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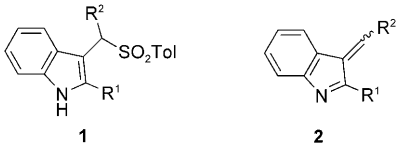
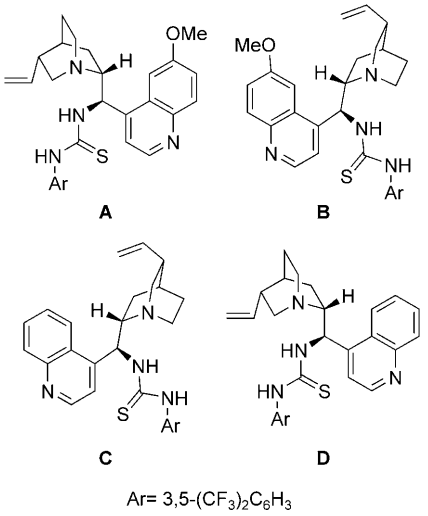
Highly Enantioselective Michael Addition of Malononitrile to Vinylogous Imine Intermediates Generated in situ from Arylsulfonyl Indoles

Linhai Jing,[a] Jiangtao Wei,[a] Li Zhou,[a] Zhiyong Huang,[a] Zhengkai Li,[a] Di Wu,[a, b] Haifeng Xiang,[a] and Xiangge Zhou*[a, b]

The conjugate addition of carbon-based nucleophiles to activated unsaturated systems represents one of the best established and most versatile carbon–carbon bond-forming reactions in organic chemistry.[1] Malononitrile, a classic equivalent of a 1,3-dicarbonyl compound, might be a valuable nucleophile, which can then be conveniently transformed into carboxylic acid,[2] ester,[3] amine,[2a,4] or amide groups.[4b] However, to the best of our knowledge, few studies of asymmetric Michael additions that use malononitrile as the nucleophile have been reported.[5]

Arylsulfonyl indoles **1**, which bear a good leaving group, are an effective precursor for vinylogous imine intermediates **2**, which are generated under basic conditions.[6] Recently, several non-asymmetric reactions that use **2** as acceptors have been carried out.[7] However, compared with the extensively studied α,β-unsaturated carbonyl compounds and nitroolefins, the study of the enantioselective conjugate addition to **2** is still in its infancy and only one asymmetric example has been reported, in which an aldehyde was reacted with a vinylogous imino ion to form the corresponding alkylation product.[8] Since 3-substituted indole frameworks have been widely found in biologically active compounds,[9] we wish to demonstrate, herein, the first highly enantioselective Michael addition of malononitrile to vinylogous imine intermediates **2**, generated in situ from arylsulfonyl indoles **1**, catalyzed by chiral thiourea catalysts **A**–**D**.[10]





Initially, the reaction of 3-[(4-methylphenylsulfonyl)phenylmethyl]-1*H*-indole and malononitrile was tested in the presence of catalyst **A** (Scheme 1).[11] Unfortunately, the reaction afforded a racemic mixture of product, although in high yield (93%). This prompted us to investigate the possible catalytic mechanism of the reaction to improve the results. Supported by the literature stating that the s-*cis*/*trans* conformations or *E*/*Z* configurations of enamines might play an important role in affecting the diastereo- and enantioselectivities of some asymmetric catalysis,[12] a plausible catalytic mode was proposed (Scheme 2). We hypothesize that vinylogous imine intermediate **2**, generated in situ from arylsulfonyl indole **1**, contains *E* and *Z* configurations **2**-**1** and **2**-

[a] L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li, Dr. D. Wu, H. Xiang, Prof. Dr. X. Zhou
Insitute of Homogeneous Catalysis, College of Chemistry
Sichuan University, Chengdu, 610041 (China)
Fax: (+86) 8-8541-2291
E-mail: zhouxiangge@scu.edu.cn

[b] Dr. D. Wu, Prof. Dr. X. Zhou
State Key Laboratory of Coordination Chemistry
Nanjing University, Nanjing, 210093 (China)

