Investigation of the Enantioselective Synthesis of 2,3-Dihydroquinazolinones Using Sc(III)–*inda*-pybox

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Abstract: Derivatives of 2,3-dihydroquinazolinones (2,3-DHQZs) are prized for their prevalent pharmaceutical applications. Although there are potential applications, methods available for the enantioselective synthesis of these valuable compounds are scarce, since the chiral aminal center is prone to racemization. We have overcome the difficulties in the catalytic enantioselective synthesis of 2,3-DHQZs using Sc(III)–*inda*-pybox as a catalyst, in a process with a broad substrate scope.

Key words: asymmetric catalysis, dihydroquinazolinones, enantioselectivity, pybox, scandium(III) triflate

The 2,3-dihydroquinazolinone (2,3-DHQZ) structure is one of the privileged scaffolds known for their important biological and medicinal properties (Figure 1).[1] Although 2,3-DHQZs possess a chiral center, which is susceptible to racemization, most of the existing pharmacological studies have been carried out using racemates. It is noteworthy that stereoisomers of chiral drugs may exhibit different pharmacological activities, because the biological matrixes present in the human body are chiral in nature.[2] Thus, determination of the binding mode and the affinity of optically pure 2,3-DHQZs is very much needed for improving ADMET properties. In 2008, Brown and co-workers reported that the *S*-enantiomer of 2-aryl-2,3-DHQZs exhibit significantly higher antitumor activity than the corresponding *R*-enantiomers.[3]

Although there are many ways to synthesize 2,3-DHQZs in racemic form,[4] accessing the nonracemic form of 2,3-DHQZs is more challenging.[5] Seminal contributions from List and co-workers[5a] and Rueping and co-workers[5b] showcased the ability of chiral Brønsted acids in the enantioselective synthesis of 2,3-DHQZs. The paucity of methods to synthesize enantiomerically enriched 2,3-DHQZs stimulated us to develop the first metal-catalyzed enantioselective synthesis of 2,3-DHQZs.[6] We hypothesized that the activation of imines with a suitable chiral Lewis acid may facilitate the cyclization in an enantioselective manner (Scheme 1).

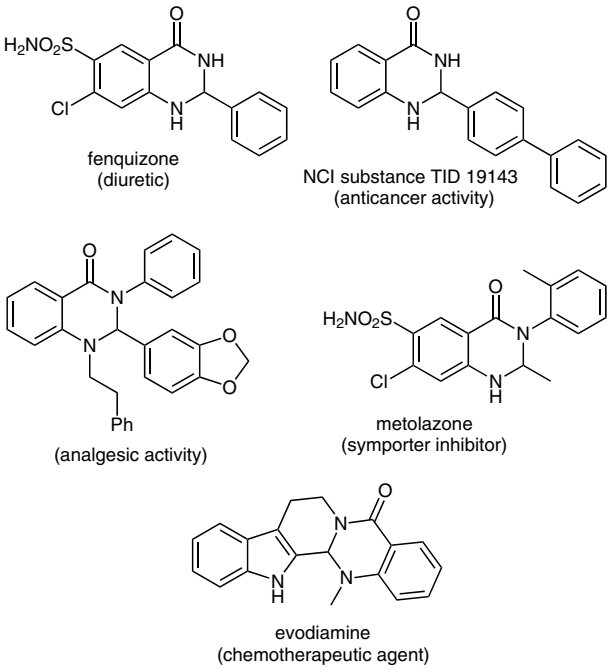
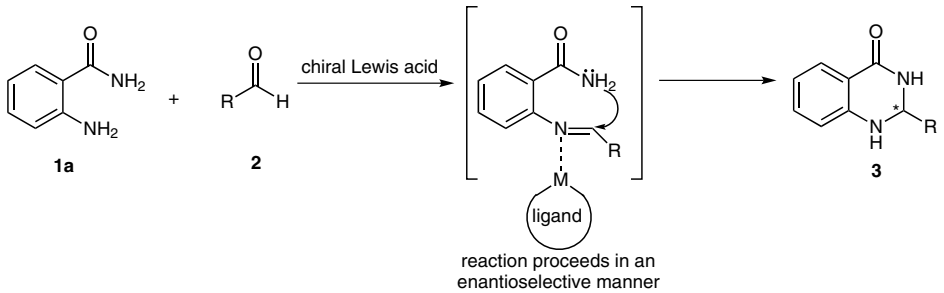


