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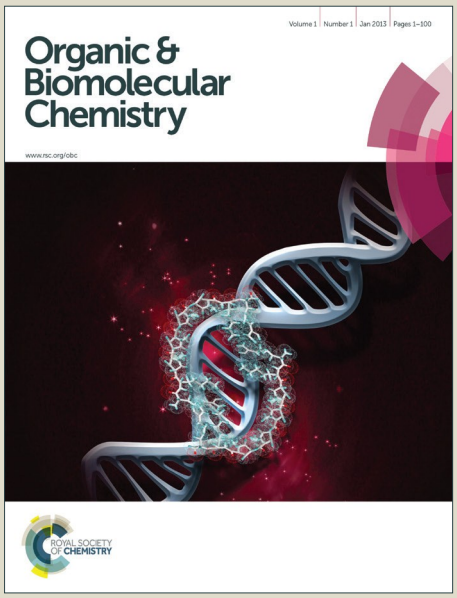




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# Catalytic enantioselective cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles with exocyclic α,β-unsaturated ketones en route to 3,2'-pyrrolidinyl bispirooxindoles

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**Cascade Michael/cyclization reactions between 3-isothiocyanato oxindoles and exocyclic α,β-unsaturated ketones are shown to proceed efficiently in the presence of a quinine-derived tertiary amino-squaramide catalyst and furnish 3,2'-pyrrolidinyl bispirooxindoles containing two spiro-quaternary and three contiguous stereocenters as a single diastereomer with excellent enantioselectivities (up to 99:1 er).**

The growing popularity of spirocyclic compounds as potential drugs as well as chiral ligands and catalysts has created a demand for their enantioselective synthesis.[1] Among various spirocyclic cores, the spirooxindole framework containing a pyrrolidine ring represents a very important class owing to their rich bioactivities.[2] In fact, the related bispirooxindole scaffold has recently drawn considerable interest not only due to its exclusive structural and stereochemical diversity but also as a result of its presence in a number of bioactive molecules (Figure 1).[3]

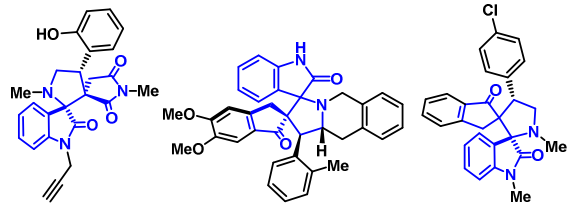
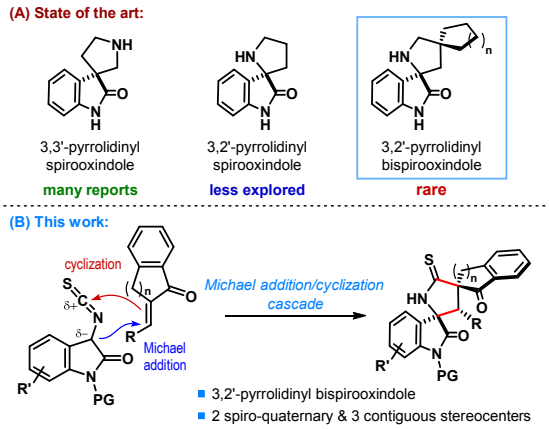



**Figure 1** Bioactive compounds bearing 3,2'-pyrrolidinyl bispirooxindole scaffold

Ever since the report by Yuan et al. in 2011,[4] 3-isothiocyanato oxindoles have been established as extremely efficient and versatile synthon for the enantioselective synthesis of spirooxindoles.[5] The increasing number of catalytic enantioselective reactions involving 3-isothiocyanato oxindole bears the testimony of its excellent reactivity profile. Owing to the ambiphilic nature of 3-isothiocyanato oxindoles, reactions with a variety of π-electrophiles have led to highly diastereo- and enantioselective synthesis of a wide range of densely functionalized spirooxindole derivatives.[6] In fact, the same strategy has also been adopted for the catalytic enantioselective synthesis of various bispirooxindole derivatives.[7,8]




