Letter

Highly Enantioselective Synthesis of Dihydroquinazolinones Catalyzed by SPINOL-Phosphoric Acids

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Highly Enantioselective Synthesis of Dihydroquinazolinones Catalyzed by SPINOL-Phosphoric Acids

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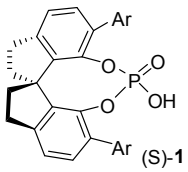
KEYWORDS: phosphoric acid, asymmetric, 2-aminobenzamide, dihydroquinazolinone, organocatalysis

ABSTRACT: The asymmetric condensation/amine addition cascade sequence of 2-aminobenzamides and aldehydes catalyzed by chiral spirocyclic SPINOL-phosphoric acids was realized. SPINOL-phosphoric acid **1j** was found to be a general, highly enantioselective organocatalyst for such cascade reactions at room temperature, affording 2,3-dihydroquinazolinones in excellent yields (up to 99%) with good to excellent ees (up to 98%). The best level of stereocontrol was obtained for aromatic aldehydes with an *ortho* substituent.

The 2,3-dihydroquinazolinone family of compounds displays extensive important pharmacological activities such as antitumor, analgesic, antifibrillatory, antibiotic, antispermatogenic, and vasodilatory efficacy.[1] In addition, it has been reported that their enantiomers have different bioacitivity.[1a, 2] Consequently, the development of new methodologies for asymmetric synthesis of 2,3-dihydroquinazolinones has been an intense focus. In this context, a few methods have been documented.[3] The first suxxess in the field was reported by List *et al.* who applied chiral BINOL-phosphoric acids[4,5] as the catalysts in the asymmetric synthesis of 2,3-dihydroquinazolinones (limited to aliphatic aldehydes, 72-94% yields and 50-98% ees, -45 ^{o}C).[3a] Simultaniously, Rueping *et al.* also reported the corresponding enantioselective synthesis using the same class of phosphoric acids (limited to aromatic aldehydes without an *ortho* substituent, 73-93% yields and 80-92% ees).[3b] Tian *et al.* recently 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% ees, -20 ^{o}C).[3c] More recently, Kesavan et al. described the first Sc(III)-*inda*-pybox-catalyzed enantioselective version (limited to aromatic aldehydes without an *ortho* substituent and aliphatic aldehydes, 80-97% yields and 80-98% ees, -20 ^{o}C – rt).[3d] Despite these elegant examples, a general, efficient and mild enantoselective protocol has yet to be described and would be of a great value due to the importance of optically active 2,3-dihydroquinazolinones.

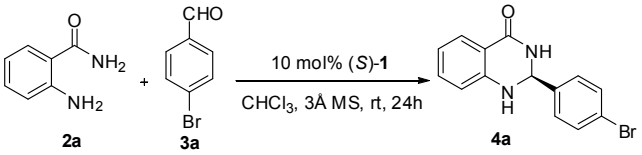
Our group has great interest in the development of chiral 1,1'-spirobiindane-7,7'-diol (SPINOL) based spirocyclic phosphoric acids **1** (Figure 1) and derivatives as novel organocatalysts for asymmetric reactions, and has showed their excellent catalytic reactivity as chiral Brønsted acid catalysts.[6-8] These previous successes led us to envision that SPINOL-phosphoric acids might be highly enantioselective catalysts for the asymmetric condensation/amine addition cascade sequence of 2-aminobenzamides and aldehydes. Herein, we present our preliminary results on this subject.



1a: Ar = Ph
1b: Ar = 4-ClC$_6$H$_4$
1c: Ar = 4-FC$_6$H$_4$
1d: Ar = 4-NO$_2$C$_6$H$_4$
1e: Ar = 4-biphenyl
1f : Ar = 3,5-(CH$_3$)$_2$C$_6$H$_3$
1g: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
1h: Ar = 1-naphthyl
1i : Ar = 9-phenanthryl
1j : Ar = 9-anthracenyl

Figure 1. Chiral SPINOL-phosphoric acids

Table 1. Catalyst Investigation.[a]



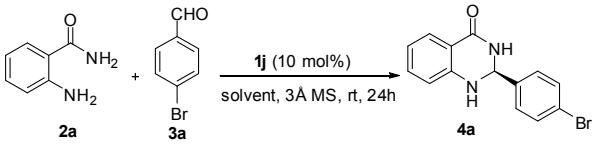
2a **3a** **4a**

entry	catalyst	yield[b] (%)	ee[c] (%)
1	**1a**	96	72
2	**1b**	99	73
3	**1c**	97	70
4	**1d**	96	70
5	**1e**	98	66
6	**1f**	97	23
7	**1g**	96	82
8	**1h**	98	74
9	**1i**	98	59
10	**1j**	98	88

[a]Reaction conditions: catalyst **1** (10 mol%)), **2a** (0.05 mmol), **3a** (0.055 mmol), $CHCl_3$ (1.0 mL), molecular sieves (3Å, 75 mg), rt, 24 h. [b]Isolated yields; [c] Determined by chiral HPLC.

