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Asymmetric Multicomponent Sulfa-Michael/Mannich Cascade Reaction: Synthetic Access to 1,2-Diamino-3-Organosulfur Compounds and 2-Nitro Allylic Amines

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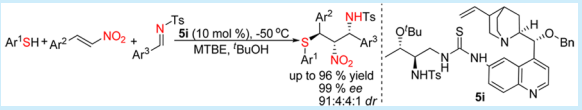
Supporting Information

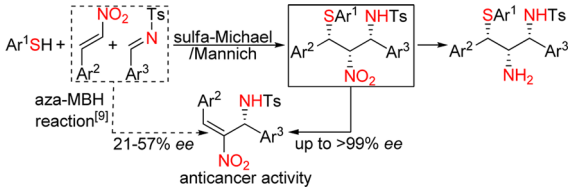
ABSTRACT: A novel catalytic asymmetric three-component intermolecular sulfa-Michael/Mannich cascade reaction has been developed using a chiral multifunctional catalyst. This reaction provides facile access to 1-amino-2-nitro-3-organosulfur compounds bearing three consecutive stereocenters in high yields (up to 96%) with good diastereo- (up to 91:4:4:1 *dr*) and excellent enantioselectivities (93−99% *ee*). Furthermore, the products of this reaction could be facilely transformed into potentially bioactive 1, 2-diamino-3-organosulfur compounds and 2-nitro allylic amines.



The prevalence of chiral organosulfur compounds in natural products and other bioactive compounds has provided a major impetus for the development of efficient methods for their construction.[1] In this regard, the catalytic asymmetric sulfa-Michael addition has distinguished itself as a powerful tool for the synthesis of organosulfur compounds, and significant progress has been achieved in this area.[2] In contrast, reports pertaining to the development and application of sulfa-Michael addition-triggered catalytic asymmetric multicomponent reactions, which could be used as an efficient method for the synthesis of diverse sets of relatively complex chiral structures,[3] have been scarce.[4] Chiral 1,2-diamino-3-organosulfur compounds are ubiquitous in living organisms (e.g., glutathione and biotin),[1] and subunits of this type can also be found in a wide range of bioactive natural products[5] and drugs.[6] It was envisaged that the use of a catalytic asymmetric multicomponent sulfa-Michael/Mannich reaction would provide efficient access to 1-amino-2-nitro-3-organosulfur compounds as the precursor of 1,2-diamino-3-organosulfur compounds. Notably, the products of this reaction could also be readily converted[7] to the corresponding chiral bioactive 2-nitro allylic amines,[8] which are otherwise difficult to prepare with a high level of enantioselectivity via the direct asymmetric aza-Baylis−Hillman reaction of nitroalkenes.[9] The potential retro-sulfa-Michael[10] or retro-Mannich[11] reaction constitutes a major obstacle for achieving the catalytic asymmetric sulfa-Michael/Mannich reaction.[12] The difficulties associated with these issues could also be the main reason why only three examples of a sulfa-initiated catalytic asymmetric three-component sulfa-Michael/Michael intermolecular domino reaction have been reported to date.[4a−c] Recently, our group reported the enantioselective three-component intermolecular sulfur-Michael/Mannich domino reaction in the catalysis of chiral quaternary ammonium salts using chalcones as Michael acceptors.[4d] However, when we tried to expand this catalytic system to nitroolefins as Michael acceptors, only racemic products resulted. Thus, the development of an efficient catalytic system for the asymmetric multicomponent sulfa-Michael/Mannich reaction that accommodates other substrates is therefore still highly desired and represents a significant challenge to synthetic chemistry.

As part of ongoing work toward the development of new methods for the asymmetric construction of biologically active sulfur-containing complex compounds, herein, we report the development of a novel enantioselective asymmetric multicomponent sulfa-Michael/Mannich reaction for the construction of 1-amino-2-nitro-3-organosulfur compounds using a multifunctional organocatalyst (Scheme 1).

