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Catalytic Asymmetric Synthesis of Dihydroquinazolinones from Imines and 2-Aminobenzamides

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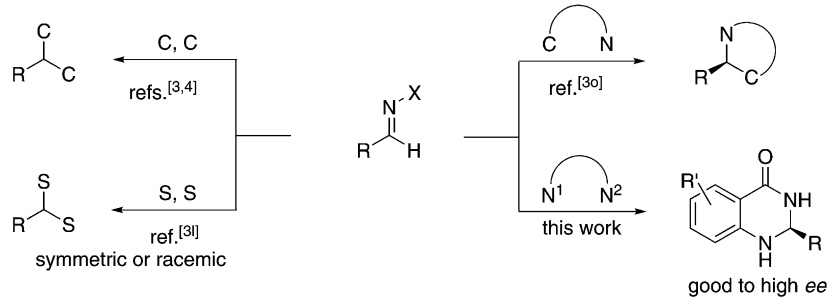
Abstract: An unprecedented catalytic asymmetric synthesis of aminal-containing heterocyclic compounds has been developed from imines and tethered nitrogen/nitrogen nucleophiles. In the presence of 10 mol% of a commercially available chiral phosphoric acid, a range of aromatic, α,β-unsaturated, and aliphatic imines react with 2-aminobenzamides to give dihydroquinazolinones in good to excellent yields and *ee*. The enantioselectivity is significantly affected by the imine N-substituent through nonbonding interactions with the chiral phosphoric acid and the 2-aminobenzamide.

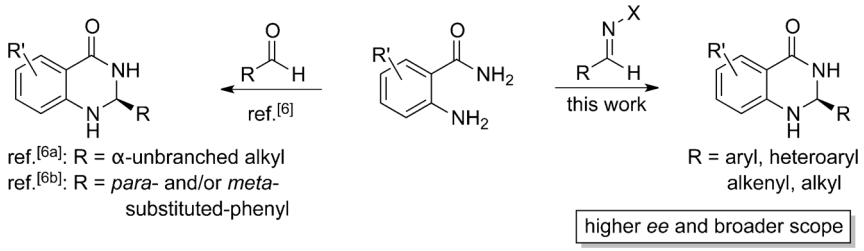
Keywords: aminals; 2-aminobenzamides; carbon-nitrogen bond cleavage; dihydroquinazolinones; imines

A wide variety of nucleophiles undergo additions to imines by breaking the C–N π bonds but delivering the stronger C–N σ bonds to the final products.[1] In contrast, the transformation of imines has rarely been reported through the complete cleavage of C=N bonds. Other than olefination,[2] the C=N bonds of imines can be transformed into geminal σ bonds in the presence of carbon, sulfur, or nitrogen nucleophiles (Scheme 1).[3,4] Recently, we reported a catalytic asymmetric formation of geminal C–C/C–N σ bonds from imines and tethered carbon/nitrogen nucleophiles, wherein the imine N-substituents significantly affect the reactivity and enantioselectivity.[3] Inspired by this study, we investigated the reaction of imines with tethered nitrogen/nitrogen nucleophiles for the formation of aminal-containing heterocyclic compounds and developed a highly enantioselective synthesis of dihydroquinazolinones (Scheme 1).

Dihydroquinazolinones display a variety of important biological and medicinal properties such as antitumor, analgetic, anti-inflammatory, choleretic, antifibrillatory, antibiotic, antispermatogenic, and vasodilatory efficiency.[5] They are usually prepared from aldehydes and 2-aminobenzamides under acidic conditions, and recently List and Rueping reported remarkable breakthroughs toward the corresponding asymmetric synthesis using chiral phosphoric acids as the catalysts.[6–8] List et al. obtained excellent enantioselectivity from the reaction of α-unbranched aliphatic aldehydes with 2-aminobenzamides, but poor enantioselectivity from the reaction with α-branched aliphatic aldehydes (e.g., Me_2CHCHO: 50% *ee*) or aromatic aldehydes (e.g., PhCHO: 26% *ee*).[6a] Rueping et al. obtained 80–92% *ee* from the reaction with



Scheme 1. Transformation of imine C=N bonds into geminal σ bonds.

