Synthesis I. Karakaya et al. Paper

Synthesis and Catalytic Asymmetric Applications of Quinazolinol Ligands

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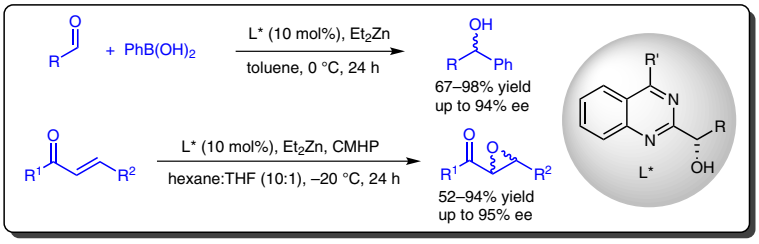

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Abstract A range of chiral quinazolinol ligands were efficiently synthesized and subsequently investigated for catalytic chiral induction in both the asymmetric phenylation of aryl aldehydes and the asymmetric epoxidation of chalcones. Encouragingly, high enantioselectivities (up to 95%) and yields (up to 98%) were achieved under the optimized reaction conditions.

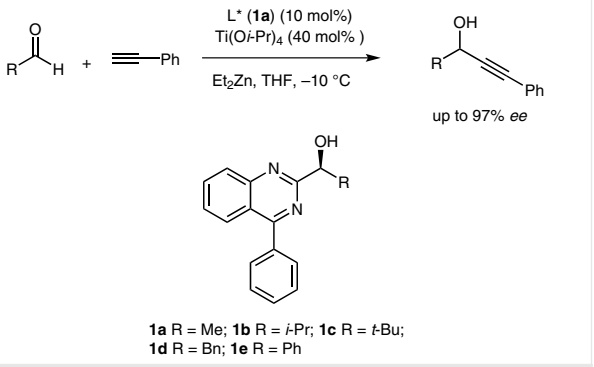
Key words quinazolines, quinazolinones, enantioselective arylations, Weitz–Scheffer epoxidation, α,β-unsaturated ketones

Enantioselective C–C bond formation is one of the most frequently studied operations to construct chiral organic compounds. Therefore, significant efforts have been devoted to designing efficient catalytic systems in recent years. Among the variety of enantioselective reactions, the arylation of aldehydes is one of the most attractive research areas, because optically active aryl carbinols are important and common precursors for the preparation of pharmacologically and biologically active compounds such as (*R*)-neobenodine, (*S*)-carbinoxamine and (*R*)-orphenadrine.[1] To date, several useful catalytic approaches have been developed that employ aryltitanium, phenyllithium,[2] diphenylzinc,[1b,3] arylboronic acids,[4] aryl Grignard reagents,[5] aryl bromides[6] and aryltrifluoroborates[7] as aryl sources in aldehyde addition chemistry. Although some of these reagents are commercially available, many are very expensive and, therefore, their cost limits their widespread application. Of those reagents commonly employed, arylboronic acids are most attractive due to their low-cost, widespread availability, and their chemical robustness (air- and moisture-insensitivity). Furthermore, the widespread availability of boronic acid and benzaldehyde partners enables access to both enantiomers using the same chiral ligand by simply interchanging the reactive groups on both reaction partners: the arylboronic acid and aldehyde.[8]

Another exciting field of asymmetric catalysis is asymmetric epoxidation of α,β-unsaturated ketones. Containing both ketone and epoxide moieties, these remarkable chiral synthons can be easily converted into large quantities of enantiomerically enriched molecules in a few simple steps. A wide variety of methods, which are inspired from the Weitz–Scheffer epoxidation, have been developed for the enantioselective epoxidation of electron-deficient olefins.[9] In general, chiral metal peroxides,[10] asymmetric phase-transfer catalysts,[11] enantiomerically pure hydroperoxides,[12] polyamino acid catalysts,[13] chiral dioxiranes,[14] L-proline-based derivatives, cinchona alkaloids,[15] or other organocatalysts have been used. Although these methods have been successful in a number of contexts, the potential of these catalyst systems has not been fully realized due to the requirements for large quantities of expensive chiral ligands. Several other procedures have been developed that employ chiral metal complexes bearing zinc, magnesium,[16] lithium[17] and some lanthanides.[18] In particular, Enders has reported the asymmetric epoxidation of α,β-unsaturated ketones under oxygen using stoichiometric quantities of diethylzinc and a chiral amino-alcohol,[19] while Pu and coworkers improved this stoichiometric process obtaining similar results with catalytic amounts of diethylzinc and chiral polybinaphthyl ligands with stoichiometric *tert*-butyl hydroperoxide as the oxidant.[20]

