1H), 0.73 (s, 9H), −0.21 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 162.9, 151.5, 138.7, 135.0, 130.2, 128.9, 128.7, 128.3, 126.5, 126.0, 122.8, 78.3, 44.1, 25.9, 18.5, −4.9, −5.0; IR (KBr cm^{-1}) 3025, 2924, 2851, 1567, 1476, 1309, 1253, 1102; Anal. Calcd for $C_{22}H_{27}ClN_2OSi$: C, 66.22; H, 6.82; N, 7.02. Found: C, 66.17; H, 6.92; N, 7.10; MS (FAB) m/z 399 (MH^+); HRMS (FAB) calcd for $C_{22}H_{27}ClN_2OSi$ (MH^+) 399.1659, found 399.1654; $[\alpha]_D^{20} = -1.5$ (c 6.5, CH_2Cl_2).

4.6. General procedure for the Ni(0)-mediated coupling of chloroquinazoline 7

To a solution of triphenyl phosphine (11 g, 42 mmol) in 30 mL of DMF was added $NiCl_2{\cdot}6H_2O$ (2.85 g, 12 mmol) and heated to 50 °C under nitrogen atmosphere. After 5 min, zinc dust (15 mmol, 0,975 g) was added and the mixture was stirred for 1 h. Then, a solution of 4-chloro-quinazoline **7** (10 mmol) in 5 mL of DMF was injected into the mixture using a syringe. After stirring for 1–12 h, the mixture was cooled to room temperature, treated with ammonia (50 mL, 28% in water), and the crude mixture was extracted with hexane (3 × 100 mL and washed with brine). The organic layer was dried with Na_2SO_4, the solvents were removed under reduced pressure (20 °C, 15 mbar). The residue was chromatographed with silica gel column by eluting with hexane to give triphenyl phosphine as the first fractions. Later fractions eluted with EtOAc–hexane (5:95) afforded **8**, **9** and **6**, respectively.

4.6.1. 2,2′-Bis-[1-(*tert*-Butyldimethylsilanyloxy)-ethyl]-[4,4′]-biquinazoline 8a

Crystallization from hexane gave colorless needles. Yield: 50%; mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (d, J = 8.5 Hz, 2H), 7.96–7.90 (m, 2H), 7.89–7.85 (m, 2H), 7.57–7.48 (m, 2H), 5.32 (q, J = 6.5 Hz, 2H), 1.67 (d, J = 6.5 Hz, 6H), 0.92 (s, 18H), 0.11 (s, 6H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.5, 164.2, 151.8, 134.4, 129.2, 128.0, 126.7, 122.4, 73.2, 26.1, 24.1, 18.7, −4.2, −4.5; IR (KBr cm^{-1}) 3467, 2924, 2851, 1611, 1561, 1488, 1367, 1253, 1096; Anal. Calcd for $C_{32}H_{46}N_4O_2Si_2$: C, 66.85; H, 8.06; N, 9.75. Found: C, 67.23; H, 8.23; N, 9.74; $[\alpha]_D^{20} = +70$ (c 1.1, chloroform); ee: 99%; retention time: 7.1 min, Chiralcel OD-H, n-hexane, flow rate of 1 mL/min, 265 nm.

4.6.2. 2,2′-Bis-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]-4,4′-biquinazoline 8b

Crystallization from hexane gave colorless needles. Yield: 48%; mp 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.18 (d, J = 8.2 Hz, 2H), 7.92 (ddd, J = 8.4, 6.9, 1.4 Hz, 2H), 7.84 (ddd, J = 8.4, 1.2, 0.6 Hz, 2H), 7.51 (ddd, J = 8.2, 6.9, 1.2 Hz, 2H), 4.76 (d,

