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Catalytic Asymmetric [3 + 2] Cyclization Reactions of 3-Isothiocyanato Oxindoles and Alkynyl Ketones Via an in Situ Generated Magnesium Catalyst

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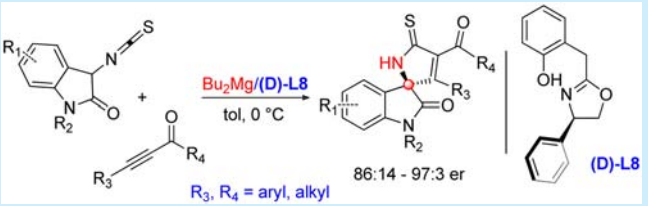
Supporting Information

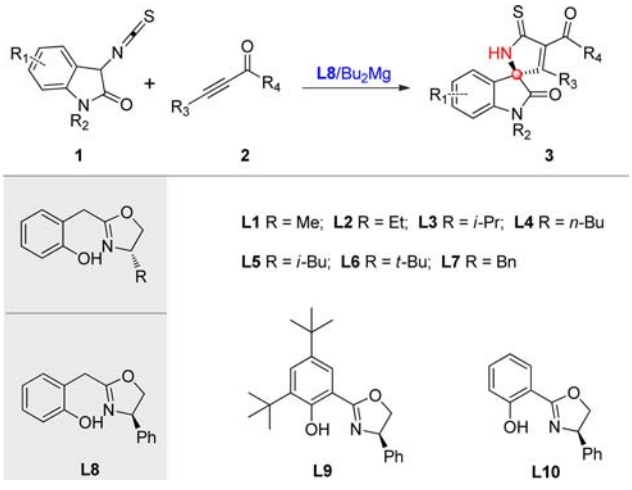
ABSTRACT: A highly enantioselective formal [3 + 2] cycloaddition reaction between 3-isothiocyanato oxindoles and alkynyl ketones is reported for the first time. An oxazoline−OH type chiral ligand derived from *o*-hydroxy-phenylacetic acid is employed to generate an effective magnesium catalyst in the current cyclization reaction and give serials of chiral spirooxindoles with good chemical yields and enantioselectivities.



Recently, 3-isothiocyanato oxindole has been recognized as a powerful synthon in the construction of chiral spirooxindole structures containing a nitrogen atom at the C-3 position. These are often present as important structural motifs in many natural products and synthetic biologically active compounds.[1,2] In 2011, Yuan and co-workers demonstrated the first example of catalytic asymmetric formal [3 + 2] cycloaddition of 3-isothiocyanato oxindoles with simple ketones.[3] Subsequently, a series of examples that applied 3-isothiocyanato oxindole as a privileged attractive reactant to construct chiral spirooxindoles were widely realized.[4] Although the catalytic asymmetrc reactions of 3-isothiocyanato oxindole with electron-deficient compounds, containing aldehydes, ketones, imines, and other types of unsaturated compounds, were successfully demonstrated respectively, the corresponding reaction of electron-deficient C≡C bond-containing compounds in this [3 + 2] cyclization has been rarely accomplished. To date, only one example has been reported using 2-butynedioic acid diesters as active reaction partners by Shi and coworkers.[5] However, in Shi's work, both ends of the C≡C bond had to be equipped with ester groups to impart high reactivity, which means that the reaction scope was relatively narrow. Herein, we tried to employ alkynyl ketones in the catalytic asymmetric [3 + 2] cyclization with 3-isothiocyanato oxindoles using an in situ generated magnesium catalyst recently designed by us.