In our previous work, we examined quinazolinones and their derivatives as chiral ligands in the catalytic enantioselective addition of diethylzinc to aldehydes resulting in secondary alcohols in good to excellent yields and ee values.[21] We also showed that the addition of phenylacetylide to aldehydes using alcohol derivatives of bisquinazolines gave the desired propargylic alcohols in modest ee values

(75%).[22] Furthermore, using 4-phenylquinazolinols **1a–e** in alkynylzinc additions to aldehydes has enabled improved enantioenrichment of the resulting propargylic alcohols from 75% to 97% (Scheme 1).[23]



Scheme 1 Catalytic enantioselective alkynylzinc additions to aldehydes

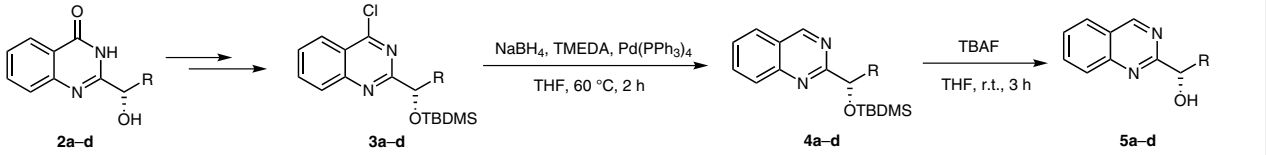
In the present work we sought to synthesize quinazoline alcohols **5a–d** containing hydrogen instead of a phenyl group at the 4-position in order to explore the catalytic activity of these ligands (not only **5a–d**, but also **1a–e**) in both the catalytic asymmetric addition of phenylzinc species to aryl aldehydes and in the catalytic enantioselective epoxidation of chalcones.

Synthesis of Chiral Ligands

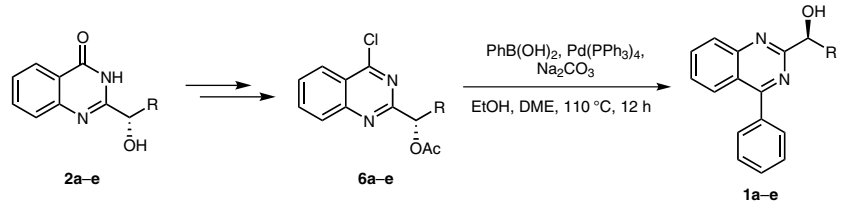
The syntheses of 4*H*-quinazolinols **5a–d** were carried out according to the general synthetic route shown in Scheme 2. The quinazolinone alcohols **2a–d** were prepared according to the literature,[22] and these alcohols were subsequently protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole by heating at reflux temperature for two hours in DMF. To obtain the chloroquinazolines **3a–d**, the TBDMS-protected quinazolinones were reacted with $POCl_3$ and *N*,*N*-diethylaniline at reflux temperature for four hours in benzene. For the dehalogenation reactions, chloroquinazolines **3a–d** were treated with $NaBH_4$ and TMEDA with a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) at reflux under an N_2 atmosphere for two hours. Finally, the synthesis of the chiral ligands was completed by removal of the TBDMS protecting groups using TBAF in THF for three hours. The chiral 4*H*-quinazoline alcohols **5a–d** were obtained in enantiopure form (99% ee). To synthesize **5a–d** we also attempted to dehalogenate the acetylated protected chloroquinazolines **6a–d**; unfortunately, this resulted in very low yields ranging between 30–40%. Switching OAc to the TBDMS protecting group improved the yields dramatically, affording 4*H*-quinazolines **4a–d** in excellent yields (71–85%).

The chiral 4-phenylquinazolinol ligands **1a–d** were easily prepared starting from (*S*)-3*H*-quinazolinones following O-protection with Ac_2O, chlorination with $POCl_3$ and Suzuki coupling with $PhB(OH)_2$ in three steps, as recently reported.[23] While we were able to synthesize the ligands **1a–d** in enantiopure form, ligand **1e** could only be obtained in 72% ee (Scheme 3).

