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Highly enantioselective synthesis of dihydroquinazolinones through $Sc(OTf)_3$-catalyzed intramolecular amidation of imines

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ABSTRACT

A $Sc(OTf)_3$-catalyzed intramolecular amidation of imines with a novel fluorous bis(oxazolines) as ligand is presented. The corresponding chiral dihydroquinazolinones were obtained in 76–94% yield with enantioselectivities up to 98%. The fluorous ligand can be easily recovered and reused at least three times without significant loss of enantioselectivity.

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1. Introduction

Pharmacologically active heterocycles/intermediates which possess a chiral center are increasingly being successfully synthesized in a stereoselective route in recent years [1]. Many biological processes involving these nitrogen containing heterocycles as markers or messenger molecules and an array of pharmaceuticals and agrochemicals based on those chemicals have been reported during the past few decades. 2,3-Dihydroquinazolinone derivatives including the oxidized form, the quinazolinones, displayed extensive important pharmacological activities, such as antitumor, analgesic, antifibrillatory, antibiotic, antispermatogenic, and vasodilatory efficacy [2]. A selection of bio-active quinazolinone derivatives are shown in Scheme 1. In addition, these compounds are relevant building blocks in organic synthesis to form more complex structures such as natural products like luotonin A, sclerotigenin, fumiquinazoline A or (±)-cruciferane (Fig. 1). Consequently, numerous methodologies are described in the literature for the preparation of these important classes of compounds.

Sharma and Kaur developed the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from anthranilamide and different aldehydes/ketones in presence of *para*-toluene sulfonic acid as catalyst under reflux conditions [3]. Rostamizadeh et al. observed formation of 2,3-dihydroquinazolin-4(1H)-ones from isatoic anhydride and aromatic aldehydes under solvent free conditions using catalytic amounts of iodine in 2008 [4]. Likewise, Lewis acid catalysts, such as gallium(III) triflate [5] and zinc(II) perfluorooctanoate [6] have also been used for catalyzing one-pot reaction for synthesis of quinazolinones. As reported by Bunce and Nammalwar, various quinazolinone derivatives can also be synthesized using 2-nitrobenzamides and carbonyl compounds as the substrates with iron powder as the promoter [7]. Another synthetic strategy to give different 2-substituted dihydroquinazolinones from anthranilamide and different aldehydes in the presence of β-cyclodextrin water was published by Ramesh et al. [8]. More recently, Langer and coworkers reported base mediated synthesis of 2-aryl-2,3-dihydroquinazolin-4(1H)-ones from 2-aminobenzonitriles and aromatic aldehydes in water [9].

Regardless of the above methods that are available to synthesize dihydroquinazolinones as racemates [10], enantioselective synthesis of 2,3-dihydroquinazolinones is not easily achieved since the aminal stereocenter is sensitive to racemization [11]. Cheng et al. reported about the asymmetric synthesis of dihydroquinazolinones using (S)-TRIP as the catalyst [12]. Singh and coworkers reported the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from isatoic anhydride, aldehyde, amine or ammonium acetate in water under microwave in the presence of L-proline [13]. Additionally, in

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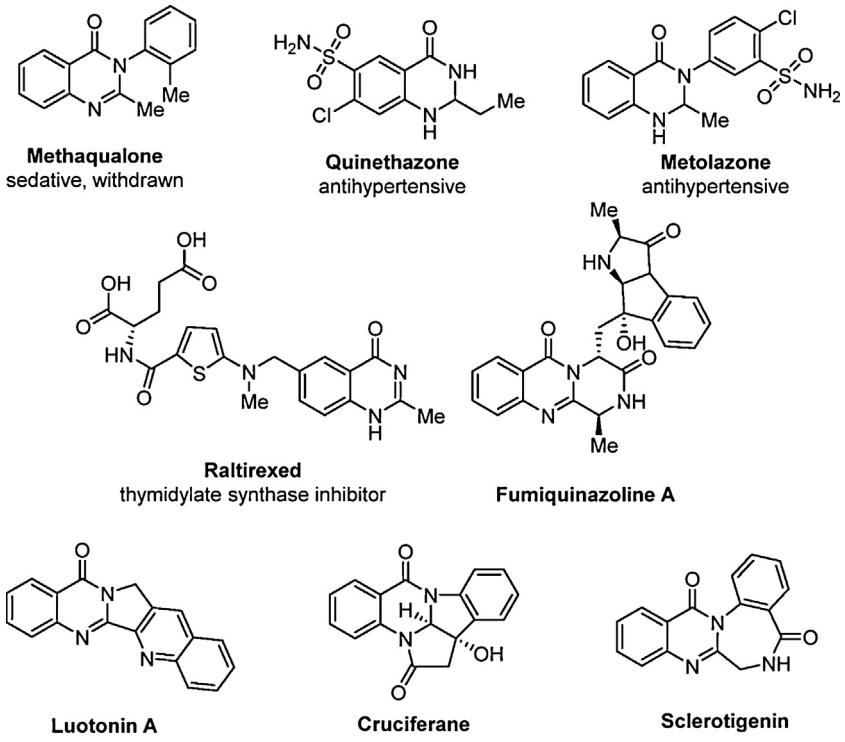


