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ROYAL SOCIETY OF CHEMISTRY

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DOI: 10.1039/C7NJ00538E

Enantioselective Synthesis of Dihydroquinazolinone derivatives Catalyzed by Chiral Organocatalyst

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Abstract: The asymmetric condensation/amine addition cascade sequence of 2-aminobenzamide and aldehydes catalyzed by novel chiral organocatalyst were realized. The organocatalyst was found to be a general, highly enantioselective catalyst for such cascade reactions at room temperature, affording 2,3-dihydroquinazolinones in an excellent yield (up to 99%) and ee's (up to 97%). The best level of stereocontrol was obtained for aromatic/aliphatic aldehydes with an ortho, para and meta substituents.

Keywords: Dihydroquinazolinone, enantioselective synthesis, organocatalyst, Cinchona alkaloid, bipyridine.

1. Introduction

The 2,3-dihydroquinazolinone derivatives were exhibited very important in pharmacological activities, such as antitumor, analgesic, antifibrillatory, antibiotic, antispermatogenic, and vasodilatory efficacy. In addition, it has been reported that their enantiomers having different bioacitivities.[1,2] Consequently, most of the researchers focused to develop a new methodology for the asymmetric synthesis of 2,3-dihydroquinazolinone derivatives. A variety of methods have been developed for the synthesis of dihydroquinazolinone derivatives, the condensation of 2-aminobenzamide with aldehyde is one of the direct method for the synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones. Number of acid catalysts, such as *p*-TSA/$NaHSO_3$,[3] $TiCl_4$/Zn,[4] $CuCl_2$,[5] ionic liquid–water,[6] TFA,[7] ammonium chloride,[8] heteropolyacid ($H_3PW_{12}O_{40}$),[9] silicabonded *N*-propylsulfamic acid,[10] and cellulose-SO_3H,[11] have been utilized to accomplish this transformation. Most of the reported synthetic protocols were

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associated with the use of expensive reagents, extended reaction times, high reaction temperatures, and also involve tedious work-up procedures.

Regardless of the above methods that are available to synthesize dihydroquinazolinones as racemates,[12] enantioselective synthesis of dihydroquinazolinone is not easily achieved since the aminal stereocenter is sensitive to racemization.[13] Cheng *et al*., reported about the asymmetric synthesis of dihydroquinazolinones using (*S*)-TRIP as a catalyst.[14] Singh and coworkers reported the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, aldehyde, amine or ammonium acetate in water under microwave in the presence of L-proline catalyst.[15] In this context, a few methods have been reported using chiral phosphoric acid as catalysts. Rueping *et al*., reported the chiral BINOL-phosphoric acid as a catalyst in the asymmetric synthesis of 2,3-dihydroquinazolinones (limited to aromatic aldehydes without an ortho substituent, 73−93% yields, and 80−92% ee's).[16] Similarly Tian *et al*.,developed a new method for the BINOL-phosphoric acid-catalyzed asymmetric synthesis of 2,3-dihydroquinazolinones from imines and 2-aminobenzamides with substrate diversity (limited to the use of preformed imines, 54−90% yields, and 83−97% ee's, at −20 °C).[17] Additionally, in 2012, Kesavan *et al*., described the Sc(III)-inda-pybox-catalyzed enantioselective version.[18] Similarly, Tao Deng and co-workers was reported $Sc(OTf)_3$-catalyzed intramolecular amidation of imines with a fluorous bis(oxazolines) as a chiral ligand.[19] In 2013 Lin and co-workers reported the application of SPINOL-phosphoric acid to this asymmetric condensation reaction.[20]

Despite these elegant examples, a general, efficient, and mild enantoselective protocol has yet to be described and would be of a great value because of the importance of optically active 2,3-dihydroquinazolinones. The synthesized new organocatalysts **2**[21] (Figure 1) was used as highly enantioselective catalyst for the asymmetric condensation/amine addition cascade sequence of 2-aminobenzamides and aldehydes. Herein, we present our preliminary results of this work. A narrow range of substituted 2,3-dihydroquinazoline-4(1*H*)-ones were obtained in high yields and good enantioselectivities (up to 99% yield, 97% ee′s).

