Asymmetric Synthesis

DOI: 10.1002/anie.200804770

Asymmetric Brønsted Acid Catalysis: Catalytic Enantioselective Synthesis of Highly Biologically Active Dihydroquinazolinones**

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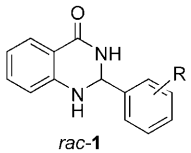
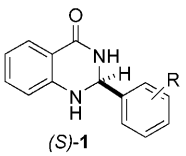
Dihydroquinazolinones are important heterocyclic compounds which influence numerous cellular processes. They display a broad range of biological, medicinal, and pharmacological properties and are constituents of antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating agents.[1]

In addition, 2,3-dihydroquinazolinones of type **1** have been shown to act as potent tubulin inhibitors with impressive



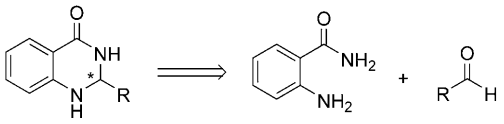
rac-**1**



(*S*)-**1**

antiprolivative activity against several human cancer cell lines, with IC_{50} values in the nanomolar concentration range.[2] They act analogously to the antimitotic agent colchicine,[3] as efficient inhibitors of tubulin polymerization.[4] In addition, the 2,3-dihydroquinazolinones inhibit the binding of cholchicine to α,β-tubulin.[5] In general, racemic mixtures of **1** have been assayed; however, it has been shown recently that the *S* enantiomer (*S*)-**1** has significantly higher activity in the inhibition of cholchinine binding and tubulin assembly. As the *S* enantiomer could be prepared only by a multistep diasteroselective synthesis sequence,[2] further investigations into these highly efficient antitumoral agents were severely restricted.

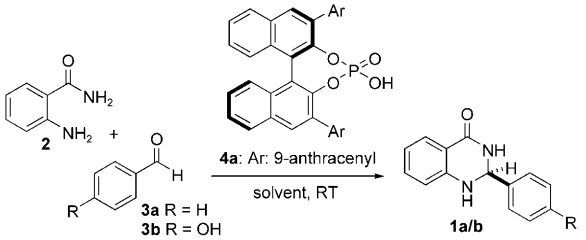
Given the importance of these valuable 2,3-dihydroquinazolinones[1–5] and in view of the significantly higher activity of the *S* enantiomer, as well as the lack of efficient methods for the preparation of these important active agents, the development of a new catalytic asymmetric synthesis of these compounds appeared to be of great importance. In this context, we decided to investigate a metal-free, catalytic enantioselective approach starting from the simplest starting materials, 2-aminobenzamide and the corresponding aldehydes [Eq. (1)]. We report herein the asymmetric, organocatalytic synthesis of these valuable enantiopure 2,3-dihydroquinazolinones by a one-step procedure using easily accessible or commercially available starting materials.



(1)

On the basis of our previous successes in the field of asymmetric ion-pair catalysis,[6] we started our investigations with the Brønsted acid catalyzed reaction of 2-aminobenzamide (**2**) with various aldehydes **3** (Table 1). Initial studies showed that the reaction can be carried out successfully using phosphoric acid diesters as the catalyst. Therefore we decided to explore chiral phosphoric acid diesters[7–10] **4a** in this transformation. This would then not only be the first example of an asymmetric condensation/amine addition sequence of 2-

Table 1: Brønsted acid catalyzed enantioselective synthesis of 2,3-dihydroquinazolinones in various solvents.



Entry[a]	R	Solvent	e.r. (*S*/*R*)[b]
1[c]	H	THF	72:28
2[c]	H	Bu_2O	81:18
3[c]	H	MTBE	87:13
4[c]	H	benzene	84:16
5[c]	H	toluene	86:14
6[c]	H	$CHCl_3$	93:7
7[c]	H	CH_2Cl_2	92:8
8[d]	OH	toluene	99:1
9[d]	OH	$CHCl_3$	99:1
10[c]	OH	$CHCl_3$	93:7

[a] Reaction conditions: 2-Aminobenzamide (**2**), aldehyde **3a/b** (1.1 equiv), **4a** (10 mol%), solvent (0.05 M), and 3 Å molecular sieves at room temperature. [b] Enantiomeric ratios were determined by HPLC on a chiral phase. [c] Enantiomeric ratios of the reaction mixtures after column chromatography. [d] Enantiomeric ratio of the reaction solution. MTBE = methyl *tert*-butyl ether.

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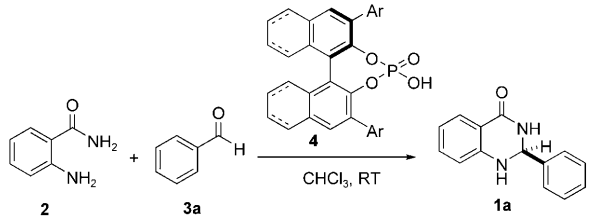
[**] We acknowledge Evonik Degussa and the DFG (Priority Programme Organocatalysis) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804770.