Fig. 1. Selected examples of biologically active quinazolinone derivatives.

2012, Prakash and Kesavan reported the enantioselective synthesis of 2,3-dihydroquinazolin-4(1H)-ones from 2-aminobenzamides with aldehydes using Sc(III) as a catalyst (limited to the use of preformed imines, 54–90% yields, and 83–97% *ee*'s, −20 °C) [14]. More recently, in 2013 Lin and co-workers reported the application of SPINOL-phosphoric acid to this asymmetric condensation [15]. Despite these elegant examples, a general, efficient, and mild enantioselective protocol has yet to be described and would be of a great value because of the importance of optically active 2,3-dihydroquinazolinones.

Our group has great interest in developing different chiral bis(oxazolines) for asymmetric reactions and has showed their excellent catalytic reactivity as chiral ligands. These previous successes led us to envision that recyclable bis(oxazolines) ligand might be suitable for the asymmetric condensation of 2-aminobenzamides and different aldehydes. Herein, we present our preliminary results on this subject. A range of substituted 2,3-dihydroquinazoline-4(1H)-ones were obtained in high yields and good enantioselectivities (up to 94% yield, 98% *ee*).

2. Results and discussion

Initial attempts were made to prove our hypothesis by screening ligands (Fig. 2, L1–L8) with various Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$ or $Zn(OTf)_2$. Intramolecular amidation of imine formed between 2-aminobenzamide (**1**) and benzaldehyde (**2a**) as the model substrates with 1 mol% of Lewis acid and 5 mol% of ligand in chloroform at room temperature in the presence of powdered 4 Å molecular sieves. A series of chiral bis(oxazolines) ligands were screened, as shown in Table 1. Although the yields of the reactions in the presence of ligands L1–L3 were good, the enantioselectivities of these reactions were frustrating (Table 1, entries 1–3). In detail, the fluorous bis(oxazolines) L3 almost had no inducing effect on the enantioselectivity (Table 1, entry 3). Since

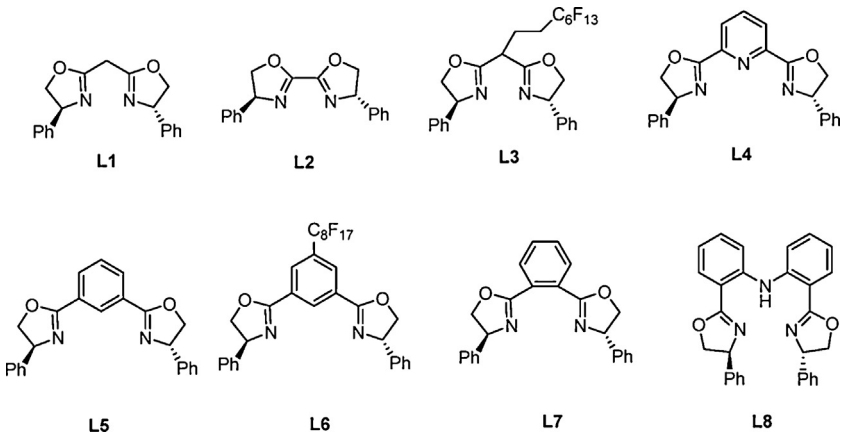
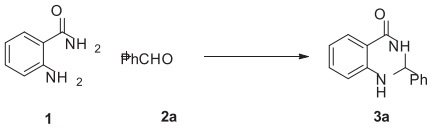


Fig. 2. Selected examples of chiral ligands examined.