Figure 1 Pharmaceutically important 2,3-DHQZ scaffolds[1]



Scheme 1 Intramolecular amidation of imines

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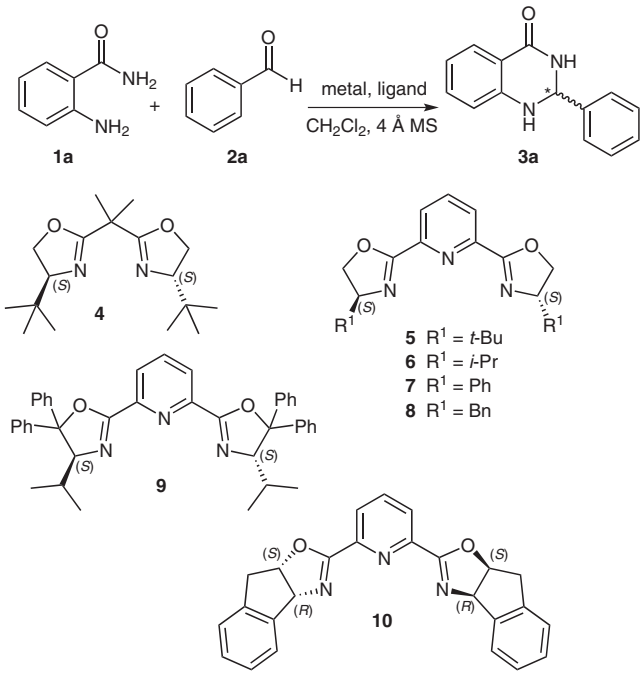
Our hypothesis was proven in the enantioselective synthesis of 2,3-DHQZs via the intramolecular amidation of imines using Sc(III)–*inda*-pybox.[6] Herein, we describe various factors which affect the enantioselectivity of the reaction and application of the protocol for the synthesis of various 2-alkyl- and 2,3-diaryl-substituted 2,3-DHQZs with fair to very good enantioselectivity in high yields.

Our exploration began with the screening of various substituted bis(oxazoline)s derived from amino alcohols in combination with various Lewis acids. The model reaction was carried out between anthranilamide (2-aminobenzamide, **1a**) and benzaldehyde (**2a**) at 25 °C in the presence of 5 mol% of various Lewis acids [CuOTf, $Cu(OTf)_2$ or $Zn(OTf)_2$], 10 mol% of bis(oxazoline) ligand **4** and powdered 4 Å molecular sieves (Scheme 2). All of these catalytic systems failed to promote the cyclization; imine was observed as a major product and less than 20% of the desired product was isolated with no chiral induction (Table 1, entries 1–3). After these unsuccessful experiments, we focused on the tridentate pyridine–bis(oxazoline)s **5**–**9** (Scheme 2), and the reactions were performed under similar conditions. Metal triflates (Cu, Zn) in combination with pybox **5** were not efficient enough to catalyze the intramolecular amidation of imine to form 2,3-DHQZ **3a** (Table 1, entries 4–6). In our continued effort to identify a suitable Lewis acid, we explored rare earth metal triflates in combination with pybox **5**, since the catalytic efficiency of such complexes is well known.[7,8] The scandium(III)–pybox complex promoted intramolecular amidation of imine to form 2,3-DHQZ **3a** in excellent yield with non-neglectable enantioselectivity (Table 1, entry 7). Encouraged by this observation, efforts were dedicated to improve the enantioselectivity. The employment of other well-known pybox ligands **6**–**9** did not realize the desired results (Table 1, entries 8–11).



Scheme 2 Enantioselective synthesis of 2-phenyl-2,3-DHQZ **3a**

Table 1 Optimization Study[a]

Entry	Ligand	Lewis acid	Yield[b] (%) of **3a**	er[c] (*R*/*S*)
1	**4**	CuOTf	20	*rac*
2	**4**	$Cu(OTf)_2$	10	*rac*
3	**4**	$Zn(OTf)_2$	10	*rac*
4	**5**	CuOTf	15	*rac*
5	**5**	$Cu(OTf)_2$	10	*rac*
6	**5**	$Zn(OTf)_2$	10	*rac*
7	**5**	$Sc(OTf)_3$	90	62:38
8	**6**	$Sc(OTf)_3$	80	50:50
9	**7**	$Sc(OTf)_3$	82	68:32
10	**8**	$Sc(OTf)_3$	89	58:42
11	**9**	$Sc(OTf)_3$	90	65:35

