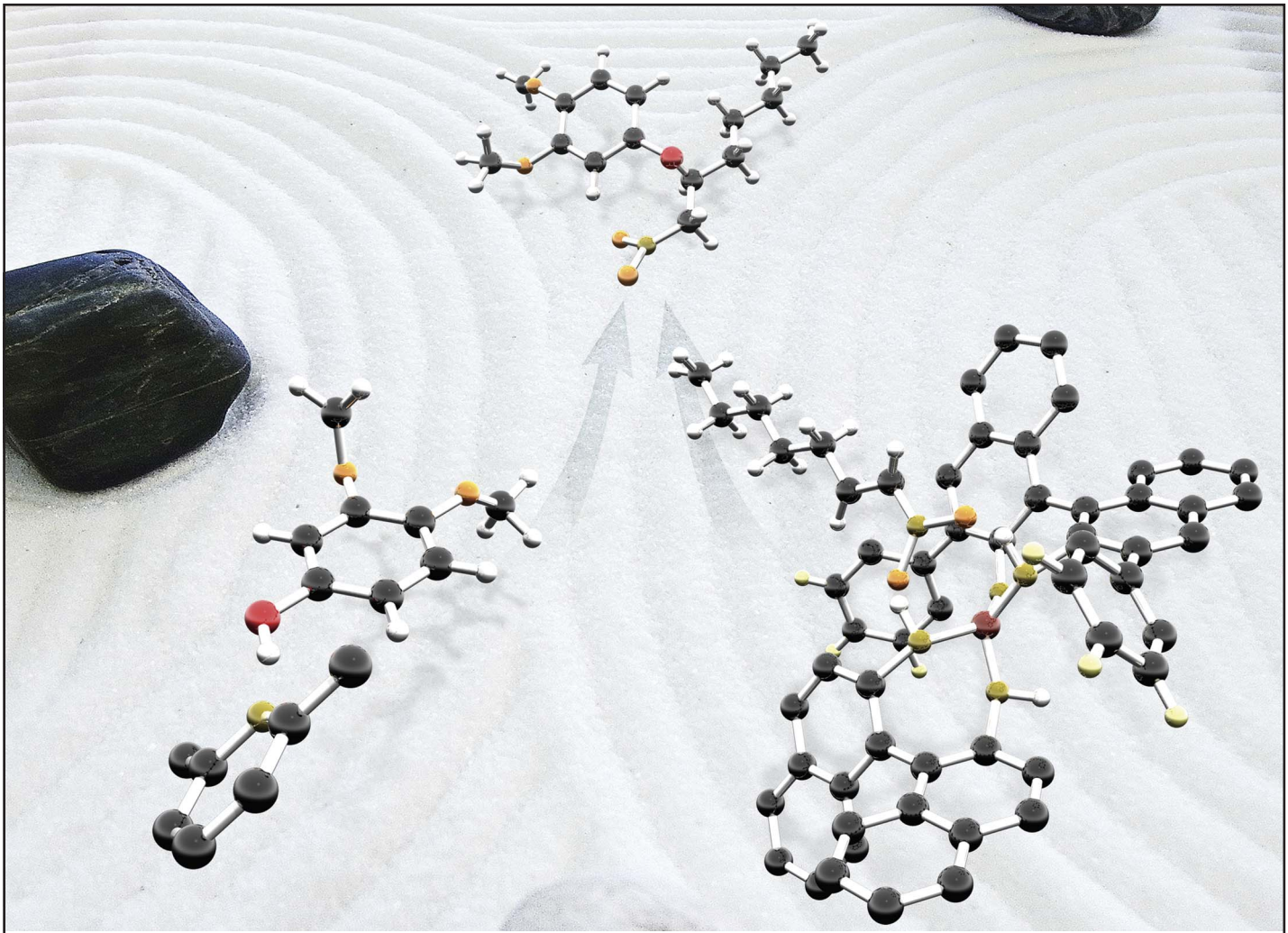

Showcasing research from Professor Takashi Ooi's Laboratory, Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Japan.

Chiral ionic Brønsted acid–achiral Brønsted base synergistic catalysis for asymmetric sulfa-Michael addition to nitroolefins

An acid–base synergistic catalysis of chiral *P*-spiro arylaminophosphonium barfate and 2,6-lutidine enables simultaneous activation of a broad range of nitroolefins and 3,4-dimethoxythiophenol for affording structurally diverse, highly enantioenriched 2-thionitroalkanes. This system greatly expands the potential of the asymmetric catalysis of the weakly acidic, aminophosphonium ions.