Scheme 1. Asymmetric Multicomponent Sulfa-Michael/Mannich Cascade Reaction



The reaction of thiophenol **1a** with nitrostyrene **2a** and *N*-sulfonylaldimine **3a** was selected as a model reaction. Following a series of preliminary experiments, we investigated the use of bifunctional catalysts **5a**−**5c**[13] to evaluate their performance on the reaction in DCM at −40 °C. Pleasingly, all three of these catalysts could promote the model reaction to give the desired products in excellent yields (87−97%) (Table 1, entries 1−3). Takemoto catalyst **5a**[13a] afforded the desired product **4aaa** with good diastereoselectivity (87:13 *dr*), but only moderate

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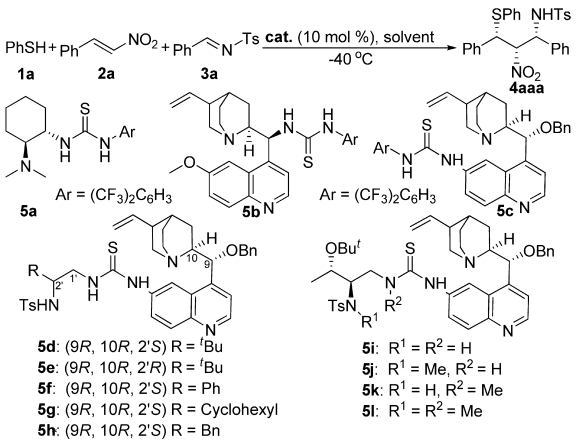
Table 1. Catalytic Asymmetric Sulfa-Michael/Mannich Reaction under Various Conditions[a]



entry	cat.	solvent	t (h)	yield (%)[b]	dr[c,d]	ee (%)[d]
1	**5a**	DCM	28	97	87:13	45
2	**5b**	DCM	43	94	76:24	35
3	**5c**	DCM	43	87	64:36	65
4	**5d**	DCM	43	77	65:35	98
5	**5e**	DCM	43	71	65:35	80
6	**5f**	DCM	43	75	47:53	92
7	**5g**	DCM	43	79	57:43	95
8	**5h**	DCM	43	77	62:38	94
9	**5i**	DCM	43	79	69:31	98
10[e,f]	**5i**	MTBE	24	90	82:18	99
11[e,f,g]	**5i**	MTBE	67	90	83:17	99
12[e,f,g,h]	**5i**	MTBE	70	83	83:17	99
13[e,f,g]	**5j**	MTBE	67	90	72:28	96
14[e,f,g]	**5k**	MTBE	67	10	78:22	76
15[e,f,g]	**5l**	MTBE	67	10	67:33	75

[a]Unless noted, all of the reactions were carried out with **1a** (0.15 mmol), **2a** (0.15 mmol), **3a** (0.1 mmol), and the cat. (10 mol %) in 0.5 mL of solvent at −40 °C. [b]Combined isolated yields of the isomers. [c]Ratio of the major diastereomer to the total of the other three pairs. [d]Determined by chiral HPLC of the major stereoisomer. [e]Reactions were carried out with **1a** (0.3 mmol), **2a** (0.3 mmol), **3a** (0.2 mmol), and the cat. (10 mol %) in 0.5 mL of solvent. [f]38 μL of ^{t}BuOH were added. [g]Performed at −50 °C. [h]5 mol % **5i** was used as the catalyst.