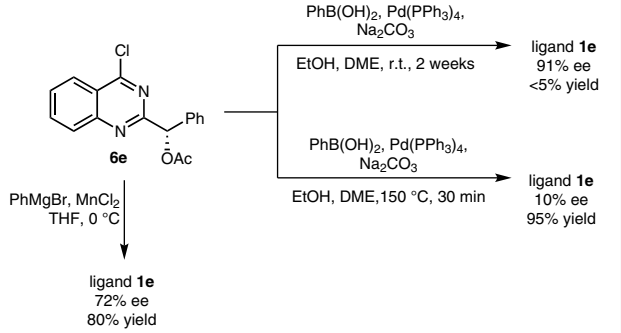
The reaction conditions were revised in an attempt to achieve an enantiopure form of ligand **1e**. It was reasoned that high temperature and basic conditions could be the cause of the racemization. Lowering the reaction temperature to room temperature allowed the isolation of ligand **1e** with much higher enantiopurity (91%), but even when continued for two weeks the reaction yield remained less than 5%. Also, we attempted to accelerate the reaction and avoid racemization by performing the reaction in a Schlenk tube at high temperature (about 150 °C). Although the reaction was completed in 30 minutes, the enantiopurity remained around 10%. Additionally, employing a Grignard protocol with chloroquinazolines following established literature[24] failed to give better enantiopurity, affording ligand **1e** with identical enantioinduction to that obtained in the first method (Scheme 4).



Scheme 2 Synthesis of 4*H*-quinazolinols **5a–d**



Scheme 3 Synthesis of 4-phenylquinazolinol ligands **1a–e**



Scheme 4 Revised reaction conditions for the synthesis of ligand **1e**

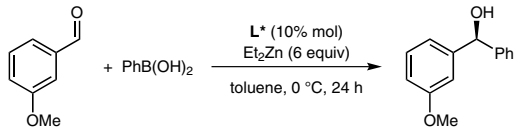
Application of Enantioselective Phenylboronic Acid Addition to Aldehydes

In order to examine the catalytic asymmetric induction abilities of the ligands, we initiated our research by choosing *m*-methoxybenzaldehyde as a model substrate for phenylation. As model reaction conditions, 10 mol% of the ligand in toluene at 0 °C was initially selected. The phenylzinc reagent was prepared in situ by transmetalation using diethylzinc and phenylboronic acid in toluene at 60 °C for 12 hours. All the ligands (**1a**–**e** and **5a**–**d**) were then screened in the model reaction and furnished the desired alcohol in moderate to high yields with varying levels of enantiocontrol (15–75% ee) (Table 1).

In general, the 4-phenylquinazoline ligands **1a**–**e** gave better enantioselectivities than the 4*H*-quinazoline ligands **5a**–**d**. In light of these results, it can be argued that the strong electron-donating phenyl substitution at the 4-position of the ligand provides a favorable effect on the enantioselection compared to the weak electron-donating hydrogen. For both ligand families, as the size of the alkyl group attached to the chiral center increased, the enantiomeric excess of the diarylmethanols gradually improved, with the bulkiest ligand **1c** giving the best enantioselectivity (75%). Benzyl and phenyl substituents at the chiral center of the 4-phenylquinazoline ligands **1d**,**e** resulted in the desired alcohol having enantioselectivities of 29% and 35%, respectively. While the product yield improved with a 20% catalyst loading, the enantiomeric excess remained the same. However, in the presence of less ligand (5 mol%), the enantioselectivity and yield of the alcohol were slightly diminished. Therefore, 10 mol% of **1c** was selected to explore the effects of other reaction parameters such as solvent, co-catalyst, equivalents of Et_2Zn and temperature.

Hexanes, THF and diethyl ether gave similar enantioselectivity (70% ee for hexanes, 64% ee for THF, 60% ee for diethyl ether), but worse than when using toluene. We also investigated the effects of co-catalysts such as molecular sieves, HMPA, *N*-ethylimidazole and Ti(O*i*-Pr)$_4$ in this addition reaction. However, none of these provided improvements in the ee values. It was apparent that the standard

Table 1 Asymmetric Addition of Phenylzinc to *m*-Methoxybenzaldehyde Catalyzed by Ligands **1a**–**e** and **5a**–**d**



Entry	Ligand (mol%)	Co-cat.	ee (%)[a]	Yield (%)[b]	Config[c]
1	**1a** (10)	–	24	74	*S*
2	**1b** (10)	–	39	84	*S*
3	**1c** (10)	–	**75**	**80**	*S*
4	**1d** (10)	–	29	65	*S*
5	**1e** (10)	–	35	70	*S*
6	**5a** (10)	–	15	72	*S*
7	**5b** (10)	–	23	67	*S*
8	**5c** (10)	–	40	77	*S*
9	**5d** (10)	–	26	85	*S*
10	**1c** (20)	–	75	90	*S*
11	**1c** (5)	–	63	75	*S*
12	**1c** (10)	molecular sieves	66	89	*S*
13	**1c** (10)	HMPA	54	76	*S*
14	**1c** (10)	*N*-ethylimidazole	69	73	*S*
15	**1c** (10)	Ti(O*i*-Pr)$_4$	70	89	*S*
16	**1c** (10)[d]	–	70	89	*S*
17	**1c** (10)[e]	–	75	50	*S*
18	**1c** (10)[f]	–	62	94	*S*
19	**1c** (10)[g]	–	61	76	*S*