The initial studies were carried out using the reaction of 2-aminobenzamide (**2a**) and 4-bromobenzaldehyde (**3a**) as the model substrates with 10 mol% of catalyst in chloroform at room temperature in the presence of powdered 3Å molecular sieves. We first investigated the influence of catalyst. A series of chiral SPINOL-phosphoric acids (*S*)-**1a**–**j** were screened, as shown in Table 1. Indeed, the reaction proceeded to afford the desired optically active 2,3-dihydroquinazolinone **4a** in excellent yields using catalyst (*S*)-**1**. The screening of SPINOL-phosphoric acids (*S*)-**1a**–**j** showed that the 6,6'-substituents on the SPINOL backbone remarkably affected the enantioselectivity. The catalyst (*S*)-**1j** (Ar = 9-anthracenyl) revealed the highest enantioselectivity at room temperature to afford 2,3-dihydroquinazolinone **4a** in 98% yield with 88% ee (entry 10, Table 1).

Table 2. Optimization of the Reaction Conditions.[a]



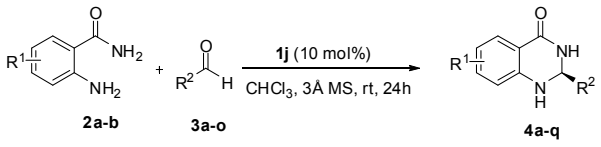
2a 3a 4a

entry	solvent	yield[b] (%)	ee[c] (%)
1	THF	77	11
2	Toluene	88	43
3	$ClCH_2CH_2Cl$	89	58
4	CH_2Cl_2	98	58
5	CCl_4	60	61
6	$CHCl_3$	98	88
7[d]	$CHCl_3$	97	69
8[e]	$CHCl_3$	79	73
9[f]	$CHCl_3$	97 (95)	88 (88)

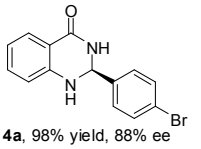
[a]General conditions: catalyst **1j** (10 mol%), **2a** (0.05 mmol), **3a** (0.055 mmol), solvent (1.0 mL), 3Å MS (powdered, 75mg), rt, 24 h. [b]Isolated yields; [c]Determined by chiral HPLC; [d]Amberlite CG50 (50 mg) was added; [e]48h at 0 °C; [f]1.0-mmol scale experiment, data in parentheses was obtained using the recovered catalyst **1j**.

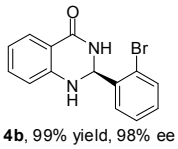
Then, the reaction was studied in different reaction conditions, and the results are summarized in Table 2. A solvent screen revealed that chloroform gave the corresponding product **4a** in both the highest yield and enantioselectivity (entries 1-6, Table 2). While other solvents such as THF, toluene, $ClCH_2CH_2Cl$, CH_2Cl_2 and CCl_4 also gave the desired product with good to excellent yields but poor enantioselectivity (entries 1-5, Table 2). The reaction with Amberlite CG50 as an additive led to remarkably lowered enantioselectivity (97% yield, 69% ee, entry 7, Table 2). Lowering the temperature to 0 °C remarkably lowered the yield and enantioselectivity (79% yield, 73% ee, entry 8, Table 2). Thus, the optimized reaction conditions for the model reaction were established (entry 6, Table 2). Furthermore, the scalability of the newly investigated method was proven with a 1.0-mmol scale experiment (entry 9, Table 2). The 2,3-dihydroquinazolinone **4a** was achieved in 97% yield and 88% ee at room temperature. In order to illustrate the recycling of the catalyst (*S*)-**1j**, the recovered catalyst 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 compared catalytic

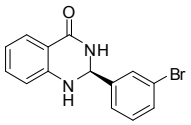
Table 3. Substrate Scope. [a]