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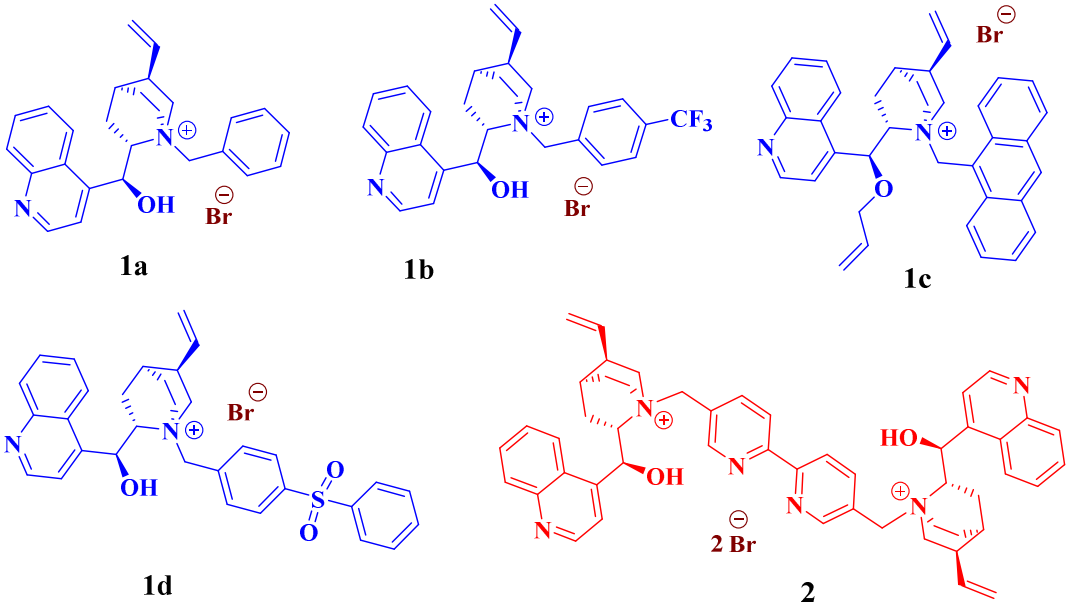
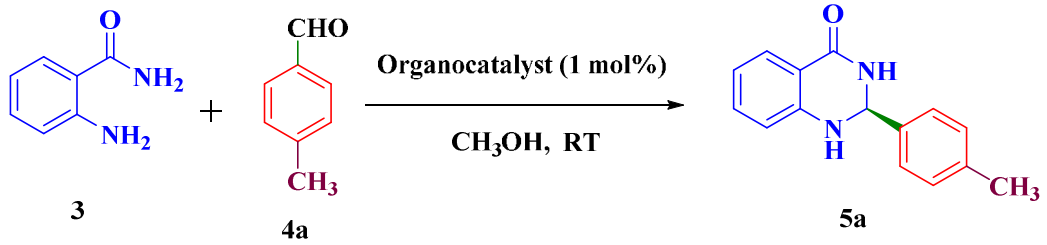


Figure 1: Single-site and Multi active-site containing chiral organocatalysts.

2. Results and Discussion

Table 1: Catalytic asymmetric condensation/amine addition reaction of 2-aminobenzamide **3** and 4-methylbenzaldehyde **4a** with different organocatalysts **1(a-d)** and **2** at room temperature



Entry	Organocatalyst	Time (h)[a]	Yield (%)[b]	ee's (%)[c] Abs.Conf.[d]
1	**1a**	12	87	42
2	**1b**	20	89	50
3	**1c**	26	73	26
4	**1d**	36	65	30
5	**2**	0.5	99	96

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[a]The condensation/amine addition reaction of 2-aminobenzamide **3** (0.07 mmol), 4-methylbenzaldehyde **4a** (0.07 mmol), organocatalysts **1(a-d)** and **2**, with 1 ml of methanol at room temperature (30 ºC). [b]Isolated yield of purified material. [c]Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexane–IPA as an eluent. (See supporting information (Figure: S34-S38). [d]Absolute configuration was determined by comparison of the previously reported HPLC retention time.[16-20]

The initial studies were carried out using the reaction of 2-aminobenzamide **3** and 4-methylbenzaldehyde **4a** as the model substrates with 1 mol % of different organocatalyst in methanol at room temperature (30 ºC). This revealed that **1a-1d** are indeed able to act as catalysts, though their activity and stereoselectivity are insufficient, even with increased their reaction time from 12 to 36 hrs (entries 1–4 in Table 1). However, our newly synthesized organocatalyst **2** influenced the reaction rate and we achieved very good yields up to 99% and ee's up to 96% (entry 5, Table 1) under the same reaction conditions in less time (only 30 min). This is due to the multiple active sites are presented in the organocatalysts **2** which can be increased the number of ion pair interactions between the catalyst and the substrate and also π-π interaction between the quinoline moiety of the catalyst and aromatic aldehyde substrate. Further, we believe that the simultaneous cooperative neighboring group of the cinchonium cation interacts with the substrates.

Then, the asymmetric condensation/amine addition reaction was carried out in different solvents using organocatalyst **2** at room temperature, with other parameters kept as constant. The optimization of the condensation/amine addition reaction of 2-aminobenzamide **3** with 4-methylbenzaldehyde **4a**, was carried out under organocatalytic conditions, the obtained results (Table 2) show that the change of solvent is found to be an important, crucial factor in the condensation/amine addition reaction due to the polarity of the solvents. The product yields and ee's have been found to be poor using aprotic solvents, such as acetone, chloroform and DCM (entries 1-3, Table 2), and we found very good yields and ee's of **5a** when using protic polar solvents, such as methanol and ethanol (entries 4-5, Table 2). Further, lowering the temperature to 0 °C remarkably reduced the chemical yield and enantioselectivity (entry 6, Table 2). Furthermore, the reaction was carried out room temperature condition in presence of polar aprotic solvents obtained moderate yields and good ee's (entry 7 and 8, Table 2). From the observed results of Table 2, using non polar solvents we got better yield and moderate ee's

