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Organocatalytic Enantioselective Formal [4 + 2] Cycloaddition of Enones with Cyclic *N*-Sulfonylimines and Methylene Chromene for Chiral Spirocyclic Compounds

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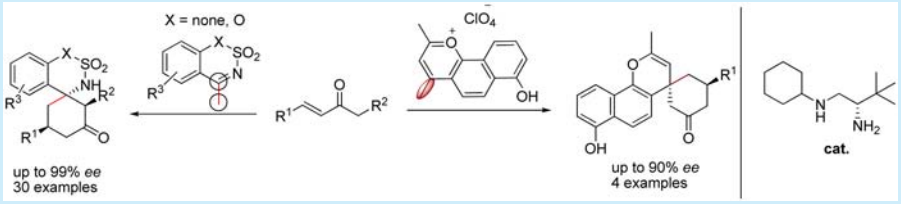
Supporting Information



ABSTRACT: A highly enantioselective synthesis of spirocycles and bridged rings has been developed through a formal [4 + 2] cycloaddition reaction between enones and *N*-sulfonylimines. The unprecedented strategy has been realized utilizing *N*-sulfonylimine as a novel dienophile through enamine−iminium tautomerism of *N*-sulfonylimine. In addition, a *γ*,*ε*-regioselective cycloaddition reaction proceeded by employing methylene chromene species as dienophiles.

The spirocyclic framework featuring unique structural properties commonly appears in bioactive molecules and nature products synthesis and functioned as a versatile intermediate for powerful ligands and catalyst synthesis.[1] Consequently, its construction in an enantioselective manner is highly desirable.

Cyclic sulfonamides have been extensively studied owing to their broad spectrum of biological activities[2] and great potential to serve as chiral auxiliaries[3] and important synthetic reagents.[4] Traditional enantioselective approaches to these building blocks include transition metal catalyzed asymmetric reduction,[5] addition of boric reagents[6] and *β*-ketoacids,[7] and cycloaddition reactions.[8] More recently, the utilization of cyclic sulfonylimine **1a** as a nucleophile through enamine generation has been accomplished. In 2011, Chen[9] and co-workers first applied these imine species via direct asymmetric Michael addition to *α*,*β*-unsaturated aldehydes. In the following years, Bode[10] and Ye[11] successfully developed the *N*-heterocyclic carbene catalyzed cyclization of corresponding imines with enals and *α*,*β*-unsaturated carboxylic acids, respectively. Both of these cascade sequences undergo a formal [3 + 3] cycloaddition pathway affording polycyclic adducts. In 2014, Zhang[12] and co-workers found that even simple aldehyde can also be cyclized with cyclic *N*-sulfonylimines by employing a *trans*-perhydroindolic acid catalysis to afford biologically important piperidine derivatives. They proposed an aza-Diels−Alder reaction pathway from a mechanistic perspective. Subsequently, they developed another approach to these piperidine derivatives through an organocatalytic tandem reaction between enals and *N*-sulfonylimines. In 2015, Chen[14] reported an alternative work to access spirocyclic sulfonamide architectures through formal [3 + 3] cycloadditions between ketones and cyclic *N*-sulfonyl-1-azadienes.

Inspired by studies, we envisioned that, by taking advantage of enamine−iminium tautomerism of *N*-sulfonylimines, the enamine intermediates generated from the corresponding imine could be trapped by an appropriate activated diene, and a novel [4 + 2] type cycloaddition[15] reaction should proceed to afford the desired spirocyclic compound. The enones can serve as a capable chiral aminodiene[16] through chiral primary amine catalysis in our design. To test the feasibility of our plan, we first explored the formal [4 + 2] cycloaddition reaction between cyclic *α*-methyl-*N*-sulfonylimine **1a** and linear enone **2a** catalyzed by a series of *tert*-leucine derived primary amine catalyst **4a**−**c** at ambient temperature.