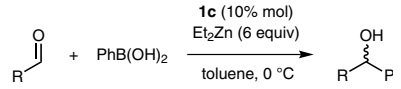
[a] Determined by chiral HPLC (Chiralcel OD-H).
[b] Yield of isolated product.
[c] The absolute configuration of the adduct was assigned in accordance with the literature.25
[d] Et_2Zn (4 equiv) was used.
[e] Et_2Zn (7 equiv) was used.
[f] The reaction was conducted at r.t.
[g] The reaction was conducted at –10 °C.

screening conditions employed an excess of Et_2Zn/PhB(OH)$_2$ because reducing or increasing the amount had no effect on the enantioselectivities nor the product yields. With optimized conditions in hand, we next studied the phenylboronic acid addition to several aromatic aldehydes (Table 2).

The electron-deficient *o*-, *m*- and *p*-chlorobenzaldehydes, *m*-bromobenzaldehyde and 1-naphthylaldehyde (Table 2, entries 2–5 and 9) gave moderate enantioselectivities, ranging between 50% and 66% ee, and good to excellent yields. Remarkably, the best enantioselectivity (94%) was obtained from the reaction with *p*-bromo-substituted benzaldehyde (Table 2, entry 6). Electron-rich *m*-methoxybenzaldehyde and *m*- and *p*-substituted methylbenzaldehydes (Table 2, entries 1, 7 and 8) produced very good enantioselection (75–92% ee) and yields (77–98%) of the corresponding diaryl carbinols. *p*-Nitrobenzaldehyde gave only

41% ee but returned a good yield (86%) (Table 2, entry 10). To ensure the scalability of this process, a gram-scale reaction was established with *p*-methylbenzaldehyde and the desired carbinol was produced with the same enantioselectivity and in a higher yield (Table 2, entry 8).[25]

Table 2 Asymmetric Addition of Phenylboronic Acid to Aromatic Aldehydes Using Ligand **1c** as the Catalyst



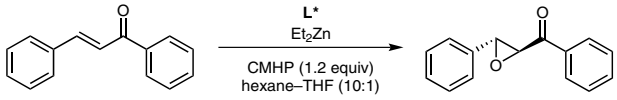
Entry	R	ee (%)[a]	Yield (%)[b]	Config[c]
1	*m*-$MeOC_6H_4$	75	98	*S*[26]
2	*o*-ClC_6H_4	65	67	*R*[27]
3	*m*-ClC_6H_4	66	96	*S*[28]
4	*p*-ClC_6H_4	50	95	–
5	*m*-BrC_6H_4	61	78	*S*[28]
6	*p*-BrC_6H_4	94	82	*R*[29]
7	*m*-MeC_6H_4	92	98	–
8	*p*-MeC_6H_4	85	77 (85)[d]	*S*[27]
9	1-naphthyl	51	75	*S*[26]
10	*p*-$O_2NC_6H_4$	41	86	*S*[4d]

[a] Determined by chiral HPLC (Chiralcel OD-H).
[b] Yield of isolated product.
[c] The absolute configuration of the adduct was assigned in accordance with the literature.
[d] Reaction run on gram scale.

Application to the Enantioselective Epoxidation of Chalcones

To determine optimum reaction conditions for the epoxidation of chalcones, a model reaction was performed using (*E*)-chalcone in the presence of a chiral ligand (20 mol%) and cumene hydroperoxide (CMHP) (1.2 equiv) at ambient temperature in hexanes for 24 hours under an inert atmosphere. The results are summarized in Table 3. All the chiral quinazolinols (**1a**–**e**, **5a**–**d**) were examined under these conditions and interestingly, the best enantioselection was obtained in the presence of ligand **1e** which can be synthesized in up to 72% ee from L-mandelic acid. The other ligands (**1a**–**d** and **5a**–**c**) gave much lower enantioselectivities (between 33–54%), except for ligand **1d** (68% ee) derived from L-phenylalanine. Further examination was carried out to obtain better enantioselectivity via screening the ligand and Et_2Zn loadings. It was observed that the best ligand and Et_2Zn loading ratio was 10 mol%. To optimize the process further, different temperatures were screened and the best result was achieved at –20 °C. A series of solvents were also screened, but with no apparent improvements being identified.

