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Organocatalytic Direct Asymmetric Aldol Reactions of 3-Isothiocyanato Oxindoles to Ketones: Stereocontrolled Synthesis of Spirooxindoles Bearing Highly Congested Contiguous Tetrasubstituted Stereocenters

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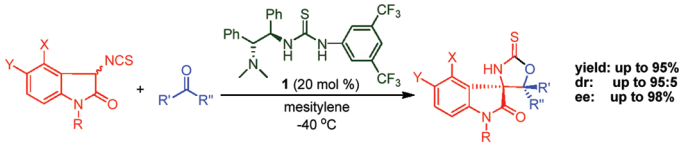
ABSTRACT



The first example of a direct catalytic asymmetric intermolecular aldol reaction of 3-isothiocyanato oxindoles to simple ketones with bifunctional thiourea-tertiary amine as catalyst is reported. This strategy provides a promising approach for the asymmetric synthesis of a range of enantioenriched spirocyclic oxindoles bearing two highly congested contiguous tetrasubstituted carbon stereocenters. Versatile transformations of the spirocyclic oxindole products into other structurally diverse spirocyclic oxindoles have also been demonstrated.

The catalytic asymmetric aldol reaction is one of the most important methods for the asymmetric formation of C−C bonds and has found widespread application in organic synthesis.[1] In this respect, in contrast to the remarkable advances that have been made with aldehydes as electrophiles,[1,2] the development of aldol additions to ketones was quite slow.[3] This state is attributable, at least in part, to the lower reactivity of ketones and the decreased steric discrimination compared to aldehydes.[4] Therefore, the direct asymmetric ketone−aldol reactions to date mainly focus on the activated ketone electrophiles[5] or intramolecular aldol additions based on enamine catalysis.[6] Furthermore, the intermolecular aldol reactions for simple

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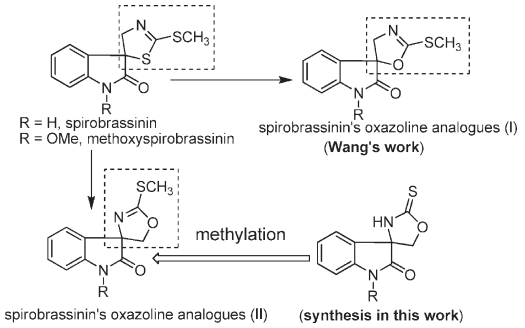
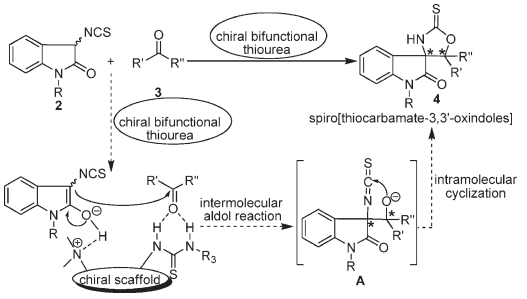
ketones as electrophiles are closely tied to either preformed enolates[7] or in situ-generated enolates with stoichiometric reducing reagents.[8] In these conditions, the direct catalytic asymmetric *intermolecular* aldol reactions of unmodified carbonyl compounds to simple ketones for the construction of optically active β-hydroxy (tertiary alcohols) carbonyl compounds should pose a far more difficult challenge.[9] To our knowledge, there is only one method for the direct asymmetric intermolecular aldol addition to simple ketones that has been developed to date, by Shibasaki and co-workers:[10] Mg Schiff base complexes catalyzed the direct aldol reaction/cyclization sequence of α-isothiocyanato esters to simple ketones under proton-transfer conditions. Herein, we report *the first organocatalytic direct asymmetric intermolecular aldol reactions of 3-isothiocyanato oxindoles to simple ketones with bifunctional thiourea-tertiary amines as catalysts*; this reaction readily afforded a new family of enantioenriched spirocyclic oxindoles bearing highly congested contiguous tetrasubstituted carbon stereocenters in up to 95% yield, 95:5 dr, and 98% ee.