[a] Reaction conditions: Lewis acid (5 mol%), ligand **4**–**9** (10 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL).
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

These results indicate that pybox ligands derived from amino alcohols do not provide optimal encircling of activated imine to induce very good asymmetric induction. We hoped that pybox derived from (1*R*,2*S*)-1-amino-2-indanol would provide such an environment around imine leading to the formation of enantiomerically enriched 2,3-DHQZs. It is evident from Table 1 that pybox ligands derived from (*S*)-amino alcohols are responsible for formation of the *R*-isomer of 2,3-DHQZ **3a**. Hence, *inda*-pybox (**10**) (Scheme 2) was synthesized from (1*R*,2*S*)-1-amino-2-indanol in order to obtain the most-wanted *S*-isomer of 2,3-DHQZ **3a**. As expected, the most-wanted *S*-stereoisomer of 2,3-DHQZ **3a** was isolated with very good enanti-

Table 2 Influence of Metal Triflates on the Enantioselectivity[a]

Entry	Metal	Yield[b] (%) of **3a**	er[c] (*R*/*S*)
1	Sc^{3+}	94	8:92
2	Yb^{3+}	72	12:88
3	Y^{3+}	65	18:82
4	La^{3+}	20	*rac*

[a] Reaction conditions: $M(OTf)_3$ (5 mol%), ligand **10** (10 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL).
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

oselectivity (84% ee) under the previously established conditions (Table 2, entry 1).

Other rare earth metal triflates were evaluated in an attempt to further improve the enantioselectivity (Table 2, entries 2–4); however, it is beyond any doubt that scandium(III) triflate is the most suitable rare earth metal, catalyzing the intramolecular amidation of imine to afford 2,3-DHQZ **3a** in very good enantioselectivity.

An optimization study of the reaction medium was carried out with various solvents, including acetonitrile, chloroform, dichloromethane, methyl *tert*-butyl ether, tetrahydrofuran, benzene and toluene. Use of acetonitrile and tetrahydrofuran, as well as nonpolar solvents such as benzene and toluene, yielded the product **3a** with moderate enantioselectivity and conversion (Table 3, entries 3–6). When ethanol was used as the solvent, complete racemization of the product occurred (Table 3, entry 7). Methyl *tert*-butyl ether did not play any important role in further improving the enantioselectivity (Table 3, entry 8). This study identified dichloromethane or chloroform as the most suitable reaction medium for the synthesis of 2,3-DHQZ **3a** in an enantioselective manner using Sc(III)–(1*R*,2*S*)-*inda*-pybox (Table 3, entries 1 and 2).

Table 3 Impact of the Reaction Medium[a]

Entry	Solvent	Yield[b] (%) of **3a**	er[c] (*S*/*R*)
1	CH_2Cl_2	94	92:8
2	$CHCl_3$	92	92:8
3	THF	78	83:17
4	MeCN	81	88:12
5	toluene	60	81:19
6	benzene	54	76:24
7	EtOH	74	*rac*
8	MTBE	30	67:33

[a] Reaction conditions: $Sc(OTf)_3$ (5 mol%), ligand **10** (10 mol%), powdered 4 Å MS (50 mg), solvent (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), solvent (1 mL).
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

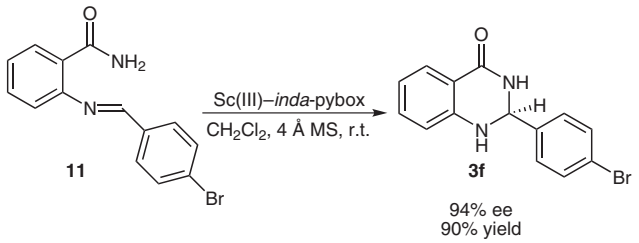
The ratio of metal to ligand was studied in order to improve the efficiency and selectivity of the reaction. Perhaps the most interesting observation was that a higher loading of metal ion resulted in a negative effect on the enantioselectivity (Table 4, entry 1); the enantioselectivity was strongly affected when excess Lewis acid was used. Hence, we performed the reaction with a low catalyst loading of 1 mol% of Lewis acid and 2 mol% of ligand **10**. These conditions provided a significant increase in the enantioselectivity while maintaining a high yield within four hours (Table 4, entry 3). Employment of an excess of the ligand (2.5 mol%), which ensures complete suppression of any competitive, achiral background reaction by efficient complexation, resulted in the achievement of an excellent level of enantioselection (98% ee) at room temperature (Table 4, entry 4).