**Scheme 1** Catalytic enantioselective synthesis of bispirooxindoles

Despite these advancements, construction of differently substituted and diversely functionalized spirooxindoles containing multiple contiguous stereogenic centers continues to be a formidable challenge. In addition, compared to the large number of reports describing the enantioselective synthesis of 3,3'-pyrrolidinyl spirooxindoles,[9] 3,2'-pyrrolidinyl spirooxindoles are relatively less explored.[10] Particularly the catalytic enantioselective syntheses of 3,2'-pyrrolidinyl bispirooxindoles are rather rare (Scheme 1A).[7]

As part of our ongoing research program directed toward the enantioselective synthesis of spirocyclic compounds, we became interested in developing an efficient route to 3,2'-pyrrolidinyl bispirooxindoles. We surmised that the reaction between 3-isothiocyanato oxindole and an electron-deficient exocyclic olefin would lead to the formation of

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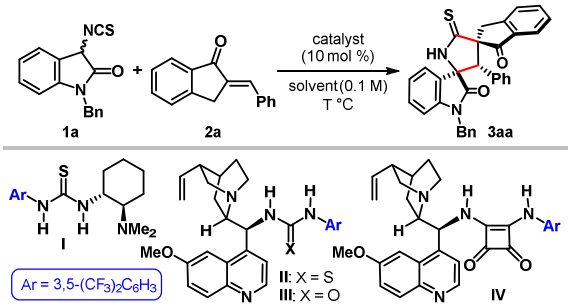
3,2'-pyrrolidinyl bispirooxindoles bearing two spiro-quaternary and three contiguous stereocenters in a single step (Scheme 1B). While similar reactions of 3-isothiocyanato oxindole with alkylidene heterocycles have been reported,[7] to the best of our knowledge, the same reaction with alkylidene carbocycles has not been explored till date. Here we report the first catalytic enantioselective cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles with exocyclic α,β-unsaturated ketones.

**Table 1** Reaction optimization[a]

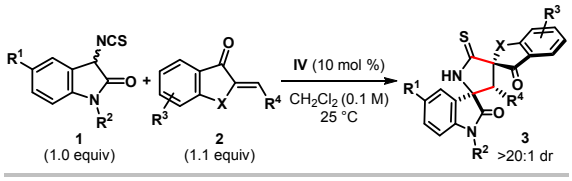



| Entry | Cat. | Solvent | T/°C | *t*/h[b] | dr[c] | er[d] |
|---|---|---|---|---|---|---|
| 1 | - | toluene | 25 | 1 | n.d. | - |
| 2 | **I** | toluene | 25 | 1 | 10:1 | 29:71 |
| 3 | **II** | toluene | 25 | 1 | 6:1 | 83:17 |
| 4 | **II** | toluene | 0 | 3 | 4:1 | 85:15 |
| 5 | **II** | toluene | –20 | 3 | 9:1 | 75:25 |
| 6 | **II** | toluene | –60 | 48 | >20:1 | 78:22 |
| 7 | **III** | toluene | 25 | 1 | 3:1 | 77:23 |
| 8 | **IV** | toluene | 25 | 1 | 10:1 | 97.5:2.5 |
| 9 | **IV** | $CH_2Cl_2$ | 25 | 1 | >20:1 | 98:2 |
| 10 | **IV** | $CHCl_3$ | 25 | 1 | >20:1 | 97.5:2.5 |
| 11 | **IV** | $PhCF_3$ | 25 | 1 | >20:1 | 95:5 |
| 12 | **IV** | 2-MeTHF | 25 | 1 | >20:1 | 96:4 |
| 13 | **IV** | TBME | 25 | 1 | >20:1 | 95.5:4.5 |
| 14[e] | **IV** | $CH_2Cl_2$ | 25 | 1.5 | >20:1 | 97:3 |

[a] Reactions were performed using 1.0 equiv of **1a** and 1.1 equiv of **2a** on a 0.05 mmol scale. [b] Time required for complete consumption of **1a**. [c] Diastereomeric ratio (dr) as determined by $^1$H NMR analysis of the crude reaction mixture; n.d. = not determined. [d] Enantiomeric ratio (er) as determined by HPLC analysis using a chiral stationary phase. [e] Reaction using 5 mol % catalyst. TBME = *tert*-Butyl methyl ether.