Table 1
Optimization of the conditions.[a]



1 2a 3a

Entry	Ligand	Metal	Solvent	Yield[b]/%	*ee*[c]/%
1	L1	$Sc(OTf)_3$	$CHCl_3$	62	19(R)
2	L2	$Sc(OTf)_3$	$CHCl_3$	81	Racemic
3	L3	$Sc(OTf)_3$	$CHCl_3$	70	12(R)
4	L4	$Sc(OTf)_3$	$CHCl_3$	82	30(R)
5	L5	$Sc(OTf)_3$	$CHCl_3$	79	93(S)
6	L6	$Sc(OTf)_3$	$CHCl_3$	78	94(S)
7	L7	$Sc(OTf)_3$	$CHCl_3$	69	Racemic
8	L8	$Sc(OTf)_3$	$CHCl_3$	72	27(R)
9	L6	$Zn(OTf)_2$	$CHCl_3$	13	5
10	L6	$Cu(OTf)_2$	$CHCl_3$	17	8
11	L6	$Sc(OTf)_3$	CH_2Cl_2	87	97
12	L6	$Sc(OTf)_3$	CCl_4	59	62
13	L6	$Sc(OTf)_3$	THF	35	26
14	L6	$Sc(OTf)_3$	Dioxane	39	45
15	L6	$Sc(OTf)_3$	Toluene	42	58
16[d]	L6	$Sc(OTf)_3$	CH_2Cl_2	46	98
17[e]	L6	$Sc(OTf)_3$	CH_2Cl_2	84	97
18[f]	L6	$Sc(OTf)_3$	CH_2Cl_2	85	96
19[g]	L6	$Sc(OTf)_3$	CH_2Cl_2	84	95
20[h]	L6	$Sc(OTf)_3$	CH_2Cl_2	81	92

[a] Reactions were carried out using 0.3 mmol of 2 aminobenzamide, 0.36 mmol of benzaldehyde, 5 mol% of ligand, 1 mol% of metal salt and powdered 4 Å molecular sieves in solvent for 48 h.
[b] Isolated yields.
[c] The *ee* value of the compound was checked by chiral HPLC using a Venusil CA column.
[d] At 0 °C for 72 h.
[e] 1.0 mmol scale experiment.
[f] First reuse by F-SPE.
[g] Second reuse by F-SPE.
[h] Third reuse by F-SPE.

these attempts were not successful, we turned our attention to commercial pybox ligand L4 with $Sc(OTf)_3$ as Lewis acid, these complexes can be used in different reactions and their catalytic efficiencies is well demonstrated in the literature [16,17]. We were delighted to observe that pybox/$Sc(OTf)_3$ catalyzed the intramolecular amidation of imine with great efficiency and with an enantiomeric excess of 30% (Table 1, entry 4). Encouraged by this observation, we sought other suitable ligand to enhance the enantioselectivity of this transformation. The reaction proceeded to afford the desired optically active 2,3-dihydroquinazolinone **2a** in excellent enantiomeric excess using ligand L5 (Table 1, entry 5). As we expected, the fluorous bis(oxazolines) L6 revealed similar enantioselectivity at room temperature to afford 2,3-dihydroquinazolinone **2a** in 79% yield with 93% *ee* (Table 1, entry 6). However, L7 and L8 failed to improve the enantioselectivity of the reaction (Table 1, entries 7 and 8).

Scandium(III) triflate was found to be the most suitable metal partner since reactions catalyzed by other metal triflates such as $Cu(OTf)_2$ and $Zn(OTf)_2$ in combination with L6 did not improve either the yield or the enantioselectivity (Table 1, entries 9 and 10). It was observed that 2,3-dihydroquinazolinone **2a** was isolated in very low yields (10–20%) with almost no chiral induction.