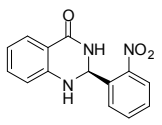


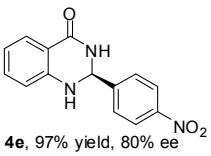
2a-b 3a-o 4a-q

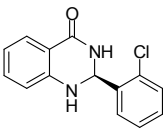

4a, 98% yield, 88% ee

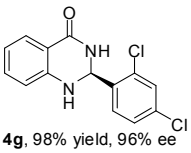

4b, 99% yield, 98% ee

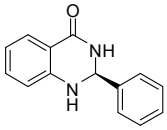

4c, 98% yield, 87% ee

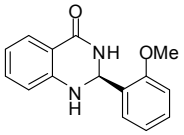

4d, 99% yield, 95% ee

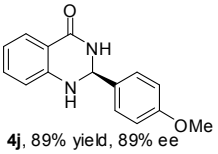

4e, 97% yield, 80% ee

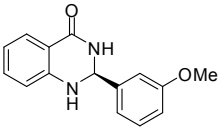

4f, 99% yield, 98% ee

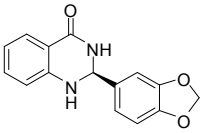

4g, 98% yield, 96% ee

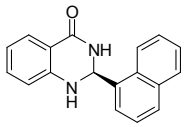

4h, 99% yield, 90% ee

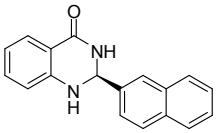

4i, 99% yield, 94% ee

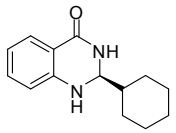

4j, 89% yield, 89% ee

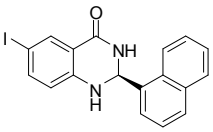

4k, 95% yield, 93% ee

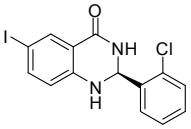

4l, 95%, 87% ee

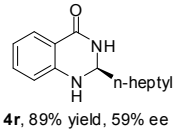

4m, 99% yield, 97% ee


4n, 89% yield, 89% ee


4o, 98% yield, 84% ee


4p,88%, 93% ee


4q, 88% yield, 94% ee


4r, 89% yield, 59% ee

[a]Reaction conditions: catalyst **1j** (10 mol%)), **2** (0.05 mmol), **3** (0.055 mmol), $CHCl_3$ (1.0 mL), 3Å MS (powdered, 75 mg), rt, 24 h. [b] Isolated yields; [c] Determined by chiral HPLC.

activity and enantioselectivity (95% yield, 88% ee, entry 9, Table 2).

With these reaction conditions identified, our attention turned to examination of the scope of catalytic asymmetric condensation/amine addition cascade reaction. The reactions were carried out using catalyst **1j** under the optimized conditions and the results are summarized in Table 3. All reactions proceeded in generally excellent yields with good to excellent enantioselectivities. The influence of the aldehyde substrates was first investigated. Either electron-withdrawing or -donating substituents (-Br, -NO_2, -Cl, -OMe, -OCH_2O-) on the phenyl group of aromatic aldehydes could be well tolerated, affording their desired products **4a-l**. It is noteworthy that different position-substituent on the the phenyl group of aromatic aldehydes appears to have a remarkably effect on the enantioselectivity. We found that the best level of stereocontrol was obtained for aromatic aldehydes with an *ortho* substituent, such as **4b** (98%ee), **4d** (95%ee), **4f** (98%ee), **4g** (96%ee) and **4i** (94%ee). The 1-naphthyl bearing substrate also led to product **4m** in 99% yield and 97% ee, while 2-naphthyl bearing substrate only gave product **4n** in 89% yield and 89% ee. When a cyclohexyl substituent was introduced, the reaction ran smoothly, affording the product **4o** in 98% yield and 84% ee. We further expanded the scope of this cascade reaction to substituted 2-aminobenzamide. Reaction of 1-naphthaldehyde and *ortho*-chlorobenzaldehyde with 5-iodo-2-aminobenzamide, which can participate in subsequent transformations such as cross-coupling reactions, gave the corresponding 2,3-dihydroquinazolinone **4p** and **4q** in good yields with excellent ees.

The absolute stereochemistry of product **4c**, obtained by using the catalyst (*S*)-**1j**, was determined to be *S* by comparison of its optical rotation with the literature data.[3b] Thus, a possible transition state of this reaction is proposed in Figure 2. It is clear that the enantioselectivity is determined by the step of intramolecular amidation of imine. SPINOL-phosphoric acid (*S*)-**1j** as a bifunctional organocatalyst brings together two groups (amine and imine) through hydrogen bonding. In this model, the amine attacks the imine from the *Si* face preferentially due to less steric hindrance, resulting in the *S*-stereoisomer.

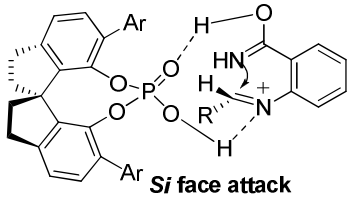


Figure 2. Possible transition state of the reaction

In summary, we have developed an efficient and practical protocol to synthesize optically active 2,3-dihydroquinazolinones by chiral SPINOL-phosphoric acid-catalyzed asymmetric condensation/amine addition cascade sequence of 2-aminobenzamides and aldehydes. Following this methodology, a series of 2,3-dihydroquinazolinones were obtained in excellent yields (up to 99%) with good to excellent ees (up to 98%) at room temperature. In addition, we found that different position-substituent on the the phenyl group of aromatic aldehydes appears to have a remarkably effect on the enantioselectivity. The best level of stereocontrol was obtained for aromatic aldehydes with an *ortho* substituent. Furthermore, the scalability of the newly investigated method was proven with a 1.0-mmol scale experiment and the recycling of the catalyst was illustrated.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy. S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem.* **2008**, *51*, 4620. (b) Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348. (c) Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136. (d) Russel, H. E.; Alaimo, R. J. *J. Med. Chem.* **1972**, *15*, 335. (e) Neil, G. L.; Li, L. H.; Buskirk, H. H.; Moxley, T. E. *Cancer Chemother.* **1972**, *56*, 163. (f) Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1141.