As part of our continuing investigations of the asymmetric cyclization reactions of isothiocyanato esters[4c,g,l] and the development of in situ generated magnesium catalysts in asymmetric reactions,[6,7] we examined the reaction between 3-isothiocyanato oxindole **1a** and alkynyl ketone **2a** in the presence of a series of in situ generated magnesium catalysts. At the outset, we screened some chiral oxazoline−OH ligands derived from *o*-hydroxy-phenylacetic acid, which were

Scheme 1. Proposed Asymmetric [3 + 2] Cycloaddition of 3-Isothiocyanato Oxindoles with Alkynyl Ketones and Representative Chiral Ligands



developed by us recently,[8] in the current cyclization reaction. We found the reaction proceeded well under the catalytic conditions. Notably, however, the enantioselectivities varied greatly, even occurring with opposite stereoselectivities, when different substituents were introduced into the chiral oxazoline−OH ligands (Table 1, entries 1−8).[9] Fortunately, the enantioselectivity was strongly enhanced when a phenyl group was introduced into the oxazoline−OH ligand (Table 1, entry 8, 84:16 er). However, a further trial of other chiral ligands

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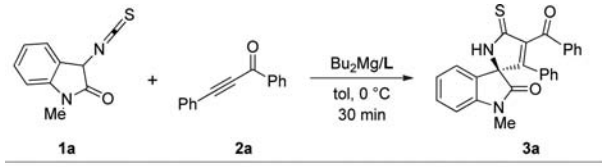
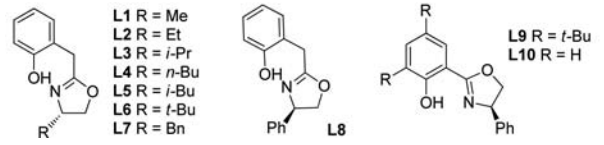
Table 1. Screening for the Optimized Conditions[a]





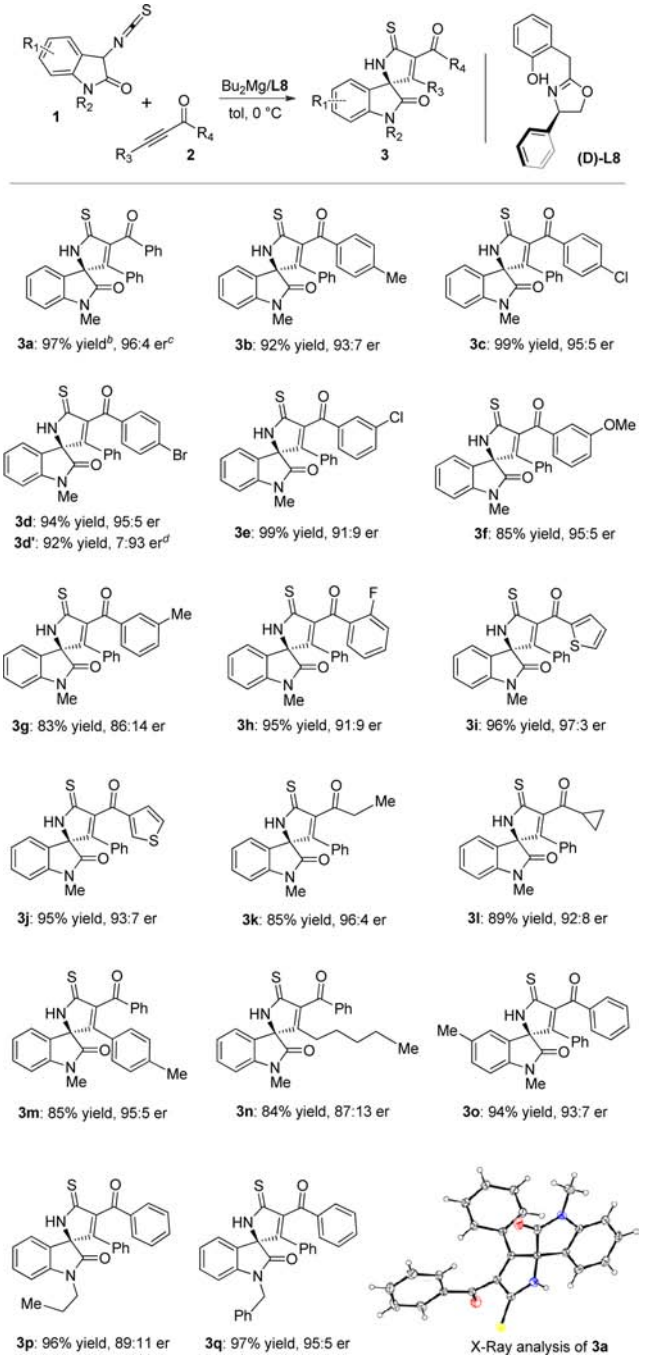
entry	L	method	yield (%)[b]	er (%)[c]
1	**L1**	Method A	93	54:46 (R)
2	**L2**	Method A	92	55:45 (R)
3	**L3**	Method A	89	66:34 (R)
4	**L4**	Method A	92	71:29 (R)
5	**L5**	Method A	90	31:69 (S)
6	**L6**	Method A	87	64:36 (R)
7	**L7**	Method A	91	48:52 (S)
8	**L8**	Method A	91	84:16 (R)
9	**L9**	Method A	90	53:47 (R)
10	**L10**	Method A	94	60:40 (R)
11[d]	**L8**	Method A	93	84:16 (R)
12	**L8**	Method B	92	87:13 (R)
13[e]	**L8**	Method B	90	85:15 (R)
14	**L8**	Method C	93	92:8 (R)
15	**L8**	Method D	93	94:6 (R)
16[f]	**L8**	Method D	86	90:10 (R)
17[g]	**L8**	Method D	97	96:4 (R)

