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Organocatalytic asymmetric desymmetrization: efficient construction of spirocyclic oxindoles bearing a unique all-carbon quaternary stereogenic center *via* sulfa-Michael addition†

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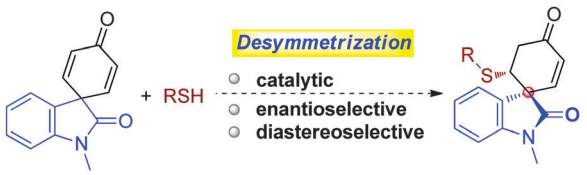
An unprecedented enantioselective desymmetrization of spiro cyclohexadienone oxindoles has been developed successfully *via* organocatalyzed asymmetric SMA, which provides facile access to spirocyclic oxindoles bearing a unique all-carbon quaternary stereogenic center with excellent levels of stereoselectivity.

Spirocyclic oxindoles widely occur in a large number of natural products and biologically active molecules,[1] especially those bearing a unique all-carbon quaternary stereogenic center at the C-3-position.[2] With the development of asymmetric catalysis, the past decade has witnessed great progress in the construction of the tetrasubstituted carbon stereogenic center at the C-3 position of oxindoles, which was popularly carried out through asymmetric addition reactions of 3-substituted oxindoles employing various types of chiral metal catalysts[3] and organocatalysts.[4] Enantioselective desymmetrization is an efficient and economical protocol to generate enantiomerically enriched and highly functionalized compounds bearing multiple stereogenic centers, and this strategy is effected by differentiation of two enantiotopic groups on the readily available symmetric or prochiral molecules.[5,6] Although impressive advances have been made in the catalytic asymmetric synthesis of spirocyclic oxindoles, to our knowledge, a desymmetrization strategy has never been applied in the synthesis of such motifs so far. Chiral sulfur-containing compounds also have important applications in many areas of chemistry and biology, for example, serving as antibiotics, ligands for metal-based catalysts, catalysts themselves, and chiral auxiliaries.[7] In sharp contrast to the well-documented approaches to access either optically active oxindole compounds[2] or chiral sulfur-containing compounds,[8] the development of an effective method for the construction of spirocyclic oxindoles bearing a unique all-carbon quaternary and a contiguous sulfur-substituted tertiary stereogenic center remains not only a demand for biochemists and medicinal chemists, but also a challenge for synthetic organic chemists. We envisioned that excellent stereoselective control achieved in catalytic asymmetric sulfur-Michael addition reactions rendered them well suitable for the facile access to highly functionalized spirocyclic oxindoles containing a unique all-carbon stereogenic center *via* enantio-selective desymmetrization of prochiral spiro-[cyclohexadienone-oxindole] (Scheme 1). In this communication, we reported the first desymmetrical construction of chiral spirocyclic oxindoles bearing two contiguous stereogenic centers *via* a highly efficient asymmetric sulfa-Michael addition reaction.

Considering the significant role of acid–base bifunctional organocatalysts[9] in asymmetric catalysis, we reasoned that an amine–thiourea catalyst could efficiently enhance the nucleophilicity of the thiols and simultaneously activate the conjugated double bond in the prochiral spiro-[cyclohexadienone-oxindole] through hydrogen bonding interactions with the carbonyl group, and therefore generate the two contiguous stereogenic centers with high stereoselective control. Hence, we initiated our study by evaluating the reaction of spiro-[cyclohexadienone-oxindole] **1a** with thiophenol **2a** in DCM at room temperature with the fine-tunable amine–thiourea catalyst developed in the lab recently.[10] To our gratification, the reaction was finished smoothly in less than 20 h with catalyst **I-a**, affording the desired adduct **3aa** as a single diastereomer (>20 : 1 dr) although the enantioselectivity is pretty low (Table 1, entry 1). Encouraged by the promising results, a series of fine-tunable bifunctional amine–thiourea catalysts **I** were subsequently screened. Among the tested bifunctional amine–thiourea catalysts, **I-d** was revealed to be the best



Scheme 1 Enantioselective desymmetrization of prochiral spirocyclic oxindoles *via* SMA.