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EDGE ARTICLE

Chiral ionic Brønsted acid–achiral Brønsted base synergistic catalysis for asymmetric sulfa-Michael addition to nitroolefins†

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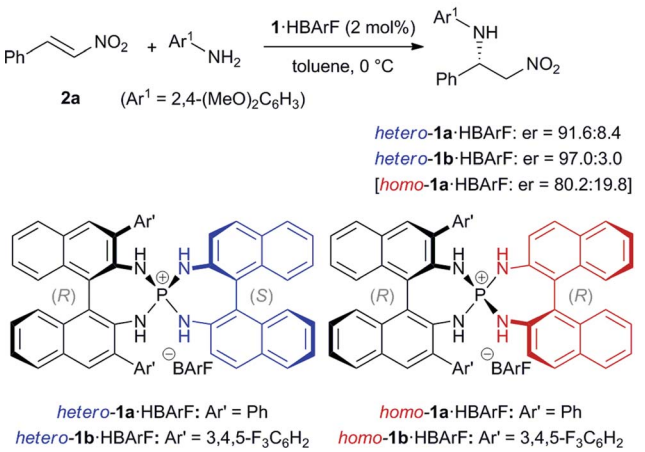
A highly enantioselective sulfa-Michael addition to aromatic and aliphatic nitroolefins is achieved under the synergistic catalysis of chiral, ionic Brønsted acid *homo*-**1b**·HBArF and 2,6-lutidine. The potential utility of this new method is clearly demonstrated by its application to the syntheses of a novel, optically active taurine derivative and β-sultam.

Introduction

Since the cinchona alkaloid-catalyzed asymmetric sulfa-Michael addition was first reported in 1977,[1] considerable progress has been made in the development of effective catalytic systems for sulfa-Michael reactions of different sulfur donors and Michael acceptors, providing useful tools for constructing sulfur-containing, chiral organic compounds of biological significance.[2] However, efforts toward developing the catalytic asymmetric conjugate addition of sulfur nucleophiles to β-substituted nitroolefins have been very limited in spite of the versatility of the Michael adducts as intermediates for the synthesis of chiral 1,2-amino thiols and 2-thiocarbonyl compounds. This is probably due to the difficulty associated with the potential reversibility of the transformation.[1a,3–6] To address this problem, the use of Brønsted acid or base catalysts featuring appropriate pK_a values would be suitable, because the intermediary formed nitronate could be rapidly protonated under characteristic proton transfer conditions, which would be crucial for efficient *in situ* derivatization of the desired Michael adduct. In fact, Ellman demonstrated the effectiveness of the bifunctional catalysis of chiral *N*-sulfinyl urea-tertiary amines in achieving the highly enantioselective sulfa-Michael addition of thioacetic acid to nitroolefins.[4c,d] Recently, Connon introduced a C-5′ substituted cinchona alkaloid-derived bifunctional catalyst for promoting the additions of alkyl thiols to aromatic nitroolefins with high levels of enantioselectivity.[4e] Despite these impressive contributions, however, the full potential of this type of reaction is yet to be realized in terms of substrate generality and synthetic applicability.

Herein, we disclose our own solution to this problem by developing a unique acid–base synergistic catalysis[7] of chiral *P*-spiro arylaminophosphonium barfate *homo*-**1b**·HBArF[8] and 2,6-lutidine, which enabled a highly enantioselective Michael addition of an aromatic thiol to a series of aromatic and aliphatic nitroolefins **2**. Furthermore, the significant synthetic value of this new protocol is clearly demonstrated in the asymmetric synthesis of novel taurine derivative and β-sultam.

Earlier, we reported the design of *homo* and *hetero* chiral **1**·HBArF as ionic Brønsted acid catalysts[9] and demonstrated the effectiveness of *hetero*-**1b**·HBArF for achieving the asymmetric aza-Michael reaction of nitroolefins **2** (Scheme 1).[10] The catalysis relied on the ability of **1**·H to recognize non-ionic substrate **2** even in the presence of basic nucleophiles such as 2,4-dimethoxyaniline. This distinct feature of designer chiral cation **1**·H prompted us to explore the possibility of establishing a system in which a achiral Brønsted base catalytically activates a relatively acidic nucleophile, such as a thiol, for stereoselective bond formation with **2**, which is electrophilically activated by **1**·H.



Scheme 1 Previous study.