[a]Reactions were performed with 0.11 mmol of **2a** and 0.10 mmol of **1a** in toluene (1 mL) in the presence of **L** (20 mol %) and Bu_2Mg (1.0 M in heptanes) (20 mol %) at 0 °C for 0.5 h. [b]Isolated yield. [c]Enantiomeric excesses were determined by chiral stationary phase HPLC. [d]100 mg of 4 Å MS was added. [e]Reaction was carried out in 2 mL of toluene with 0.11 mmol of **2a** and 0.10 mmol of **1a**. [f]Reaction was carried out at −10 °C. [g]0.20 mmol of **2a** and 0.10 mmol of **1a** was used. Method A: **1a** and **2a** were added together in one portion to the in situ generated catalyst. Method B: **1a** was added in one portion to the in situ generated catalyst, then **2a** was added dropwise over 2 min. Method C: **2a** was added in one portion to the in situ generated catalyst, then **1a** was added dropwise over 2 min. Method D: **2a** was added in one portion to the in situ generated catalyst, then **1a** was added dropwise over 15 min.

derived from the salicylic acid skeleton did not give improved results (Table 1, entries 9, 10). The addition of 4 Å MS into the reaction mixture made no difference to the enantioselectivity (Table 1, entry 11). To improve the er value of product **3a**, we tried to add one substrate more slowly. After a detailed screening process, we were pleased to find the enantioselectivity could be enhanced to 96:4 by extending the addition time of **1a** to 15 min and increasing the loading amount of **2a** to 2.0 equiv (Table 1, entry 17).[10]

Having established optimized methods for the current [3 + 2] cyclization reaction between 3-isothiocyanato oxindoles and alkynyl ketones, next the substrate scope of the current cyclization reaction was investigated. Aromatic enones **2** with various substituents at *para*-, *meta*-, and *ortho*-positions on the aromatic ring or heteroaryl enones were amenable to the [3 + 2] cyclization reactions (Scheme 2, **3a**−**3j**). Aliphatic ketones also engaged in the reactions, and reasonable yields and er values were observed (Scheme 2, **3k** and **3l**). Variation of R_3

Scheme 2. Substrate Scope of the Asymmetric [3 + 2] Cyclization Reaction[a]



[a]Reactions were performed with 0.20 mmol of **2** and 0.10 mmol of **1** in toluene (1 mL) in the presence of **L8** (20 mol %) and Bu_2Mg (1.0 M in heptanes) (20 mol %) at 0 °C for 0.5 h. [b]Isolated yield. [c]Enantiomeric excesses were determined by chiral stationary phase HPLC (OD-H; *n*-hexane/*i*-PrOH = 40/60; flow rate, 1.0 mL/min). [d]The reaction was carried out with (L)-**L8**.