J = 7,5 Hz, 2H), 2.40–2.34 (m, 2H), 1.07 (d, J = 6,7 Hz, 6H), 0.88 (s, 18H), 0.87 (d, J = 6.7 Hz, 6H), 0.08 (s, 6H), −0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 164.1, 151.6, 134.4, 129.2, 128.0, 126.7, 122.4, 82.5, 34.8, 22.6, 19.5, 18.7, 18.6, −4.1, −4.6; IR (KBr cm^{-1}) 3067, 2926, 2851, 2711, 1725, 1615, 1560, 1467, 1383, 1255, 1069, 1006; Anal. Calcd for $C_{36}H_{54}N_4O_2Si_2$: C, 68.52; H, 8.63; N, 8.88. Found: C, 68.35; H, 8.81; N, 8.93; $[\alpha]_D^{20} = -49$ (c 1, EtOH); ee: 99%; retention time: 4.3 min, Chiralcel OD-H, n-hexane, flow rate of 1 mL/min, 265 nm.

4.6.3. 2,2′-Bis-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpropyl)-4,4′-biquinazoline 8c

Crystallization from hexane gave colorless needles. Yield: 52%; mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.18 (d, J = 8.4 Hz, 2H), 7.95–7.84 (m, 2H), 7.51 (ddd, J = 8.2, 6.9, 1.1 Hz, 2H), 4.84 (s, 2H), 1.04 (s, 18H), 0.86 (s, 18H), 0.03 (s, 6H), −0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 163.5, 151.4, 134.1, 129.2, 127.7, 126.7, 122.2, 84.1, 37.1, 26.6, 26.1, 18.5, −4.9, −5.0; IR (KBr cm^{-1}) 3064, 2969, 2927, 2851, 1723, 1615, 1560, 1473, 1362, 1251, 1100, 1032; Anal. Calcd for $C_{38}H_{58}N_4O_2Si_2$: C, 69.25; H, 8.87; N, 8.50. Found: C, 69.19; H, 8.87; N, 8.46; $[\alpha]_D^{20} = -87$ (c 1, EtOH); retention time: 3.8 min, Chiralcel OD-H, n-hexane, flow rate of 1 mL/min, 265 nm.

4.6.4. 2,2′-Bis-((*S*)-(*tert*-Butyldimethylsilyloxy)(phenyl)methyl)-4,4′-biquinazoline (8d)

Crystallization from ethanol gave colorless needles. Yield: 30%; mp 138.5–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (d, J = 8.5 Hz, 2H), 7.91–7.85 (m, 2H), 7.77–7.74 (m, 2H), 7.66–7.63 (m, 4H), 7.41–7.28 (m, 8H), 6.26 (s, 2H), 0.94 (s, 18H), 0.10 (s, 6H), 0.09 (s, H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 163.6, 152.0, 142.8, 134.1, 129.1, 128.3, 127.9, 127.5, 127.3, 126.9, 122.3, 78.9, 26.1, 18.7, −4.3, −4.5; IR (KBr cm^{-1}) 2928, 2851, 1611, 1560, 1541, 1488, 1356, 1306, 1255, 1219, 1127, 1099, 1065; Anal. Calcd for $C_{42}H_{50}N_4O_2Si_2$: C, 72.16; H, 7.21; N, 8.01. Found: C, 72.48; H, 7.46; N, 8.12 $[\alpha]_D^{20} = -114$ (c 1, EtOH); ee: 99%, retention time: 7.4 min, Chiralcel OD-H, n-hexane, flow rate of 1 mL/min, 265 nm.

4.6.5. 2,2′-Bis-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-phenylethyl)--4,4′-biquinazoline 8e

Crystallization from ethanol gave colorless needles. Yield: 42%; mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (d, J = 8.4 Hz, 2H), 8.03–7.87 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.37–7.17 (m, 10H), 5.31 (dd, J = 9.1, 4.3 Hz, 2H), 3.36 (dd, A part of AB system, J = 13.3, 4.3 Hz, 2H), 3.23 (dd, B part of AB system, J = 13.3, 9.1 Hz, 2H), 0.77 (s, 18H), −0.17 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 164.2, 151.9, 138.8, 134.5, 130.3, 129.2, 128.3, 128.1, 126.7, 126.5, 122.5, 78.9, 44.4, 26.0, 18.6, −4.7, −4.9; IR (KBr cm^{-1}) 3470, 2930, 2857, 2401, 1744, 1563, 1488, 1382, 1258, 1092; Anal. Calcd for $C_{44}H_{54}N_4O_2Si_2$: C, 72.68; H, 7.49; N, 7.71. Found: C, 72.40; H, 7.64; N, 7.80; $[\alpha]_D^{20} = +56$ (c 1, EtOH); retention time: 8.0 min, Chiralcel OD-H, n-hexane–iPrOH, 98:02, flow rate of 1 mL/min, 265 nm.