Table 4 Optimization of the Metal/Ligand Ratio[a]

Entry	Metal/ligand (mol%:mol%)	Yield[b] (%) of **3a**	er[c] (*S*/*R*)
1	10:20	96	88:12
2	5:10	94	93:7
3	1:2	92	96:4
4	1:2.5	92	99:1

[a] Reaction conditions: $Sc(OTf)_3$ (1–10 mol%), ligand **10** (2–20 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL).
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

To prove that the cyclization occurs through an imine intermediate, (*E*)-2-[(4-bromobenzylidene)amino]benzamide (**11**) was treated with Sc(III)–*inda*-pybox. The corresponding 2,3-dihydroquinazolinone **3f** was isolated in very good yield and enantioselectivity (Scheme 3), thus demonstrating that imine **11** is the intermediate that undergoes cyclization to afford the 2,3-DHQZ.



Scheme 3 Enantioselective cyclization of (*E*)-2-[(4-bromobenzylidene)amino]benzamide (**11**)

After studying the influence of various parameters, we experienced difficulties in reproducing the results with the same enantioselectivity. The only parameter which had not been fixed was the molecular sieves, so more attention was given to optimizing the amount of molecular sieves. The purpose of molecular sieves is to absorb the water molecules produced during the course of the reaction. Although scandium(III) triflate is a water-tolerant Lewis acid, molecular sieves need to be added to obtain an enantiomerically enriched compound because the generation of a trace amount of triflic acid is sufficient enough to catalyze the cyclization, which may lead to poor enantioselection. The quantity and the nature of the molecular sieves has a profound effect on the enantioselectivity and yield of the reaction. Under our standard conditions, a clean reaction occurred when 200 mg of molecular sieves were used as beads instead of in powdered form, but a

poor enantioselection of 32% was observed. This implies that the nature of the molecular sieves plays a crucial role. The presence of an excess amount of molecular sieves in powdered form promotes the formation of imine rather than generation of the product through the catalytic cycle; this retards the rate of the reaction and, even after longer reaction time, a poor yield of 2,3-DHQZ **3a** was isolated (Table 5, entries 1–3).

Table 5 Role of Molecular Sieves (MS)[a]

Entry	Powdered 4 Å MS (mg)	Yield[b] (%) of **3a**	er[c] (*S*/*R*)
1	200	30	99:1
2	150	52	99:1
3	100	76	99:1
4	50	92	99:1
5	–	93	*rac*

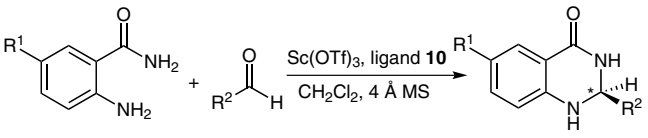
[a] Reaction conditions: $Sc(OTf)_3$ (1 mol%), ligand **10** (2.5 mol%), powdered 4 Å MS (0–200 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL).
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

Molecular sieves not only act as a desiccant, which in powdered form in larger amounts affects the yield of the reaction, in their absence complete racemization of the product was observed (Table 5, entry 5). This clearly indicates that the water molecules produced in the reaction mixture are efficiently trapped with an adequate amount of molecular sieves (Table 5, entry 4).

After investigating the influence of various parameters on the enantioselectivity, we started surveying the substrate scope. Simple aromatic aldehydes like benzaldehyde and 2-naphthaldehyde provided excellent enantioselectivity and yield (Table 6, entries 1 and 2). The cyclization of various *meta*- and *para*-substituted aldehydes was also achieved with excellent enantioselectivity and yield (Table 6, entries 3–9). 3,4-Disubstituted aldehydes were successfully employed as substrates; the corresponding cyclized products were isolated in admirable yield and enantioselectivity (Table 6, entries 10–13). The presence of a free hydroxy group did not pose any negative effect on the enantioselectivity (Table 6, entry 11). Substituted anthranilamides were also found to be suitable substrates under our catalytic conditions (Table 6, entries 14 and 15).