Then, in the presence of L6, the preliminary evaluation of other solvents such as CH_2Cl_2 and CCl_4 disclosed that CH_2Cl_2 was much superior to $CHCl_3$ and CCl_4 with regard to enantioselectivity, delivering the chiral 2,3-dihydroquinazolinone **2a** in 97% *ee* (Table 1, entries 11 vs. 5 and 12). However, further screening of other solvents including THF, toluene and 1,4-dioxane could not realize better results than CH_2Cl_2 did (entries 13–15 vs. 11). Hence, CH_2Cl_2 was chosen as the most suitable solvent for further optimization of the reaction conditions. Lowering the temperature to 0 °C remarkably lowered the yield but with higher enantioselectivity (46% yield, 98% *ee*, Table 1, entry 16). Thus, the optimized reaction conditions for the model reaction were established.

Furthermore, the scalability of the newly investigated method was proven with a 1.0 mmol scale experiment (Table 1, entry 17). The 2,3-dihydroquinazolinone **2a** was obtained in 84% yield and 97% *ee* at room temperature. To illustrate the recycling of the ligand L6, the recovered ligand in the above reaction was then reused directly in the next reaction with a 1.0 mmol scale experiment, and the same procedure was repeated to exhibit the comparable activity and enantioselectivity (85% yield, 96% *ee*, entry 18 vs. 84% yield, 95% *ee*, entry 19, respectively, Table 1).

With these reaction conditions identified, our attention turned to extend the scope of our methodology in synthesizing various optically 2,3-dihydroquinazolinones. The reactions were carried out using ligand L6 under the optimized conditions, and the results are summarized in Table 2. To our delight, all reactions proceeded in generally excellent yields with good to excellent enantioselectivities. Substituted benzaldehydes bearing either electronically poor, neutral, or rich group have remarkable differences in enantioselectivities of this reaction although the corresponding products **3a**–**3k** were obtained in generally high yields and favorable to good enantioselectivities (76–94% yield, 87–98% *ee*). In detail, the presence of an electron-withdrawing group (–Cl, $–NO_2$ or $–CF_3$) in the *para*-position of benzaldehyde is well tolerated in synthesizing substituted 2,3-dihydroquinazolinones **3b**–**3d** (Table 2, entries 2–4). Among them, *p*-nitrobenzaldehyde **3d** had the highest capability in enantioselective control with an excellent enantioselectivity of 98% (Table 2, entry 4). When electron-donating groups were introduced, the reactions ran smoothly, affording the products **3e**–**3g** in high yields with enantiomeric excess ranging from 92 to 95% (Table 2, entries 5–7).

Moreover, the position of electron-withdrawing substituents appeared to exert some impact on the enantioselectivity. The

Table 2
Scope of substrates.[a]

Entry	R	Product	Yield[b]/%	*ee*[c]/%
1	C_6H_5	**3a**	84	97
2	4-ClC_6H_4	**3b**	89	98
3	4-$CF_3C_6H_4$	**3c**	94	97
4	4-$NO_2C_6H_4$	**3d**	92	98
5	4-$OMeC_6H_4$	**3e**	86	92
6	4-$Me_2NC_6H_4$	**3f**	83	93
7	4-MeC_6H_4	**3g**	86	95
8	3-BrC_6H_4	**3h**	84	88
9	2-BrC_6H_4	**3i**	91	89
10	3-$NO_2C_6H_4$	**3j**	81	91
11	2-$NO_2C_6H_4$	**3k**	90	92
12	2-Pyridinyl	**3l**	82	87
13	1-Naphthyl	**3m**	79	92
14	(E)-PhCH=CH	**3n**	76	94
15	$PhCH_2CH_2$	**3o**	85	93
16	Cyclohexanyl	**3p**	90	89
17	CH_3CH_2	–	nr	–

[a] Reactions were carried out using 1 mmol of 2-aminobenzamide, 1.2 mmol of aldehyde, 1 mol% of $Sc(OTf)_3$, 5 mol% of L6 and powdered 4 Å molecular sieves at room temperature in CH_2Cl_2 for 48 h.
[b] Isolated yields.
[c] The *ee* value of the compound was checked by chiral HPLC using a Venusil CA column and Venusil CO column.

presence of bromo as well as nitro group on benzaldehyde at either the *ortho* or *meta* position obviously reduced the enantiomeric excesses of the transformation (Table 2, entries 8–11). The steric effect of a bromine atom contributed to the diminished enantioselectivity in the case of *o*-bromobenzaldehyde (Table 2, entry 9). A similar steric effect was observed when *o*-nitrobenzaldehyde was treated with 2-aminobenzamide to afford **3k** with slightly decreased enantioselectivity (92% *ee*, Table 2, entry 11).