Catalyst **4a** successfully delivered the cycloadduct **3a** which has a similar structure with the products in ref 14 as a single diastereoisomer albeit affording a relatively low conversion and poor enantioselectivity (Table 1, entry 1, 49% *ee*). A slightly better result was observed by the employment of **4b** as the catalyst (entry 2, 53% conversion, 65% *ee*). Changing the tertiary amine moiety to a secondary amine led to a significant improvement of the reaction rate and enantioselectivity (entry 3, full conversion, 96% *ee*). Ultimately, the *tert*-leucine derivative **4c** which had been found to effectively catalyze the stereoselective conjugate addition and cascade reactions of enones[17] was selected for the generation of the product **3a** according to both conversion and enantioselectivity.

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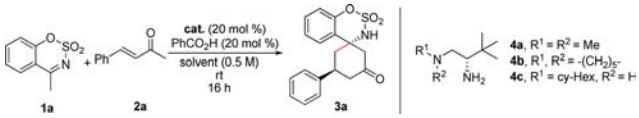
Table 1. Optimization of Reaction Conditions



1a 2a 3a

entry[a,b]	cat.	solvent	conv (%)[c]	ee (%)[d]
1	**4a**	toluene	12	49
2	**4b**	toluene	53	65
3	**4c**	toluene	full	96
4	**4c**	CH_2Cl_2	87	97
5	**4c**	EtOAc	full	97
6	**4c**	THF	full	96
7[e]	**4c**	EtOAc	87	95
8[f]	**4c**	EtOAc	41	89
9[g]	**4c**	EtOAc	n.r.	–
10[h]	**4c**	EtOAc	89	96

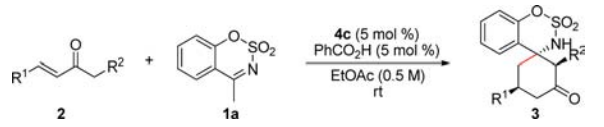
[a]Unless otherwise noted, all the reactions were performed with **1a** (0.1 mmol), **2a** (0.2 mmol), additive (0.02 mmol) and cat. (0.02 mmol) in solvent (0.2 mL). [b]All products were formed as a single diastereoisomer. [c]Determined by GC analysis. [d]Determined by HPLC analysis on a chiral stationary phase. [e]$PhCO_2H$ was replaced by $TsOH{\cdot}H_2O$. [f]No additive was added. [g]Reaction was carried out with $PhCO_2H$ (0.04 mmol). [h]$PhCO_2H$ (0.005 mmol) and **4c** (0.005 mmol).

Then, we draw our attention to further optimization of other parameters. Changing the solvent to EtOAc improved the *ee* value slightly without any loss in conversion (entry 5). Apparently, a Brønsted acid additive exhibited great impact on the reaction. In the absence of catalytic benzoic acid, both the reaction rate and the enantioselectivity dropped significantly (entry 7). Meanwhile, no reaction occurred when the acid loading was increased to 40 mol % (entry 9). The ratio of catalyst **4c** and benzoic acid (1:1) was found to be optimal for the enamine−iminium tautomerism of *N*-sulfonylimine, which is very critical for the formal [4 + 2] cycloaddition reaction. Subsequently, a lowering of the catalyst loading was carried out. The catalyst still remained effective while its loading was down to 5 mol %. Thus, the optimized reaction conditions had been established (entry 10).

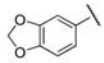
The optimized catalyst system displayed a broad scope of the *α*-methyl-*N*-sulfonylimines and conjugated enones. Highly enantioenriched cycloadducts were obtained with linear enones possessing *β*-aryl and hetero aryl substituents as well as linear aliphatic enones in high yields (Table 2, entries 1−12, 70−94% yield, 95−99% *ee*; entries 16−18, 75−93% yield, 97−99% *ee*). Specifically, structurally complex spiro-bridged-ring products **3m−3o** were obtained when cyclic enones were employed. Switching the substrate ratio from 2:1 (**2:1a**) to 1:1.5 improved the yields significantly (entries 13−14, 64−97% yield, 94−96% *ee*). Particularly, a higher catalyst loading was required for 2-cycloheptenone (entry 15, 70% yield, 96% *ee*).