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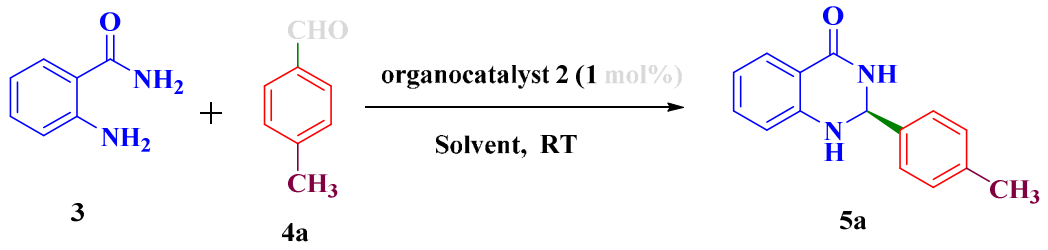
(entry 9 and 10, Table 2). Through extensive screening, the optimized reaction conditions are found to be 1 mol% of organocatalyst **2**, and methanol as solvent at room temperature.

Table 2: Effect of solvent and reaction condition on the asymmetric condensation/amine addition reaction of 2-aminobenzamide **3** and 4-methylbenzaldehyde **4a** with organocatalyst **2** at room temperature.



3 **4a** **5a**

Entry	Solvent	Time (h)[a]	Yield (%)[b]	ee's (%)[c] Abs.Conf.[d]
1	Chloroform	12	57	36
2	Acetone	12	52	34
3	Dichloromethane	12	49	27
4	Ethanol	6	87	64
5	Methanol	0.5	99	96
6	Methanol[e]	1.0	85	59
7	DMF	7	75	84
8	DMSO	7	80	86
9	Toluene	10	57	67
10	Cyclohexane	10	63	60

[a]The condensation/amine addition reaction of 2-aminobenzamide **3** (0.07 mmol), 4-methylbenzaldehyde **4a** (0.07 mmol), organocatalyst **2**, with 1 ml of methanol at room temperature (30 ºC). [b]Isolated yield of purified material. [c] Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexane–IPA as an eluent. (See supporting information (Figure: S39-S48). [d]Absolute configuration was determined by comparison of the previously reported HPLC retention time.[16-20] [e] Reaction carried out under cold condition (0 ºC).

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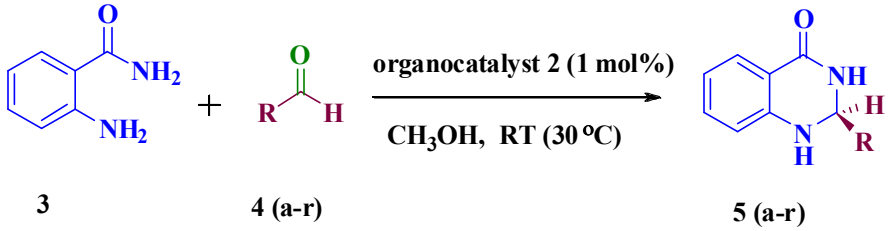
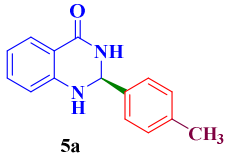
Table 3: Catalytic asymmetric condensation/amine addition reaction of 2-aminobenzamide **3** and various substituted aromatic aldehydes **4 (a-o)** under optimized conditions[a,b,c,d]

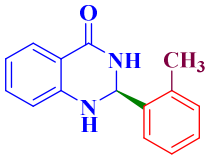


3 **4 (a-r)** **5 (a-r)**

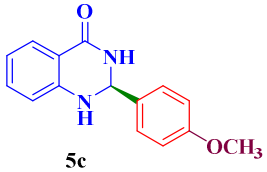
R = Ph, 4-CH_3Ph, 2-CH_3Ph, 4-OCH_3Ph, 3,4-OCH_3Ph, 4-ClPh, 2-ClPh, 2,4-ClPh, 2-OHPh, 4-FPh, 2,4-FPh, 4-BrPh, 4-NO_2Ph, 2-NO_2Ph, 4-CNPh, -cyclohexyl, -CH_3, -CH_2CH_3