Table 3 Asymmetric Epoxidation of (*E*)-Chalcone Catalyzed by Ligands **1a**–**e** and **5a**–**d**



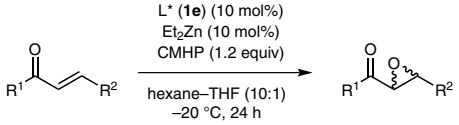
Entry	Ligand (mol%)	Et_2Zn (mol%)	Temp (°C)	ee (%)[a]	Yield (%)[b]
1	**1a** (20)	20	r.t.	33	95
2	**1b** (20)	20	r.t.	45	86
3	**1c** (20)	20	r.t.	42	79
4	**1d** (20)	20	r.t.	68	92
5	**1e** (20)	20	r.t.	72	90
6	**5a** (20)	20	r.t.	40	98
7	**5b** (20)	20	r.t.	40	88
8	**5c** (20)	20	r.t.	33	78
9	**5d** (20)	20	r.t.	54	67
10	–	20	0	0	78
11	**1e** (30)	30	0	87	86
12	**1e** (20)	20	0	81	75
13	**1e** (10)	10	0	88	83
14	**1e** (5)	5	0	84	65
15	**1e** (10)	5	0	65	77
16	**1e** (10)	15	0	47	80
17	**1e** (10)	10	–10	92	82
18	**1e (10)**	**10**	**–20**	**95**	**94**
19	**1e** (10)	10	–30	96	65
20[c]	**1e** (10)	10	–20	94	79
21[d]	**1e** (10)	10	–20	94	86
22[e]	**1e** (10)	10	–20	70	90

[a] Determined by chiral HPLC (Chiralcel OD-H).
[b] Yield of isolated product.
[c] Reaction in heptanes.
[d] Reaction in decane.
[e] Reaction in toluene.

With suitable conditions in hand [chalcone (1.0 equiv), CMHP (1.2 equiv), ligand **1e** (10 mol%), Et_2Zn (10 mol%), hexanes–THF (10:1), –20 °C, 24 h], an exploration of the scope of the chalcones was initiated. As shown in Table 4, different chalcones were converted into the corresponding epoxides with modest to high enantiomeric excess. Electron-rich methoxy groups at the *para* positions of the phenyl rings at both sides of the chalcones showed similar effects on the asymmetric epoxidation (induction) (Table 4, entries 2 and 3). Interestingly, an *o*-methoxy substituent at the α-position of the chalcone gave enhanced enantioselectivity and a high reaction yield (Table 4, entry 4). Similarly, the substrate bearing an *o*-chlorophenyl at the β-position of the chalcone gave high selectivity and yield (Table 4, entry 6), while the *p*-chlorophenyl substituent on the phenacyl group at the α-position of the chalcone resulted in moder-

ate selectivity (Table 4, entry 7). Although the high reaction yield was maintained, the enantiopurity of the product remained very low in the presence of an electron-deficient *p*-bromophenyl substituent at the β-position (Table 4, entry 5).

Table 4 Asymmetric Epoxidation of Chalcones Using Ligand **1e**[a] as the Catalyst



Entry	R^1	R^2	ee (%)	Yield (%)	Config[b]
1	Ph	Ph	95	94	2*R*,3*S*[30]
2	*p*-$MeOC_6H_4$	Ph	82	65	2*S*,3*R*[30]
3	Ph	*p*-$MeOC_6H_4$	81	52	2*S*,3*R*[13b]
4	Ph	*o*-$MeOC_6H_4$	92	86	–
5	*p*-BrC_6H_4	Ph	26	93	–
6	*o*-ClC_6H_4	Ph	90	88	2*R*,3*S*[30]
7	Ph	*p*-ClC_6H_4	67	85	2*R*,3*S*[13b]
8	Ph	*p*-MeC_6H_4	75	88	2*R*,3*S*[30]

[a] Ligand **1e** (72% enantioenriched) was used.
[b] The absolute configuration of the adduct was assigned in accordance with the literature.

In summary, we have successfully developed methods for the catalytic asymmetric phenylation of arylaldehydes and the epoxidation of chalcones in the presence of chiral quinazolinols (**1a**–**e** and **5a**–**d**). Contrary to the more expensive diphenylzinc, phenylboronic acids proved to be highly effective reagents for phenyl group transfer in the asymmetric phenylation of aromatic aldehydes. Our results demonstrate that the chiral environment at the 2-position of the quinazolinol has a crucial effect on enantioinduction, where greater steric bulk (increasing from methyl to *tert*-butyl) provides significant enhancement. Generally, electron-donating aldehydes brought about higher enantioselection, while the addition of phenylboronic acid to aldehydes with electron-withdrawing substituents afforded the corresponding carbinols with moderate enantioselectivities. Additionally, in Weitz–Scheffer epoxidations, chalcones with electron-deficient substituents were converted into the corresponding optically active epoxyketones, with high yields and enantioselectivities, via reactions involving nucleophilic CMHP. We anticipate that due to the simplicity of the ligand synthesis and the ease of ligand modification, these chiral quinazolinols may establish a new set of functional catalysts for other enantioselective reactions.