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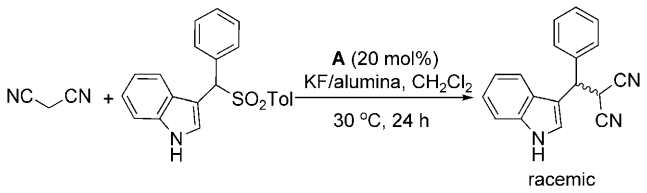
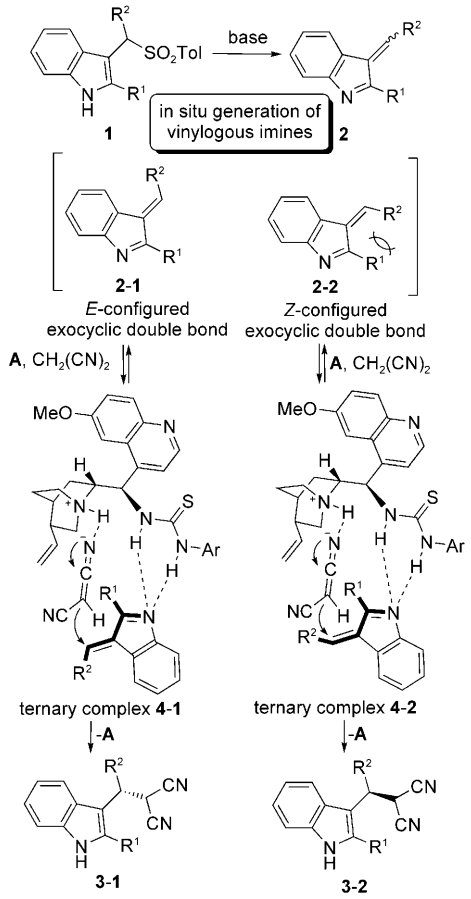


Scheme 1. The reaction between malononitrile and 3-[(4-methylphenylsulfonyl)phenylmethyl]-1*H*-indole; Tol = 4-methylphenyl.

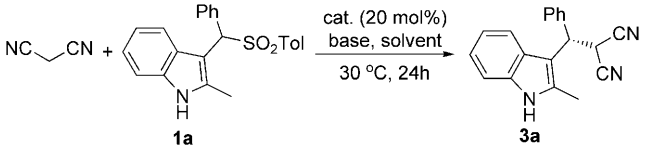


Scheme 2. Proposed catalytic mode through double activation.

2, as shown in Scheme 2. The thiourea moiety of catalyst **A** acts as a Brønsted acid and interacts with the nitrogen atom of **2** through hydrogen bonding, enhancing the electrophilicity.[10e,13] Meanwhile, the aliphatic tertiary amine unit in **A** acts as a Brønsted base to deprotonate and activate malononitrile by forming a hydrogen bond with its anion,[5e–h,14] generating ternary-complex transition states **4-1** and **4-2**, respectively. Consequently, nucleophilic attack to **2-1** and **2-2** affords the correspondingly configured products **3-1** and **3-2**, respectively. Thus, the formation of hydrogen bonds, as well as the ratio of *E*/*Z* configurations of the exocyclic double bond, are important factors in determining the ultimate enantioselectivity. During the reaction shown in Scheme 1, the lack of steric effects in vinylogous imine **2** ($R^1 = H$) might induce the ratio of *E*/*Z* isomers to be around 1:1 and, therefore, results in the formation of a racemic product mixture.