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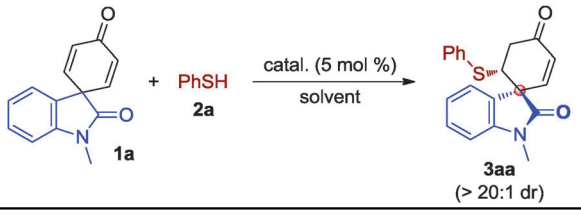
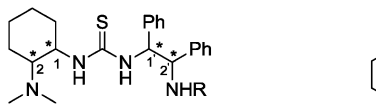
† Electronic supplementary information (ESI) available: Experimental section. CCDC 932106. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc42587h

Table 1 Screening studies of enantioselective desymmetrization of spiro cyclohexadienone oxindole **1a** *via* organocatalytic asymmetric SMA[a]

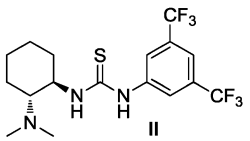


Entry	Catal.	Solvent	T (°C)	Yield[b] (%)	ee[c] (%)
1	**I-a**	CH_2Cl_2	rt	86	18
2	**I-b**	CH_2Cl_2	rt	85	30
3	**I-c**	CH_2Cl_2	rt	81	20
4	**I-d**	CH_2Cl_2	rt	89	74
5	**II**	CH_2Cl_2	rt	88	65
6	**III**	CH_2Cl_2	rt	75	59
7	**IV**	CH_2Cl_2	rt	79	72
8	**V**	CH_2Cl_2	rt	81	−61
9	**VI**	CH_2Cl_2	rt	72	−68
10	**I-d**	Et_2O	rt	67	47
11	**I-d**	THF	rt	75	52
12	**I-d**	EtOAc	rt	72	54
13	**I-d**	PhMe	rt	85	46
14	**I-d**	$CHCl_3$	rt	96	74
15[d]	**I-d**	$CHCl_3$	−20	92	84

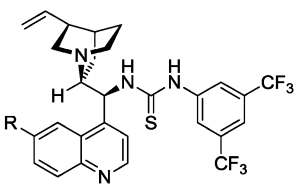
[a] All reactions were carried out with 0.20 mmol of **1a** and 0.22 mmol of **2a** in 0.5 mL solvent in 10–18 h. [b] Isolated yield. [c] dr was determined by crude ^{1}H NMR and ee was determined by HPLC analysis. [d] In 16 h.



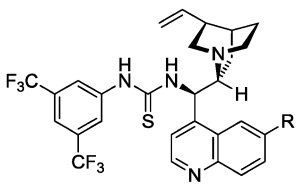
(1*R*,2*R*,1'*S*,2'*S*)-**Ia**: R = Ts
(1*R*,2*R*,1'*R*,2'*R*)-**Ib**: R = Ts
(1*R*,2*R*,1'*R*,2'*R*)-**Ic**: R = Ms
(1*R*,2*R*,1'*R*,2'*R*)-**Id**: R = 3,5-$(CF_3)_2C_6H_3SO_2$



II



III: R = H;
IV: R = MeO

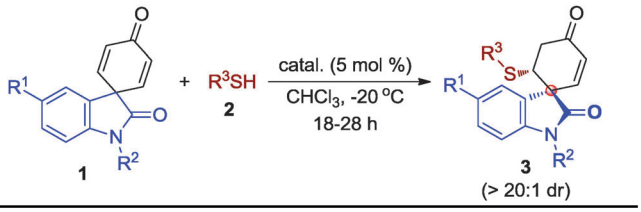


V: R = H;
VI: R = MeO

catalyst in terms of diastereoselectivity and enantioselectivity (entries 1–4). Other chiral bifunctional amine–thiourea catalysts derived from 1,2-diaminocyclohexane or cinchona alkaloid[11] were also tested in this transformation, producing the desired adducts with a little lower ee (entries 5–9). Subsequent evaluation of solvent effects improved the enantioselectivity to 74% when chloroform was used as the solvent (entries 10–14). Reducing the temperature to −20 °C led to full conversion with >20 : 1 dr and 84% ee for the desymmetrical adduct within 16 h (entry 15).