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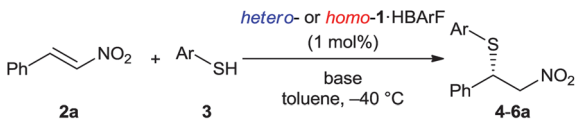
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of *homo*-**1b**·HBArF, **6–9**. CCDC 884839–884840. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc20698f

Results and discussion

An initial attempt was made by the reaction of 4-methoxythiophenol (**3a**) with *trans*-β-nitrostyrene (**2a**) in the presence of *hetero*-**1a**·HBArF (1 mol%) in toluene at −40 °C, revealing that virtually no bond formation had taken place after 26 h of stirring (Table 1, entry 1). This indicated that the electrophilic activation of **2a** by *hetero*-**1a**·HBArF, which was effective for the aza-Michael reaction in terms of both reactivity and selectivity (Scheme 1),[10] was insufficient for facilitating the addition of sulfur nucleophile **3a**. In marked contrast however, the use of 2,6-lutidine (1 mol%) as an activator of **3a** in combination with *hetero*-**1a**·HBArF under otherwise identical conditions led to the formation of **4** in 77% yield, albeit with almost negligible enantioselectivity (entry 2). In addition, the reaction with 2,6-lutidine as the sole base catalyst proceeded, though sluggishly, to give **4** in only 17% yield (entry 3). These results strongly suggested that an acid–base synergistic catalysis of *hetero*-**1a**·HBArF and 2,6-lutidine is operative and is of critical importance for allowing the C–S bond-forming event to occur smoothly through the productive activation of both electrophile **2a** and nucleophile **3a**. Encouraged by these observations, we next examined the effect of the structure of the ionic Brønsted acid catalyst on the reaction profile. Interestingly, employment of the homochiral catalyst, *homo*-**1a**·HBArF, substantially improved the enantioselectivity (entry 4). This preference is opposite to that observed in the aza-Michael reaction under simple acid catalysis of **1**·HBArF, although the absolute configuration of the newly created stereocenter is identical (*cf.* Scheme 1). This phenomenon could be ascribed to the three-dimensional structural difference in the transition state, which is probably caused by the interaction between 2,6-lutidine and **3a**. However, the precise structure of the transition state remains open for discussion. The electronic attributes of the aromatic substituents at the 3,3′-positions of the binaphthyl subunit (Ar′) were also important, and introduction of 3,4,5-trifluorophenyl groups (*homo*-**1b**·HBArF) delivered a notable increase in catalytic efficiency and stereoselectivity (entry 5). At this stage, we turned our attention to the relationship between the structure of the sulfur nucleophile and the stereochemical outcome of the reaction. While comparable enantioselectivity was observed with 2,4-dimethoxythiophenol (**3b**) (entry 6), critical enhancement of the selectivity was attained in the addition of the commercially available 3,4-dimethoxythiophenol (**3c**) and the corresponding adduct **6a** was obtained in 99% yield with the enantiomeric ratio of 97.2 : 2.8 (entry 7). Considering the competing base-catalyzed background reaction, we finally tuned the amount of 2,6-lutidine and found that a half molar equivalent of *homo*-**1b**·HBArF was optimal for realizing the full potential of this synergistic catalysis (entries 8 and 9).[11] It should be noted that the use of other organic bases such as triethylamine (Et_3N) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in place of 2,6-lutidine caused a slight decrease in the enantiomeric ratio of **6a** (entries 10 and 11).[12]

With the optimized reaction conditions in hand, we undertook an extensive survey of the scope of the reaction with respect to the substrate. As summarized in Table 2, a wide range of nitroolefins **2** bearing β-substituents with different steric and electronic properties were employable, and the desired sulfa-Michael adducts **6** were isolated uniformly in quantitative yields with excellent enantioselectivities (entries 1–8). The presence of fused and heteroaromatic rings in the Michael acceptors scarcely affected the catalytic and chiral efficiencies (entries 9 and 10). Particularly emphasized is the fact that the present system based on the intermolecularly operative, synergistic catalysis enabled a highly enantioselective sulfa-Michael addition to a variety of simple aliphatic nitroolefins and thus tolerated the incorporation

Table 1 Optimization of reaction conditions[a]