Besides, this protocol could also be applied to heteroaromatic aldehydes as exemplified by 2-pyridinecarboxaldehyde in 82% yield and 87% *ee* (Table 2, entry 12). The 1-naphthyl-bearing substrate delivered the corresponding product with high enantioselectivity of 92% albeit with slightly decreased yield (Table 2, entry 13). The α,β-unsaturated aldehyde (cinnamaldehyde) also led to product **3n** in only 76% yield and 94% *ee*, whereas a saturated aldehyde (phenylpropyl aldehyde) gave product **3m** in 85% yield and 93% *ee* (Table 2, entries 14 vs. 15).

We further expanded the scope of this reaction to aliphatic aldehydes. When a cyclohexyl substituent was introduced, affording the product **3p** in 90% yield and 89% *ee* (Table 2, entry 16) while no desired product was obtained for propionaldehyde (Table 2, entry 17).

3. Conclusions

In summary, we have presented an efficient protocol for the synthesis of dihydroquinazolinones through $Sc(OTf)_3$-catalyzed intramolecular amidation of imines with a fluorous bis(oxazolines) as ligand. This process was carried out in mild conditions and gave the corresponding dihydroquinazolinones with moderate to high yields and good enantiomeric excesses. The reaction expands the scope of the asymmetric addition with a variety of aldehydes. The fluorous ligand can be easily recovered and reused at least three times without significant loss of enantioselectivity. Further explorations of the chiral bis(oxazolines) type ligands' applications in asymmetric catalysis are underway.

4. Experimental

4.1. General information

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer and tetramethylsilane (TMS) was used as a reference. All of the products were known compounds and were identified by comparison of their physical and spectra data with those of authentic samples. Enantiomeric excesses (ee) were determined by chiral HPLC using a Venusil CA column and Venusil CO column.

4.2. General procedure for the enantioselective synthesis of 2,3-dihydroquinazolinones.

A mixture of 2-aminobenzamide (1 mmol), aldehyde (1.2 mmol), 1 mol% of $Sc(OTf)_3$, 5 mol% of L6 and powdered 4 Å molecular sieves in 1.0 mL anhydrous CH_2Cl_2 was stirred for 48 h at room temperature under a nitrogen atmosphere. Completion of the reaction was ascertained by TLC, and the product was purified by flash column chromatography to afford desired product.

4.3. General procedure for recovery of fluorous bis(oxazolines)

After the reaction was finished, the mixture was concentrated and then loaded onto a FluoroFlash® silica gel for F-SPE. The residue was eluted by methanol:water (v/v = 80:20) at first for the seperation of non-fluorous component, pure methanol was then added onto the fluorous gel column continuously for obtaining the elutant of fluorous bis(oxazolines). When the bulk of solvent was removed and the residue was dried in vacuo at 50 °C for 8 h to give the fluorous bis(oxazolines). The recovered ligand could be used directly for the next run.

4.4. 2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (**3a**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (84% yield). The *ee* (97%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 254 nm, major enantiomer t_1 = 29.1 min, minor enantiomer t_2 = 33.9 min. White solid; ^1H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.39–7.33 (m, 3H), 7.24–7.21(m, 1H), 7.09 (s, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.67–6.64 (m, 1H), 5.73 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.05, 147.32, 141.13, 132.77, 127.91, 127.79, 126.82, 126.32, 116.58, 114.43, 113.87, 66.03.

4.5. 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3b**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (89% yield). The *ee* (98%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 210 nm, major enantiomer t_1 = 18.0 min, minor enantiomer t_2 = 22.6 min. White solid; ^1H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.23–7.21 (m, 1H), 7.12 (s, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.68–6.65 (m, 1H), 5.75 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.04, 148.18, 141.26, 133.97, 133.52, 129.29, 128.87, 127.92, 117.85, 115.49, 115.02, 66.30.