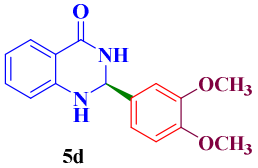
5a
99% yield, 96% ee′s



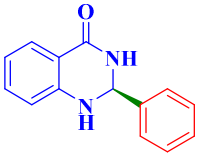
5b
99% yield, 91% ee′s



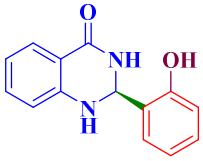
5c
98% yield, 95% ee′s



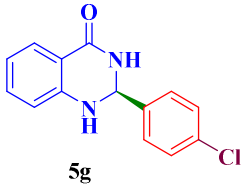
5d
98% yield, 97% ee′s



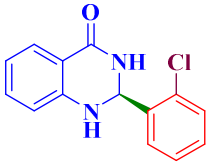
5e
97% yield, 95% ee′s



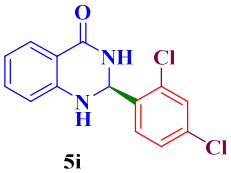
5f
97% yield, 84% ee′s



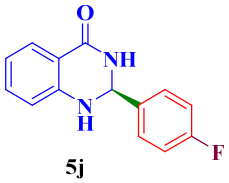
5g
97% yield, 80% ee′s



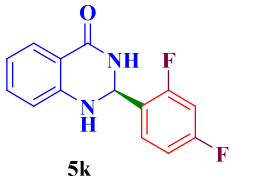
5h
96% yield, 95% ee′s



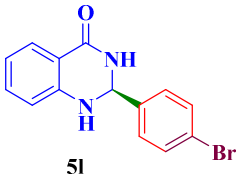
5i
95% yield, 70% ee′s



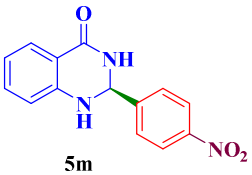
5j
98% yield, 85% ee′s



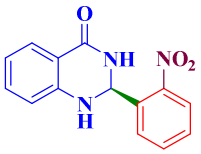
5k
98% yield, 75% ee′s



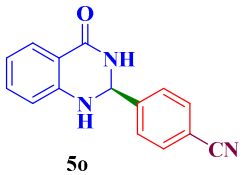
5l
98% yield, 83% ee′s



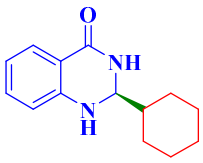
5m
99% yield, 90% ee′s



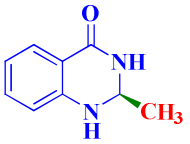
5n
97% yield, 95% ee′s



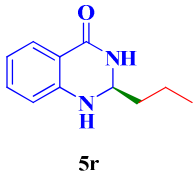
5o
98% yield, 87% ee′s



5p
94% yield, 90% ee′s



5q
[e] No reaction



5r
[e] No reaction

[a]The condensation/amine addition reaction of 2-aminobenzamide **3** (0.07 mmol), various aromatic aldehydes **4 (a-o)** (0.07 mmol), organocatalyst **2**, with 1 ml of methanol at room

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temperature (30 ºC). [b]Isolated yield of purified material. [c]Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexane–IPA as an eluent. [d]Absolute configuration was determined by comparison of the HPLC retention time.[16-20] [e]No reaction was observed under optimised reaction condition.

With these optimized reaction conditions identified, our attention turned to an examination of the scope of catalytic asymmetric condensation/amine addition cascade reaction. The reactions were carried out using organocatalyst **2** under the optimized conditions, and the results are summarized in Table 3. All reactions proceeded in generally excellent yields with good to excellent enantioselectivities. In general, for the first time, a number of different aromatic aldehydes with electron-donating and -withdrawing substituents were successfully applied in the reaction with 2-aminobenzamide. The corresponding (*S*)-2,3-dihydroquinazolinones **5a-5o** were isolated in good yields (up to 99%) and excellent enantioselectivities (up to 97%, Table 3). Further, the rate of the reaction does not affect in the presence of electron donating/withdrawing substitution on the aromatic ring of the aldehyde at various positions. In addition to that the reaction were carried out in the presence of aliphatic aldehydes such as cyclohexanecarbaldehyde, acetaldehyde, propionaldehyde with 2-aminobenzamide. Among these aliphatic aldehyde, cyclohexanecarbaldehyde mediated reaction gave better yield (94%) and ee's (90%) than the other two aliphatic aldehydes (Table 3, entry 5p-5r) under optimised reaction conditions. This may be due to the lack of π- π interaction between the quinoline moity of the catalyst with the substrate.