The full experimental details for **1a**–**e** are provided in our previous publication.[23] Reagents and solvents were purchased from chemical suppliers and purified to match the reported physical and spectroscopic data. Column chromatography was performed on Aldrich silica gel (230–400 mesh). Solvents were concentrated under reduced pressure. Melting points were determined with a Gallenkamp apparatus. IR spectra (KBr pellets) were obtained on a Perkin–Elmer spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian (200, 400) and Bruker 400 spectrometers in $CDCl_3$. Enantiomeric excesses were determined by HPLC analysis using a chiral column (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 are given in g/100 mL.

(*S*)-2-{1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}quinazoline (4a); Typical Procedure 1

To a solution of (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-4-chloroquinazoline (**3a**) (2 g, 6.19 mmol) in dry THF (15 mL) was added TMEDA (1.22 g, 10.53 mmol), $Pd(PPh_3)_4$ (190 mg, 0.165 mmol) and $NaBH_4$ (398 mg, 10.53 mmol), and the mixture was heated at reflux temperature for 2 h under an N_2 atm. The mixture was cooled to r.t., diluted with CH_2Cl_2 (100 mL) and washed with H_2O (3 × 50 mL). The separated organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexanes–EtOAc, 20:1) to give (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}quinazoline (**4a**) as a colorless oil in 80% yield (1.42 g).

$[\alpha]_D^{20}$ –16 (*c* 2.5, CH_2Cl_2).

IR (KBr): 2928, 2855, 1620, 1585, 1488, 1251, 1098 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.98 (d, *J* = 6.53 Hz, 1 H), 7.86–7.55 (m, 3 H), 5.17 (q, *J* = 6.51 Hz, 1 H), 1.58 (d, *J* = 6.51 Hz, 3 H), 0.83 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 160.8, 150.2, 134.0, 128.4, 127.4, 127.1, 123.8, 73.1, 25.9, 25.7, 23.9, 18.5, –3.6, –4.6, –4.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2OSi$: 289.1738; found: 289.1733.

(*S*)-2-{1-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl}quinazoline (4b)

Typical procedure 1 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-4-chloroquinazoline (**3b**) (550 mg, 1.56 mmol), TMEDA (309 mg, 2.66 mmol), $Pd(PPh_3)_4$ (89 mg, 0.078 mmol) and $NaBH_4$ (100.6 mg, 2.66 mmol) in a solution of THF (10 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 20:1) to give (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}quinazoline (**4b**) as a colorless oil in 85% yield (420 mg).

$[\alpha]_D^{20}$ –48.8 (*c* 2.5, CH_2Cl_2).

IR (KBr): 3063, 2957, 2856, 1620, 1585, 1487, 1252, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 8.02 (dd, *J* = 8.5 Hz, 0.74 Hz, 1 H), 7.89–7.58 (m, 3 H), 4.62 (d, *J* = 7.7 Hz, 1 H), 2.28 (m, 1 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.80 (s, 9 H), 0.76 (d, *J* = 6.6 Hz, 3 H), 0.00 (s, 3 H), –0.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 160.5, 150.0, 134.0, 128.4, 127.4, 127.1, 123.7, 82.5, 34.8, 25.9, 19.1, 18.7, 18.4, –4.6, –4.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{29}N_2OSi$: 317.2051; found: 317.2054.

(*S*)-2-{1-[(*tert*-Butyldimethylsilyl)oxy]-2,2-dimethylpropyl}quinazoline (4c)

Typical procedure 1 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl}-4-chloroquinazoline (**3c**) (1.4 g, 3.84 mmol), TMEDA (0.76 g, 6.54 mmol), $Pd(PPh_3)_4$ (0.22 g, 0.192 mmol) and $NaBH_4$ (0.25 g, 6.54 mmol) in a solution of THF (10 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 20:1) to give (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl}quinazoline (**4c**) as a colorless oil in 71% yield (0.9 g).

$[\alpha]_D^{20}$ –51.1 (*c* 1.8, CH_2Cl_2).

