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Organocatalytic Construction of Spirooxindole Naphthoquinones through Michael/hemiketalization using *L*-Proline derived Bifunctional Thiourea

V Pratap Reddy Gajulapalli, Kanduru Lokesh, Manjunatha Vishwanath and Venkitasamy Kesavan*

**Michael/hemiketalization of 2-hydroxy-1,4-naphthoquinone to oxindole ketoester was studied using a series of chiral bifunctional organocatalysts. Good yields (up to 91%) and excellent enantioselectivities (up to 98%) were achieved by using Proline derived thiourea catalyst. This method provides an elegant synthetic route to access oxindole containing naphthoquinone derivatives.**

In chemical biology, researchers employ chemical probes to explore biological systems. Due to the unmet need of identifying small molecules binding partners for biological targets, access to compound collections with wide biological activities is highly desirable. This need of novel molecules to decipher cellular processes inspires synthetic chemists to construct new molecules around privileged structural motifs.[1] Creation of chiral molecular complexity around a biologically active scaffolds, is an ongoing challenge for synthetic organic chemists.[2] Enantiomerically pure spirooxindoles are being used to unravel biological pathways in recent years.[3a,b,f,d] Hence, heterocyclic spirooxindoles are widely targeted by synthetic chemists due to their prevalent presence in various pharmacologically active scaffolds and natural products.[3c,e,g,h] Intrigued by the biological activities of spirooxindoles, various groups have developed scaffold inspired enantioselective synthesis of novel spirooxindoles.[4] Development of these efficient methodologies make significant contribution in guiding the discovery of new chemical entities.

A large number of natural products and biologically active molecules contain quinine and naphthoquinone structural motifs.[5] Hence these derivatives have been explored for their antitumor,[6,7] antifungal,[8] molluscicidal,[9] anti-inflammatory,[10] trypanocidal,[11] and leishmanicidal biological activities.[12]

Intrigued by the pharmacological activities of spirooxindole motifs and naphthoquinone derivatives, we wish to synthesize molecules which comprise both of these pharmacophores. The hybrid molecule, spirooxindole naphthoquinone **3**, may inherit biological activities of both spirooxindole and naphthoquinone skeletons. Synthesis of **3** could be easily achieved by tandem Michael/hemiketalization of ketoester **1** with 2-hydroxy-1,4-naphthoquinone **2**. However identification of suitable catalyst to facilitate this transformation is a formidable task.

Organocatalysts are emerging as a method of choice to perform C-C bond formation for the efficient enantioselective assembly of complex molecular architecture enantioselectively.[13] Especially chiral bifunctional thioureas play a vital role in various asymmetric transformations in C-C bond formation reactions.[14] In our continuing efforts in identifying new catalysts for enantioselective transformations, we have developed a novel bifunctional thiourea and uncovered its potential in various asymmetric transformations.[15] Having demonstrated the capability of chiral proline thiourea in catalyzing C-C bond formation, we sought to explore the same catalyst for the assembly of novel spirooxindole naphthaquinones **3.**
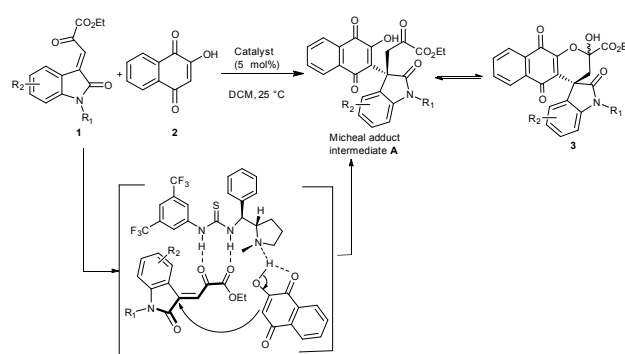
Scheme 1 Strategy for enanioselective synthesis of spirooxindole naphthoquinones.