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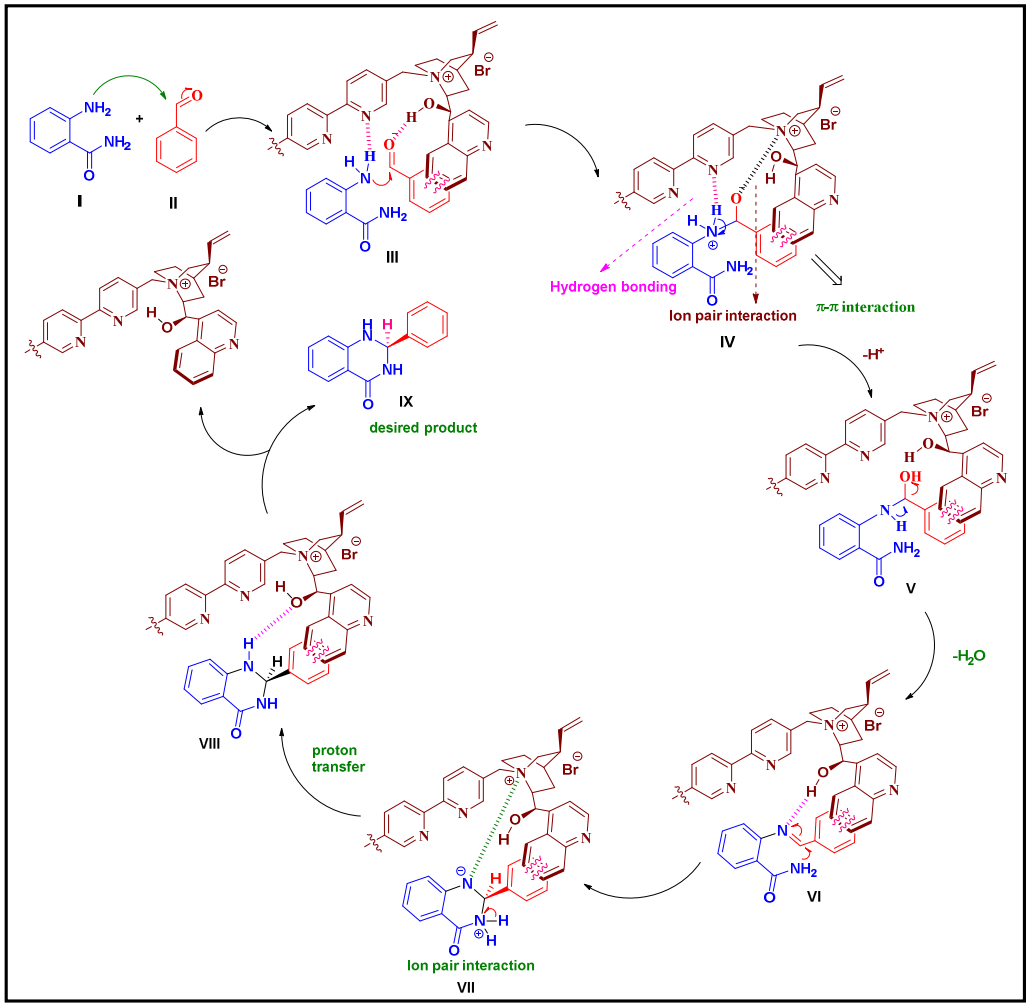

Figure 2: Plausible mechanism for the condensation/amine addition reaction.

Further, we proposed a possible mechanism (Figure 2) for the formation of dihydroquinazolinone derivatives, the amine is more reactive than the amide, hence amine is reacted with aldehyde to form imine at the same time hydrogen bonded with the catalyst (bipyridine, free –OH group containing catalyst) in intermediate **III** and also strong ion pair interaction between the enolate anion of the intermediate **IV** with the quaternary ammonium ion of the catalyst. Simultaneously π–π interaction is more between the catalyst as well as the aromatic ring of the substrate in intermediate **IV**. Further, the intermediate **IV** loss of one proton to form intermediate **V**. Furthermore, the intermediate **V** consecutively loss of water molecule and to form an imine derivative **VI**, then the amide group containing nitrogen lone pair attack the

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imine carbon to form cyclized intermediate **VII**. After that the proton transfer taking place in intermediate **VII** to form intermediate **VIII**. Finally the 2-(benzylideneamino)benzamide was cyclised to form our desired product **IX** with high yield and ee's and eliminate the catalyst which is used for another cycle.

3. Conclusions

In conclusion, we have developed an efficient and practical protocol to synthesize optically active dihydroquinazolinones derivatives by chiral organocatalyzed asymmetric condensation/amine addition cascade sequence of 2-aminobenzamide and wide range of aromatic/aliphatic aldehydes. Following this methodology, a series of 2,3-dihydroquinazolinones were obtained in excellent yields (up to 99%) with excellent ee's (up to 97%) at room temperature. In addition, we found that a different position-substituent on the aryl group of aromatic aldehydes appears to have a remarkable effect on the enantioselectivity. The best level of stereocontrol was obtained for aromatic aldehydes with an ortho, para and meta substituents.

4. Experimental Methods

4.1. Materials and Methods

All the chemicals and reagents were used in this work as an analytical grade. *p*-Tolualdehyde, veratraldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,4-diflurobenzaldehyde, 4-flurobenzaldehyde, and salicylaldehyde, were purchased from Sigma Aldrich. 2-Aminobenzamide, 4-cyanobenzaldehyde, 2-methylbenzaldehyde and 4-methoxybenzaldehyde were purchased from Alfa Aesar and benzaldehyde was obtained from Merck and all the solvents were obtained from laboratory grade. The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard, $CDCl_3$ & DMSO-d^6 as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethyl acetate as an eluent. The HPLC was recorded in SHIMADZU LC-6AD with a chiral column (Chiralcel OD-H), using HPLC grade n-hexane and isopropanol as solvents.