With the optimized desymmetrization reaction conditions in hand, a series of experiments was performed to investigate the substrate scope for this sulfa-Michael addition. As summarized in Table 2, a wide array of aryl thiols reacted smoothly with spiro-[cyclohexadienone-oxindole] **1a** to afford the expected adducts in high yields and excellent diastereoselectivities and good to high enantioselectivities in the presence of 5 mol% of catalyst **I-d**. Aryl thiols bearing electron-rich (Table 2, entries 2–4), electron-neutral (entries 1),

Table 2 Substrate scope of enantioselective desymmetrization of spiro cyclohexadienone oxindoles *via* organocatalytic asymmetric SMA[a]



	1					
Entry	R^1	R^2	R^3	**3**	Yield[b] (%)	ee[c] (%)
1	H	Me (**1a**)	Ph (**2a**)	**3aa**	92	84
2[d]	H	Me (**1a**)	*o*-Me-C_6H_4 (**2b**)	**3ab**	85	83
3	H	Me (**1a**)	*p*-Me-C_6H_4 (**2c**)	**3ac**	85	82
4	H	Me (**1a**)	*m*-Me-C_6H_4 (**2d**)	**3ad**	83	82
5[d]	H	Me (**1a**)	*o*-F-C_6H_4 (**2e**)	**3ae**	77	88
6	H	Me (**1a**)	*p*-F-C_6H_4 (**2f**)	**3af**	85	88
7	H	Me (**1a**)	*m*-F-C_6H_4 (**2g**)	**3ag**	84	85
8	H	Me (**1a**)	*p*-Cl-C_6H_4 (**2h**)	**3ah**	95	86
9	H	Me (**1a**)	1-Naphthyl (**2i**)	**3ai**	86	92
10	H	Me (**1a**)	2-Naphthyl (**2j**)	**3aj**	89	88
11	H	Me (**1a**)	2-Thienyl (**2k**)	**3ak**	83	95
12	MeO	Me (**1b**)	2-Naphthyl (**2j**)	**3bj**	85	84
13	Cl	Me (**1c**)	2-Naphthyl (**2j**)	**3cj**	80	84
14	Me	Me (**1d**)	2-Naphthyl (**2j**)	**3dj**	81	82
15	H	Bn (**1e**)	2-Naphthyl (**2j**)	**3ej**	82	92

[a] All reactions were carried out with 0.20 mmol of **1** and 0.22 mmol of **2** in 0.5 mL $CHCl_3$. [b] Isolated yield. [c] dr was determined by crude ^{1}H NMR and ee was determined by HPLC analysis. [d] In 48 h.

and electron-deficient substituents (entries 5–8) all worked well, providing optically active adducts in high yields (77–95%) and good to excellent enantioselectivities (82–88% ee). Remarkably, the substitution pattern of the arene had little effect on the stereoselectivity of the reaction, and *ortho*-substituted thiols **2b** and **2e** underwent this transformation leading to desired adducts **3ab** and **3ae** with 82% and 88% ee, respectively (entries 2 and 5). Heteroaromatic 2-thienyl thiol **2k** was also a viable substrate as the condensed-ring thiol in this transformation leading to the corresponding adducts in 95% ee (entry 11). The scope of this SMA reaction with respect to the prochiral electrophile partner was also explored. Spirocyclic oxindoles, which bear electron-donating or electron-withdrawing groups on the phenyl ring, proved to be excellent Michael acceptors for this reaction providing high diastereoselectivity and good enantioselectivity (entries 12–14). To our delight, *N*-benzyl substituted spirocyclic oxindole **1e** can be well tolerated in this catalytic system and lead to the desired adduct **3ej** in 82% yield and 92% ee (entry 15).

To determine the relative and absolute configuration of cycloadduct **3aj**, the derived oximes **4** were synthesized in a 1 : 1 *E*/*Z* ratio *via* a simple condensation protocol. X-ray analysis of the crystal of **4E** revealed the (1*R*,6*R*) configuration for the spiro all-carbon quaternary stereogenic center and the adjacent tertiary stereogenic center, and therefore also for the corresponding moieties in **3aj** (Fig. 1).‡

The optically active adducts contain functional groups that are amenable towards further transformations as exemplified in Scheme 2. Direct hydrogenation of the adduct **3aj** with MeOH as the solvent at room temperature in the presence of a catalytic amount of $Pd(OH)_2/C$ afforded compound **5** in 92% yield without loss of diastereomeric and enantiomeric excess. Upon treatment with two