4.6. 2-(4-(Trifluoromethyl) phenyl)-2,3-dihydroquinazolin-4(1H)-one (**3c**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (94% yield). The *ee* (97%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 210 nm, major enantiomer t_1 = 11.9 min, minor enantiomer t_2 = 18.0 min. White solid; ^1H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.28–7.18 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.69–6.66 (m, 1H), 5.84 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.93, 148.32, 136.28, 133.80, 132.40, 132.19, 129.29, 128.92, 128.69, 128.21, 127.93, 127.20, 117.70, 115.09, 66.33. ^{19}F NMR (500 MHz, DMSO-d_6) δ −60.94.

4.7. 2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3d**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (92% yield). The *ee* (98%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 230 nm, major enantiomer t_1 = 21.2 min, minor enantiomer t_2 = 31.0 min. Yellow solid; ^1H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.24 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 7.3 Hz, 1H), 7.31 (s, 1H), 7.26–7.23 (m, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.69–6.66 (m, 1H), 5.89 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.82, 149.89, 147.77, 135.37, 134.14, 129.90, 128.58, 127.97, 126.51, 124.14, 118.05, 115.48, 115.12, 65.85.

4.8. 2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**3e**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (86% yield). The *ee* (92%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min,

UV = 230 nm, major enantiomer t_1 = 17.7 min, minor enantiomer t_2 = 19.2 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.23–7.20 (m, 1H), 6.99 (s, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.67–6.64 (m, 1H), 5.69 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.18, 147.56, 147.47, 134.15, 132.97, 129.13, 127.66, 1117.56, 114.89, 114.53, 113.11, 65.77, 54.98.

4.9. 2-(4-(Dimethylamino) phenyl)-2,3-dihydroquinazolin-4(1H)-one (**3f**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (83% yield). The *ee* (93%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 210 nm, major enantiomer t_1 = 26.2 min, minor enantiomer t_2 = 28.4 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.21 (s, 1H), 6.90 (s, 1H), 6.72–6.65 (m, 4H), 5.62 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.32, 150.19, 147.69, 132.62, 128.12, 127.17, 126.82, 116.43, 114.50, 113.87, 111.41, 66.11, 39.63.

4.10. 2-(p-Tolyl)-2,3-dihydroquinazolin-4(1H)-one (**3g**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (86% yield). The *ee* (95%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 210 nm, major enantiomer t_1 = 26.1 min, minor enantiomer t_2 = 31.4 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.26–7.12 (m, 3H), 7.04 (s, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.66–6.63 (t, J = 7.4 Hz, 1H), 5.69 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.12, 147.38, 138.13, 137.19, 132.73, 128.28, 126.81, 126.26, 116.54, 114.47, 113.88, 65.84, 20.20.

4.11. 2-(3-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3 h**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (84% yield). The *ee* (88%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 90:10, flow rate = 0.7 mL/min, UV = 230 nm, major enantiomer t_1 = 37.6 min, minor enantiomer t_2 = 40.7 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.65 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.35–7.32 (m, 1H), 7.26–7.23 (m, 1H), 7.19 (s, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.68–6.65 (m, 1H), 5.76 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.99, 148.03, 145.19, 134.06, 131.73, 131.17, 130.18, 127.94, 126.33, 122.16, 117.91, 115.43, 115.04, 66.05.

4.12. 2-(2-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3i**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (91% yield). The *ee* (89%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 230 nm, major enantiomer t_1 = 27.5 min, minor enantiomer t_2 = 33.9 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.67–7.64 (m, 3H), 7.45–7.42 (m, 1H), 7.33–7.30 (m, 1H), 7.26–7.23 (m, 1H), 6.98 (s, 1H), 6.80–6.60 (m, 2H), 6.08 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.09, 147.16, 138.62, 132.90, 132.27, 130.17, 128.59, 127.54, 126.86, 121.68, 116.99, 114.19, 114.08, 65.86.

4.13. 2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3j**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (81% yield). The *ee* (91%) was determined by HPLC analysis, Venusil CO column, Hexane/i-PrOH 70:30, flow rate = 0.5 mL/min, UV = 230 nm, major enantiomer t_1 = 30.9 min, minor enantiomer t_2 = 35.5 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.34 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.70–7.67 (m, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.33 (s, 1H), 7.27–7.24 (m, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.70–6.67 (m, 1H), 5.92 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.92, 148.28, 147.83, 144.85, 134.16, 133.90, 130.61, 127.97, 123.83, 122.09, 118.11, 115.49, 115.15, 65.72.