from phenyl group to *p*-Me-Ph had no obvious effect on the chemical yield and enantioselectivity of the cyclization product **3m**, but when R_3 was changed to an alkyl group, the er value of product **3n** reduced to 87:13. Then several representative 3-isothiocyanato oxindoles were examined in the [3 + 2] cyclization reaction and provided the corresponding product with satisfactory results (Scheme 2, **3o**−**3q**). To prove the

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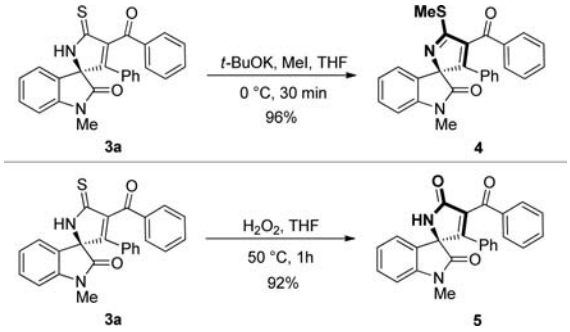
absolute configuration of the product, we recrystallized compound **3a** and determined this by X-ray crystallography studies. Moreover, the enantiomer product could be obtained by employing (L)-**L8** as a chiral ligand with similar results (Scheme 2, **3d′**).

Furthermore, product **3a** could be further transformed to other spirooxindole derivatives, as presented in Scheme 3,

Scheme 3. Transformations of the Conjugate Adducts



direct methylation of **3a** could provide **4** in good yield. Alternately, the C═S bond in **3a** could be smoothly converted into a C═O bond by an oxidation reaction employing H_2O_2 as a simple oxidant.

Finally, a possible mechanism for this [3 + 2] cyclization reaction is proposed on the basis of our recent work on the magnesium catalyst generated in situ from oxazoline−OH ligands and Bu_2Mg.[8] It is illustrated in Figure 1, which has the

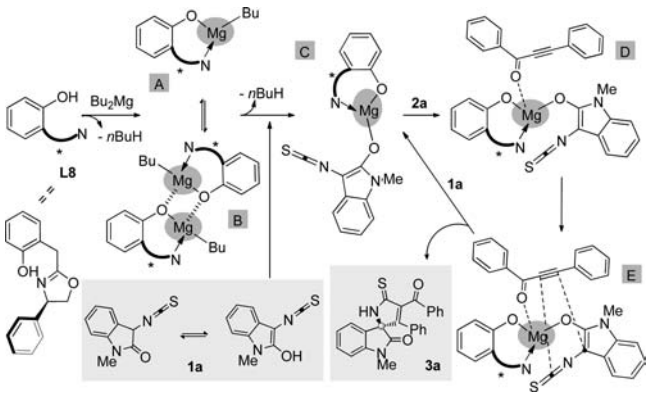


Figure 1. Proposed mechanism of the [3 + 2] cyclization reaction.

alkynyl ketone **2a** coordinating to the magnesium center in the manner shown to bring about the formal [3 + 2] cycloaddition process. Then another molecule of **1a** could participate in the process to allow the cyclization product to release and regenerate the precatalyst to allow the next catalytic cycle to proceed.

In summary, we have developed an enantioselective [3 + 2] cyclization reaction between 3-isothiocyanato oxindoles and alkynyl ketones for the first time. An in situ generated magnesium catalyst is employed and provides a series of chiral spirooxindoles in high yield and enantioselectivity. Further investigation of the in situ generated magnesium catalyst in other cyclization reactions is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02052.

CIF files of **3a** (CIF)

Experimental details, characterization data, X-ray crystal structure (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(10) We speculate the overloading of **2a** might coordinate to the metal center to give a more favorable chiral environment.

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