aminobenzamide **2** and aldehydes **3**, but also the first efficient access to various enantioenriched 3-dihydroquinazolinones **1**. Indeed, our initial investigations proved that 2,3-dihydroquinazolinone **1a** and **1b** could be obtained in very good enantiomeric ratios (up to e.r. 99:1)[11] when the reactions were performed in aromatic or halogenated solvents and in the presence of chiral Brønsted acid **4a** (Table 1, entries 4–10). A detailed inspection of the reaction showed that a heterogeneous reaction mixture was formed in the reaction of **2** with **3b**. When the precipitate was removed by filtration or a sample was taken from the supernatant for analysis, almost enantiopure product was obtained (Table 1, entries 8 and 9). Subsequent analysis of the precipitate revealed this corresponded to product **1** with a lower enantiomeric ratio. The unified and completely dissolved reaction mixture of **1b** formed , therefore, in lower overall enantioselectivity (Table 1, entry 10).[12,13] We decided to perform further experiments in chloroform because of the generally better solubility of both reactants and products. For most reaction mixtures we observed homogeneous solutions, and typically, better enantioselectivities could be obtained.

To further optimize the reaction conditions, in addition to the variation in temperature and catalyst loading, the chiral phosphoric acid diesters **4a–f** were tested (Table 2). The best results with regard to selectivity and reactivity were obtained using the Brønsted acid **4a** in chloroform at room temperature. At either lower temperatures or lower catalyst loading (1 mol% **4a**) similar enantioselectivity was obtained but the reaction time was prolonged. With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. In general, for the first time, a number of different aliphatic and aromatic aldehydes with electron-donating and -withdrawing substituents were successfully applied in the reaction with 2-aminobenzamide. The corresponding (*S*)-2,3-dihydroquinazolinones **1a–1j** were isolated in good yields and excellent enantioselectivity (up to e.r. 99:1; Table 3).

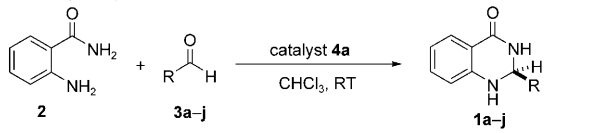
Table 2: Evaluation of chiral Brønsted acids as catalysts in the new reaction.



Entry[a]	Cat.	Ar	e.r. (*S*/*R*)[b]
1	**4a**	9-anthracenyl	93:7
2	**4b**	1-naphthyl	73:27
3	**4c**	2-naphthyl	58:42
4	**4d**	9-phenanthryl	72:28
5	**4e**	phenyl	55:45
6	**4f**	4-biphenyl	75:25
7	**4g**	3,5-$(CF_3)C_6H_3$	53:47

[a] Reaction conditions: 2-Aminobenzamide (**2**), benzaldehyde **3a** (1.1 equiv), **4** (10 mol%) $CHCl_3$ (0.05 M) and 3 Å molecular sieves at room temperature. [b] Enantiomeric ratios were determined by HPLC on a chiral phase.

Table 3: Substrate scope[a,b] of the organocatalytic enantioselective synthesis of dihydroquinazolinones **1**.[13]



1a: e.r. 93:7, 86%

1b: e.r. 93:7 (e.r. 99:1)[c,d], 86%

1c: e.r. 96:4, 87%

1d: e.r. 93:7, 93%

1e: e.r. 90:10, 90%

1f: e.r. 90:10 (e.r. 99:1)[c], 93%

1g: e.r. 96:4, 85%

1h: e.r. 93:7 (e.r. 99:1)[d], 92%

1i: e.r. 93:7[c], 73%

1j: e.r. 90:10, 93%

[a] Reaction conditions: 2-Aminobenzamide (**2**), aldehyde **3a–j** (1.1 equiv), **4a** (10 mol%), $CHCl_3$ (0.05 M), and 3 Å molecular sieves at room temperature. [b] Yield of isolated product after column chromatography of reaction mixtures. Enantiomeric ratios were determined by HPLC on a chiral phase. [c] Enantiomeric ratio of the chloroform reaction solution. [d] Enantiomeric ratio of the toluene reaction solution.

In summary, we report on the development of a new metal-free, highly enantioselective, Brønsted acid catalyzed condensation/amine addition reaction for the synthesis of 2,3-dihydroquinazolinones starting from the simplest and most readily available starting materials. Thus, a highly efficient and general approach to valuable enantiomerically enriched 2,3-dihydroquinazolinones with preference for the more active *S* enantiomers has been established. This extremely simple and practical protocol is not only of great importance and considerable interest for additional drug design and development of dihydroquinazolinones, but it also simplifies further examination of tubulin polymerization inhibition in antitumor research. This in turn may provide insights into the mechanism of the ligand binding at the colchicine binding site. Moreover, certain dihydroquinazolinones show an inherent fluorescence which allows explicit intracellular localization.

Additional studies on these aspects and further applications of this reaction are topics of current investigations.

Received: September 30, 2008
Published online: December 19, 2008

Keywords: antitumor agents · inhibitors · organocatalysis · phosphoric acid diester

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[11] The absolute configuration of the products was assigned by comparison of the optical rotation value of **1a** with the value reported in Ref. [2].

[12] The observation that the precipitate and reaction solution in heterogeneous mixtures display different enantioselectivities is not surprising. In such cases it is possible to obtain almost enantiopure product by simple filtration. However, to determine the true enantioselectivity of this reaction, we prepared the HPLC sample from a solution of both the precipitate and the supernatant.

[13] A detailed experimental procedure and characterization of all products is given in the Supporting Information.