enantioselectivity (45% *ee*). Based on this result and the structural framework of catalyst **5a**, a series of bi- and multifunctional catalysts[14] were also screened in an attempt to increase the enantioselectivity. Unfortunately, however, none of these catalysts provided the desired product with a satisfactory yield and enantioselectivity (see the Supporting Information (SI)). Good enantioselectivity was achieved using catalyst **5c**, which indicated that the presence of a C-6′-thiourea substituted quinine moiety was important for controlling the stereochemistry of the reaction. Based on this result, we designed and synthesized a series of trifunctional C-6′ substituted quinine derivatives **5d**−**5i**, bearing tertiary amine, thiourea, and sulfonamide functional groups. These catalysts were then evaluated in terms of their efficiency (Table 1, entries 4−9). The results of these experiments revealed that catalyst **5i** bearing a bulky *tert*-butyl ether moiety gave the best results, which were attributed to the steric hindrance of this group (79% yield, 69:31 *dr*, 98% *ee*) (Table 1, entry 9). Several other multifunctional catalysts were also investigated (see SI), but they all failed to provide better results than catalyst **5i**. A variety of solvents were also screened, and MTBE was found to provide the best performance in terms of the diastereoselectivity (74:26 *dr*) and enantioselectivity (99% *ee*) (see SI). The addition of a small amount of ^{t}BuOH led to a significant improvement in the yield and selectivity of the reaction (90% yield, 99% *ee* and 82:18 *dr*) (Table 1, entry 10), although the reason for these improvements in the catalytic performance remains unclear. The addition of ^{t}BuOH could lead to the formation of synergistic hydrogen bonding interactions between the catalyst, reactive substrates, and ^{t}BuOH.[15] It was also noted that lowering the reaction temperature to −50 °C led to a slight improvement in the diastereoselectivity of the desired product (83:17 *dr*) (Table 1, entry 11). To gain insight into the effect of the multiple hydrogen bonds of the catalyst, catalysts (**5j**−**5l**) were synthesized and evaluated. When the sulfonamide moiety was methylated (**5j**), the catalytic performance of the reaction was maintained to some extent, albeit with a slightly reduced diastereoselectivity (Table 1, entry 13 vs 11). In sharp contrast, once the nitrogen of the thiourea moiety of the catalyst was methylated (**5k** and **5l**), the reactivities and enantioselectivities decreased dramatically and only 10% yields were obtained (Table 1, entries 14 and 15). Apparently these results show the thiourea and the sulfonamide of the catalyst **5i** may synergistically fix and activate the substrate via multiple hydrogen bonding.

With the optimized reaction conditions in hand, a series of substituted thiophenols (**1a**−**1k**) as the nucleophile was investigated (see SI). The use of 4-*tert*-butylbenzenethiol (**1b**) as a nucleophile gave the best diastereoselectivity (91:4:4:1 *dr*) of all of the thiophenols tested, and the corresponding product was obtained in 80% yield with 99% *ee*.

4-*tert*-Butylbenzenethiol was selected for study to further expand the substrate scope (Table 2). Various nitrostyrenes **2** were investigated in this cascade reaction. The results revealed that the cascade reaction proceeded smoothly, regardless of the position (Table 2, entries 5−9) or the electronic nature (Table 2, entries 3−6 or 7−13) of the substituents on the aromatic ring of the nitrostyrene substrate to give the desired products in good yields (65−95%), diastereoselectivities (72:5:16:7−90:5:5:0 *dr*), and excellent enantioselectivities (98−99% *ee*) (Table 2, entries 1−13). Nitroalkenes bearing heteroaromatic rings also reacted smoothly under the optimized reaction conditions to give the corresponding 1-amino-2-nitro-3-organosullfur products in 85−90% yields, 88:4:8:0−89:7:4:0 *dr*, and 98% *ee* (Table 2, entries 14−16). Subsequently, we turned our attention to the scope of the imine **3** (Table 2, entries 17−23). The results of these experiments revealed that the position of the substituent on the aryl ring of the imine had a significant effect on the outcome of the reaction. For example, imines with a *meta*- or *para*-substituted phenyl ring gave better results than those with an *ortho*-substituted phenyl ring (Table 2, entries 18 and 19 vs 20). It is noteworthy that the diastereoselectivity of the products could be improved by recrystallization. For example, a single recrystallization of **4aaa** (99% *ee*, 83:17 *dr*) from methanol gave almost optically pure material (70% yield, >99% *ee*, >99:1 *dr*).