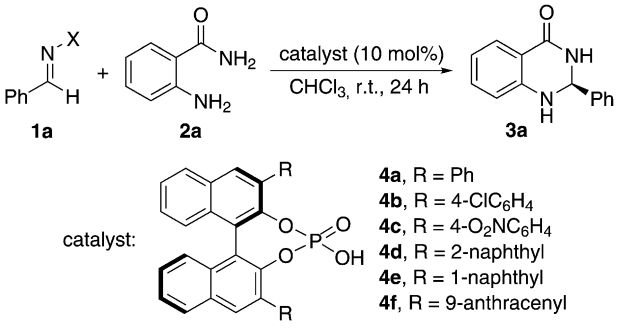


Scheme 2. Catalytic asymmetric synthesis of dihydroquinazolinones.

para- and/or *meta*-substituted benzaldehydes and 80% *ee* from the reaction with cyclohexanecarboxaldehyde.[6b] Our goal was to improve the enantioselectivity and extend the scope. Reasoning that imines have additional N-substituents to interact with the acidic catalysts and 2-aminobenzamides, we replaced the aldehydes in the aminal-forming reaction with imines and found that the modified reaction not only gave better enantioselectivity in the synthesis of some known 2-aryl- and 2-alkyldihydroquinazolinones, but also extended the scope to 2-(2-substituted-phenyl)-, 2-(1- or 2-naphthyl)-, 2-heteroaryl-, and 2-alkenyldihydroquinazolinones (Scheme 2).

Treatment of *N*-benzylidene-*p*-toluenesulfonamide (**1aa**) with 2-aminobenzamide (**2a**) and 10 mol% of chiral phosphoric acid **4a** in chloroform at room temperature resulted in the formation of dihydroquinazolinone **3a** in 90% yield and with 24% *ee* (Table 1, entry 1). Notably, the enantioselectivity is significantly better than that for the synthesis of the same product from a previously reported reaction of benzaldehyde with 2-aminobenzamide (**2a**) in the presence of catalyst **4a** (10% *ee*).[6b] Encouraged by this result, we evaluated a range of substituents on the imine nitrogen atoms including the sulfonyl, diphenylphosphinyl, and aryl groups (Table 1, entries 2–20). The reactivity and enantioselectivity were dramatically affected by the imine *N*-substituents, and the *N*-(1-naphthalenesulfonyl) group was identified as the best one, the use of which led to the formation of dihydroquinazolinone **3a** with 64% *ee* (Table 1, entry 9). It is noteworthy that the reaction with *N*-benzylidene-*p*-methoxyaniline (**1ap**) afforded comparable enantioselectivity (Table 1, entry 16, 63% *ee*). While deteriorated *ee* and/or unsatisfying yields were observed when replacing chloroform with a number of other common organic solvents,[9] chiral phosphoric acids **4b–f** were able to improve the enantioselectivity significantly (Table 1, entries 21–25). Taken together, the employment of commercially available phosphoric acid **4f** in combination with low temperature (−20 °C) and 3 Å molecular sieves allowed the synthesis of dihydroquinazolinone **3a** with up to 96% *ee* (Table 1, entry 26), which is much higher than that reported in literature (26% *ee*[6a] and 86% *ee*[6b]). For further comparison, we applied our optimized conditions to the

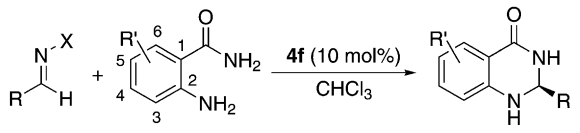
Table 1. Survey of the imine N-substituents and catalysts.[a]



