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Highly Enantioselective Synthesis of 2,3-Dihydroquinazolinones through Intramolecular Amidation of Imines

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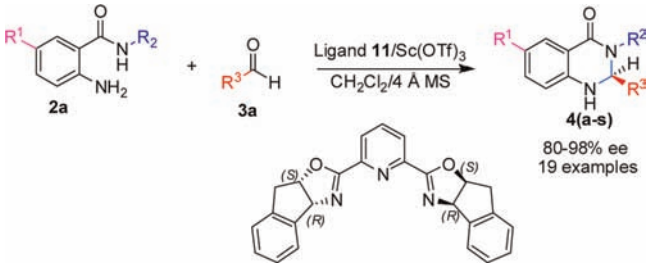
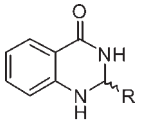
ABSTRACT



Enantioselective synthesis of 2,3-dihydroquinazolinones (DHQZs) was accomplished using readily available Sc(III)-*inda*-pybox as the catalyst. This is the first report on the metal catalyzed asymmetric intramolecular amidation of imines to synthesize DHQZs.

Pharmacologically active heterocycles/intermediates which possess a chiral center are increasingly being synthesized in a stereoselective manner in recent years.[1] Nitrogen containing heterocycles are an integral part of many drug molecules or physiologically active natural products and/or synthetic molecules. One such heterocycle is 2,3-dihydroquinazolinone (DHQZ-**1**) which contains a cyclic aminal chiral center. DHQZ is a privileged scaffold because of its extensive pharmacological activities including antibacterial, antifertility, antitumor, antifibrilatory, vasodilatory, antifungal, and analgesic efficacy.[2]



Regardless of various methods that are available to synthesize DHQZs as racemates,[3] enantioselective synthesis of 2,3-DHQZs is not easily achieved since the aminal stereocenter is sensitive to racemization.[4] Development of synthetic methodology to synthesize *S*-enantiomers is very much wanted because they are more potent antiproliferative agents than *R*-enantiomers.[4] The reported higher anticancer activity of *S*-enantiomer is possible only if racemization of DHQZs does not occur under physiological conditions (pH $\approx$ 7.0−7.4). Catalytic asymmetric synthesis of 2,3-DHQZ has been a challenge for a long

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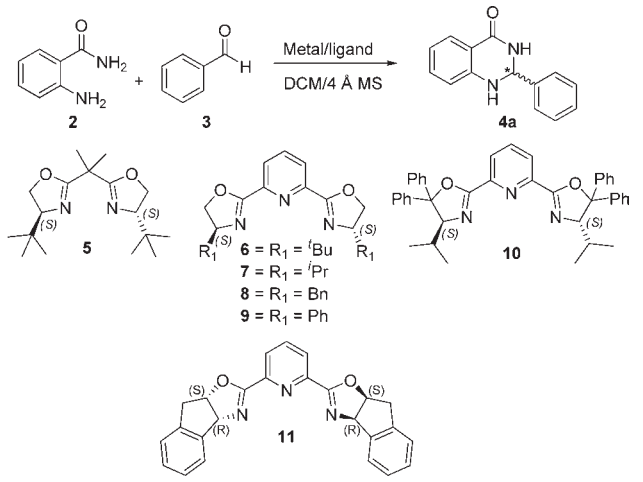
Scheme 1. Enantioselective Synthesis of DHQZ **4a**



time.[5] List et al.[5a] and Rueping et al.[5b] developed methodologies for enantioselective synthesis of DHQZs using chiral Brønsted acids. The first method[5a] worked well only for linear aliphatic aldehydes or α-unbranched aldehydes, and poor enantioselectivity was observed for α-branched aldehydes including aromatic aldehydes. The method by Rueping et al. lacks substrate diversity. Except for these chiral Brønsted acid catalyses, there is no other catalytic method available to the best of our knowledge for the asymmetric synthesis of DHQZs. That stimulated us to develop a high yield metal catalyzed enantioselective intramolecular amidation of imines to synthesize 2,3-dihydroquinazolinones. To circumvent the racemization of an aminal stereocenter, we sought to activate the imine formed by the reaction between 2-aminobenzamide (**2**) and benzaldehyde (**3**) through a chiral Lewis acid catalyst.

