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Stereoselective synthesis of benzosulfamidate-fused tetrahydroquinazoline scaffold via organocatalytic [4+2] cycloaddition of 2-amino-β-nitrostyrenses of cyclic *N*-sulfimines

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ABSTRACT

A concise synthetic route to valuable highly functionalized benzosulfamidate-fused tetrahydroquinazoline is presented. The [4+2] cycloaddition of *o*-*N*-Cbz-amino-β-nitrostyrene with benzoxathiazine 2,2-dioxide using an imidazole as the catalyst afforded tetrahydroquinazolines with high diastereoselectivities. Furthermore, a chiral quinine-derived squaramide organocatalyst promoted an asymmetric [4+2] cycloaddition reaction, providing enantioenriched benzosulfamidate-fused tetrahydroquinazolines with good enantiopurities (up to 69:31 er).

Introduction

The synthesis of *N*-heterocyclic motifs bearing complex side chains, particularly containing other atoms or chiral moieties in an enantioenriched form, is of high significance and great interest to synthetic chemists because such motifs are ubiquitous in biologically active compounds and natural products.[1] Among the known *N*-heterocycles, cyclic aminals, although possibly considered metabolically unstable, are the key units or building blocks of diverse commercially available pharmaceuticals and biologically active compounds.[2] Therefore, the development of generally applicable synthetic tools for cyclic aminals is highly desirable and recently has attracted much attention.[3] List et al. and Rueping et al. independently disclosed a highly enantioselective organocatalytic reaction of 2-aminobenzamides to aldehydes using a phosphoric acid as the catalyst.[3f,g] Tian et al. employed an imine instead of an aldehyde for the asymmetric synthesis of aminals from 2-aminobenzamides.[3d] Kesavan et al. developed a metal-catalyzed enantioselective synthesis of cyclic aminals through the intramolecular amidation of imine.[3c] In these cases, the resulting aminals are dihydroquinazolinones bearing an oxo group in the 4-position. However, the asymmetric synthesis of 4-alkyl substituted cyclic aminals have rarely been pursued; only one example is reported by Gong and co-workers to date. Gong's group developed a cascade hydroamination/redox reaction of 1-(2-ethynylphenyl)pyrrolidine with amine to afford a cyclic aminal using a Au(I) complex and Brønsted acid as the combined catalyst.[3b] We envisioned the development of an effective method to synthesize 4-alkyl substituted cyclic aminal derivatives by the [4+2] cycloaddition reaction of 2-amino-β-nitrostyrenes with cyclic *N*-sulfimines (benzoxathiazine 2,2-dioxides).

Cyclic *N*-sulfimines attracted much attention and have been proven to be powerful building blocks in the synthesis of functionalized benzosulfamidate heterocycles.[4] These sulfamidate compounds exhibit important biological activities such as antibiotic, antiviral, anticancer, anticonvulsant, antiobesity, antiarthritis, and antiosteoporosis activities.[5] Therefore, several reactions using cyclic *N*-sulfimines have been reported for the synthesis of sulfamidate derivatives including addition, allylation, annulation, cycloaddition, and Mannich reaction.[6] However, to the best of our knowledge, the cycloaddition reaction of amide nucleophiles with cyclic *N*-sulfimines to afford cyclic aminals has not been reported (Scheme 1).

Results and discussion

The [4+2] cycloaddition reaction of *o*-*N*-Cbz-2-amino-β-nitrostyrene (**1a**)[7] with benzoxathiazine 2,2-dioxide (**2a**) was selected

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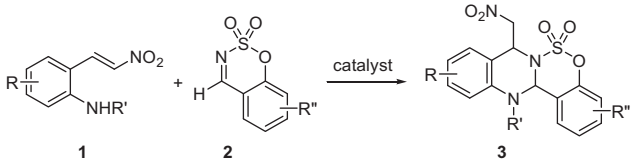
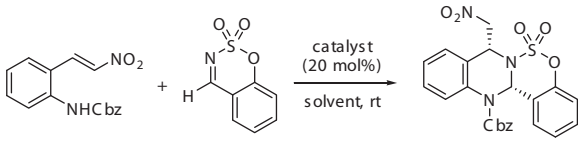


Scheme 1. Catalytic reaction of 2-amino-β-nitrostyrene with cyclic *N*-sulfimine.

Table 1
Optimization of reaction conditions.[a]



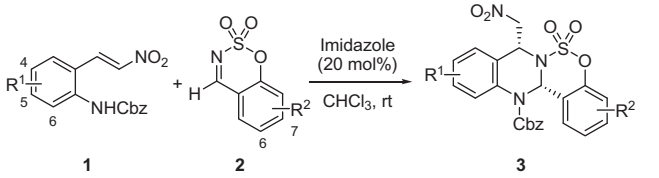
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	DBU	$CHCl_3$	48	17
2	Pyrrolidine	$CHCl_3$	72	30
3	DABCO	$CHCl_3$	72	48
4	Imidazole	$CHCl_3$	60	32
5[c]	Imidazole	$CHCl_3$	96	62
6[d]	Imidazole	$CHCl_3$	96	56
7	Imidazole	CH_2Cl_2	24	53
8	Imidazole	THF	72	42
9	Imidazole	CH_3CN	72	55
10	Imidazole	Toluene	72	46
11	Imidazole	MeOH	72	28