After achieving the cyclization of various aromatic aldehydes, and to highlight the efficiency of our catalytic protocol, aliphatic aldehydes were investigated, for which butyraldehyde (**12b**) was chosen as a model substrate (Table 7). Initial screening experiments revealed that the use of various ligands under the standard conditions failed to induce good enantioselectivity in cyclized product **13b** and only 10% enantiomeric excess was obtained when *inda*-pybox (**10**) was used as the chiral ligand (Table 7, entry 6). Hence, we performed the reaction at low temperature. Cyclization occurred with the maximum enantioselectivity (86% ee) at –20 °C (Table 7, entry 7). Further lowering of the temperature failed to enhance the enantioselectivity nor the yield of the reaction (Table 7, entry 8).

Table 6 Substrate Scope (Aromatic Aldehydes)[a]



1a–o **2** **3a–o**

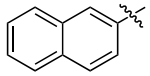
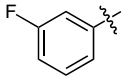
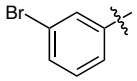
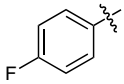
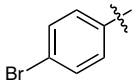
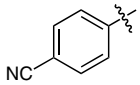
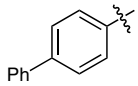
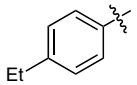
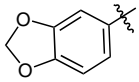
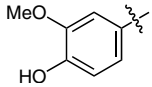
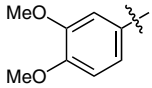
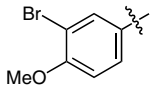
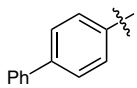
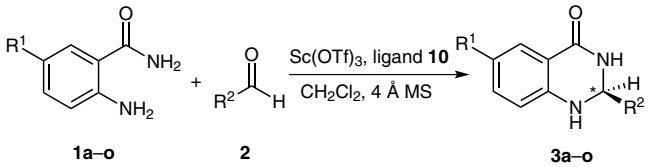
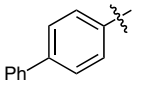
Entry	R^1	R^2	Yield[b] (%)	er[c] (*S*/*R*)
1	H		**3a**: 94	99:1
2	H		**3b**: 92	99:1
3	H		**3c**: 91	99:1
4	H		**3d**: 94	90:10
5	H		**3e**: 92	95:5
6	H		**3f**: 90	97:3
7	H		**3g**: 88	95:5
8	H		**3h**: 95	98:2
9	H		**3i**: 91	93:7
10	H		**3j**: 95	95:5
11	H		**3k**: 90	95:5
12	H		**3l**: 95	95:5
13	H		**3m**: 93	96:4
14	OCF_3		**3n**: 95	97:3

Table 6 Substrate Scope (Aromatic Aldehydes)[a] (continued)



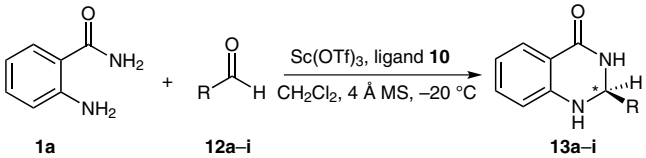
1a–o 2 3a–o

Entry	R^1	R^2	Yield[b] (%)	er[c] (*S*/*R*)
15	Cl		**3o**: 95	98:2

[a] Reaction conditions: $Sc(OTf)_3$ (1 mol%), ligand **10** (2.5 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; amide (0.3 mmol, 1 equiv), aldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL), r.t., 3–8 h.
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

After optimizing the reaction conditions for the formation of 2-propyl-2,3-DHQZ **13b**, we synthesized various 2-alkyl-substituted 2,3-DHQZs **13a**–**i** in an enantioenriched manner (Table 8). Linear as well as branched aliphatic aldehydes were subjected to cyclization with anthranilamide (2-aminobenzamide, **1a**). Reaction proceeded smoothly with good yield and enantioselectivity when linear aliphatic aldehydes were employed as substrates (Table 8, entries 1–4). In the case of branched aldehydes like isobutyraldehyde (**12e**) and isovaleraldehyde (**12f**), fair enantioselectivity and good yield was achieved (Table 8, entries 5 and 6). Improvement in enantioselectivity and yield was obtained when aromatic substitution was present at the β-position (Table 8, entry 8) rather than at the α-position (Table 8, entry 7) of the chain. When cyclohexanecarboxaldehyde (**12i**) was employed as the substrate, the corresponding cyclized product **13i** was isolated with moderate enantioselectivity and yield (Table 8, entry 9).