We hoped that a suitable chiral Lewis acid would mediate intramolecular amidation of imines to form enantiomerically pure 2,3-DHQZ **4a** (Scheme 1). Although there are many chiral ligands that can be employed for Lewis acid mediated catalysis, we initially selected bis(oxazoline) **5** and pyridine bis(oxazoline) **6** for evaluation because they are renowned for their ability to catalyze various mechanistically different asymmetric transformations with a wide variety of Lewis acids.[6−8] Initial attempts were made to prove our hypothesis by screening ligands **5** and **6** with various metal salts. Intramolecular amidation of imine formed between 2-aminobenzamide (**2**) and benzaldehyde (**3**) was carried out at 25 °C with various Lewis acids such as Cu(I)OTf, $Cu(OTf)_2$, or $Zn(OTf)_2$ (5 mol %) and 10 mol % of ligand **5** or **6** in the presence of powdered 4 Å molecular sieves in dichloromethane. It was observed that DHQZ **4a** was isolated in very low yields (10−20%) with no chiral induction. Since these attempts were not successful, we turned our attention to pybox ligand complexes with rare metal triflates. The catalytic efficiency of these complexes as Lewis acids is well demonstrated in the literature.[9,10] We were delighted to observe that pybox **6**/$Sc(OTf)_3$ catalyzed the intramolecular amidation of imine with great efficiency and with an enantiomeric excess of 34% (Table 1, entry 1). Encouraged by this observation, we sought to identify the suitable pybox ligand to enhance the enantioselectivity of this transformation. Valinol, phenylalaninol, phenyl glycinol, and 1,1-diphenyl valinol derived pybox ligands **7**−**10**, respectively, failed to

Table 1. Evaluation of Box and Pybox Ligands in Lewis Acid Catalyzed Enantioselective Synthesis of 2,3-Dihydroquinazolinone[a] **4a**

entry	ligand	metal	yield (%)[b]	ee (%)[c,d]
1	**6**	$Sc(OTf)_3$	90	34 (R)
2	**7**	$Sc(OTf)_3$	80	racemic
3	**8**	$Sc(OTf)_3$	82	16 (R)
4	**9**	$Sc(OTf)_3$	89	36 (R)
5	**10**	$Sc(OTf)_3$	90	30 (R)
6	**11**	$Sc(OTf)_3$	94	84 (S)
7	**11**	$Yb(OTf)_3$	72	76 (S)
8	**11**	$Y(OTf)_3$	65	64 (S)
9	**11**	$La(OTf)_3$	60	racemic
10[e]	**11**	$Sc(OTf)_3$	93	98 (S)

[a] Reactions were carried out using 300 μmol of 2-aminobenzamide (**2**), 360 μmol of benzaldehyde (**3**), 5 mol % of Lewis acid, 10 mol % of ligand, and powdered 4 Å molecular sieves at 25 °C in CH_2Cl_2 for 6−48 h. [b] Isolated yields. [c] Enantiomeric excess were determined on a chiral stationary phase. [d] Absolute configuration of the product is indicated in the parentheses. [e] Lewis acid/Ligand ratio (1:2.5 mol %) was used.

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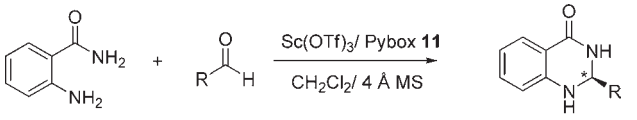
improve the enantioselectivity of the reaction (entries 2−5). It is important to note that, in all these reactions, DHQZ **4a** was observed to possess an *R*-configuration. Since *S*-amino alcohol derived pybox ligands yielded the *R*-stereoisomer of DHQZ **4a**, we evaluated the efficiency of the scandium(III)-(1*R*,2*S*)-*Inda*-pybox **11** catalytic system in the asymmetric synthesis of DHQZ **4a** to obtain the *S*-stereoisomer. As we expected the *S*-stereoisomer of DHQZ **4a** formed under the reaction conditions with very good enantioselectivity (84% ee, entry 6). Scandium(III) triflate was found to be the most suitable metal partner since reactions catalyzed by other rare earth metal triflates such as $Yb(OTf)_3$, $Y(OTf)_3$, and $La(OTf)_3$ in combination with (1*R*,2*S*)-*Inda*-pybox **11** did not improve either the yield or the enantioselectivity (entries 7−9). Screening of various solvents identified dichloromethane or chloroform as the most suitable reaction medium in which remarkable enantioselectivity was obtained. When ethanol was used as the reaction medium, complete racemization of the product occurred. To optimize the catalyst loading, we lowered the metal to 1 mol % and increased the ligand ratio to 2.5 times, i.e., 2.5 mol % for efficient complex formation. We hoped that this would suppress the synthesis of DHQZ **4a** catalyzed by metal alone which in turn will enhance the enantioselectivity. Indeed DHQZ **4a** was obtained in 98% ee, with a catalyst loading of 1 mol % of $Sc(OTf)_3$ and 2.5 mol % of *Inda*-pybox **11** under standard reaction conditions (entry 10). Thus we have achieved the first metal catalyzed synthesis of 2,3-dihydroquinazolinone **4a** in quantitative yield and admirable enantioselectivity with a catalytic loading of 1 mol % at ambient temperature. With these optimized conditions in hand, we extended the scope of our methodology in synthesizing various optically pure 2,3-dihydroquinazolinones.