[a] All of the reactions were carried out in solvent (0.3 M) with **1a** (0.10 mmol) and **2a** (0.20 mmol) in the presence of catalyst.
[b] Isolated yield after chromatographic purification.
[c] 1.0 equiv. of imidazole was used.
[d] Reaction performed at 50 °C.

as the model reaction (Table 1). First, the reaction was conducted in the presence of DBU as the catalyst, furnishing the desired tetrahydroquinazoline **3a**. However, the yield was relatively low (17%) when the reaction was carried out in $CHCl_3$ at room temperature (Table 2, entry 1). Then, several bases were screened in this cycloaddition reaction to select the best catalyst. Pyrrolidine and DABCO showed slightly increased catalytic activities, providing product **3a** in 30% and 48% yields, respectively (Table 2, entries 2 and 3). In contrast, imidazole exhibited good catalytic activity, affording a single diastereomer tetrahydroquinazoline **3a** in 62% yield (Table 1, entry 4). Next, various solvents were investigated to further optimize the reaction efficiency. CH_2Cl_2, THF, CH_3CN, and toluene were compatible for this [4+2] cycloaddition reaction, providing product **3a** in 42–55% yields (Table 1, entries 7–10). However, polar protic solvents such as MeOH gave poor results (Table 1, entry 11).

With the optimized reaction conditions in hand (1 equiv of **1**, 2 equiv of **2**, 20 mol% of imidazole in $CHCl_3$ at rt), the substrate scope and generality of the reaction was investigated.[8] First, several substituted *o*-*N*-Cbz-2-amino-β-nitrostyrenes **1** were investigated to determine the generality of this [4+2] cycloaddition reaction with benzoxathiazine 2,2-dioxide (**2a**). In general, the electronic nature of substituent and its position on the phenyl ring did not significantly affect the reaction efficiency, and the reactions of the substrates afforded the desired benzosulfamidate-fused tetrahydroquinazolines in moderate to good yields (50–77% yields, Table 2, entries 2–5). Notably, 6-methyl-*o*-*N*-Cbz-amino-β-nitrostyrene provided a relatively high yield in this reaction (Table 2, entry 3). Next, the substrate scope of cyclic *N*-sulfimines was investigated. The cyclic *N*-sulfimines with electron-donating

Table 2
Substrate scope for the cycloaddition of *o*-*N*-Cbz-amino-β-nitrostyrenes with cyclic *N*-sulfimines.[a]



Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	H	H	96	**3a**	62
2	4-Me	H	48	**3b**	52
3	6-Me	H	48	**3c**	77
4	4-Br	H	72	**3d**	50
5	4-Cl	H	72	**3e**	54
6	H	6-Me	96	**3f**	40
7	H	7-Me	96	**3g**	65
8	H	6-OMe	72	**3h**	53
9	H	6-Cl	96	**3i**	27
10	H	6-Br	96	**3j**	45

[a] All of the reactions were carried out in solvent (0.3 M) with **1** (0.10 mmol) and **2** (0.20 mmol) in the presence of imidazole (0.02 mmol).
[b] Isolated yield after chromatographic purification.

groups (Me and OMe) at the 6-position of the phenyl ring reacted with **2a**, providing the corresponding products **3f** and **3h** in moderate yields (Table 1, entries 6 and 8). The substrate containing a methyl group at the 7-position of the phenyl ring afforded the corresponding product in a higher yield than that at the 6-position (Table 2, entry 7 vs entry 8). The cyclic *N*-sulfimines with electron-withdrawing groups (Cl and Br) on the phenyl ring showed slightly decreased reactivity and produced the corresponding tetrahydroquinazoline products in moderate yields (Table 2, entries 9 and 10).

The relative configuration of benzosulfamidate-fused tetrahydroquinazoline **3** was determined based on 2D ^{1}H NOESY NMR spectroscopy. NOESY studies confirmed the *cis* configuration in the compound **3a**, since intense NOE cross-peaks were observed between H-2′ and H-4′ (Fig. 1).

Encouraged by these successful imidazole-catalyzed cycloaddition reactions for the synthesis of benzosulfamidate-fused tetrahydroquinazoline derivatives, we investigated the asymmetric variant of the organocatalytic [4+2] cycloaddition reaction of *o*-*N*-Cbz-2-amino-β-nitrostyrenes with cyclic *N*-sulfimines. Because thiourea- and squaramide-based bifunctional catalysts (Fig. 2) exhibit excellent enantioselective catalytic capability,[9–11] bifunctional chiral organocatalysts (**I**–**V**) were prepared and screened. In the initial exploration, *o*-*N*-Cbz-2-amino-β-nitrostyrene (**1a**) was treated with benzoxathiazine 2,2-dioxide (**2a**) in dichloromethane at room temperature in the presence of 20 mol% organocatalyst (Table 3). To our delight, the Takemoto bifunctional thiourea catalyst **I**[9] afforded the desired product in a moderate yield (40%) and with an er of 62:38 after 60 h (Table 3, entry 1). Cinchona-derived thiourea catalysts **IIa**–**IIIb**[10] did not give better result (Table 3, entries 2–5). Thus, cinchona-based squaramide catalysts **IV** and **V**[11] were investigated; although catalyst **IV** provided a similar result as catalyst **I** (Table 3, entry 7), catalyst **V** provided

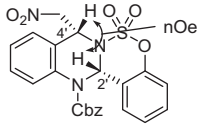


Fig. 1. NOE correlation in *cis*-**3a**.