Table 8 Substrate Scope (Aliphatic Aldehydes)[a]

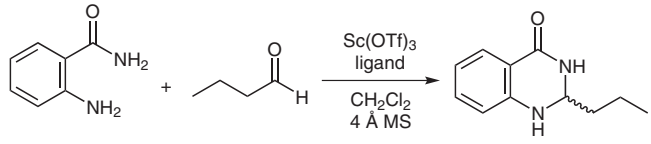


1a 12a–i 13a–i

Entry	Aldehyde **12**	Yield[b] (%)	er[c] (*S*/*R*)
1	propionaldehyde (**12a**)	**13a**: 80	89:11
2	butyraldehyde (**12b**)	**13b**: 82	93:7
3	hexaldehyde (**12c**)	**13c**: 79	88:12
4	heptaldehyde (**12d**)	**13d**: 84	96:4
5	isobutyraldehyde (**12e**)	**13e**: 78	82:18
6	isovaleraldehyde (**12f**)	**13f**: 81	83:17
7	phenylacetaldehyde (**12g**)	**13g**: 77	82:18
8	hydrocinnamaldehyde (**12h**)	**13h**: 87	93:7
9	cyclohexanecarboxaldehyde (**12i**)	**13i**: 79	82:18

[a] Reaction conditions: $Sc(OTf)_3$ (1 mol%), ligand **10** (2.5 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), aldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL), –20 °C, 48–80 h.
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralcel OD-H or Chiralpak AD-H column).

Table 7 Influence of Temperature[a]



1a 12b 13b

Entry	Ligand	Temp (°C)	Yield[b] (%) of **13b**	er[c] (*S*/*R*)
1	**5**	25	80	*rac*
2	**6**	25	78	*rac*
3	**7**	25	80	*rac*
4	**8**	25	83	*rac*
5	**9**	25	75	*rac*
6	**10**	25	88	55:45
7	**10**	–20	85	93:7
8	**10**	–40	79	92:8

[a] Reaction conditions: $Sc(OTf)_3$ (1 mol%), ligand **5**–**10** (2.5 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; anthranilamide (0.3 mmol, 1 equiv), butyraldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL), at the given temperature, 48 h.
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralpak AD-H column).

After achieving the enantioselective synthesis of various 2-aryl- and 2-alkyl-substituted 2,3-DHQZs, we proceeded to optimize the reaction conditions for 2,3-diaryl-2,3-DHQZs, which are potent analgesic and antimicrobial agents.[1e] To the best of our knowledge, there is no general synthetic method available for obtaining enantiomerically enriched 2,3-diaryl-2,3-DHQZ analogues, because they are more sterically hindered and less nucleophilic than 2-substituted 2,3-DHQZs. The importance of these valuable 2,3-diaryl-2,3-DHQZs, as well as the lack of methods for their enantioselective synthesis, stimulated us to develop a catalytic protocol for the asymmetric synthesis of such compounds. We initially carried out the condensation reaction between *N*-phenylanthranilamide (**14**) and benzaldehyde (**2a**) with scandium(III) triflate (5 mol%) and *inda*-pybox (10 mol%) in dichloromethane at room temperature. No chiral induction was observed at room temperature, hence the reactions were performed at –20 °C. Various substituted pybox ligands **5**–**10** were tested at this low temperature and the results are shown in Table 9. This screening revealed that ligand **10** induces the best asym-

Table 9 Screening of pybox Ligands[a]

Entry	Ligand	Yield[b] (%) of **15a**	er[c] (*S*/*R*)
1	**5**	60	68:32
2	**6**	57	53:47
3	**7**	54	84:16
4	**8**	60	86:14
5	**9**	64	67:33
6	**10**	72	90:10

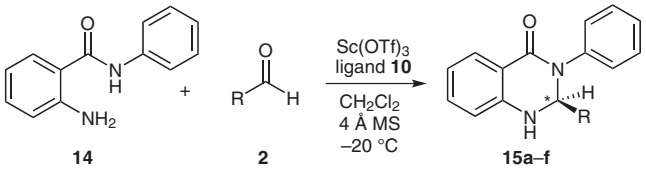
[a] Reaction conditions: $Sc(OTf)_3$ (5 mol%), ligand **5**–**10** (10 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; *N*-phenylanthranilamide (0.3 mmol, 1 equiv), benzaldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL), –20 °C.
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralcel OD-H or Chiralpak AD-H column).

metric induction (Table 9, entry 6). Further lowering of the temperature, as well as the mole ratio of the metal, significantly lowered the rate of the reaction.