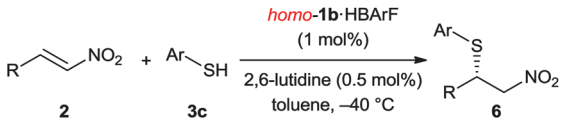


3a: Ar = 4-$MeOC_6H_4$
3b: Ar = 2,4-$(MeO)_2C_6H_3$
3c: Ar = 3,4-$(MeO)_2C_6H_3$

Entry	Acid	Base (mol%)	3	Time (h)	Yield (%)[b]	Er[c]	Prod.
1	*hetero*-**1a**·H	None	**3a**	26	Trace	—	**4**
2	*hetero*-**1a**·H	2,6-Lutidine (1)	**3a**	26	77	53.0 : 47.0	**4**
3	None	2,6-Lutidine (1)	**3a**	42	17	—	**4**
4	*homo*-**1a**·H	2,6-Lutidine (1)	**3a**	26	88	66.5 : 33.5	**4**
5	*homo*-**1b**·H	2,6-Lutidine (1)	**3a**	8	95	74.6 : 25.4	**4**
6	*homo*-**1b**·H	2,6-Lutidine (1)	**3b**	12	99	74.3 : 25.7	**5**
7	*homo*-**1b**·H	2,6-Lutidine (1)	**3c**	9	99	97.2 : 2.8	**6a**
8	*homo*-**1b**·H	2,6-Lutidine (0.5)	**3c**	5	99	97.8 : 2.2	**6a**
9	*homo*-**1b**·H	2,6-Lutidine (0.1)	**3c**	7	99	97.6 : 2.4	**6a**
10	*homo*-**1b**·H	Et_3N (0.5)	**3c**	3	99	95.9 : 4.1	**6a**
11	*homo*-**1b**·H	DBU (0.5)	**3c**	3	99	95.8 : 4.2	**6a**

[a] The reaction was performed with 0.1 mmol of **2a**, 0.11 mmol of **3**, 1–0.1 mol% of base, and 1 mol% of *hetero*- or *homo*-**1**·HBArF in toluene (5.0 mL) at −40 °C. See ESI for details.† [b] Isolated yield. [c] Enantiomeric ratios were analyzed by chiral stationary phase HPLC. Absolute configurations of **4** and **6a** were determined to be *S* by X-ray diffraction analysis, respectively, and that of **5** was assigned by analogy.

Table 2 Substrate scope (Ar = 3,4-$(MeO)_2C_6H_3$)[a]

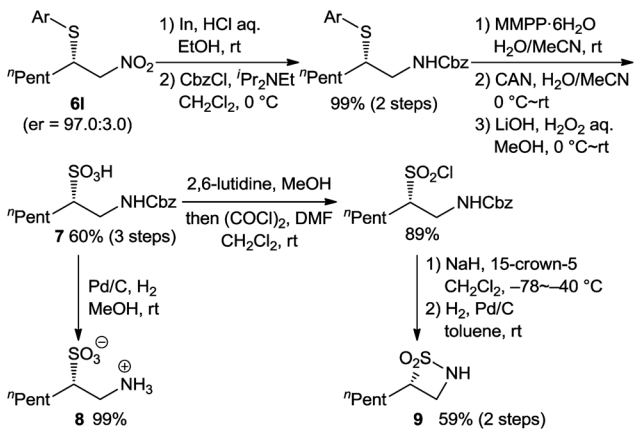


Entry	R	Time (h)	Yield (%)[b]	Er[c]	6
1	2-FC_6H_4	8	99	98.4 : 1.6	**6b**
2	2-MeC_6H_4	12	99	95.5 : 4.5	**6c**
3	3-BrC_6H_4	20	99	94.8 : 5.2	**6d**
4	3-$MeOC_6H_4$	11	97	96.6 : 3.4	**6e**
5	4-FC_6H_4	8	99	96.9 : 3.1	**6f**
6	4-BrC_6H_4	21	99	95.5 : 4.5	**6g**
7	4-MeC_6H_4	11	99	96.0 : 4.0	**6h**
8	4-$MeOC_6H_4$	23	99	94.8 : 5.2	**6i**
9[d]	1-Naphthyl	52	99	94.8 : 5.2	**6j**
10	3-Furyl	23	99	95.9 : 4.1	**6k**
11[e,f]	$Me(CH_2)_4$	24	99	97.0 : 3.0	**6l**
12[f,g]	Me_2CH	24	99	95.1 : 4.9	**6m**
13[f,g]	Cyclohexyl	24	98	97.8 : 2.2	**6n**
14[e,f]	^{t}BuCOO$(CH_2)_4$	26	99	95.9 : 4.1	**6o**
15[e,f]	^{t}BuMe$_2$SiO$(CH_2)_3$	24	98	97.6 : 2.4	**6p**