The absolute and relative configurations of the products were unambiguously determined to be (1*R*, 2*S*, 3*S*), (1*R*, 2*S*, 3*R*) and the mixture of (1*R*, 2*R*, 3*R*) and (1*S*, 2*S*, 3*S*) by X-ray crystallographic analysis of **4aaa-A**, **4aaa-B**, and (±)-**4aaa-C**, respectively (see Figure 1).

A series of control experiments were conducted to achieve a deeper understanding of the mechanism of this reaction (Scheme 2). Under the optimum reaction conditions, the Michael

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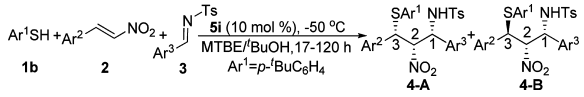
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Asymmetric Sulfa-Michael/Mannich Reactions of *p*-^{t}BuC$_6$H$_4$SH (1b) with Nitrostyrenes 2 and Imines 3 in the Presence of Catalyst 5i[a]



entry	Ar^2	Ar^3	yield (%)[b]	*dr* (A:B:C:D)[c]	*ee* (%) (A/B)[d]
1	Ph	Ph	**4baa**, 80	91:4:4:1	99/99
2	Ph	*m*-$CH_3C_6H_4$	**4bab**, 88	89:6:4:1	98/98
3	*p*-MeC_6H_4	*m*-$CH_3C_6H_4$	**4bbb**, 91	89:6:4:1	98/98
4	*m*-MeC_6H_4	*m*-$CH_3C_6H_4$	**4bcb**, 76	83:8:6:3	98/99
5	*p*-$OMeC_6H_4$	*m*-$CH_3C_6H_4$	**4bdb**, 91	90:5:5:0	98/98
6	*m*-$OMeC_6H_4$	*m*-$CH_3C_6H_4$	**4beb**, 95	81:7:11:1	98/98
7	*p*-FC_6H_4	*m*-$CH_3C_6H_4$	**4bfb**, 83	86:8:5:1	98/98
8	*m*-FC_6H_4	*m*-$CH_3C_6H_4$	**4bgb**, 72	84:10:5:1	98/98
9	*o*-FC_6H_4	*m*-$CH_3C_6H_4$	**4bhb**, 83	72:5:16:7	99/98
10	*p*-ClC_6H_4	*m*-$CH_3C_6H_4$	**4bib**, 96	83:9:5:3	98/98
11	*m*-ClC_6H_4	*m*-$CH_3C_6H_4$	**4bjb**, 72	79:13:6:2	98/99
12	*p*-BrC_6H_4	*m*-$CH_3C_6H_4$	**4bkb**, 85	83:12:4:1	98/98
13[f]	*m*-BrC_6H_4	*m*-$CH_3C_6H_4$	**4blb**, 65	78:12:7:3	98/98
14	Furyl	*m*-$CH_3C_6H_4$	**4bmb**, 89	89:2:9:0	98/–[e]
15	Furyl	Ph	**4bma**, 90	88:4:8:0	98/–[e]
16	Thiophen	Ph	**4bna**, 85	89:7:4:0	98/–[e]
17[f]	*p*-MeC_6H_4	*p*-$CH_3C_6H_4$	**4bbc**, 64	85:6:6:3	98/97
18[f]	*p*-MeC_6H_4	*p*-FC_6H_4	**4bbd**, 72	83:8:5:4	93/93
19[f]	*p*-MeC_6H_4	*m*-FC_6H_4	**4bbe**, 93	85:10:4:1	98/98
20	*p*-MeC_6H_4	*o*-FC_6H_4	**4bbf**, 28	82:11:5:2	98/97
21	*p*-MeC_6H_4	*m*-ClC_6H_4	**4bbg**, 76	83:10:5:2	98/99
22	*p*-MeC_6H_4	*m*-BrC_6H_4	**4bbh**, 93	83:11:5:1	97/–[e]
23	*p*-MeC_6H_4	*m*-$MeOC_6H_4$	**4bbi**, 90	89:6:4:1	98/91