Benzaldehyde and 2-naphthaldehyde underwent cyclization with 2-aminobenzamide (**2**) with ease and in excellent enantioselectivity to afford DHQZs **4a** and **4b** respectively (Table 2, entries 1 and 2). The presence of fluorine on benzaldehyde at either the *meta* or *para* position did not have any bearing on the outcome of the transformation. Fluorine containing DHQZs **4c** and **4e** (entries 3 and 5) were obtained in superior yield and enantioselectivity. The steric effect of a bromine atom contributed to the diminished enantioselectivity in the case of *m*-bromobenzaldehyde (**3d**) (entry 4). A similar steric effect was not observed when *p*-bromobenzaldehyde (**3f**) was treated with 2-aminobenzamide (**2**) to afford DHQZ **4f** (entry 6) with excellent enantioselectivity (94% ee). The presence of an electron withdrawing nitrile group, as well as ethyl and phenyl substituents in the *para*-position of benzaldehyde, is well tolerated in synthesizing DHQZs **4g**−**4i**. These DHQZs were obtained in high yields and with enantiomeric excess ranging from 86 to 96% (entries 7−9). Although a moderate enantioselectivity was observed for aliphatic aldehydes at ambient temperature, lowering the temperature to −20 °C resulted in the desired asymmetric induction. DHQZs **4j**−**4l** were obtained in very good yields (80−85%) by reacting respective aldehydes **3j**−**3l** with 2-aminobenzamide (**2**) at −20 °C. The asymmetric induction observed (86−92% ee) in these aliphatic aldehydes was comparable to that in aromatic aldehydes (entries 10−12). In all of these experiments the *S*-enantiomer was obtained as the major product. We further expanded the scope of our methodology to 3,4-disubstituted benzaldehydes and substituted 2-aminobenzamides (Figure 1). It is evident from Figure 1 that 3,4-disubstituted benzaldehydes are very well tolerated substrates under the protocol. The presence of a hydroxyl group and electron donating groups did not hamper the catalytic efficiency of the scandium(III)-*inda*-pybox system in the intramolecular amidation of imines. 2,3-Dihydroquinazolinones **4m**−**4p** were synthesized under optimized reaction conditions in admirable yields and enantioselectivities (90−92% ee). Similarly substitution on 2-aminobenzamide did not have any negative influence on the enantioselectivity. Reaction of 4-phenylbenzaldehyde with 5-chloro and 5-OCF_3 substituted 2-aminobenzamides gave rise to corresponding 2,3-dihydroquinazolinones **4q** and **4r** in quantitative yields.

Encouraged by this success, we proceeded to highlight the efficiency of our catalytic system in synthesizing 2,3-dihysdroquinazolinone **4s** by reacting 4-phenylbenzaldehyde with 2-amino-*N*-phenylbenzamide. DHQZs derived from 2-amino-*N*-phenylbenzamide are potent anti-inflammatory and analgesic agents.[11] The scandium(III)-*inda*-pybox system catalyzed the intramolecular amidation of imines to form dihydroquinazolinone **4s** in 95% yield and with an

Table 2. Substrate Scope of Scandium(III)-*Inda*-Pybox Catalyst in Enantioselective Synthesis of 2,3-Dihydroquinazolinones[a]