4.7. General procedure for the desilylation of 8: synthesis of 2

To a solution (*S*,*S*)-**8** (1 mmol) in 5 mL of THF was slowly added tetrabutylammonium fluoride (3 mmol) in portions within 1 h at room temperature. The reaction proceeding was monitored by TLC. After the total conversion of the starting material the crude mixture was diluted with NH_4Cl (15 mL) and extracted with dichloromethane (2 × 25 mL). The solvent was removed under reduced pressure (15 mbar, 20 °C) and the residue was chromatographed on a small silica gel column by eluting with EtOAc–hexane (40:60) to give desilylated (*S*,*S*)-biquinazoline alcohol **2**.

4.7.1. (1*S*,1′*S*)-1,1′-(4,4′-Biquinazoline-2,2′-diyl)diethanol 2a

Crystallization from a mixture of EtOAc–hexane gave colorless needles. Yield: 95%; mp 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.18 (d, J = 8.5 Hz, 2H), 8.01–7.97 (m, 2H), 7.86 (d, J = 8.5, 0.7 Hz, 2H), 7.59 (td, J = 5.8, 3.8 Hz, 2H), 5.25–5.19 (m, 2H), 4.41 (d, J = 5.2 Hz, 2H), 1.71 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.3, 164.1, 151.3, 135.1, 128.8, 128.4, 126.6, 122.4, 70.2, 23.5; IR (KBr cm^{-1}) 3467, 2974, 2929, 1613, 1558, 1485, 1376, 1306, 1264, 1104, 1034; Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.20. Found: C, 69.21; H, 5.20; N, 16.20; MS (FAB) m/z 347 (MH^+); HRMS (FAB) calcd for $C_{20}H_{18}N_4O_2$ (MH^+) 347.1508, found 347.1504; $[\alpha]_D^{20} = +83$ (c 1, chloroform); ee: 98.5%; retention time: 19.1 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 265 nm.

4.7.2. (1*S*,1′*S*)-1,1′-(4,4′-Biquinazoline-2,2′-diyl)-*bis*-(2-methylpropan-1-ol) 2b

Crystallization from a mixture of dichloromethane–hexane gave colorless needles. Yield: 95%; mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19 (d, J = 8.4 Hz, 2H), 7.99 (ddd, J = 8.4, 6.9, 1.4 Hz, 2H), 7.84–7.80 (m, 2H), 7.59 (ddd, J = 8.2, 6.9, 1.1 Hz, 2H), 4.96 (dd, J = 6.1, 3.4 Hz, 2H), 4.28 (d, J = 6.1 Hz, 2H), 2.48 (d sept., J = 6.9, 3.4 Hz, 2H), 1.18 (d, J = 6.9 Hz, 6H), 0.82 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.1, 163.9, 151.0, 135.1, 128.9, 128.4, 126.5, 122.3, 78.0, 34.2, 20.1, 15.7; IR (KBr cm^{-1}) 3459, 3064, 2961, 2930, 2872, 1714, 1615, 1562, 1488, 1466, 1383, 1317, 1245, 1175, 1139, 1020; Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.39; H, 6.45; N, 13.72; MS (FAB) m/z 403 (MH^+); HRMS (FAB) calcd for $C_{24}H_{26}N_4O_2$ (MH^+) 403.2134, found 403.2126; $[\alpha]_D^{20} = -20$ (c 1, EtOH); ee: 99%; retention time: 6.8 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 265 nm.