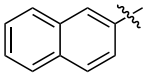
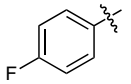
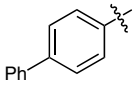
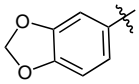
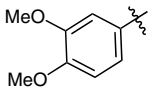
With the optimized conditions for the formation of 2,3-diphenyl-2,3-DHQZ **15a** in hand, we started investigating the substrate scope. Cyclization occurred smoothly with good yield and enantioselectivity when benzaldehyde or 2-naphthaldehyde was employed as the substrate in the reaction with *N*-phenylanthranilamide (Table 10, entries 1 and 2). The presence of fluoro substitution at the *para* position of the aldehyde yielded the desired product **15c** with moderate enantioselectivity (Table 10, entry 3); better yield and enantioselectivity were observed when 4-phenyl-substituted benzaldehyde was employed as the substrate (Table 10, entry 4). In the case of disubstituted aldehydes, the cyclized products **15e** and **15f** were isolated with good yields and moderate enantioselectivities (Table 10, entries 5 and 6).

In summary, we have accomplished the first metal-catalyzed enantioselective synthesis of 2-aryl-, 2-alkyl- and 2,3-diaryl-substituted 2,3-DHQZs, in a process with a broad substrate scope. Detailed experimental studies have revealed the influence of various factors, such as the mole ratio of the chiral catalyst, temperature and molecular sieves, which are prone to affect the enantioselective synthesis of 2,3-DHQZs. This work will pave the way to finding better lead compounds, in optically enriched form, against various drug targets. Currently, we are expanding this methodology to the synthesis of cyclothiazides in an enantioselective manner.

Table 10 Enantioselective Synthesis of 2-Aryl-3-phenyl-2,3-DHQZs[a]



14 **2** **15a–f**

Entry	R	Time (d)	Yield[b] (%)	er[c] (*S*/*R*)
1		4	**15a**: 74	90:10
2		4	**15b**: 78	87:13
3		6	**15c**: 70	81:19
4		4	**15d**: 92	91:9
5		7	**15e**: 70	78:22
6		7	**15f**: 73	76:24

[a] Reaction conditions: $Sc(OTf)_3$ (5 mol%), ligand **10** (10 mol%), powdered 4 Å MS (50 mg), CH_2Cl_2 (1 mL), r.t., 3 h; *N*-phenylanthranilamide (0.3 mmol, 1 equiv), aldehyde (0.36 mmol, 1.2 equiv), CH_2Cl_2 (1 mL), –20 °C.
[b] Isolated yield after column purification.
[c] Determined by HPLC (Chiralcel OD-H or Chiralpak AD-H column)

Chiral ligands **4**–**10** were synthesized according to reported procedures.[9] Amino alcohols required for the synthesis of ligands, anthranilamide and aldehydes were purchased from Aldrich Chemicals and used without further purification. *N*-Phenylanthranilamide was obtained from Alfa Aesar. All reactions were carried out in a flame-dried flask. Solvents used for reactions and column chromatography were of commercial grade and distilled prior to use. Toluene, benzene and THF were dried over sodium/benzophenone; CH_2Cl_2 and $CHCl_3$ were dried over CaH_2. Solvents for HPLC analysis were bought as HPLC grade and used without further purification. TLC was performed on precoated Merck silica gel 60 aluminum plates with F_{254} indicator, which were visualized by irradiation with UV light. Column chromatography was performed using Merck silica gel 60–100 mesh. Melting points were determined by the open glass capillary method and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 500-MHz instrument using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra were obtained by ESI using a Waters Micromass Q-TOF mass spectrometer. IR spectra were recorded on a Perkin Elmer FT/IR-420 spectrometer. Enantiomeric excesses were obtained by HPLC analysis on a chiral stationary phase column (Chiralpak AD-H, Chiralpak AS-H or Chiralcel OD-H). Optical rotations were recorded on a Jasco DIP polarimeter with a sodium lamp at $\lambda = 589$ nm and are reported as $[\alpha]_D^T$ (T = temperature in °C).