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†Electronic Supplementary Information (ESI) available: CCDC 985882. For ESI and crystallographic data in CIF or other format See DOI: 10.1039/b000000x/

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Table 1 Organocatalyst screening of Michael reaction between 2-hydroxy-1,4-naphthaquinone and oxindole ketoester[a]
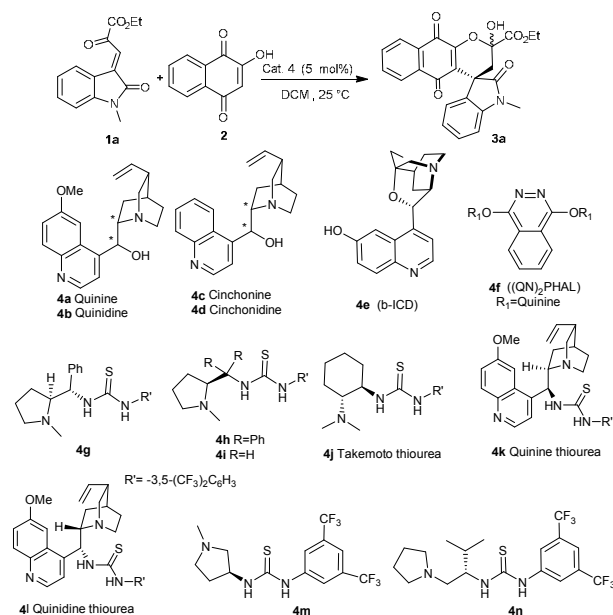
Entry	catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**4a**	2	81	-40
2	**4b**	2	84	-70
3	**4c**	2	82	-60
4	**4d**	2	82	27
5	**4e**	2	81	37
6	**4f**	2	86	-27
7	**4g**	5	81	98
8	**4h**	10	-	-
9	**4i**	5	86	-72
10	**4j**	4	80	-84
11	**4k**	3	81	-90
12	**4l**	3	83	83
13	**4m**	5	79	-75
14	**4n**	5	84	-93

[a] The reactions were carried out with **1a** (0.1 mmol), **2** (0.1 mmol), and catalyst **4** (0.005 mmol) in 1 ml of DCM at 25 °C. [b] Isolated yield. [c] Determined by chiral HPLC stationary phase. A minus sign indicate opposite enantiomer.

On the basis of our hypothesis (Scheme 1), ketoester **1** was reacted with 2-hydroxy-1,4- naphthoquinone **2** in the presence of various bases and bifunctional organocatalysts (5 mol%) at room temperature in dichloromethane. The results are summarized in the Table 1.

It is evident from these observations that although chiral bases efficiently catalyzed the reaction to afford the expected spirooxindole naphthoquinone **3a** in very good yields, the enantioselectivity of the reaction was found to be poor. Only quinidine **4b** yielded the expected product with a moderate enantiomeric excess of 70% (Table 1, entry 2). In screening bifunctional organocatalysts, we decided to firstly evaluate *L*-proline derived thiourea **4g** developed by our group. To our delight, organocatalyst **4g** efficiently transformed the reactants into spirooxindole naphthoquinone **3a** in very good
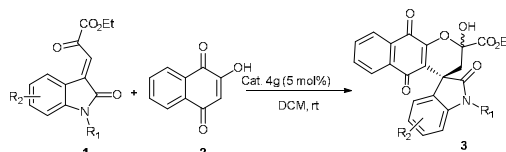
yield and excellent enantioselectivity (Table 1, entry 7). To demonstrate the requirement of stereogenic centre at the carbon bearing thiourea moiety, catalysts **4h** and **4i** were evaluated in the synthesis of spirooxindole naphthoquinone **3a**.

Diphenyl substitutions on stereogenic center suppressed the catalytic efficiency of **4h** entirely and no product formation was observed (Table 1, entry 8). Although employment of organocatalyst **4i** furnished the expected product in 86% yield and the enantimeric excess was only moderate (Table 1, entry 9). HPLC profile proved that the opposite stereoisomer was obtained when organocatalyst **4i** was employed. This shows that stereochemical outcome in assembling spirooxindole naphthaquinones, is controlled by the newly created stereogenic carbon which bears thiourea moiety.