Scheme 1. Spirobrassinin and Its Related Analogues



On the other hand, spirocyclic oxindoles are important subunits frequently found in biologically active compounds.[11] Spirobrassinin and its related analogues (Scheme 1),[12,13] a particular class of spirocyclic oxindole-type phytoalexins that exhibit potent antimicrobial, antitumor, and oviposition-stimulant biological activities, are awakening intense interest in the development of efficient methodologies for their synthesis and related biological studies.[12,14] Very recently, a highly efficient strategy for the construction of spirobrassinin oxazoline analogues (I) through the organocatalyzed asymmetric synthesis of spirocyclic thiocarbamates was established by Wang and co-workers (Scheme 1), and a promising antipyretic activity was revealed by the preliminary biological evaluation.[13] Taking the correlation between the molecular structural diversities and the potential biological activities into account, we notice that the synthesis of another family of spirobrassinin oxazoline analogues (II) has not been realized up until now (Scheme 1), let alone relevant further biological studies of them. We envisioned that this type of spirobrassinin oxazoline analogues (II) would be readily accessed via the methylation of the corresponding spiro[thiocarbamate-3,3′-oxindole] precursors (Scheme 1).[13]

Scheme 2. Strategy for the Direct Asymmetric Intermolecular Aldol Reaction of 3-Isothiocyanato Oxindoles **2** to Simple Ketones with Chiral Bifunctional Thiourea



On the basis of the above considerations and our recent success in asymmetric organocatalysis,[15] we reasoned that a new class of nucleophilic 3-isothiocyanato oxindoles **2** would be generated by installing an isothiocyanato group into the

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(16) For the synthesis of 3-isothiocyanato oxindoles **2**, see the Supporting Information.

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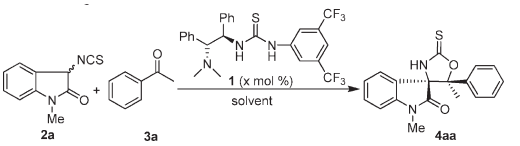
3-position of oxindoles.[16] Furthermore, we surmised that the asymmetric intermolecular aldol reaction of **2** to simple ketones would occur in the presence of chiral bifunctional thiourea-tertiary amines, and the subsequent intramolecular cyclization could yield a variety of spiro[thiocarbamate-3,3′-oxindoles] with two contiguous chiral quaternary carbon centers (Scheme 2).[17] To our delight, this working hypothesis (Scheme 2) was demonstrated by the initial experiment between 3-isothiocyanato oxindole **2a** and acetophenone (**3a**) catalyzed by DABCO to proceed smoothly for generating racemic **4aa** in CH_2Cl_2 at room temperature (Table 1). Among the chiral bifunctional thiourea-tertiary amine catalysts with diverse structural scaffolds surveyed, catalyst **1** turned out to be the most effective catalyst (for details, see the Supporting Information).

Afterward, our studies focused on a comprehensive screen of other reaction conditions in the presence of catalyst **1**. As shown in Table 1, probing of solvents revealed that mesitylene was better than other solvents in terms of enantioselectivity (entry 1 vs 2−7). Further investigation of catalyst loading in mesitylene was carried out; it was found that 20 mol % catalyst loading was beneficial to this process in view of both reaction yield and enantioselectivity compared to 10 mol % and 5 mol % catalyst loading (entry 9 vs 1 and 8). Lowering the reaction temperature resulted in a high, to 91%, ee without sacrificing the yield, although with an extension of the reaction time to 28 h (entry 10). Adding 4 Å molecular sieves (MS) as additive did not lead to any improvement to this reaction (entry 11). In addition, the probe into the concentration effects of the reaction revealed that a low concentration did not lead to an obvious increase in enantioselectivity or to a detrimental effect on the diastereoselectivity and yield (entries 12−13). Based on the comprehensive consideration of reaction time, yield, diastereoselectivity, and enantioselectivity, the optimal reaction conditions were established as shown in Table 1, entry 12.

With optimized conditions in hand, the scope of the reaction was investigated for 3-isothiocyanato oxindoles **2** and simple ketones **3**. As shown in Table 2, various acetophenone derivatives **3b**−**f** with either an electron-donating or electron-withdrawing group at the meta or para position of the aromatic ring gave their corresponding spiro[thiocarbamate-3,3′-oxindole] products in good yield, good diastereoselectivity, and high enantioselectivity (entries 1−5). Excellent results could be obtained smoothly by 2-acetonaphthone (**3g**) and its derivative **3h**, respectively (entries 6, 7). Aliphatic ketones **3i** and **3j** also proved to be amenable to this procedure, with high yields and moderate ee values (entries 8, 9). Additionally, the 3-isothiocyanato oxindole core may also be modified. Thus, both the benzo moiety (entries 10−14) and the N-protecting group may be changed as well (entry 15). For example, the reactions of different 3-isothiocyanato oxindoles **2b** and **2c** with various aryl methyl ketones proceeded smoothly to generate the desired products in good yield, dr, and ee values (entries 10−14). Furthermore, incorporating different protecting groups on the N1 of 3-isothiocyanato oxindole led to different effects on the reactivity and stereoselectivity (entry 15). However, when we further expanded the substrate scope to ortho-substituted