Entry	Imine	X	Catalyst	Yield [%][b]	*ee* [%][c]
1	**1aa**	4-$MeC_6H_4SO_2$	**4a**	90	24
2	**1ab**	4-$O_2NC_6H_4SO_2$	**4a**	80	42
3	**1ac**	3-$O_2NC_6H_4SO_2$	**4a**	70	10
4	**1ad**	2-$MeC_6H_4SO_2$	**4a**	90	43
5	**1ae**	2-$O_2NC_6H_4SO_2$	**4a**	83	48
6	**1af**	2,6-$Cl_2C_6H_3SO_2$	**4a**	70	42
7	**1ag**	2,4,6-(*i*-Pr)$_3C_6H_2SO_2$	**4a**	88	41
8	**1ah**	2-naphthalenesulfonyl	**4a**	85	51
9	**1ai**	1-naphthalenesulfonyl	**4a**	77	64
10	**1aj**	2-thiophenesulfonyl	**4a**	85	39
11	**1ak**	$MeSO_2$	**4a**	38	35
12	**1al**	*n*-$C_{16}H_{33}SO_2$	**4a**	90	22
13	**1am**	Me_2NSO_2	**4a**	94	34
14	**1an**	Ph_2PO	**4a**	94	44
15	**1ao**	Ph	**4a**	80	48
16	**1ap**	4-$MeOC_6H_4$	**4a**	70	63
17	**1aq**	2-HOC_6H_4	**4a**	30	36
18	**1ar**	2-$O_2NC_6H_4$	**4a**	65	45
19	**1as**	2,4,6-$Me_3C_6H_2$	**4a**	50	45
20	**1at**	1-naphthyl	**4a**	40	62
21	**1ai**	1-naphthalenesulfonyl	**4b**	70	74
22	**1ai**	1-naphthalenesulfonyl	**4c**	73	75
23	**1ai**	1-naphthalenesulfonyl	**4d**	79	76
24	**1ai**	1-naphthalenesulfonyl	**4e**	77	78
25	**1ai**	1-naphthalenesulfonyl	**4f**	74	87
26[d]	**1ai**	1-naphthalenesulfonyl	**4f**	64	96

[a] *Reaction conditions:* imine **1a** (0.11 mmol), 2-aminobenzamide (**2a**) (0.10 mmol), catalyst **4** (10 mol%), chloroform (2.0 mL), room temperature, 24 h.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC analysis.
[d] The reaction was run at −20 °C for 4 d in the presence of 3 Å molecular sieves (10 mg).

Table 2. Catalytic asymmetric synthesis of dihydroquinazolinones.[a–c]



1 **2** **3**

Entry	1, R	2, R'	3	Yield [%][d]	*ee* [%][e]
1[f]	**1ai**, Ph	**2a**, H	**3a**	64	96[k]
2[f]	**1b**, 4-MeOC$_6$H$_4$	**2a**, H	**3b**	70	95
3[g]	**1c**, 4-FC$_6$H$_4$	**2a**, H	**3c**	74	90
4[f]	**1d**, 2-MeOC$_6$H$_4$	**2a**, H	**3d**	71	94
5[g]	**1e**, 2-ClC$_6$H$_4$	**2a**, H	**3e**	70	90
6[f]	**1f**, 2-naphthyl	**2a**, H	**3f**	63	93
7[f]	**1g**, 1-naphthyl	**2a**, H	**3g**	61	94
8[g]	**1h**, 3-pyridinyl	**2a**, H	**3h**	70	92
9[h]	**1i**, (*E*)-PhCH=CH	**2a**, H	**3i**	74	92[l]
10[h]	**1j**, (*E*)-2-MeOC$_6$H$_4$CH=CH	**2a**, H	**3j**	81	95
11[i]	**1k**, hexyl	**2a**, H	**3k**	70	83
12[j]	**1l**, cyclohexyl	**2a**, H	**3l**	54	86[m]
13[f]	**1g**, 1-naphthyl	**2b**, 5-Me	**3m**	82	95
14[h]	**1i**, (*E*)-PhCH=CH	**2b**, 5-Me	**3n**	73	95
15[f]	**1g**, 1-naphthyl	**2c**, 5-Br	**3o**	80	90
16[f]	**1g**, 1-naphthyl	**2d**, 6-Me	**3p**	90	92
17[h]	**1j**, (*E*)-2-MeOC$_6$H$_4$CH=CH	**2e**, 6-Cl	**3q**	90	97
18[f]	**1g**, 1-naphthyl	**2f**, 5-Cl-3-Me	**3r**	80	93