The scope of the formal [4 + 2] cycloaddition reaction with respect to *α*-methyl-*N*-sulfonylimines including substituents at the phenyl ring and different ring size were investigated then. Presumably due to the poor solubility of imines possessing a five-membered ring, a prolonged reaction time were needed to obtain satisfactory yields (Scheme 1, **5a−5d**: 60−83% yield, 95−98% *ee*). Increasing the catalyst loading to 20 mol % gave the product **5e** in 68% yield and 97% *ee*. Variation of the phenyl ring involving electron-rich and -deficient substituents did not significantly affect the outcomes; the products **3s−3y** were

Table 2. Scope of Enones



2 1a 3

entry[a]	product	R^1	R^2	*t* (h)	yield (%)[b]	ee (%)[c]
1	**3a**	Ph	H	72	90	96
2	**3b**	*p*-ClC_6H_4	H	48	90	95
3	**3c**	*m*-BrC_6H_4	H	60	85	99
4	**3d**	*p*-BrC_6H_4	H	48	86	98
5	**3e**	*o*-FC_6H_4	H	48	85	96
6	**3f**	*p*-$OMeC_6H_4$	H	60	92	97
7	**3g**	*o*-$OMeC_6H_4$	H	60	89	96
8	**3h**	*p*-MeC_6H_4	H	60	94	96
9	**3i**	*p*-CNC_6H_4	H	72	84	99
10	**3j**		H	60	95	97
11	**3k**		H	72	70	99
12	**3l**	Me	H	72	77	96
13[d]	**3m**	-(CH_2)		72	64	94
14[d]	**3n**	-$(CH_2)_2$		72	97	96
15[d,e]	**3o**	-$(CH_2)_3$		48	70	96
16	**3p**	3-thienyl	H	72	86	99
17	**3q**	2-furanyl	H	72	75	97
18	**3r**	2-naphthyl	H	60	93	98

[a]Unless otherwise noted, all the reactions were performed with **1a** (0.2 mmol), **2** (0.4 mmol), benzoic acid (0.01 mmol), and **4c** (0.01 mmol) in EtOAc (0.4 mL). [b]Yields of isolated product following flash column chromatography on silica gel. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Reactions were performed with **1a** (0.3 mmol), **2** (0.2 mmol). [e]Benzoic acid (0.04 mmol) and **4c** (0.04 mmol).

obtained with good yields and excellent enantioselectivities (80−90% yield, 94−98% *ee*). The absolute configuration of adduct **3p** bearing a 3-thienyl group was determined by X-ray crystallographic analysis.[18] Based on the above results, we proposed a Michael−Mannich tandem reaction pathway for the formal [4 + 2] reaction. As indicated in Scheme 2, first, an enantioselective Michael addition reaction proceeded between sulfonyl enamine and conjugated iminium intermediate **A** which was formed through the condensation of enone and catalyst **4c**. Subsequently, the enamine intermediate **B** underwent an intramolecular Mannich reaction and then hydrolyzed to yield the product **3**.

Beyond the *N*-sulfonyl imines, methylene chromenes in situ generated from the corresponding perchlorates **7** were then successfully employed to this [4 + 2] type cycloaddition

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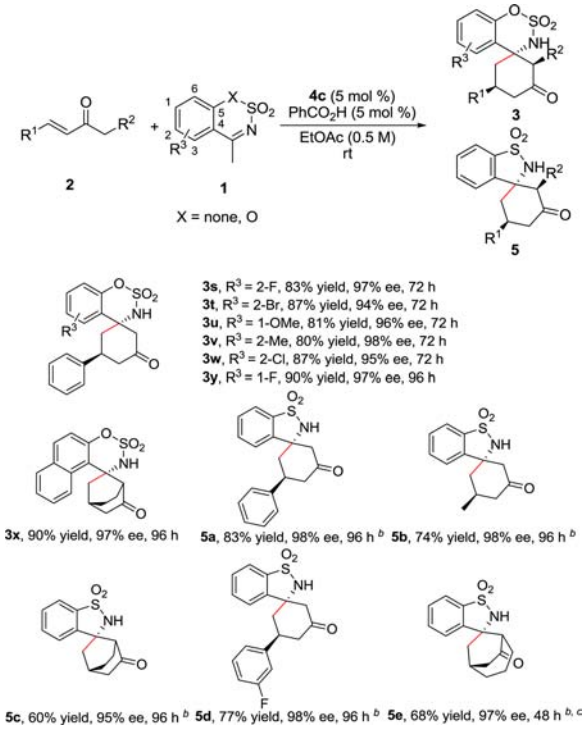
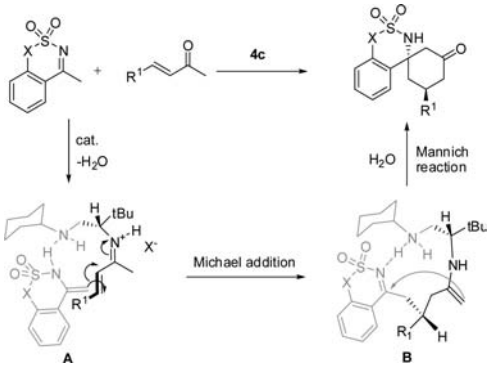
Scheme 1. Scope of *N*-Sulfonylimines[a]