IR (KBr): 3063, 2955, 2857, 1675, 1620, 1566, 1472, 1101 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 7.90–7.58 (m, 3 H), 4.75 (s, 1 H), 0.99 (s, 9 H), 0.85 (s, 9 H), –0.01 (s, 3 H), –0.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 159.6, 149.8, 133.8, 128.5, 127.3, 127.0, 123.6, 84.1, 40.6, 36.7, 26.4, 25.9, 25.7, 18.3, 18.1, –2.9, –4.7, –5.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{31}N_2OSi$: 331.2200; found: 331.2206.

(*S*)-2-{1-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylethyl}quinazoline (4d)

Typical procedure 1 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethyl}-4-chloroquinazoline (**3d**) (260 mg, 0.65 mmol), TMEDA (128.5 mg, 1.1 mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) and $NaBH_4$ (41.9 mg, 1.1 mmol) in a solution of THF (5 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 20:1) to give (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethyl}quinazoline (**4d**) as a colorless oil in 80% yield (189 mg).

$[\alpha]_D^{20}$ –20.0 (*c* 3.5, CH_2Cl_2).

IR (KBr): 3063, 2954, 2855, 1619, 1570, 1471, 1255, 1098 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.43 (s, 1 H), 8.06 (d, *J* = 8.56 Hz, 1 H), 7.93–7.16 (m, 8 H), 5.18 (dd, *J* = 9.25 Hz, 4.09 Hz, 1 H), 3.19 (m, 2 H), 0.69 (s, 9 H), –0.21 (s, 3 H), –0.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 160.8, 150.2, 138.7, 134.1, 130.1, 128.4, 128.1, 127.5, 127.2, 126.3, 123.8, 78.7, 44.3, 25.7, 25.7, 18.3, –2.9, –5.2, –5.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}N_2OSi$ for: 365.2044; found: 365.2029.

(*S*)-1-(Quinazolin-2-yl)ethan-1-ol (5a); Typical Procedure 2

TBAF (2.65 g, 8.42 mmol) was added in portions to a solution of (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}quinazoline (**4a**) (810 mg, 2.8 mmol) in THF (5 mL), and the resulting mixture was stirred for 3 h at ambient temperature. The reaction was quenched with sat. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexanes–EtOAc, 6:1) to give (*S*)-1-(quinazolin-2-yl)ethan-1-ol (**5a**) as a colorless oil in 91% yield (443 mg).

$[\alpha]_D^{20}$ –6.67 (*c* 1.5, CH_2Cl_2); ee 99%; t_R = 6.4 min (Chiralcel OD-H; *n*-hexane–*i*-PrOH, 90:10; flow rate = 1 mL/min; 254 nm).

IR (KBr): 3430, 2975, 1620, 1586, 1489, 1377, 1103 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 8.03 (d, *J* = 8.47 Hz, 1 H), 7.96–7.64 (m, 3 H), 5.12 (m, 1 H), 4.50 (d, *J* = 4.67 Hz, 1 H), 1.67 (d, *J* = 6.64 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 160.9, 149.5, 134.6, 127.9, 127.6, 127.3, 123.7, 69.9, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_2O$: 175.0873; found: 175.0872.

(*S*)-2-Methyl-1-(quinazolin-2-yl)propan-1-ol (5b)

Typical procedure 2 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}quinazoline (**4b**) (275 mg, 0.87 mmol) and TBAF (315 mg, 2.61 mmol) in a solution of THF (5 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 6:1) to give (*S*)-2-methyl-1-(quinazolin-2-yl)propan-1-ol (**5b**) as a colorless solid in 88% yield (155 mg).

Mp 25–27 °C; $[\alpha]_D^{20}$ +2.5 (*c* 0.4, CH_2Cl_2); ee 99%; t_R = 8.4 min (Chiralcel OD-H; *n*-hexane–*i*-PrOH, 90:10; flow rate = 1 mL/min; 254 nm).

IR (KBr): 3452, 3063, 2961, 1620, 1585, 1488, 1376, 1019 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 8.04 (d, *J* = 8.12 Hz, 1 H), 7.97–7.64 (m, 3 H), 4.87 (dd, *J* = 6.01 Hz, 3.35 Hz, 1 H), 4.32 (d, *J* = 6.01 Hz, 1 H), 2.44 (m, 1 H), 1.17 (d, *J* = 6.93 Hz, 3 H), 0.74 (d, *J* = 6.72 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 160.5, 149.3, 134.5, 128.0, 127.6, 127.3, 123.7, 34.0, 19.9, 15.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_2O$: 203.1186; found: 203.1187.