[a]Unless noted, all of the reactions were carried out with **1b** (0.3 mmol), **2** (0.3 mmol), **3** (0.2 mmol), **5i** (10 mol %), and ^{t}BuOH (38 uL) in 0.5 mL of MTBE for the specified reaction times, which are shown in the Supporting Information. [b]Combined isolated yields of the isomers. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture; A–D represent the four pairs of enantiomers of the product, respectively. [d]Determined by chiral HPLC of the stereoisomers A and B. [e]Not determined. [f]Performed at −40 °C.

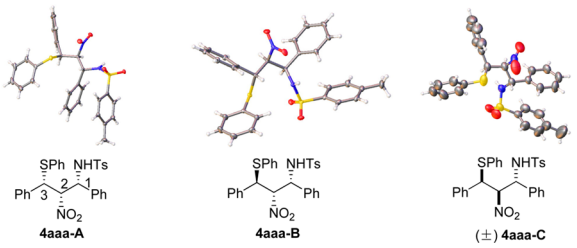
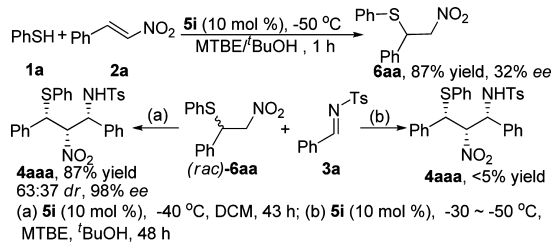


Figure 1. X-ray crystal structures of **4aaa-A**, **4aaa-B**, and (±)-**4aaa-C**.

Scheme 2. Mechanistic Investigations



addition reaction of thiophenol **1a** with nitrostyrene **2a** proceeds smoothly to give adduct **6aa** in good yield with poor enantioselectivity (87% yield, 32% *ee*), which contrasted sharply with the excellent enantioselectivity observed for the catalytic asymmetric multicomponent domino reaction (90% yield, 99% *ee*, and 83:17 *dr*) (Table 1, entry 11). The differences in the outcome of these reactions could be attributed to the occurrence of a dynamic kinetic resolution (DKR) in the multicomponent reaction in the presence of catalyst **5i**. Further evaluation revealed that when DCM was used as solvent, racemic **6aa** could smoothly react with imine **3a** to afford **4aaa** with almost the same stereoselectivities that were observed from the direct reaction of **1a**, **2a**, and **3a** (Table 1, entry 9); this is similar to literature reported for the DKR model.[10d−f] While under the optimum reaction conditions, the alkalinity of the tertiary amine moiety of the catalyst was not strong enough to deprotonate the acidic nitroalkane **6aa**. The treatment of a mixture of nitroalkane **6aa** and imine **3a** under the same reaction conditions resulted in almost no reaction (Scheme 2). Based on the experiment results, we proposed a possible mechanism of this reaction. As shown in Figure 2, the reaction proceeded in two steps. First, the tertiary

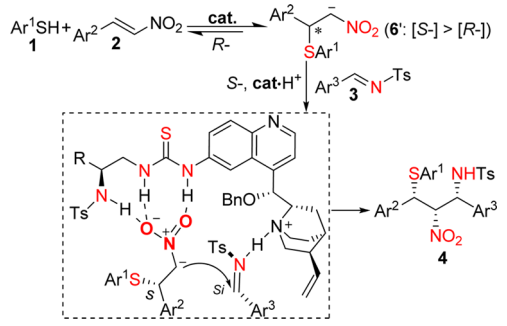


Figure 2. Proposed mechanism and main transition-state model.