4.7.3. (1*S*,1′*S*)-1,1′-(4,4′-Biquinazoline-2,2′-diyl)-*bis*-(2,2-dimethylpropan-1-ol) 2c

Crystallization from a mixture of dichloromethane–hexane gave colorless needles. Yield: 95%; mp 209–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.18 (d, J = 8.4 Hz, 2H), 7.97 (ddd, J = 8.4, 7.0, 1.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.56 (ddd, J = 8.4, 7.0, 1.1 Hz, 2H), 4.75 (d, J = 8.1 Hz, 2H), 4.22 (d, J = 8.1 Hz, 2H), 1.05 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 163.1, 150.8, 134.9, 128.9, 128.3, 126.5, 122.3, 81.3, 37.3, 26.4; IR (KBr cm^{-1}) 3462, 3064, 2957, 2862, 1614, 1560, 1487, 1311, 1236, 1070, 1019; Anal. Calcd for $C_{26}H_{30}N_4O_2$: C, 72.53; H, 7.02; N, 13.01. Found: C, 72.57; H, 7.33; N, 12.97; MS (FAB) m/z 431 (MH^+); HRMS (FAB) calcd for $C_{26}H_{30}N_4O_2$ (MH^+) 431.2447, found 431.2439; $[\alpha]_D^{20} = -18$ (c 1, EtOH); ee: 99%; retention time: 9.3 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 265 nm.

4.7.4. (1*S*,1′*S*)-4,4′-Biquinazoline-2,2′-diyl-*bis*-(phenylmethanol) 2d

Crystallization from a mixture of dichloromethane–hexane gave colorless needles. Yield: 48%; mp 223.5–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (d, J = 8.5 Hz, 2H), 7.94 (t, J = 7.7 Hz, 2H), 7.58 (d, J = 6.8 Hz, 4H), 7.53 (d, J = 8.4 Hz, 2H), 7.42–7.31 (m, 8H), 6.12 (d, J = 5.4 Hz, 2H), 5.28 (d, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.8, 163.4, 151.2, 142.3, 134.9, 128.6, 128.6, 128.3, 128.0, 127.3, 127.2, 122.3, 75.8; IR (KBr cm^{-1}) 3725, 2918, 2862, 1734, 1611, 1541, 1558, 1507, 1485, 1451, 1306, 1230, 1054.

4.7.5. (1*S*,1′*S*)-1,1′-(4,4′-Biquinazoline-2,2′-diyl)*bis*(2-phenylethanol) 2e

Crystallization from a mixture of ethanol gave colorless needles. Yield: 93%; mp 205–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (d, J = 8.5 Hz, 2H), 8.02–7.92 (m, 2H), 7.59–7.51 (m, 4H), 7.28–7.19 (m, 10H), 5.42 (m, 2H), 4.34 (br s, 2H), 3.53 (dd, A part of AB

system, J = 13.8, 4.0 Hz, 2H), 3.27 (dd, B part of AB system, J = 13.8, 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.6, 163.7, 151.2, 137.8, 135.0, 130.0, 128.8, 128.5, 128.3, 126.6, 126.5, 122.2, 74.5, 43.6; IR (KBr cm^{-1}) 3781, 3450, 3064, 3025, 1611, 1568, 1482, 1451, 1376, 1309, 1267, 1118, 1085; MS (FAB) m/z 499 (MH^+); HRMS (FAB) calcd for $C_{32}H_{27}N_4O_2$ (MH^+) 499.2134, found 499.2128; $[\alpha]_D^{20} = -193$ (c 1, chloroform); ee: 99%; retention time: 26.3 min, Chiralcel OD-H, n-hexane–iPrOH, 90:10, flow rate of 1 mL/min, 265 nm.

4.8. Typical procedure for the addition of phenylacetylene to arylaldehyde

Phenylacetylene (2 mmol) and diethylzinc (2 mmol, 1.6 M in hexane) were dissolved in dry THF (2 mL) and refluxed for 1 h and cooled to room temperature under a nitrogen atmosphere. Then, a suspension of chiral ligand **2** (0.1 mmol) and $Ti(OiPr)_4$ (0.25 mmol) in THF (2 mL) was added to the above solution and stirred at room temperature for 1 h. The mixture was cooled to 0 °C and arylaldehyde (1 mmol in 1 mL THF) was added. After 20 h stirring at 0 °C under a nitrogen atmosphere, the reaction was quenched with saturated ammonium chloride solution, extracted with diethyl ether (2 × 50 mL), washed with brine (2 × 25 mL), and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the conversion and yield were determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as internal standard directly on the crude mixture.