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	x	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	mesitylene	10	16	88	74:26	87
2	toluene	10	16	88	71:29	77
3	EtOAc	10	16	65	73:27	45
4	CH_2Cl_2	10	16	86	70:30	60
5	$CHCl_3$	10	16	90	70:30	71
6	THF	10	16	70	43:57	56
7	hexane	10	16	90	60:40	61
8	mesitylene	5	16	82	73:27	87
9	mesitylene	20	16	93	71:29	88
10	mesitylene	20	28	92	84:16	91[e]
11	mesitylene	20	28	90	84:16	91[e,f]
12	mesitylene	20	48	90	86:14	92[e,g]
13	mesitylene	20	108	90	87:13	93[e,h]

[a] Reaction was performed with **2a** (0.1 mmol), **3a** (0.2 mmol), and catalyst **1** (specified loading) in 2.0 mL of solvent at 0 °C, unless otherwise noted. [b] Isolated yields of both diastereoisomers. [c] Determined by HPLC. [d] Determined by chiral HPLC for the major diastereoisomer. [e] Run at −40 °C. [f] 4 Å MS (30 mg) was used. [g] In 4 mL of solvent. [h] In 8 mL of solvent.

acetophenone **3l** (entry 16) and propiophenone (**3m**) (entry 17), unfortunately, the corresponding products were observed only in trace amount.

A large-scale experiment was conducted under the optimized conditions to evaluate the applicability of our method. The reaction between **2a** and **3g** proceeded cleanly in 28 h on a 6.0 mmol scale (1.23 g of **2a**) and afforded **4ag** with excellent results (95% yield, 94:6 dr, and 97% ee) (Scheme 3). Meanwhile, the absolute configuration of the major stereoisomer of product **4ag** was unambiguously determined by X-ray crystallography; it contains a (C7*S*, C10*S*) configuration.[18] The absolute configuration for all other products was assigned by analogy.

Remarkably, the versatile transformations of **4ag** into other structurally diverse spirocyclic oxindoles, such as compounds **5**−**9** bearing two contiguous tetrasubstituted carbon stereocenters, were smoothly realized (for details, see Supporting Information). As illustrated in Scheme 4, the oxazolidinethione ring of **4ag** was readily transformed into the *N*-Boc oxazolidinone ring contained in spirocyclic oxindole compound **5**. With the removal of the Boc group in **5** under basic or acidic conditions, an N-unprotected oxazolidinone ring formed in compound **6**.[19a] Meanwhile, an alternative direct approach to the construction of **6** from **4ag** would be via oxidation reaction in a solution of 30% aqueous hydrogen peroxide and formic acid in 61% yield. In addition, the oxazolidinethione moiety of **4ag** also could be smoothly converted into a 2-alkylthio-oxazoline ring as in compounds

(18) CCDC 810232 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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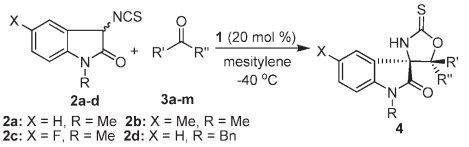
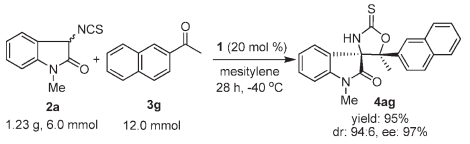
Table 2. Scope of the Reaction[a]