[a] *Reaction conditions:* imine **1** (0.11 mmol), 2-aminobenzamide **2** (0.10 mmol), phosphoric acid **4f** (10 mol%), chloroform (2.0 mL), −20 °C (or 10 °C for entries 3, 5, 7, 8, 13, and 15-18), 1.5–4 d.

[b] For entries 1, 9–11, and 14, 3 Å molecular sieves (10 mg) were used.

[c] The absolute configuration of product **3e** was determined by single crystal X-ray analysis (CCDC 816904; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif), and that of the rest of new products was assigned by analogy.

[d] Isolated yield.

[e] Determined by chiral stationary phase HPLC analysis.

[f] X = 1-naphthalenesulfonyl.

[g] X = *p*-methoxyphenyl.

[h] X = 2,6-dichlorobenzenesulfonyl.

[i] X = *p*-toluenesulfonyl.

[j] X = 2,4,6-triisopropylbenzenesulfonyl.

[k] The *ee* reported in literature: 26%[6a] and 86%.[6b]

[l] Product **3i** was obtained in 83% *ee* from the reaction with (*E*)-PhCH=CHCHO under the same conditions.

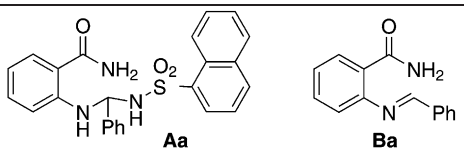
[m] The *ee* reported in literature: 80%.[6b]

reaction of benzaldehyde with 2-aminobenzamide (**2a**) and obtained dihydroquinazolinone **3a** in 73% yield and with 84% *ee*.

In the presence of 10 mol% of phosphoric acid **4f**, a range of aromatic and heteroaromatic imines, having an *N*-(1-naphthalenesulfonyl) or *N*-(*p*-methoxyphenyl) group, smoothly reacted with 2-aminobenzamide (**2a**) to afford the corresponding dihydroquinazolinones in good yields and with excellent *ee* (Table 2, entries 1–8). It is noteworthy that both electron-withdrawing and electron-donating groups were successfully introduced into the heterocyclic products by employing the imines bearing such groups on the aromatic rings. For the reaction with α,β-unsaturated imines, alternative employment of a 2,6-dichlorobenzenesulfonyl group as the N-substituent afforded much better enantioselectivity relative to that with the 1-naphthalenesulfonyl group,[9] and 2-alkenyldihydroquinazolinones were obtained with excellent *ee* (Table 2, entries 9 and 10). Switching the imine N-substituents allowed the reaction with aliphatic imines to afford very good enantioselectivity (Table 2, entries 11 and 12). Moreover, a variety of 2-aminobenzamides having substituted benzene rings were transformed into the corresponding dihydroquinazolinones in good to excellent yields and with excellent *ee* (Table 2, entries 13–18). When compared to the catalytic asymmetric synthesis of dihydroquinazolinones from aldehydes,[6] the reaction with imines not only significantly enhances the enantioselectivity by tuning the electronic and steric properties of the N-substituents, but also extends the scope to 2-(2-substituted-phenyl)-, 2-(1- or 2-naphthyl)-, 2-heteroaryl-, and 2-alkenyldihydroquinazolinones in a highly enantioselective manner.