(*S*)-2,2-Dimethyl-1-(quinazolin-2-yl)propan-1-ol (5c)

Typical procedure 2 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2,2-dimethylpropyl}quinazoline (**4c**) (720 mg, 2.17 mmol) and TBAF (2.06 g, 6.53 mmol) in a solution of THF (5 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give (*S*)-2,2-dimethyl-1-(quinazolin-2-yl)propan-1-ol (**5c**) as a colorless solid in 75% yield (352 mg).

Mp 62–65 °C; $[\alpha]_D^{20}$ –21.54 (*c* 1.3, CH_2Cl_2); ee 99%; t_R = 6.0 min (Chiralcel OD-H; *n*-hexane–*i*-PrOH, 90:10; flow rate = 1 mL/min; 254 nm).

IR (KBr): 3462, 2955, 1620, 1574, 1489, 1377, 1067 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.04–7.27 (m, 4 H), 4.66 (d, *J* = 7.69 Hz, 1 H), 4.32 (d, *J* = 7.69 Hz, 1 H), 1.02 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 159.4, 149.3, 134.3, 128.1, 127.6, 127.2, 123.7, 81.0, 36.9, 26.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O$: 217.1342; found: 217.1345.

(*S*)-2-Phenyl-1-(quinazolin-2-yl)ethan-1-ol (5d)

Typical procedure 2 was followed using (*S*)-2-{1-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethyl}quinazoline (**4d**) (1 g, 2.74 mmol) and TBAF (2.59 g, 8.22 mmol) in a solution of THF (10 mL). The crude residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give (*S*)-2-phenyl-1-(quinazolin-2-yl)ethan-1-ol (**5d**) as a colorless solid in 86% yield (590 mg).

Mp 85–87 °C; $[\alpha]_D^{20}$ –78.67 (*c* 1.5, CH_2Cl_2); ee 99%; t_R = 12.8 min (Chiralcel OD-H; *n*-hexane–*i*-PrOH, 90:10; flow rate = 1 mL/min; 254 nm).

IR (KBr): 3251, 1619, 1565, 1087 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 7.99–7.93 (m, 3 H), 7.67 (ddd, *J* = 8.09 Hz, 6.91 Hz, 1.17 Hz, 1 H), 7.25–7.22 (m, 4 H), 7.20–7.15 (m, 1 H), 5.57 (dd, *J* = 7.65 Hz, 3.80 Hz, 1 H), 4.34 (br s, 1 H), 3.49 (dd, *J* = 13.76 Hz, 3.83 Hz, 1 H), 3.12 (dd, *J* = 13.77 Hz, 7.68 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 160.9, 149.6, 138.1, 134.8, 129.9, 128.4, 128.4, 128.2, 127.9, 127.5, 126.5, 123.9, 74.5, 43.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1186; found: 251.1189.

Catalytic Asymmetric Addition of Phenylzinc Species to Aldehydes; General Procedure

Et_2Zn (2.41 mL, 1 M in hexanes) was added in one portion to a solution of phenylboronic acid (100 mg, 0.81 mmol) in toluene (2 mL) in a 10 mL oven-dried sealed tube (N_2 atm), and the mixture was heated for 12 h at 60 °C. The mixture was cooled to r.t. and a solution of chiral ligand **1c** (12 mg, 0.04 mmol) in toluene (0.5 mL) was syringed into the sealed tube and the contents stirred for a further 30 min. The reaction mixture was then cooled to 0 °C. After 10 min, a solution of freshly distilled aldehyde (0.41 mmol) in toluene (0.5 mL) was added and the mixture was stirred for 24 h at 0 °C. The reaction mixture was quenched with HCl (5 wt%, 6 mL) and extracted with EtOAc (3 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography (EtOAc and hexane) to give the product. The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

Catalytic Asymmetric Epoxidation of Chalcones; General Procedure

Chiral ligand **1e** (0.024 mmol) was added to a sealed tube and the tube was purged with N_2 (× 3). Dry hexanes (ca. 1 mL) was added and the mixture stirred for 10 min. Et_2Zn (0.024 mmol, 1 M in hexanes) was then added to the reaction mixture. After stirring for 1 h at ambient temperature, a solution of the chalcone (0.24 mmol) in hexanes–THF (1.2 mL, 5:1) was added to the suspension and stirring was continued for 30 min. The temperature was decreased to –20 °C and CMHP (0.36 mmol, 1.6 M in toluene) was added to the reaction mixture. The resulting mixture was stirred for 24 h, and then quenched with sat. $NaHSO_3$ (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the residue purified by column chromatography (EtOAc and hexane) to afford the corresponding epoxide.

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Supporting Information

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