4.9. X-ray structure analysis

For the crystal structure determination, the single-crystal of compound **2c** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[34] The structures were solved by direct methods using the program SHELXS-97[35] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[35] The hydroxy H atom was positioned with the AFIX 147 command (idealized hydroxy group, torsion angle from electron density) and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **2c**: $C_{26}H_{30}N_4O_2$, crystal system, space group: orthorhombic, $C2221$; (no:20); unit cell dimensions: a = 11.085(2), b = 21.440(3), c = 10.146(3) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; volume: 2411.3(2) Å^3; Z = 4; calculated density: 1.19 mg/m^3; absorption coefficient: 0.076 mm^{-1}; F(0 0 0): 920; θ range for data collection 2.1–30.5°; refinement method: full-matrix least-square on F^2; data/parameters: 3712/148; goodness-of-fit on F^2: 1.017; final R indices [$I > 2\sigma(I)$]: R_1 = 0.078, wR_2 = 0.166; R indices (all data): R_1 = 0.178, wR_2 = 0.212; largest diff. peak and hole: 0.159 and −0.161 e Å^{-3}; CCDC-743971.

Acknowledgments

Financial support from the Scientific and Technological Research Council of Turkey (TUBITAK) (TBAG-108T116) is gratefully acknowledged. In addition, the authors would like to thank Dr. Graham Eaton from Leicester University for the HRMS measurements.