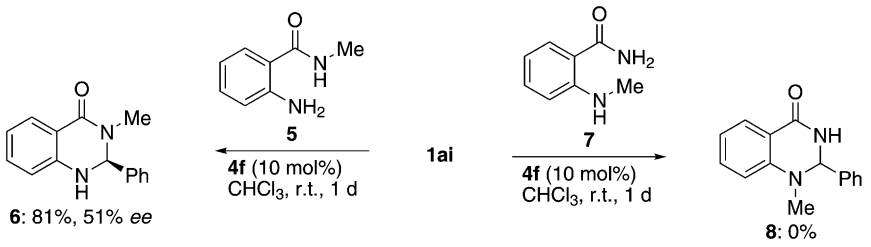
According to the ^{1}H NMR spectroscopic analysis, no reaction occurred between imine **1ai** and 2-aminobenzamide (**2a**) in deuterated chloroform at room temperature. The addition of phosphoric acid **4a** to the mixture resulted in the formation of dihydroquinazolinone **3a** and 1-naphthalenesulfonamide (byproduct), but no intermediate was observed. Nevertheless, to our delight, ESI-mass (positive mode) spectroscopic analysis of the reaction mixture allowed us to identify tentatively two intermediates, aminal **Aa** and imine **Ba**, and the complexes of 2-aminobenzamide (**2a**) and imine **Ba** with phosphoric acid **4a** according to the high resolution mass data (Table 3).[10] These results suggest that transimination occurs

Table 3. Species detected by ESI-mass spectroscopic analysis.

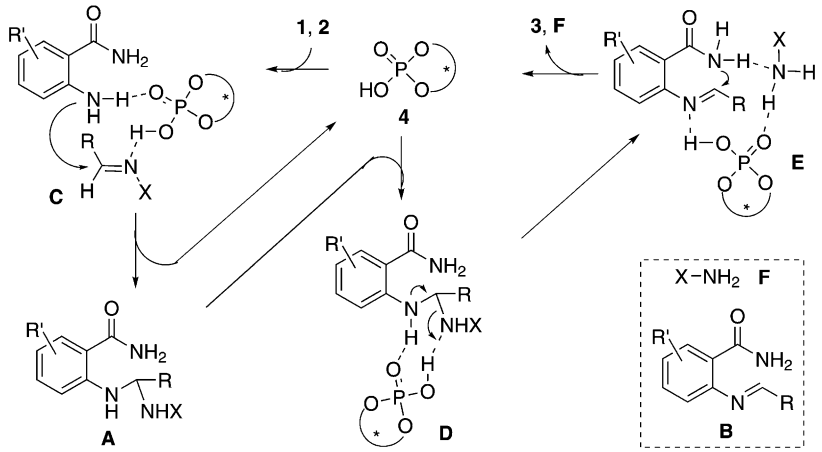


Aa **Ba**

Entry	Species	Mass (calcd.)	Mass (found)	Formula	Error [ppm]
1	[**Aa**+H]$^+$	432.13764	432.13846	$C_{24}H_{22}N_3O_3S^+$	1.9
2	[**Ba**+H]$^+$	225.10224	225.10243	$C_{14}H_{13}N_2O^+$	0.8
3	[**2a**+**4a**+H]$^+$	637.18869	637.18994	$C_{39}H_{30}N_2O_5P^+$	2.0
4	[**Ba**+**4a**+H]$^+$	725.21999	725.22168	$C_{46}H_{34}N_2O_5P^+$	2.3



Scheme 3. Treatment of imine **1ai** with 2-aminobenzamide **5** or **7**.



Scheme 4. Proposed reaction pathway.

through promotion by the phosphoric acid during the reaction.[11]

The primary amine group rather than the primary amide group in 2-aminobenzamide **2** was confirmed to undergo transimination with imine **1** at an early stage of the reaction by treatment of imine **1ai** with phosphoric acid **4f** and a 2-aminobenzamide having a methyl group either on the amide nitrogen atom or on the amine nitrogen atom (Scheme 3). While the reaction with secondary amide **5** proceeded in the presence of phosphoric acid **4f** at room temperature to give dihydroquinazolinone **6** in 81% yield and with 51% *ee*, no desired product was obtained from the reaction with secondary amine **7** under the same conditions.[12]