In view of the success of bifunctional hydrogen bonding catalysts[11] in related cascade reactions of 3-isothiocyanato oxindoles,[5-7] we decided to commence our investigation with such catalyst candidates. *N*-Benzyl-3-isothiocyanato oxindole **1a** and (*E*)-β-benzylidene-α-indanone **2a** were chosen as the model substrates, which were expected to undergo Michael addition/cyclization cascade and generate a bispirooxindole derivative containing two spiro-quaternary and three contiguous stereogenic centers (Table 1). The said cascade reaction indeed took place in toluene at 25 °C, in the absence of any catalyst, within an hour to produce the desired bispirooxindole **3aa** (entry 1). Under identical reaction conditions, 10 mol % of Takemoto catalyst[11e] (**I**) promoted the formation of **3aa** with good diastereoselectivity but with modest enantioselectivity (entry 2). Quinine-derived thiourea **II**, in contrast, appeared to be more enantioselective but less

**Table 2** Substrate scope[a]




(A)

| R | t/h | Yield (%) | er |
|---|---|---|---|
| Ph (**3aa**) | 2 | 94 | 98:2 |
| 2-$FC_6H_4$ (**3ab**) | 5 | 96 | 97:3 |
| 3-$FC_6H_4$ (**3ac**) | 5 | 96 | 98:2 |
| 4-$FC_6H_4$ (**3ad**) | 5 | 94 | 98:2 |
| 3-$ClC_6H_4$ (**3ae**) | 2 | 93 | 98:2 |
| 4-$BrC_6H_4$ (**3af**) | 2 | 92 | 97:3 |
| 4-$MeC_6H_4$ (**3ag**) | 2 | 85 | 97.5:2.5 |
| 4-(*i*-Pr)$C_6H_4$ (**3ah**) | 2 | 94 | 96:4 |
| 4-$OMeC_6H_4$ (**3ai**) | 2 | 94 | 94.5:5.5 |
| 3,4-$(OMe)_2C_6H_3$ (**3aj**) | 2 | 93 | 95:5 |
| 4-$CF_3C_6H_4$ (**3ak**) | 5 | 88 | 99:1 |
| 3-$NO_2C_6H_4$ (**3al**) | 2 | 97 | 98.5:1.5 |
| 4-$NO_2C_6H_4$ (**3am**) | 3 | 92 | 98.5:1.5 |
| $C_6F_5$ (**3an**) | 2 | 95 | 96:4 |
| 2-Furyl (**3ao**) | 1 | 94 | 90:10 (97:3) |
| 2-Thienyl (**3ap**) | 3 | 86 | 93:7 |
| PhCH=CH (**3aq**) | 3 | 97 | 95.5:4.5 |
| *i*-Bu (**3ar**) | 5 | 94 | 83:17 |
| H (**3as**) | 2 | 97 | 98.5:1.5 |

3ao (CCDC 1492583)

(B)[b]

R = Cl (**3at**) 95% yield, 99:1 er
R = Br (**3au**) 95% yield, 98.5:1.5 er
R = F (**3av**) 96% yield, 98.5:1.5 er
**3ay**[c] 88% yield, 79:21 er
**3aw** 96% yield, 97.5:2.5 er
**3ax** 95% yield, 99:1 er
**3az** 97% yield, 97:3 er

(C)[b]

R = Me (**3ba**) 94% yield, 98:2 er
R = *n*-Pr (**3ca**) 91% yield, 97:3 er
R = PMB (**3da**) 96% yield, 97:3 er
**3ea** 94% yield, 97:3 er

[a] Reactions were performed on a 0.1 mmol scale. Yields correspond to the isolated yield. Diastereomeric ratio (dr) was determined by $^1$H NMR analysis of the crude reaction mixture and found to be >20:1 in all the cases. Enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase. Values in the parenthesis indicate er of the product after a single recrystallization. [b] Reaction time = 2-3 h. [c] Reaction time = 24 h.