4.14. 2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3k**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (90% yield). The *ee* (92%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 80:20, flow rate = 0.5 mL/min, UV = 210 nm, major enantiomer t_1 = 39.5 min, minor enantiomer t_2 = 41.9 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.81–7.73 (m, 1H), 7.65–7.59 (m, 2H), 7.29–7.21 (m, 1H), 6.99 (s, 1H), 6.80–6.68 (m, 2H), 6.32 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.87, 147.15, 146.59, 135.40, 133.38, 133.05, 129.37, 128.39, 126.80, 124.19, 117.18, 114.40, 114.00, 61.67.

4.15. 2-(Pyridin-2-yl)-2,3-dihydroquinazolin-4(1H)-one (**3l**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1(82% yield). The *ee* (87%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 230 nm, major enantiomer t_1 = 22.9 min, minor enantiomer t_2 = 29.1 min. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 4.2 Hz, 1H), 8.38 (s, 1H), 7.83–1.80 (m, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.35–7.20 (m, 3H), 6.75 (d, J = 8.1 Hz, 1H), 6.67–6.64 (m, 1H), 5.72 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.44, 149.54, 147.70, 138.58, 137.85, 135.50, 134.31, 127.22, 124.16, 120.99, 117.99, 115.10, 67.30.

4.16. 2-(Naphthalen-1-yl)-2,3-dihydroquinazolin-4(1H)-one (**3m**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (79% yield). The *ee* (92%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 273 nm, miajor enantiomer t_1 = 18.4 min, minor enantiomer t_2 = 22.1 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, J = 7.8 Hz, 1H), 8.30 (s, 1H), 8.01–7.97 (m, 2H), 7.73–7.71 (m, 2H), 7.58–7.52 (m, 3H), 7.29–7.26 (m, 1H), 7.11 (s, 1H), 6.78–6.72 (m, 2H), 6.50 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.54, 147.93, 134.65, 133.25, 132.76, 130.02, 128.85, 128.08, 127.02, 125.55, 125.30, 124.68, 124.07, 116.75, 114.47, 114.01, 65.41.

4.17. (E)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (**3n**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (76% yield). The *ee* (94%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 230 nm, major enantiomer t_1 = 21.0 min, minor enantiomer t_2 = 23.4 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.32 (d, J = 7.7 Hz, 2H), 7.28–7.21 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.68–6.63 (m, 2H), 6.37–6.34 (m, 1H), 5.28 (d, J = 6.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.98, 148.22, 148.00, 146.96, 146.54, 134.07, 128.19, 127.95, 125.87, 117.95, 115.46, 115.05, 66.24.

4.18. 2-Phenethyl-2,3-dihydroquinazolin-4(1H)-one (**3o**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (85% yield). The *ee* (93%) was determined by HPLC analysis,

Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 280 nm, major enantiomer t_1 = 17.2 min, minor enantiomer t_2 = 20.3 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.61–7.59 (m, 1H), 7.28–7.16 (m, 6H), 6.76–6.65 (m, 3H), 4.74–4.72 (m, 1H), 2.74 (d, J = 5.0 Hz, 2H), 1.94–1.90 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.58, 148.03, 141.07, 132.62, 127.85, 127.78, 126.91, 125.28, 116.58, 114.55, 113.90, 63.46, 36.15, 28.77.

4.19. 2-Cyclohexyl-2,3-dihydroquinazolin-4(1H)-one (**3p**)

Purified by column chromatography eluting with Hexane/EtOAc 2:1 (90% yield). The *ee* (89%) was determined by HPLC analysis, Venusil CA column, Hexane/i-PrOH 85:15, flow rate = 0.7 mL/min, UV = 254 nm, major enantiomer t_1 = 10.9 min, minor enantiomer t_2 = 16.2 min. White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.20–7.18 (m, 1H), 6.74 (d, J = 10.0 Hz, 1H), 6.62–6.59 (m, 1H), 6.55 (s, 1H), 4.44 (s, 1H), 1.69 (d, J = 12.2 Hz, 4H), 1.58 (d, J = 30.8 Hz, 2H), 1.11 (s, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.20, 147.82, 132.49, 126.70, 115.89, 114.26, 113.55, 68.05, 42.34, 26.47, 26.16, 25.41, 25.09, 25.03.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.11.008.

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