(2) Uzunov, D. P.; Zivkovich, I.; Pirkle, W. H.; Costa, E.; Guidotti, A. *J. Pharm. Sci.* **1995**, *84,* 937.

(3) (a) Cheng. X; Vellalath. S; Goddard, R; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (b) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 908. (c) Cheng, D. J.; Tian, Y.; Tian, S. K. *Adv. Synth. Catal.* **2012**, *354*, 995. (d) Prakash, M.; Kesavan, V. *Org. Lett.* **2012**, *14*, 1896.

(4) For recent reviews of chiral phosphoric acid catalysis, see: (a) Terada, M. *Synthesis* **2010**, 1929. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (d) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (e) Terada, M. *Chem. Commun.* **2008**, 4097. (f) Yu, J.; Shi, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (g) You, S.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (h) Yu, X.; Wang, W. *Chem.–Asian J.* **2008**, *3*, 516.

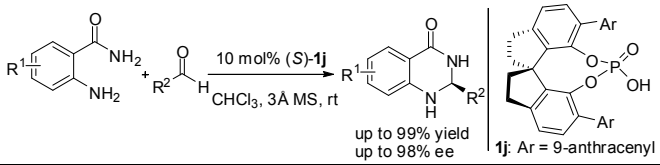
(5) For selected examples of the application of chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Rowland, G.; Zhang, H. Rowland, E.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (d) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (e) Magnus, R.; Sugiono, E.; Azap C.; Theissmann, T.; Bolte, M. *Org. Lett.*, **2005**, *7*, 3781. (f) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (g) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang,Y. Z; Gong, L. Z. *Org. Lett.* **2006**, *8*, 6023. (h) Xu, S.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840. (i) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, Bin; Xu, Z.; Zhong G. *J. Am. Chem. Soc.* **2009**, *131*,

4562. (j) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J.-P. *J. Am. Chem. Soc.*, **2009**, *131*, 4598.

(6) (a) Xu, F.; Huang, D.; Han, C.; Shen, W.; Lin, X. F.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 8677. (b) Huang, D.; Xu, F. X.; Lin, X. F.; Wang, Y. *Chem. Eur. J.* **2012**, *18*, 3148. (c) Xu, F.; Huang, D.; Lin, X. F.; Wang, Y. *Org. Biomol. Chem.* **2012**, *10*, 4467. (d) Huang, D.; Xu, F.; Chen, T.; Wang, Y.; Lin, X. F. *RSC Adv.*, **2013**, *3*, 573. (e) Li, X.; Zhao, Y.; Qu, H.; Mao, Z.; Lin, X. F. *Chem. Commun.* **2013**, *49*,1401. (f) Zhao, Y.; Li, X.; Mo, F. Li, L.; Lin, X. F. *RSC Adv.*, **2013**, *3*, 11895.

(7) For a simultaneous report on the development of chiral SPINOL-phosphoric acid, see: Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.

(8) For selected examples of the other application of chiral SPINOL-phosphoric acid catalysis, see: (a) Xing, C.; Liao, Y.; Ng, J.; Hu, Q. *J. Org. Chem.* **2011**, *76*, 4125. (b) Xu, B.; Zhu, S.; Xie, X.; Shen, J.; Zhou, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 11483. (c) Müller, S.; Webber, M.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534. (d) Xing, C.; Liao, Y.; Zhang, Y.; Sabarova, D.; Assous, B.; Hu, Q. *Eur. J. Org. Chem.* **2012**, 1115. (e) Rubush, D.; Morges, M.; Rose, B.; Thamm, D.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554. (f) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027. (g) Guin, J.; Varseev, G.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 2100. (h) Chen, Z.; Wang, B.; Sun, J. *Chem. Eur. J.* **2013**, *19*, 8426. (i) Wang, B.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685. (j) Martinez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9486. (k) Cai, Q; Liang, X.; Wang, S.; You, S. *Org. Biomol. Chem.* **2013**, *11*, 1602.


10 mol% (S)-1j
CHCl3, 3Å MS, rt
up to 99% yield
up to 98% ee
1j: Ar = 9-anthracenyl