diastereoselective (entry 3). Conducting the reaction at lower temperature did not offer any beneficial effect on the enantioselectivity of the reaction (entries 4-6). While similar level of selectivities was observed with urea derivative **III** as the catalyst (entry 7), the corresponding squaramide derivative **IV**[12] furnished the product with 10:1 dr and 97.5:2.5 er (entry 8). A survey of solvents revealed $CH_2Cl_2$ to be the optimum and afforded the product as a single diastereomer with 98:2 er (entry 9). The reaction could also be carried out using only 5

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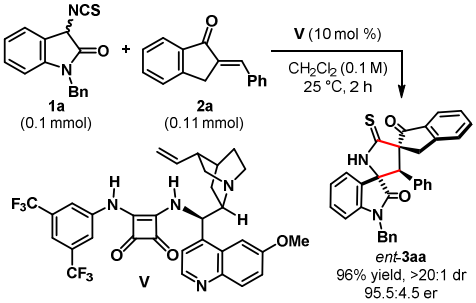
mol % of **IV**, when the product was obtained with 97:3 er (entry 14).

The scope of the Michael addition/cyclization cascade reaction was then evaluated under the optimized catalyst and reaction conditions (Table 1, entry 9). A variety of β-arylidene-α-indanones (**2a**-**n**) with diverse steric and electronic character were well tolerated and the desired products (**3aa**-**an**) were obtained as a single diastereomer in high yields and with good to excellent enantioselectivities (Table 2A). β-Heteroarylidene-α-indanones (**2o**-**p**) were also found to be suitable substrates and furnished the products (**3ao**-**ap**) in high yields and moderate to good enantioselectivities. α-Indanone-derived α,β,γ,δ-unsaturated ketone **2q** led to the formation of the desired product (**3aq**) in excellent yield and high er along with exclusive regioselectivity. β-Alkylidene-α-indanone (**2r**), however, turned out to be somewhat less reactive and delivered the product (**3ar**) with significantly reduced er. We were surprised to find that the product (**3as**) derived from unsubstituted β-methylene-α-indanone (**2s**) was generated as a single diastereomer with outstanding chemical and optical yield. The same conditions were found to be suitable for different β-arylidene-α-indanones (**2t**-**x**) having substituents on the aromatic ring of α-indanone (Table 2B). In all these cases, the products were formed, once again as a single diastereomer, in high yields with excellent enantioselectivities. When (*E*)-2-benzylidenecyclopentan-1-one (**2y**) was used as the substrate the corresponding product (**3ay**) was formed only with modest er. However, the product (**3az**) derived from (*Z*)-2-benzylidenebenzofuran-3-one was obtained in 97% yield with 97:3 er.

Our protocol was found to be equally efficient for various 3-isothiocyanato oxindoles (**1b-d**) with different *N*-substituents and also for 1,5-dimethyl derivative (**1e**) (Table 2C). The limited accessibility of 3-isothiocyanato oxindoles and their precursors deterred the demonstration of further scope with respect to differently substituted 3-isothiocyanato oxindoles. However, given the high yields and enantioselectivities observed for a variety of substrates, as shown in Table 2, similar outcome may be expected for differently substituted 3-isothiocyanato oxindoles.

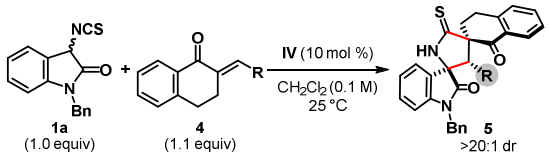
The relative and absolute configurations of **3ao** were established by the X-ray diffraction analysis of its single crystals obtained from $CHCl_3$ (Table 2A).[13] Assuming an analogous catalytic mechanism operates for the other substrates, the configurations of the other products were assigned as the same.