These experiments allow us to propose the following reaction pathway for the catalytic asymmetric synthesis of dihydroquinazolinones (Scheme 4). Both imine **1** and 2-aminobenzamide **2** are activated by phosphoric acid **4**, a bifunctional catalyst acting as a hydrogen bond donor and acceptor,[8] and an initial imine addition results in the formation of aminal **A**. Elimination of the original imine N-substituent from aminal **A** is promoted by phosphoric acid **4**, and the resulting complex, **E**, undergoes intramolecular imine addition to give dihydroquinazolinone **3** and releases phosphoric acid **4**. It is clear that the enantioselectivity is determined by the step of intramolecular imine addition. The significant influence of the imine N-substituent on enantioselectivity should be attributable to the nonbonding interactions among by-product **F** (a primary sulfonamide or a primary amine), intermediate **B**, and phosphoric acid **4** as tentatively shown in complex **E**.

In summary, we have developed, for the first time, an efficient catalytic asymmetric synthesis of aminal-containing heterocyclic compounds from imines and tethered nitrogen/nitrogen nucleophiles. In the presence of 10 mol% of a commercially available chiral phosphoric acid, a range of aromatic, α,β-unsaturated, and aliphatic imines react with 2-aminobenzamides to give dihydroquinazolinones in good to excellent yields and *ee*. The enantioselectivity is significantly affected by the imine N-substituent through non-bonding interactions with the chiral phosphoric acid and the 2-aminobenzamide.

Experimental Section

General Procedure for the Catalytic Asymmetric Synthesis of Dihydroquinazolinones

With molecular sieves: To a flame dried reaction vial equipped with a magnetic stirring bar were added 3 Å molecular sieves (10 mg). The molecular sieves were thermally activated under vacuum for 30 min, and cooled down to room temperature under nitrogen. To the reaction vial were added 2-aminobenzamide **2** (0.10 mmol), chiral phosphoric acid **4f** (7.0 mg, 0.010 mmol), and chloroform (2.0 mL). The mixture was stirred at −20 or 10 °C for 10 min, and imine

1 (0.11 mmol) was added. The resulting mixture was stirred for 1.5–4 d, and directly charged onto silica gel. The product was isolated using hexane/chloroform/ethanol (10/10/1) or hexane/ethyl acetate (2/1) as eluent.

Without molecular sieves: To a flame dried reaction vial equipped with a magnetic stirring bar under nitrogen were added 2-aminobenzamide **2** (0.10 mmol), chiral phosphoric acid **4f** (7.0 mg, 0.010 mmol), and chloroform (2.0 mL). The mixture was stirred at −20 or 10 °C for 10 min, and imine **1** (0.11 mmol) was then added. The resulting mixture was stirred for 1.5–4 d, and directly charged onto silica gel. The product was isolated using hexane/chloroform/ethanol (10/10/1) or hexane/ethyl acetate (2/1) as eluent.

Acknowledgements

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[8] For reviews of asymmetric catalysis using chiral phosphoric acids, see: a) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156–1171; b) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262–5276; c) M. Terada, *Synthesis* **2010**, 1929–1982; d) M. Terada, *Chem. Commun.* **2008**, 4097–4112; e) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758.

[9] For details, see the Supporting Information.

[10] Product **3a** and imine **Ba** have the same molecular formula. Nevertheless, distinct relative abundances of the relevant peaks were observed in the ESI-mass spectrum for the mixture of product **3a** and phosphoric acid **4a**, and this control experiment substantially supports the formation of imine **Ba** and its complex with phosphoric acid **4a** during the reaction of imine **1ai** with 2-aminobenzamide (**2a**). For details, see the Supporting Information.

[11] For examples on transimination, see: a) W. W. Zajac Jr, T. R. Walters, M. G. Darcy, *J. Org. Chem.* **1988**, *53*, 5856–5860; b) N. Giuseppone, J.-L. Schmitt, E. Schwartz, J.-M. Lehn, *J. Am. Chem. Soc.* **2005**, *127*, 5528–5539.

[12] No desired product was obtained even after the mixture was heated at 70 °C for 1 day.