The efficiency of widely used thioureas was also examined in constructing spirooxindole naphthoquinone **3a** (Table 1, entries 10-12). Takemoto **4j**, quinine **4k** and quinidine **4l** derived thioureas catalysed the transformation to afford the expected product **3a** in good yields. The enantioselectivity of the product **3a** was found to be little lower in case of Takemoto thiourea **4j** and quinidine thiourea **4l** (Table 1, entries 10 and 11), when compared with quinine derived thiourea **4k** (Table 1, entry 12). Formation of spirooxindole naphthoquinone **3a** was carried out in the presence of thioureas containing pyrrolidine ring **4m** and **4n** (Table 1, entries 13-14). The enantioselectivity got reduced, when thiourea **4m** was employed as the catalyst (Table 1, entry 13). Valinol derived thiourea **4n** furnished the product **3a** with 84% yield and 93% ee (Table 1, entry 14). It is evident from Table 1 that proline derived bifunctional organocatalyst **4g** is the most effective catalyst in furnishing the expected product with very good yield and excellent enantioselectivity (98% ee).

Encouraged by the successful construction of optically active spirooxindole naphthoquinone **3a**, we probed the scope of this reaction with the range of oxindole ketoesters **1**. We are glad to observe that irrespective of *N*1 substitution, the expected products were obtained with no significant loss of yield and enantioselectivity. *N*-benzyl **1b**, *N*-propargyl **1c** and *N*-allyl **1d** substitutions are well tolerated in the assembly of optically active spirooxindole naphthaquinones (Table 2 entries 2-4). This suggests that organocatalyst **4g** may interact with substrate **1** in the vicinity of ketoester part preferably than oxindole moiety (Scheme 1).

Under the optimized reaction conditions the generality of our protocol was tested using various 5-substituted oxindole ketoesters having electron-withdrawing, electron-donating and other substituents. We are pleased to note that the substitution pattern on aromatic ring had limited influence on enantioselectivity and there was no negative effect on yield. Various 5-halo substituted oxindole ketoesters **1e-1h** afforded the respective products **3e-3h** in excellent yields and enantioselectivities (Table 2, entries 5-8). Irrespective of electronic nature of 5-substituents on the aryl ring of oxindole ketoesters **1i** and **1j**, the completion of reactions were confirmed within 12 hours in very good yields and enantioselectivity (Table 2, entries 9 and 10).

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Table 2 Substrate scope of asymmetric Michael/ hemiketalization reaction using organocatalyst **4g**[a]

Entry	R₁, R₂	Product	Yield[b] (%)	ee[c] (%)
1	Me, H **1a**	**3a**	84	98
2	Bn, H **1b**	**3b**	85	97
3	Propargyl, H **1c**	**3c**	81	93
4	Allyl, H **1d**	**3d**	86	97
5	Me,5-F **1e**	**3e**	91	96
6	Me,5-Cl **1f**	**3f**	88	98
7	Me, 5-Br **1g**	**3g**	91	96
8	Me,5-I **1h**	**3h**	90	98
9	Me,5-OMe **1i**	**3i**	82	95
10	Me,5-OCF₃ **1j**	**3j**	86	90
11	Me, 5,7-dimethyl **1k**	**3k**	81	89
12	Me, 7F **1l**	**3l**	81	94
13	H,H **1m**	**3m**	78	50(60)[d]

[a] The reactions were carried out with **1** (0.1 mmol), **2** (0.1 mmol), and catalyst **4g** (0.005 mmol) in 1 ml of DCM at rt for 5h. [b] Isolated yield. [c] Determined using chiral HPLC stationary phase. [d] Reaction was carried out at 5 °C

Presence of 5,7-dimethyl **1k** and 7-F **1l** of oxindole ketoesters did not affect enantioselectivity and the desired products **3k** and **3l** were isolated in good yields (Table 2, entries 11 and 12). Oxindole ketoester which is devoid of substitutions of *N*1 atom underwent Michael addition followed by intramolecular cyclisation to yield the product **3m** in 78% yield and 50% ee. Lowering of temperature to 5 °C, the enantioselectivity was improved to 60%. Further lowering the temperature did not result in expected improvement of enantioselectivity. This result suggests that when there is no substituent on *N*1 atom, there may be a competitive binding of organocatalyst with oxindole moiety of ketoester as well as interacting with ketoester portion. Activation of both reactants may not be possible if the catalyst interacts with oxindole moiety instead of ketoester portion. Thus, the moderate ee observed for oxindole ketoester **1m** may be attributed to the competitive binding (Table 2, entry 13).