**Scheme 2** Access to the enantiomeric bispirooxindole

As exemplified in Scheme 2, the enantiomeric product of this cascade reaction could easily be prepared using quinidine-derived squaramide **V**, the pseudoenantiomer of catalyst **IV**. Under otherwise identical reaction conditions, *ent*-**3aa** was obtained in 96% yield and with 95.5:4.5 er.

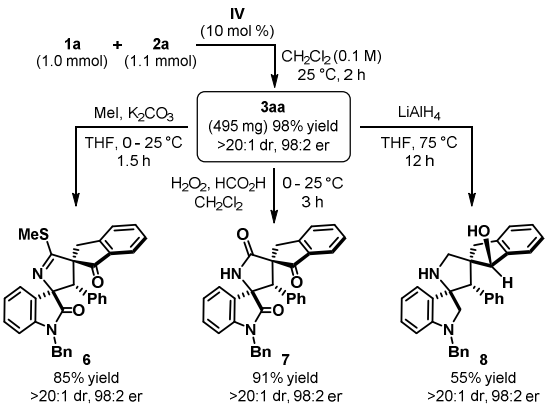
Encouraged by the excellent yields and stereoselectivities observed with a range of (*E*)-β-arylidene-α-indanones (Table 2-3), we wondered whether the exocyclic enones derived from α-tetralone could be employed in the synthesis of bispirooxindole derivatives. To our delight, the β-arylidene-α-tetralones underwent facile cascade Michael addition/cyclization reaction with 3-isothiocyanato oxindole **1a** under our optimized reaction conditions to deliver the desired bispirooxindoles (**5aa**-**ac**) as a single diastereomer in high yields with good to high er (Scheme 3).




| R | t/h | Yield (%) | er |
|---|---|---|---|
| Ph (**5aa**) | 5 | 93 | 96:4 |
| 4-$CF_3C_6H_4$ (**5ab**) | 7 | 94 | 96:4 |
| 4-$ClC_6H_4$ (**5ac**) | 8 | 91 | 94:6 |

**Scheme 3** Enantioselective Michael addition/cyclization cascade with β-arylidene-α-tetralones

The suitability of our protocol was then tested on a larger scale. Thus, a reaction between **1a** and **2a** on a 1.0 mmol scale furnished the product **3aa** in 98% yield with the same level of diastereo- and enantioselectivity as observed in the smaller scale reaction (Scheme 4).




**Scheme 4** Large-scale experiment and functionalization of the product

We next directed our efforts to demonstrate the synthetic utility of the resulting bispirooxindole derivatives. Methylation of **3aa** with methyl iodide under mild conditions resulted in bispirocyclic 2-methylthio-dihydropyrrole derivative **6** in 85% yield. Treatment of **3aa** with aqueous hydrogen peroxide under acidic conditions furnished the pyrrolidinone derivative **7** in high yield. Global reduction of **3aa** with lithium aluminium hydride led to the formation of bispiro[indoline-3,2'-pyrrolidine] **8** in 55% yield. The stereochemistry at the newly formed stereocenter was established through NMR spectroscopy.[14] It must be noted that all these transformations proceeded with complete stereochemical fidelity.

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The presence of a secondary amine functionality in a rigid stereogenic framework in **8** intrigued us to test its catalytic potential. Preliminary experiments revealed that **8** can indeed act as a catalyst for reactions proceeding via iminium activation.[14] However, both diastereo- and enantioselectivities remain modest at this stage. Our future efforts would focus on the structural modifications and functional diversifications of **8** to improve its catalytic activity and selectivity.

In conclusion, a cascade Michael addition/cyclization reaction has been developed for the highly enantioselective synthesis of 3,2′-pyrrolidinyl bispirooxindole derivatives. This cascade reaction between 3-isothiocyanato oxindoles and exocyclic α,β-unsaturated ketones is catalyzed by a quinine-derived bifunctional tertiary amino-squaramide catalyst. The products containing three contiguous stereogenic centers are obtained exclusively as a single diastereomer generally in excellent yields and enantioselectivities.

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13 CCDC 1492583 contains the crystallographic data for **3ao**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/pages/Home.aspx
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