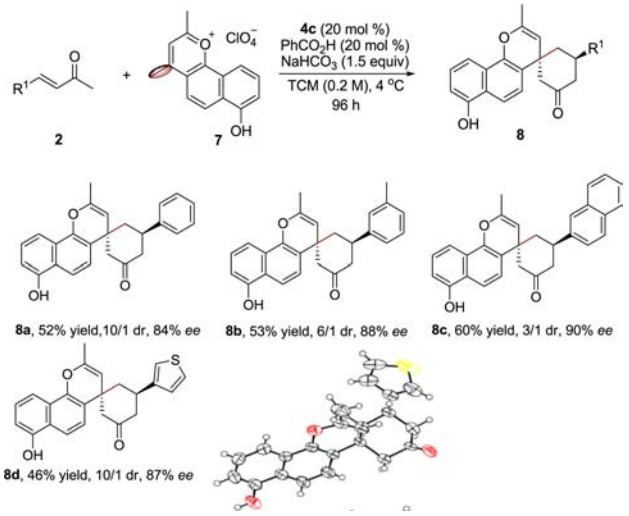
[a]Unless otherwise noted, all the reactions were performed with **1** (0.3 mmol), **2** (0.2 mmol), benzoic acid (0.01 mmol), and **4c** (0.01 mmol) in EtOAc (0.4 mL). [b]THF as the solvent. [c]Benzoic acid (0.04 mmol) and **4c** (0.04 mmol).

Scheme 2. Proposed Reaction Pathway



reaction. Interestingly, a γ,ε-regioselective, instead of the α,β-regioselective, cycloaddition reaction with different substituted linear enones was accomplished. This strategy also provided a capable alternative to afford the desired spiro-compounds **8** containing a chromene motif which usually appears in bioactive molecules.[19] It is noteworthy that the powerful catalyst **4c** still promoted the reaction effectively while a higher loading was needed (20 mol %). Generally, moderate yields and good to excellent enantioselectivities were obtained (Scheme 3). Specifically, a poor dr was obtained when 2-naphthyl was employed (**8c**, 3/1 dr). Unfortunately, no reaction occurred when cyclic enone was applied. The absolute configuration of product **8d** bearing a 3-thienyl group was determined by X-ray crystallographic analysis. We also believe that this [4 + 2] type reaction underwent a Michael−Michael tandem reaction pathway.

Scheme 3. Scope of Formal [4 + 2] Cycloaddition Reaction[a]



[a]Unless otherwise noted, all the reactions were performed with **2** (0.1 mmol), **7** (0.2 mmol), benzoic acid (0.02 mmol), sodium bicarbonate (0.15 mmol), and **4c** (0.02 mmol) in TCM (0.5 mL). Diastereomeric ratio was determined by crude ^{1}H NMR analysis.

In summary, we have developed an unprecedented formal [4 + 2] cycloaddition reaction of *N*-sulfonylimines and enones for the one-step enantioselective synthesis of stereochemically complex spiro and bridged rings. Additionally, an unexpected γ,ε-regioselective cycloaddition reaction was realized by employing the methylene chromene in situ generated from its perchlorate as the dienophile. The powerful *tert*-leucine derived primary amine promoted both of the reactions effectively and displayed a wide scope of both imine and enone substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02667.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(18) See Supporting Information. CCDC 1419090 (**3p**) and 1419089 (**8d**) contain the supplementary crystallographic data for this paper. They can be obtained from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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