In order to show the potentiality of this methodology, the reaction was carried out with 2 mmol of **1a**, in the presence of 5 mol% of catalyst **4g** under the optimized conditions. The desired product **3a** was afforded with no loss in yield and 88% enantioselectivity. Thus we established an asymmetric protocol to construct a wide range of spiro oxindole frameworks with excellent enantioselectivity.

Table 3 Conversion of spirooxindole naphthoquinones **3** to spirooxindole dihydropyridine naphthaquinones **5**
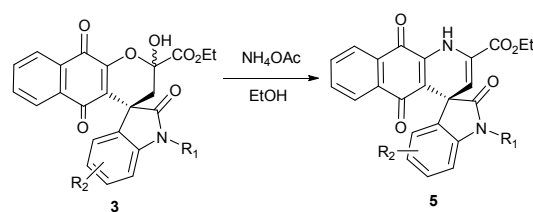
Entry	R₁, R₂	Product	Yield (%)[b]	ee (%)[c]
1	Allyl, H, **3d**	**5a**	89	89
2	Me, 5-I, **3h**	**5b**	80	96
3	Me, 5,7-dimethyl, **3k**	**5c**	85	80
4	Me, 7-F, **3l**	**5d**	90	98
5	Me, 5-Cl, **3f**	**5e**	82	97

[a] The reactions were carried out with **3** (0.1 mmol), NH₄OAc (0.15 mmol) in ethanol at rt for 6h, [b] Isolated yield. [c] Determined using chiral HPLC stationary phase.

Our efforts to crystallize synthesized compounds **3** did not yield fruitful result. Hence to demonstrate the potential application of these derivatives **3** and to determine absolute configuration at spiro centre, the compounds **3** were treated with ammonium acetate at ambient temperature in ethanol to yield spirooxindole dihydropyridine naphthoquinones derivatives **5** (Table 3, entries 1-5). To our delight structure of product **5b** was confirmed by single-crystal X-ray analysis and absolute configuration was determined to be "*R*" (Figure 1).

The reaction mechanism is proposed via Michael addition followed by hemiketalization catalyzed by bifunctional catalyst **4g** (Figure 2). Oxindole ketoester **1** is activated to nucleophilic attack through double hydrogen-bonding interactions with the thiourea group of catalyst **4g** and tertiary amine of catalyst deprotonates 2-hydroxynaphthaquinone **2**. The resulting ammonium ion forms another hydrogen bond with the enolate of **2**. The electron-rich α-carbon atom of 2-hydroxynaphthoquinone **2** predominantly attacks the *Re*-face of the electron-deficient oxindole ketoester **1** to generate the Micheal adduct intermediate **A** and subsequent intramolecular cyclization afforded the spirooxindole naphthoquinones **3** with "*R*" as absolute configuration at spirocentre of oxindole moiety (Figure 2).
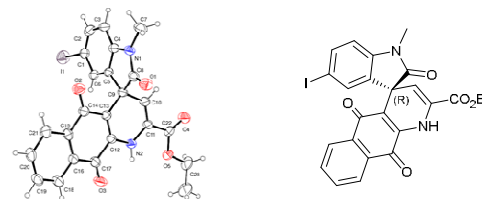
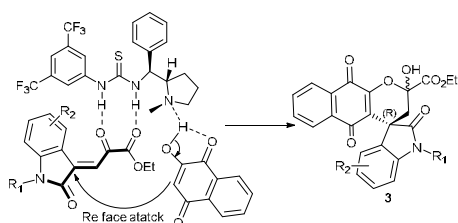**Figure 1** X-ray crystal structure of compound **5b**

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Figure 2 Plausible mechanism for Michael/hemiketalization reaction.

Conclusions

In conclusion, we have demonstrated highly efficient Michael/hemiketalization reaction for the construction of spirooxindole naphthoquinones with good yields (78-91%) and excellent enantioselectivities (up to 98% ee). To the best our knowledge, no enantioselective spirooxindole naphthoquinones have been reported previously. Proline based thiourea **4g** was identified as the efficient catalyst for this transformation.

Acknowledgements

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Graphical Abstract

upto 91% yield
upto 98% ee

upto 90% yield
upto 98% ee

5 mol% Catalyst
CH$_2$Cl$_2$, rt

NH$_4$OAc
EtOH, rt

Catalyst

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