2 **3a-l** **4a-l**

entry	DHQZ (**4a**−**l**) R =	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**4a**)	94	98
2[d]	2-naphthyl (**4b**)	92	98
3	*m*-F-C_6H_4 (**4c**)	91	98
4	*m*-Br-C_6H_4 (**4d**)	94	80
5	*p*-F-C_6H_4 (**4e**)	92	90
6	*p*-Br-C_6H_4 (**4f**)	90	94
7	*p*-CN-C_6H_4 (**4g**)	88	90
8	*p*-Ph-C_6H_4 (**4h**)	95	96
9	*p*-C_2H_5-C_6H_4 (**4i**)	91	86
10[e]	*n*-C_6H_{13} (**4j**)	86	92
11[e]	*n*-C_3H_7 (**4k**)	80	86
12[e]	Ph-C_2H_4 (**4l**)	85	86

[a] Reactions were carried out using 300 μmol of 2-aminobenzamide **2**, 360 μmol of benzaldehyde **3**, 1 mol % of metal, 2.5 mol % of pybox **11**, at rt in CH_2Cl_2 and powdered 4 Å molecular sieves for 6−48 h. [b] Isolated yields. [c] Enantiomeric excess were determined by HPLC on a chiral stationary phase. [d] Structure of **4b** was ascertained by single crystal XRD. [e] Reactions were carried out at −20 °C.

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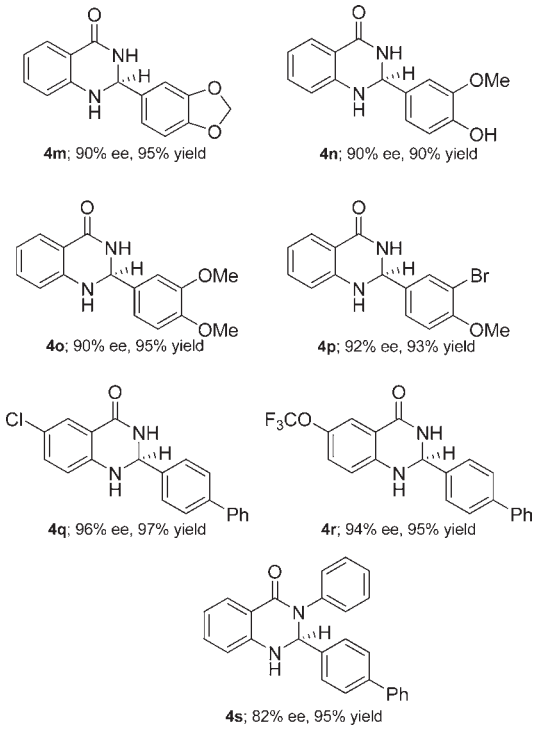

Figure 1. Efficient enantioselective synthesis of 2,3-dihydroquinazolinones using scandium(III)-*inda*-pybox.

enantiomeric excess of 82%. It is important to highlight here that there is no prior report in the literature in synthesizing optically pure 2,3-DHQZ from 2-amino-*N*-phenylbenzamide.

A plausible mechanism for the stereochemical outcome of the product can be explained by a model proposed by Evans et al.[12] The reaction may proceed through a more favored *Si* face attack rather than an unfavored *Re* face attack since less steric hindrance is expected in the approach of the reactant with the metal complex in *Si* face, which results in the formation the *S*-stereoisomer (Figure 2).

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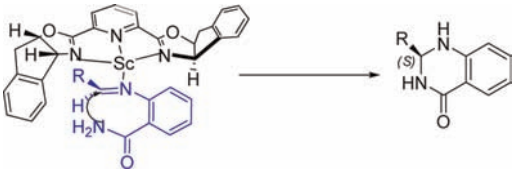

Figure 2. A plausible mechanistic pathway. *Si*-face approach; less sterically hindered and more favored. Coordinating triflate anions are not shown for clarity purposes.

In summary, we developed the first metal catalyzed highly enantioselective synthesis of 2,3-dihydroquinazolinones through intramolecular amidation of imines in very good yields. The scandium(III)-*inda*-pybox catalyst provided remarkable catalytic activation of 2-amino-*N*-phenylbenzamide to afford the corresponding 2,3-dihydroquinazolinone with very good enantioselectivity. Further application of our methodology in synthesizing enantiomerically pure 2,3-dihydroquinazolinones by condensing 2-amino-*N*-arylbenzamides and 2-amino-*N*-alkylbenzamides with various aldehydes is currently being investigated.

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Supporting Information Available. Detailed experimental procedures and characterization data by ^{1}H, ^{13}C NMR for all compounds and chiral HPLC analysis of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.