Further experiments supported the likelihood of this mechanism. As shown in Table 1, the *ee* value was dramatically increased to 54% when R^1 was changed from a proton to a methyl group, under the same catalytic conditions (Table 1, entry 1). Furthermore, the other three thiourea catalysts (**B**–**D**) gave almost the same results (Table 1, entries 2–4). Reaction conditions were then optimized; K_3PO_4 afforded the best *ee* (80%), although racemic products were obtained when organic bases, including DIPEA, DMAP, or Et_3N, were used (Table 1, entries 5–14). This is probably due to a loss of hydrogen bonding interactions between catalyst **A** and the substrates. The influence of other solvents was also examined. Protic solvents (EtOH) and polar solvents (MeCN, THF, DMF) gave inferior results (Table 1, entries 15–18), whereas a nonpolar solvent (toluene) efficiently promoted the reaction in excellent yield (91%) and high enantioselectivity (91%; Table 1, entry 19). Finally, the catalyst loading was investigated and it was observed that the catalyst loading could be decreased to 10 mol% without loss of enantioselectivity (Table 1, entry 20).

Table 1. Optimization of the reaction conditions.[a]

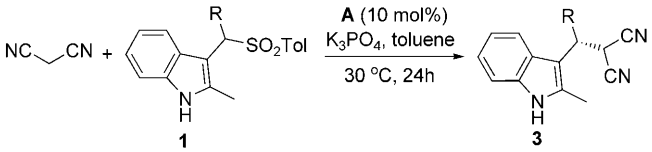


Entry	Catalyst	Base	Solvent	Yield [%][b]	*ee* [%][c]
1	**A**	KF/alumina	CH_2Cl_2	92	54
2	**B**	KF/alumina	CH_2Cl_2	90	−53
3	**C**	KF/alumina	CH_2Cl_2	90	−52
4	**D**	KF/alumina	CH_2Cl_2	89	50
5	**A**	KF	CH_2Cl_2	80	46
6	**A**	Na_2CO_3	CH_2Cl_2	82	36
7	**A**	K_2CO_3	CH_2Cl_2	88	77
8	**A**	$NaHCO_3$	CH_2Cl_2	78	31
9	**A**	NaOAc	CH_2Cl_2	70	32
10	**A**	K_3PO_4	CH_2Cl_2	87	80
11	**A**	Na_2HPO_4	CH_2Cl_2	84	52
12	**A**	DIPEA	CH_2Cl_2	78	–
13	**A**	DMAP	CH_2Cl_2	79	–
14	**A**	Et_3N	CH_2Cl_2	75	–
15	**A**	K_3PO_4	EtOH	60	–
16	**A**	K_3PO_4	MeCN	77	–
17	**A**	K_3PO_4	THF	75	–
18	**A**	K_3PO_4	DMF	72	–
19	**A**	K_3PO_4	toluene	91	91
20[d]	**A**	K_3PO_4	toluene	90	91
21[e]	**A**	K_3PO_4	toluene	72	46
22[f]	**A**	K_3PO_4	toluene	55	30

[a] Unless otherwise noted, the reactions were carried out with malononitrile (0.1 mmol), catalyst (0.02 mmol), **1a** (0.11 mmol), and base (0.11 mmol) in solvent (2.0 mL) at 30 °C for 24 h. DIPEA = *N*,*N*-diisopropylethylamine; DMAP = 4-dimethylaminopyridine. [b] Isolated yield. [c] Enantioselective excess was determined by chiral HPLC analysis. [d] 10 mol% of catalyst was used. [e] 5 mol% of catalyst was used. [f] 2 mol% of catalyst was used.

With the optimized reaction conditions in hand, we then screened a series of arylsulfonyl indoles **1a**–**m**. As portrayed in Table 2, various arylsulfonyl indoles underwent the reaction smoothly and gave the corresponding products with good to excellent results. A *para* substituent had little influence on the enantioselectivity of the reaction (Table 2, entries 2–4, 6, and 7). An *ortho* or *meta* substituent, on the other hand, seemed to be beneficial to the reaction. For example, the use of 2-Cl-substituted **1e** gave 91% *ee*, whereas 83% *ee* was obtained in the case of 4-Cl-substituted **1d** (Table 2, entries 4 and 5). The highest *ee* (more than 99%) was obtained when 3-OMe-substituted **1h** was used to form product **3h** (Table 2, entry 8). Its absolute configuration was further confirmed by single crystal structure determination (Figure 1). However, a relatively low *ee* was observed for the reaction between 2-NO_2-substituted **1j** and malononitrile (Table 2, entry 10), possibly due to an interaction between the nitro group and catalyst **A**. Finally, sulfonyl indoles with aliphatic substituents could also be employed and good yields and high enantioselectivities, ranging from 86 to 96%, were obtained (Table 2, entries 11–13).