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4.2. General procedure for the synthesis of enantioselective dihydroquinazolinones derivatives using chiral organocatalyst (5a-o)

2-Aminobenzamide (7 mmol) and aromatic aldehydes (7 mmol) were dissolved in 10 mL of methanol and 1 mol% of organocatalyst was added and the mixture was stirred at room temperature, the completion of reaction as indicated by TLC. After completion of the reaction, the solid was filtered and recrystallized with acetone, to get pure product without column chromatography.

4.3. Characterization of dihydroquinazolinones derivatives (5)

4.3.1. 2-(*p*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (5a)

White solid; m.p. 232-233°C; 99% yield; 96% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.26 min, t (minor) = 22.60 min]. $[\alpha]_D^{25}$ = +54.8 (c, 0.98, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.58 (d, 1H, *J* = 4.92 Hz), 7.34 (d, 2H, *J* = 3.99 Hz), 7.18 (t, 3H, *J* = 5.77 Hz), 6.75 (s, 1H), 6.74-6.63 (m, 2H), 5.69 (s, 1H), 2.27 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.28, 148.40, 139.09, 138.25, 138.83, 129.32, 127.87, 127.25, 117.62, 115.41, 114.93, 66.86, 21.94; ESI-MS (m/z) : $C_{15}H_{14}N_2O$: Calculated : 238.1106, Found : 239.3714.

4.3.2. 2-(*o*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (5b)

White solid; m.p. 230-232°C; 99% yield; 91% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.27 min, t (minor) = 21.91 min]. $[\alpha]_D^{25}$ = +32.6 (c, 1.05, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.60 (d, 2H, *J* = 7.68 Hz), 7.36 (d, 2H, *J* = 7.68 Hz), 7.19 (t, 3H, *J* = 9.58 Hz), 7.08 (s, 1H), 6.75-6.64 (m, 2H), 5.70 (s, 1H), 2.28 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.61, 148.74, 139.48, 138.61, 134.20, 129.69, 128.22, 127.61, 117.98, 115.79, 115.29, 67.20, 21.58; ESI-MS (m/z) : $C_{15}H_{14}N_2O$: Calculated: 238.1106, Found : 239.2410.

4.3.3. 2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5c)

White solid; m.p. 177-178°C; 98% yield; 95% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.24 min, t (minor) = 22.46

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min]. $[\alpha]_D^{25}$ = +17.7 (c, 1.57, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.60 (d, 1H, *J* = 7.53 Hz), 7.41 (d, 2H, *J* = 8.37 Hz), 7.23 (t, 1H, *J* = 7.51 Hz), 7.02 (s, 1H), 6.93 (d, 2H, *J* = 8.34 Hz), 6.73 (d, 1H, *J* = 8.01 Hz), 6.67 (t, 1H, *J* = 7.42 Hz), 5.70 (s, 1H), 3.73 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.75, 160.70, 148.88, 134.25, 134.22, 129.08, 128.27, 118.06, 115.80, 115.33, 114.50, 67.21, 55.99; ESI-MS (m/z) : $C_{15}H_{14}N_2O_2$: Calculated : 254.1055, Found : 255.1434.

4.3.4. 2-(3,4-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5d)

White solid; m.p. 211-213°C; 98% yield; 97% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.27 min, t (minor) = 14.29 min]. $[\alpha]_D^{25}$ = +27.3 (c, 2.73, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.61 (d, 1H, *J* = 7.68 Hz), 7.24 (t, 1H, *J* = 7.63 Hz), 7.12 (s, 1H), 6.99 (d, 2H, *J* = 12.81 Hz), 6.93 (d, 1H, *J* = 8.19 Hz), 6.75 (d, 1H, *J* = 8.1 Hz), 6.67 (t, 1H, *J* = 7.39 Hz), 5.69 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.67, 149.45, 148.91, 134.42, 134.13, 128.21, 120.07, 118.05, 115.89, 115.31, 112.11, 111.45, 67.42, 56.41, 56.31; ESI-MS (m/z) : $C_{16}H_{16}N_2O_3$: Calculated : 284.1161, Found (M^+) : 284.1410.

4.3.5. 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (5e)

White solid; m.p. 224-226°C; 97% yield; 95% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.37 min, t (minor) = 19.79 min]. $[\alpha]_D^{25}$ = +29.2 (c, 1.82, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.59 (d, 1H, *J* = 7.71 Hz), 7.47 (d, 2H, *J* = 7.56 Hz), 7.35 (d, 3H, *J* = 7.77 Hz), 7.23 (t, 1H, *J* = 6.94 Hz), 7.12 (s, 1H), 6.74-6.64 (m, 2H), 5.73 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.59, 148.70, 142.45, 134.27, 129.34, 129.21, 128.25, 127.68, 118.05, 115.75, 115.30, 67.40.