amine moiety of the catalyst would initially activate the thiophenol **1** by deprotonation, and the resulting thiolate anion would undergo an asymmetric sulfa-Michael addition with low enantioselectivity, which is a reversible reaction. The resulting intermediate carbanion **6′** would then undergo a DKR process, with the *S* configuration favoring the nucleophilic attack of the imine from the *Si*-face to give the desired product with the observed high level of stereoselectivity. The sulfonamide hydrogen of the catalyst strengthens the hydrogen bond interaction with the nitro group of carbanion **6′**.

To demonstrate the synthetic potential of the 1-amino-2-nitro-3-organosulfur products formed by this unprecedented catalytic asymmetric multicomponent sulfa-Michael/Mannich reaction, we converted a selection of these products to the corresponding 1,2-dimino-3-organosulfur and 2-nitro allylic amine compounds, as shown in Scheme 3. The chiral bioactive 1,2-diamino-3-organosulfur compounds were readily obtained by the reduction of the 2-nitro group in **4aaa** with Zn/HCO_2H at −5 °C, which gave **7aaa** in 63% yield without any discernible loss in the enantiomeric purity. This novel asymmetric multicomponent reaction also provided facile access to highly enantioselective chiral bioactive 2-nitro allylic amines, which would be otherwise difficult to access via the direct asymmetric aza-Baylis−Hillman reaction of nitroalkene. Oxidation of **4aaa** (>99% ee) with *m*-CPBA (1 equiv) gave the corresponding sulfoxide in quantitative yield, which subsequently underwent an elimination reaction under thermal conditions to afford the

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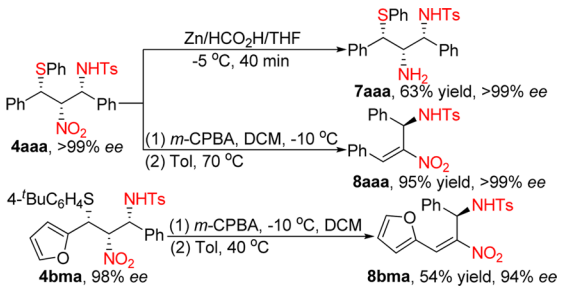
Scheme 3. Conversion of Cascade Adducts into 1,2-Diamino-3-organosulfur Compound and 2-Nitro Allylic Amines



desired aza-Baylis−Hillman equivalent **8aaa** in 95% yield without any loss in the enantiopurity of the starting material. Given that the racemic 2-nitro allylic amine **8bma** has been reported to exhibit inhibitory activity toward the growth of human cervical cancer cells,[8] the synthesis of its nonracemic variant will be of significant interest because the biological activities of these compounds are closely related to the configuration of the stereocenter. Pleasingly, chiral **8bma** was synthesized in 54% yield with 94% ee using the synthetic strategy described in this study and will be subjected to biological evaluation in due course (Scheme 3).

In summary, we have developed the catalytic asymmetric multicomponent intermolecular sulfa-Michael/Mannich reaction of thiophenol, nitrostyrene, and imine, which provided facile access to the corresponding 1-amino-2-nitro-3-organosulfur products in high yields (up to 96%) with excellent enantioselectivity (93−99% *ee*) and good diastereoselectivity. Furthermore, the products of this reaction can be readily converted chiral bioactive 1,2-diamino-3-organosulfur compounds and 2-nitro allylic amines. Further work toward expanding the application of this novel multifunctional catalyst to other asymmetric reactions is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02423.

Experimental procedures and detailed characterization data of all new compounds (PDF)
X-ray crystal details for **4aaa-A** (CIF)
X-ray crystal details for **4aaa-B** (CIF)
X-ray crystal details for (±)-**4aaa-C** (CIF)

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Notes

The authors declare no competing financial interest.

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