Table 2. Asymmetric conjugate addition of malononitrile to arylsulfonyl indoles **1**.[a]



1 **3**

Entry	**1**	R	**3**	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	**3a**	90	91
2	**1b**	4-Br-C_6H_4	**3b**	88	81
3	**1c**	4-F-C_6H_4	**3c**	93	82
4	**1d**	4-Cl-C_6H_4	**3d**	93	83
5	**1e**	2-Cl-C_6H_4	**3e**	90	91
6	**1f**	4-Me-C_6H_4	**3f**	92	84
7	**1g**	4-OMe-C_6H_4	**3g**	90	80
8	**1h**	3-OMe-C_6H_4	**3h**	95	>99[d]
9	**1i**	1-Np	**3i**	82	81
10	**1j**	2-NO_2-C_6H_4	**3j**	82	65
11	**1k**	Bn	**3k**	78	86
12	**1l**	*t*Bu	**3l**	70	96
13	**1m**	*i*Bu	**3m**	75	90

[a] The reactions were carried out with malononitrile (0.1 mmol) and **1** (0.11 mmol). Np = naphthyl; Bn = benzyl. [b] Isolated yield. [c] The *ee* value was determined by HPLC analysis on an AD-H, AS-H, or OD-H column. [d] The absolute configuration of **3h** was determined to be *S* by X-ray crystal structure analysis (Figure 1).[15] The absolute configuration of other products was assigned by analogy.

In conclusion, we have developed the first highly enantioselective Michael addition of malononitrile to vinylogous imine intermediates **2**, generated in situ from arylsulfonyl indoles **1**, catalyzed by a chiral thiourea catalyst. This organocatalytic approach provides easy and convenient access to valuable 3-indolyl derivatives **3** in high yields and enantioselectivities. We have proposed that the ratio of *E*/*Z* configurations in the intermediate and the formation of a hydrogen bond play important roles in the enantioselectivity during catalysis. Overall, we believe this approach will be an important complementary reaction to the Friedel–Crafts alkylation of indoles.[16] Further investigations to broaden the scope of this type of transformation and find evidence for the mechanism are currently ongoing in our laboratory.

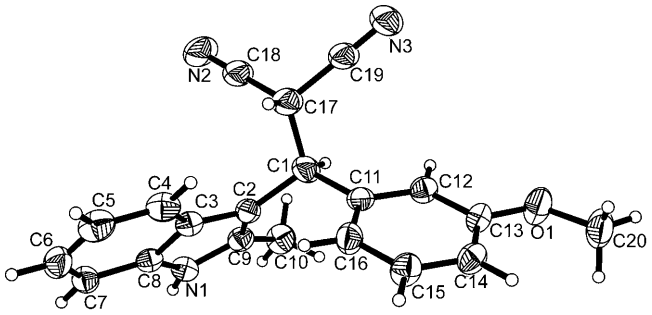


Figure 1. X-ray structure of enantiomerically pure **3h**. Thermal ellipsoids are set at 30% probability.

Experimental Section

General experimental procedure: Catalyst **A** (0.01 mmol), malononitrile (0.1 mmol), arylsulfonyl indole **1** (0.11 mmol), K_3PO_4 (0.11 mmol), and toluene (2 mL) were mixed in an ordinary test tube equipped with a magnetic stirring bar and then sealed in air. After being stirred at 30 °C for 24 h, the reaction mixture was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:6–1:10) to afford product **3**. The enantiomeric excess was determined by HPLC analysis on a chiral column. Further experimental details can be found in the Supporting Information.

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Keywords: asymmetric catalysis · imines · indoles · Michael addition · organocatalysis

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