4.3.6. 2-(2-hydroxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5f)

Orange solid; m.p. 220-221°C; 97% yield; 84% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.27 min, t (minor) = 20.53 min]. $[\alpha]_D^{25}$ = +35.8 (c, 1.73, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.89 (s, 1H), 7.66 (d, 1H, *J* = 7.65 Hz), 7.57-7.49 (m, 3H), 7.39 (d, 1H, *J* = 7.41 Hz), 7.32 (t, 1H, *J* = 7.41 Hz), 6.96-6.92 (m, 2H), 6.55 (s, 1H), 5.75 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 169.54, 163.55,

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160.52, 146.52, 133.90, 132.69, 132.34, 131.33, 128.84, 126.89, 120.16, 119.54, 119.26, 61.15; ESI-MS (m/z) : $C_{14}H_{12}N_2O_2$: Calculated : 240.0899, Found (M+1) : 241.1124.

4.3.7. 2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5g)

Pale yellow solid; m.p. 197-198°C; 97% yield; 80% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.32 min, t (minor) = 36.83 min]. $[\alpha]_D^{25}$ = +16.4 (c, 1.65, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.27 (t, 1H, *J* = 7.03 Hz), 8.15 (d, 1H, *J* = 7.71 Hz), 7.91 (s, 1H), 7.78 (t, 1H, *J* = 7.56 Hz), 7.66-7.56 (m, 3H), 7.45 (d, 1H, *J* = 7.77 Hz), 5.77 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 168.32, 161.86, 149.94, 137.66, 135.18, 132.80, 131.47, 130.68, 129.98, 128.96, 127.00, 67.42; $C_{14}H_{11}ClN_2O$: Calculated : 258.0560, Found (M+1) : 259.1007.

4.3.8. 2-(2-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5h)

Pale yellow solid; m.p. 202-204°C; 96% yield; 95% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.28 min, t (minor) = 78.29 min]. $[\alpha]_D^{25}$ = +15.02 (c, 1.29, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.14 (d, 1H, *J* = 8.19 Hz), 7.98 (s, 1H), 7.81 (d, 1H, *J* = 7.68 Hz), 7.63-7.51 (m, 4H), 7.35 (t, 1H, *J* = 7.45 Hz), 7.21 (d, 1H, *J* = 7.71 Hz), 5.75 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 168.45, 158.74, 150.00, 136.10, 134.23, 133.13, 132.63, 131.56, 131.08, 130.42, 129.71, 128.62, 127.15, 64.87.

4.3.9. 2-(2,4-dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5i)

Pale yellow solid; m.p. 162-164°C; 95% yield; 70% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.28 min, t (minor) = 19.82 min]. $[\alpha]_D^{25}$ = +36.3 (c, 1.35, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.15 (d, 1H, *J* = 8.49 Hz), 7.89 (s, 1H), 7.79 (t, 1H, *J* = 8.77 Hz), 7.61 (d, 2H, *J* = 9.09 Hz), 7.53 (t, 1H, *J* = 7.75 Hz), 7.35 (t, 1H, *J* = 7.47 Hz), 7.21 (d, 1H, *J* = 7.8 Hz), 5.75 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.99, 149.07, 134.86, 131.31, 128.79, 126.05, 118.88, 115.89, 113.04, 112.75, 105.84, 105.50, 105.15, 62.05.

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4.3.10. 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5j)

White solid; m.p. 201-203°C; 98% yield; 85% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.28 min, t (minor) = 43.72 min]. $[\alpha]_D^{25}$ = +44.6 (c, 1.29, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.20 (s, 1H), 8.02 (t, 2H, *J* = 6.18 Hz), 7.90 (d, 1H, *J* = 7.71 Hz), 7.53 (t, 1H, *J* = 6.75 Hz), 7.41-7.31 (m, 3H), 7.20 (d, 1H, *J* = 7.80 Hz), 5.75 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 167.92, 161.46, 149.54, 137.26, 134.78, 132.37, 131.07, 130.28, 129.58, 128.56, 126.61, 65.08; $C_{14}H_{11}FN_2O$: Calculated : 242.0855, Found (M^+) : 242.1211.

4.3.11. 2-(2,4-difluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5k)

White solid; m.p. 180-182°C; 98% yield; 75% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.27 min, t (minor) = 44.29 min]. $[\alpha]_D^{25}$ = +51.7 (c, 1.21, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.64-7.57 (m, 2H), 7.29-7.23(m, 2H), 7.12 (t, 1H, *J* = 8.49 Hz), 7.05 (s, 1H), 6.74-6.68 (m, 2H), 6.02 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.04, 148.12, 133.91, 130.43, 127.84, 125.10, 117.93, 114.94, 112.13, 111.80, 104.89, 104.55, 104.21, 61.15; $C_{14}H_{10}F_2N_2O$: Calculated : 260.0761, Found (M+1) : 261.1131.

4.3.12. 2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5l)

Pale yellow solid; m.p. 199-200°C; 98% yield; 83% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 8.14 min, t (minor) = 20.96 min]. $[\alpha]_D^{25}$ = +73.5 (c, 1.05, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.88 (t, 3H, *J* = 12.04 Hz), 7.76 (d, 2H, *J* = 8.28 Hz), 7.64 (s, 1H), 7.53 (t, 1H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 7.83 Hz), 5.75 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 167.85, 161.67, 149.57, 135.15, 132.52, 132.34, 131.24, 130.25, 128.29, 126.60, 126.25, 64.18; $C_{14}H_{11}BrN_2O$: Calculated : 302.0055, Found (M+1) : 303.1315.