References

1. (a) Horton, D.; Hughes, J. B.; Thomson, J. K. *J. Org. Chem.* **1968**, *33*, 728–734; (b) Eppacher, S.; Solladie, N.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1311–1330; (c) Bhardwaj, P. K.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 699–711; (d) Leeuwenburgh, M. A.; Appeldoorn, C. C. M.; van Hooft, P. A. V.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **2000**, 873–877; (e) Isobe, M.; Takai, S. *J. Organomet. Chem.* **1999**, *589*, 122–125; (f) Marco-Contelles, J.; de Opazo, E. *J. Carbohydr. Chem.* **2002**, *21*, 201–218; (g) Pal, A.; Bhattacharjya, A. *J. Org. Chem.* **2001**, *66*, 9071–9074; (h) Cohen, N.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582–588; (i) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062–4063; (k) Trost, B.; Krisch, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131–6141; (l) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493; (m) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766–4770; (n) Prakesch, M.; Gre, D.; Gre, R. *Acc. Chem. Res.* **2002**, *35*, 175–181.
2. (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939; (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; (c) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214–3217; (d) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1997**, *38*, 7511–7514; (e) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814–2816; (f) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300–1308.
3. (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105; (c) Frantz, D. E.; Fssler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381; (d) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886; (e) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736–1744; (f) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (g) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457–5460; (h) Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168–176; (i) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146; (k) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147–4149; (l) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855–1857; (m) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207–210; (n) Hui, X.-P.; Yin, C.; Chen, Z.-C.; Huang, L.-N.; Xu, P.-F.; Fan, G.-F. *Tetrahedron* **2008**, *64*, 2553–2558; (o) Wang, Q.; Chen, S.-Y.; Yu, X.-Q.; Pu, L. *Tetrahedron* **2007**, *63*, 4422–4428; (p) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427–7430; (q) Ruan, J.; Lu, G.; Xu, L.; Li, Y.-M.; Chan, A. S. C. *Adv. Synth. Catal* **2008**, *350*, 76–84; (r) Soai, K.; Kawasaki, T.; Sato, I. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons, 2006; pp 555–573; (t) Aschwanden, P.; Carreira, E. M. Acetylene Chemistry. In *Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; pp 101–134.
4. (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017–3020; (b) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carriera, E. M. *Org. Lett.* **2000**, *2*, 4233–4236; (c) Anad, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
5. (a) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172–174; (b) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637.
6. (a) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555–4557; (b) Moore, D.; Huang, W.-S.; Xu, M.-H.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831–8834; (c) Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065–1068.
7. (a) Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W.-J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747–5749; (b) Xu, Z.; Chen, C.; Xu, J.-K.; Miao, M.-B.; Yan, W.-J.; Wang, R. *Org. Lett.* **2004**, *6*, 1193–1195.
8. (a) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975–2977; (b) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147–2152; (c) Omote, M.; Eto, Y.; Tarui, A.; Sato, K.; Ando, A. *Tetrahedron: Asymmetry* **2009**, *20*, 602–604; (d) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453–1458; (e) Mao, J.; Wan, B.; Wu, F.; Lu, S. *Chirality* **2005**, *17*, 245–249.
9. (a) Braga, A. L.; Appelt, H. R.; Silveria, C. C.; Wessjohann, L. A. P.; Schneider, H. *Tetrahedron* **2002**, *58*, 10413–10416; (b) Li, M.; Zhu, X.-Z.; Yuan, K.; Cao, B.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 219–222.
10. Koyuncu, H.; Dogan, O. *Org. Lett.* **2007**, *9*, 3477–3479.
11. Han, Z.-J.; Wang, R.; Zhou, Y.-F.; Liu, L. *Eur. J. Org. Chem.* **2005**, 934–938.
12. (a) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191–1203; (b) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205–207; (c) Kwong, H.-L.; Lee, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791–3801.
13. Athanasellis, G.; Detsi, A.; Prousis, K.; Igglessi-Markopoulou, O.; Markopoulos, J. *Synthesis* **2003**, 2015–2022.
14. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2783–2793.
15. Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2005**, *70*, 3079–3088.
16. Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455.
17. Tuccinardi, T.; Martinelli, A.; Nuti, E.; Carelli, P.; Balzano, F.; Uccello-Barretta, G.; Murphy, G.; Rossello, A. *Bioorg. Med. Chem.* **2006**, *14*, 4260–4276.
18. Bergman, J. *J. Chem. Res.* **1997**, 224.
19. Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295–1310.
20. Kwong, H. L.; Lee, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791–3801.
21. Kwong, H. L.; Lee, W. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2299–2308.
22. Kwong, H. L.; Lee, W. S.; Ng, H. F.; Chiu, W. H.; Wong, W. T. *J. Chem. Soc.; Dalton Trans.* **1998**, 1043–1046.
23. Kwong, H. L.; Wong, W. L.; Lee, W. S.; Cheng, L. S.; Wong, W. T. *Tetrahedron: Asymmetry* **2001**, *12*, 2683–2694.

24. Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4413–4421.
25. Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis* **2004**, 2173–2180.
26. Cazetta, T.; Lunardi, I.; Conceicao, G. J. A.; Morana, P. J. S.; Rodrigues, J. A. R. *Tetrahedron: Asymmetry* **2007**, *18*, 2030–2036.
27. (a) Fekner, T.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2008**, 5055–5056; (b) Fekner, T.; Müller-Bunz, H.; Guiry, P. J. *Org. Lett.* **2006**, *8*, 5109–5112.
28. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4039.
29. Sugimoto, O.; Yamauchi, Y.; Tanji, K. *Heterocycles* **2002**, *57*, 323–326.
30. (a) Kendall, P. M.; Johnson, J. V.; Cook, C. E. *J. Org. Chem.* **1979**, *44*, 1421–1424; (b) Ronald, R. C.; Lansinger, J. M.; Lillie, T. S.; Wheeler, C. J. *J. Org. Chem.* **1982**, *47*, 2541–2549.
31. Janiak, C.; Deblon, S.; Wu, H.-P. *Synth. Commun.* **1999**, *29*, 3341–3352.
32. Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434–2435.
33. Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2007**, *18*, 2668.
34. Rigaku/MSC, Inc., 9009 New Trails Drive, The Woodlands, TX 77381.
35. Sheldrick, G. M. *SHELXS97* and *SHELXL97*, University of Göttingen: Germany, 1997.