2-Alkyl-, 2-Aryl- and 2,3-Diaryl-2,3-dihydroquinazolinones; General Procedure

In an oven-dried flask, pybox ligand **10** (7.5 μmol) and $Sc(OTf)_3$ (3 μmol) were taken up in anhyd CH_2Cl_2 (1 mL) [5 mol% metal/10 mol% ligand was employed in the case of *N*-phenylanthranilamide (**14**)]. Powdered 4 Å molecular sieves (50 mg) were added to the solution and the resulting mixture was stirred for a further 3 h. Then, anthranilamide (**1**) or *N*-phenylanthranilamide (**14**) (300 μmol) solubilized in CH_2Cl_2 (1 mL) was added at the indicated temperature

(see tables), followed by aldehyde (360 μmol), and the mixture was stirred until the reaction was complete as ascertained by TLC. The product was purified by using a small pad of silica gel (60–100 mesh) with PE–EtOAc (1:1) as eluent to afford the corresponding 2,3-dihydroquinazolinone as a colorless solid. Analytical data for all new compounds (**13a**, **13c**, **15e**) are provided below, and characterization data for other reported compounds are provided in detail in the Supporting Information.

(*S*)-2-Ethyl-2,3-dihydroquinazolin-4(1*H*)-one (13a)
Colorless solid; yield: 42 mg (80%); mp 148 °C.

$[\alpha]_D^{25}$ +75.2 (*c* 1.0, THF).

HPLC (OD-H column; *n*-hexane–*i*-PrOH, 80:20; flow rate = 0.8 mL·min^{-1}): t_R = 11.32 (minor enantiomer), 9.77 min (major enantiomer); er 89:11.

R_f = 0.3 (PE–EtOAc, 1:1).

FTIR (KBr): 3294, 3081, 2958, 1654, 1613, 1506, 1385, 1264, 1153, 755, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 8, 1.5 Hz, 1 H), 7.34–7.30 (m, 1 H), 6.88–6.85 (m, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.43 (br s, 1 H), 4.88–4.85 (m, 1 H), 1.86–1.81 (m, 2 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.43, 147.44, 133.85, 128.57, 119.34, 115.86, 114.69, 66.43, 28.59, 8.28.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{12}N_2O$: 199.0847; found: 119.0845.

(*S*)-2-Pentyl-2,3-dihydroquinazolin-4(1*H*)-one (13c)
Colorless solid; yield: 52 mg (79%); mp 154 °C.

$[\alpha]_D^{25}$ +79.7 (*c* 1.0, THF).

HPLC (OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate = 0.8 mL·min^{-1}): t_R = 23.45 (minor enantiomer), 20.66 min (major enantiomer); er 88:12.

R_f = 0.35 (PE–EtOAc, 1:1).

FTIR (KBr): 3329, 3206, 3069, 2953, 1643, 1614, 1507, 1387, 1261, 1152, 752, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 1.5 Hz, 1 H), 7.35–7.28 (m, 1 H), 6.90–6.87 (m, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.16 (br s, 1 H), 4.91 (t, *J* = 6 Hz, 1 H), 1.80–1.77 (m, 2 H), 1.38–1.36 (m, 5 H), 0.95–0.92 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.37, 147.42, 133.89, 128.63, 119.46, 115.91, 114.74, 65.38, 35.59, 31.45, 23.72, 22.49, 13.91.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{18}N_2O$: 241.1317; found: 241.1311.

(*S*)-2-(1,3-Benzodioxol-5-yl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (15e)
Colorless solid; yield: 71 mg (70%); mp 239 °C.

$[\alpha]_D^{25}$ +97.1 (*c* 1.0, THF).

HPLC (OD-H column; *n*-hexane–*i*-PrOH, 80:20; flow rate = 0.8 mL·min^{-1}): t_R = 32.35 (minor enantiomer), 22.42 min (major enantiomer); er 78:22.

R_f = 0.3 (PE–EtOAc, 3:1).

FTIR (KBr): 3297, 3039, 2928, 1639, 1614, 1500, 1450, 1393, 1244, 1035, 937, 856, 697 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.72 (d, *J* = 7.5 Hz, 1 H), 7.55 (m, 1 H), 7.34 (t, *J* = 8 Hz, 2 H), 7.30–7.25 (m, 3 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 6.93 (s, 1 H), 6.81 (s, 2 H), 6.77–6.71 (m, 2 H), 6.20 (d, *J* = 2.5 Hz, 1 H), 5.97 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.73, 147.82, 147.66, 147.02, 141.2, 135.07, 134.23, 129.06, 128.40, 126.72, 126.28, 120.74, 118.00, 115.76, 115.26, 108.26, 107.30, 101.64, 72.85.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{16}N_2O_3$: 345.1239; found: 345.1233.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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