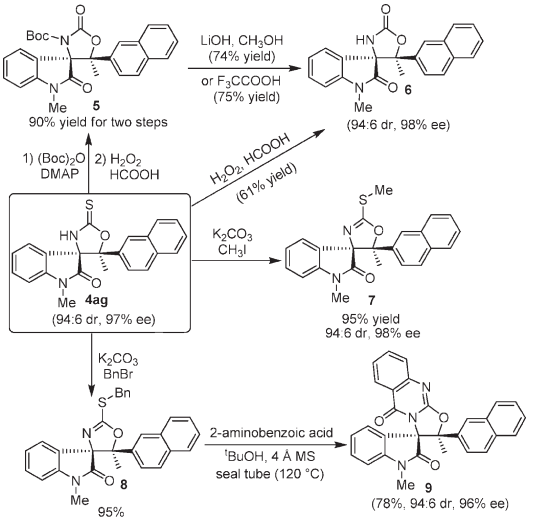
entry	2	3	time (h)	4/yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	R′ = 4-MeC$_6$H$_4$, R″ = Me (**3b**)	48	**4ab**/75	88:12	95
2	**2a**	R′ = 3-MeOC$_6$H$_4$, R″ = Me (**3c**)	28	**4ac**/81	82:18	93
3	**2a**	R′ = 4-BrC$_6$H$_4$, R″ = Me (**3d**)	28	**4ad**/95	77:23	89
4	**2a**	R′ = 4-FC$_6$H$_4$, R″ = Me (**3e**)	28	**4ae**/80	75:25	87
5	**2a**	R′ = 3-F$_3$CC$_6$H$_4$, R″ = Me (**3f**)	24	**4af**/92	70:30	91
6	**2a**	R′ = 2-naphthyl, R″ = Me (**3g**)	28	**4ag**/95	95:5	98
7	**2a**	R′ = 6-MeO-2-naphthyl, R″ = Me (**3h**)	48	**4ah**/90	90:10	98
8	**2a**	R′ = R″ = Me (**3i**)	48	**4ai**/92		64
9	**2a**	cyclohexanone (**3j**)	24	**4aj**/90		74
10	**2b**	R′ = Ph, R″ = Me (**3a**)	48	**4ba**/94	80:20	90
11	**2b**	R′ = 4-MeC$_6$H$_4$, R″ = Me (**3b**)	45	**4bb**/88	85:15	96
12	**2b**	R′ = 3-MeOC$_6$H$_4$, R″ = Me (**3c**)	48	**4bc**/80	79:21	93
13	**2b**	R′ = 3-ClC$_6$H$_4$, R″ = Me (**3k**)	48	**4bk**/95	75:25	93
14	**2c**	R′ = Ph, R″ = Me (**3a**)	48	**4ca**/82	70:30	85
15	**2d**	R′ = Ph, R″ = Me (**3a**)	28	**4da**/92	90:10	90
16	**2a**	R′ = 2-ClC$_6$H$_4$, R″ = Me (**3l**)	60	trace		
17	**2a**	R′ = Ph, R″ = Et (**3m**)	60	trace		

[a] Reaction was performed with **2** (0.15 mmol), **3** (0.30 mmol), and catalyst **1** (20 mol %) in 6.0 mL of mesitylene at −40 °C, unless otherwise noted. [b] Isolated yields of both diastereoisomers. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC for the major diastereoisomer.

Scheme 3. Large-Scale Experiment for the Synthesis of **4ag**



Scheme 4. Transformations of the Product **4ag** to Other Spirocyclic Oxindoles



7 and **8** according to a reported procedure,[19b] resulting in the formation of another family of spirobrassinin oxazoline analogues (II) (Scheme 1). Significantly, compound **8** could be further transformed into the new spirooxindole product **9** bearing an oxazolidinimine moiety.[19b] It is worth noting that no change takes place in the diastereoselectivity and enantioselectivity during the various transformations.

In conclusion, we have developed a direct catalytic asymmetric aldol reaction of 3-isothiocyanato oxindoles with simple ketones by using a bifunctional thiourea-tertiary amine as catalyst. This process provides a promising approach for the asymmetric synthesis of a range of structurally complex spirocyclic oxindoles bearing two highly congested contiguous tetrasubstituted carbon stereocenters in up to 95% yield, 95:5 dr, and 98% ee. Significantly, the potential of constructing more structurally diverse spirooxindoles has been revealed by the transformation of the oxazolidinethione moiety contained in the spirooxindole products into some other heterocyclic structures. We believe that the availability of these compounds will provide promising candidates for chemical biology and drug discovery. The biological evaluation of these compounds is currently underway in our laboratory.

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Supporting Information Available. Experimental details, characterization data for new compounds, X-ray crystal structure, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.