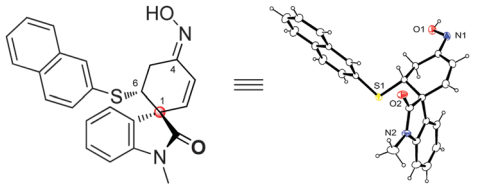
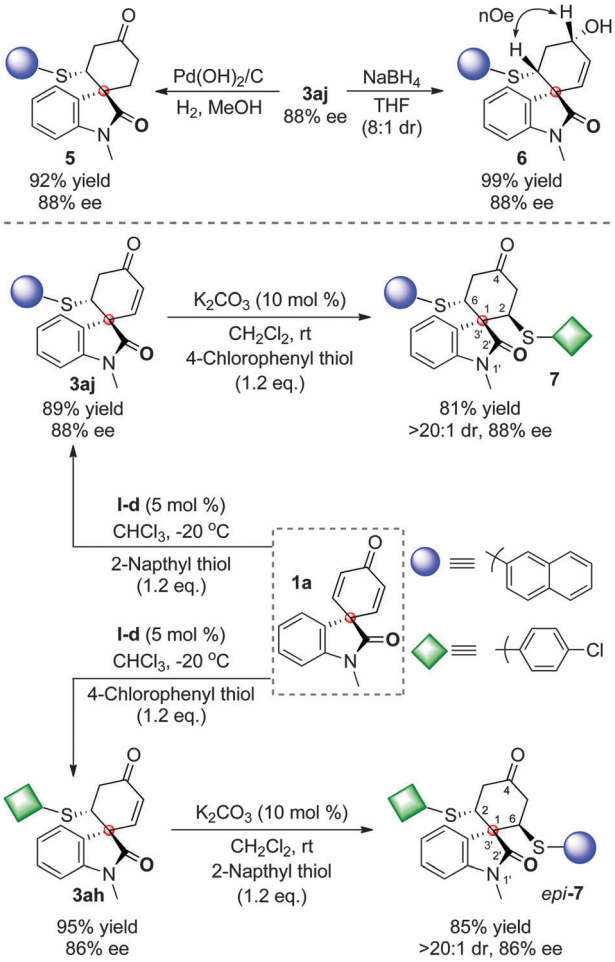


Fig. 1 X-ray structure of (1*R*,6*R*)-**4E**.



Scheme 2 Synthetic transformation and synthesis of compounds **7** and *epi*-**7** *via* double SMA by switching the adding sequence of thiols.

equivalents of $NaBH_4$ in THF at room temperature for 0.5 h, the carbonyl group in **3aj** was reduced successfully to afford the corresponding alcohol **6** containing one quaternary and two tertiary stereogenic centers in high yield and acceptable diastereoselectivity. Meanwhile, the α,β-unsaturated carbonyl moiety can be used for rapidly increasing the stereochemical and structural complexity of the SMA adducts **3**: subsequent achiral base-catalyzed SMA was successfully implemented, which provided **7** and *epi*-**7** with 2,6-*trans* configuration through simply switching the adding sequence of the two different thiols (see ESI† for more details).

In conclusion, we have developed the first catalytic asymmetric synthesis of spirocyclic oxindoles bearing a unique all-carbon quaternary and an adjacent tertiary stereogenic center *via* organocatalyzed enantioselective desymmetrization. This catalytic system exhibited high reactivity, excellent diastereo-selectivity, good enantioselectivity and broad substrate scope. The ready availability of the starting materials and the great importance of the chiral spirocyclic oxindole derivatives make the current methodology particularly interesting in synthetic chemistry. Further investigations of the scope and synthetic applications of this desymmetrization methodology are ongoing.

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Notes and references

‡ For (1*R*,6*R*)-**4E**: $C_{24}H_{20}N_2O_2S$, M_r = 400.48, T = 296 K, orthorhombic, space group $P2_12_12_1$, a = 8.8678(9), b = 9.3161(9), c = 24.972(3) Å, V = 2063.0(4) Å^3, Z = 4, 4277 reflections measured, 3493 unique (R_{int} = 0.0363) which were used in all calculations. The final wR_2 = 0.0851 (all data), flack χ = 0.02(7). CCDC 932106 (**4E**).

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