4.3.13. 2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5m)

Yellow solid; m.p. 200-201°C; 99% yield; 90% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.29 min, t (minor) = 79.28 min]. $[\alpha]_D^{25}$ = +63.7 (c, 1.32, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.37 (d, 2H,

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J = 8.58 Hz), 8.19 (d, 2H, *J* = 8.61 Hz), 7.82 (d, 1H, *J* = 7.56 Hz), 7.62 (s, 1H), 7.54 (t, 1H, *J* = 7.11 Hz), 7.34 (t, 1H, *J* = 7.32 Hz), 7.25 (d, 1H, *J* = 7.74 Hz), 5.79 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 168.45, 161.19, 149.51, 141.82, 132.55, 131.45, 130.82, 130.44, 129.79, 127.43, 124.88, 66.85.

4.3.14. 2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (5n)

Yellow solid; m.p. 191-192°C; 97% yield; 95% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 3.27 min, t (minor) = 90.53 min]. $[\alpha]_D^{25}$ = +27.3 (c, 1.02, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.15 (d, 2H, *J* = 7.92 Hz), 7.92 (d, 1H, *J* = 7.23 Hz), 7.84-7.80 (m, 2H), 7.60 (s, 1H), 7.55 (d, 1H, *J* = 7.62 Hz), 7.37 (t, 1H, *J* = 7.5 Hz), 7.19 (d, 1H, *J* = 7.89 Hz), 5.70 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 168.06, 158.72, 149.64, 149.22, 134.40, 132.76, 132.28, 130.23, 129.99, 129.63, 127.00, 125.07, 64.69; $C_{14}H_{11}N_3O_3$: Calculated : 269.0800, Found (M^+) : 269.1132.

4.3.15. 4-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (5o)

Yellow solid; m.p. 250-252 °C; 98% yield; 87% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 6.25 min, t (minor) = 91.25 min]. $[\alpha]_D^{25}$ = +60.1 (c, 1.71, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.14-8.10 (m, 3H), 8.04 (d, 1H, *J* = 1.83 Hz), 7.83 (d, 1H, *J* = 7.68 Hz), 7.61 (s, 1H), 7.54 (t, 1H, *J* = 7.62 Hz), 7.36 (t, 1H, *J* = 7.48 Hz), 7.24 (d, 1H, *J* = 7.83 Hz), 5.75 (s,1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 167.98, 161.30, 149.18, 139.84, 133.34, 132.17, 130.08, 129.93, 129.36, 129.96, 119.67, 118.94, 65.20; $C_{15}H_{11}N_3O$: Calculated : 249.0902, Found (M^+) : 249.1511.

4.3.16. 2-cyclohexyl-2,3-dihydroquinazolin-4(1*H*)-one (5p)

White solid; m.p. 178-180 °C; 94% yield; 90% ee, determined by HPLC [Chiralcel OD-H, *n*-hexane /*i*-propanol = 80/20, 1mL/min, λ = 254 nm, t (major) = 7.24 min, t (minor) = 40.25 min]. $[\alpha]_D^{25}$ = +27.4 (c, 1.07, THF). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (s, 5H), 1.54-1.70 (m, 6H), 4.44 (s, 1H), 6.57 (s, 1H), 6.58-6.62 (m, 1H), 6.74 (d, 1H, *J* = 6.39 Hz), 7.17-7.21 (m, 1H), 7.55 (d, 1H, *J* = 6.36 Hz), 7.89 (s, 1H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 164.21, 148.82, 133.49, 127.73, 116.96, 115.48, 114.74, 69.04, 43.35, 27.52, 27.29, 26.41, 26.17, 26.00. $C_{14}H_{18}N_2O$: Calculated : 230.1419, Found (M^+) : 230.1524.

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DOI: 10.1039/C7NJ00538E

Acknowledgements

This work was financially supported by the Department of Science and Technology, SERB, Extramural Major Research Project (Grant No. EMR/2015/000969), Department of Science and Technology, New Delhi, India (Grant No. SR/F/1584/2012-13), University Grants Commission, New Delhi, India (Grant No. UGC No.41-215/2012 (SR).

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DOI: 10.1039/C7NJ00538E

Graphical Abstract

Enantioselective Synthesis of Dihydroquinazolinone derivatives Catalyzed by Chiral Organocatalyst

Ayyanar Siva*, Ponmuthu Kottala Vijaya, Madhappan Mariyappan, Veeramanoharan Ashokkumar, Velu Sadhasivam, Sankar Balakrishnan, Chithiraikumar Chinnadurai and Sepperumal Murugesan*

The asymmetric condensation/amine addition cascade sequence of 2-aminobenzamide and aldehydes catalyzed by novel chiral organocatalyst are reported. The organocatalyst is found to be a good and highly enantioselective catalysts for such cascade reactions at room temperature, affording 2,3-dihydroquinazolinones in an excellent yield (up to 99%) and ee's (up to 97%).