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2**, 0.11 mmol of **3c**, 0.5 mol% of 2,6-lutidine, and 1 mol% of *homo*-**1b**·HBArF in toluene (5.0 mL) at −40 °C. See ESI for details.† [b] Isolated yield. [c] Enantiomeric ratios were analyzed by chiral stationary phase HPLC. Absolute configurations were assigned by analogy to **6a**. [d] 0.2 mol% of 2,6-lutidine was used. [e] 10 mol% of 2,6-lutidine and 2 mol% of *homo*-**1b**·HBArF were used. [f] Volume of solvent was 3.0 mL. [g] 10 mol% of 2,6-lutidine and 2 mol% of *homo*-**1b**·HBArF were used at 0 °C.

of not only linear and branched alkyl chains but also functionalized alkyl chains at the β-positions of nitroolefins through the appropriate increase in loadings of both the acid and base catalysts (entries 11–14).

The synthetic utility of this broadly useful, highly enantioselective sulfa-Michael addition to nitroolefins was demonstrated by its application to the concise asymmetric syntheses of 1-substituted taurine derivative **8** and 4-substituted β-sultam **9** (Scheme 2). Substituted taurine derivatives, a class of 2-aminoalkanesulfonic acids, are very important sulfur analogs of naturally occurring



Scheme 2 Synthesis of chiral 1-substituted taurine derivative **8** and 4-monosubstituted β-sultam **9** from **6l** (Ar = 3,4-$(MeO)_2C_6H_3$).

α-aminocarboxylic acids and are involved in various physiological processes. In recent decades, taurine derivatives have gained increasing attention due to their biological actions and potential therapeutic applications, and have stimulated considerable interest in their asymmetric synthesis.[13,14] On the other hand, β-sultams are the sulfonyl analogs of β-lactams and are intriguing molecular entities from chemical and pharmacological viewpoints because they are approximately 10^3-fold more reactive than β-lactams.[15,16] However, research toward the asymmetric construction of the simple architectures of these biologically relevant β-amino organosulfur compounds has been surprisingly limited. Our synthetic route exemplified in Scheme 2 started from the reduction of the nitro group of the Michael adduct **6l** (er = 97.0 : 3.0, entry 11 in Table 2) under the influence of indium metal and hydrochloric acid followed by Cbz-protection of the resulting primary amine functionality. Then, oxidation of the sulfide moiety by magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) afforded the corresponding aryl sulfone, which was successively treated with ceric ammonium nitrate (CAN) and lithium hydroperoxide to furnish sulfonic acid **7** in good yield. Through the simple hydrogenation of **7** with palladium on charcoal, optically active taurine derivative **8** was obtained quantitatively. Meanwhile, sulfonic acid **7** also served as a key intermediate for the synthesis of chiral 4-monosubstituted β-sultam **9**. After the 2,6-lutidinium salt of **7** was formed, it was converted to the corresponding sulfonyl chloride in a usual manner in 89% yield. Subsequent intramolecular cyclization was effected by the combination of NaH and 15-crown-5,[17] and final hydrogenative removal of the Cbz group gave (–)-4-pentyl β-sultam **9**.

Conclusions

In conclusion, we have developed an intermolecularly operative, synergistic catalysis of chiral, ionic Brønsted acid *homo*-**1b**·HBArF and 2,6-lutidine for establishing a highly enantioselective sulfa-Michael reaction of a broad range of aromatic and aliphatic nitroolefins. The synthetic utility of this new method has also been clearly demonstrated through the first catalytic asymmetric syntheses of 1-substituted taurine derivative **8** and 4-monosubstituted β-sultam **9**. We believe this approach greatly expands the potential of the asymmetric catalysis of the weakly acidic arylaminophosphonium ions.

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12 Judging from the pK_a values of DBU (24.34 in CH_3CN) and *homo*-**1b**·H (15.8 in CD_3CN), the corresponding iminophosphorane *homo*-**1b** can be generated. This possibility prompted us to use separately prepared *homo*-**1b** as a chiral base catalyst for the present sulfa-Michael addition under otherwise similar reaction conditions, which afforded **6a** in a nearly racemic form. In addition, a synergistic catalysis of *homo*-**1b**·HBArF and *homo*-**1b** resulted in the formation of **6a** in good yield at the slight expense of enantioselectivity. See ESI† for further details.

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17 The enantiomeric ratio of the resulting *N*-Cbz-β-sultam was determined to be 96.3 : 3.7, revealing the conservation of enantiopurity through the synthetic processes.

