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# Isatin *N,N′*-Cyclic Azomethine Imine 1,3-Dipole and Abnormal [3 + 2]-Cycloaddition with Maleimide in the Presence of 1,4-Diazabicyclo[2.2.2]octane

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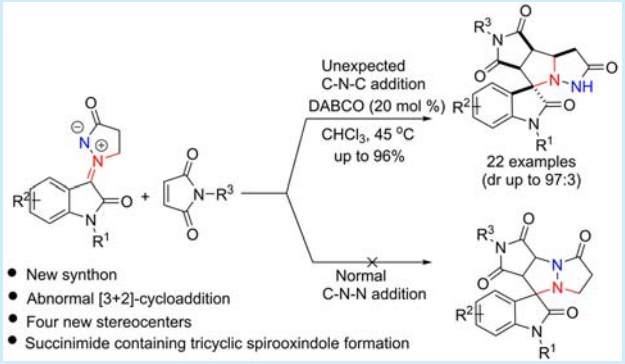
Supporting Information

**ABSTRACT:** A new isatin *N,N′*-cyclic azomethine imine synthon was devised, and an unexpected abnormal [3 + 2]-cycloaddition with maleimide catalyzed by 1,4-diazabicyclo-[2.2.2]octane (DABCO) has been disclosed. A variety of tricyclic spiropyrrolidine oxindoles bearing a dinitrogen heterocycle and succinimide scaffold were obtained in excellent yields (up to 96%) and diastereoselectivities (up to 97:3) under mild conditions.




1,3-Dipolar cycloaddition (1,3-DC) has been widely studied as one of the most powerful approaches for the construction of carbon−carbon and heterocycles from simple building blocks.[1] Until now, several 1,3-dipoles, such as azomethine ylides,[2] nitrones,[3] and carbonyl ylides,[4] have been studied. Among them, *N,N′*-cyclic azomethine imines, used as readily accessible and efficient 1,3-dipoles,[5−8] have been increasingly employed in cycloadditions for the synthesis of pyrazolones and the related dinitrogen-fused heterocyclic derivatives with significant biological activities[9] (Figure 1). Reviewing recent advances in this area, asymmetric metal-catalyzed and organocatalytic cycloadditions of *N,N′*-cyclic azomethine imines with a variety of dipolarophiles have been successfully developed.[7,8] However, the reported *N,N′*-cyclic azomethine imine 1,3-dipoles were mainly prepared by the condensation of pyrazolidin-3-one with aldehydes. Different sorts of azomethine imines for diversity of reactions and compounds are still underdeveloped and highly desirable. To the best of our knowledge, isatin *N,N′*-cyclic azomethine imine, devised as a new 1,3-dipole and a useful synthon in this work, has not been reported yet.

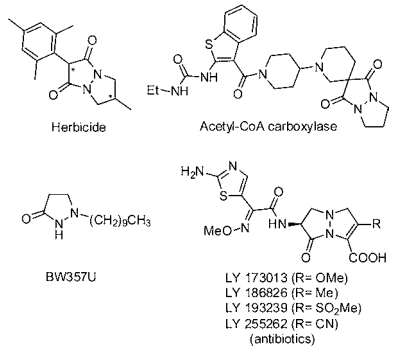



**Figure 1.** Selected examples of bioactive molecules with pyrazolone skeleton.

On the other hand, spirooxindole scaffolds, especially spiro heterocyclic oxindoles, have become the focus for many synthetic chemists recently, for their frequent occurrence in a wide range of natural products and pharmacological entities with diverse bioactive properties.[10] Accordingly, numerous elegant synthetic approaches have been developed for the construction of those structural skeletons over the past years.[11] Although spiro heterocyclic oxindoles fused with a five- or six-membered ring system at the C3-position have been well investigated, there are still limited reports on the synthesis of spiro heterocyclic oxindoles through *N,N′*-cyclic azomethine imines.[12] In 2013, Wang et al. disclosed the first asymmetric 1,3-dipolar cycloaddition of methyleneindolinones and azomethine imines catalyzed by a chiral bis-phosphoric acid bearing triple axial chirality.[12a] Later, they also developed a base-catalyzed formal [3 + 3]-annulation of azomethine imines with 3-isothiocyanatooxindoles.[12b] In 2014, Shi and co-workers

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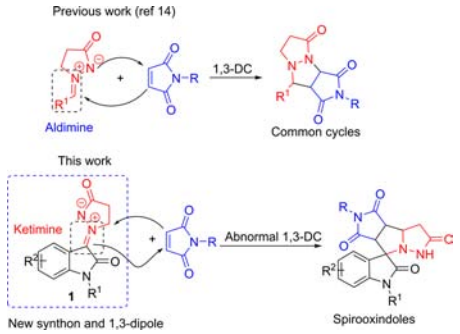
reported a novel one-pot tandem reaction of vinylcyclopropanes, 3-diazooxindoles, and maleimides in the presence of $[Pd_2(dba)_3CHCl_3]$.[12c] Afterward, Feng disclosed an asymmetric [3 + 2]-cycloaddition of methyleneindolinones with azomethine imines catalyzed by a *N,N′*-dioxide−$Mg(OTf)_2$ complex.[12d] In 2016, Zhao's group reported a 1,3-diplar cycloadditions of azomethine imines with iminooxindoles in the presence of CuI.[12e]

In view of the importance of pyrazolones and spirocyclic oxindoles and based on our continuing interest in the construction of spirooxindoles,[13] we devised a new 1,3-dipole based on isatin (shown as **1** in Scheme 1) and hope to use it as

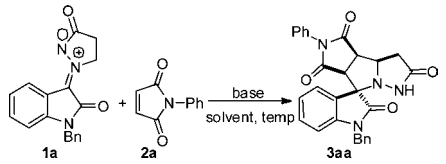
**Scheme 1. 1,3-Dipolar Cycloaddition of *N,N′*-Cyclic Azomethine Imines with Maleimides**




a new synthon for the construction of spirooxindoles with potential biological and pharmaceutical activities. During the development of a new [3 + 2]-cycloaddition, we started to investigate the model reaction of **1a** with maleimide **2a**. The reaction proceeded smoothly under mild conditions. Surprisingly, when we fully analyzed the spectra of the product after obtaining its single-crystal structure, we found that this reaction proceeded via an unexpected C−N−C [3 + 2]-cycloaddition, which was different from the previous report (Scheme 1).[14]

This abnormal observation prompted us to further study the reaction under various conditions (Table 1). Our studies were initiated in $CHCl_3$ with 1 equiv of $Et_3N$ at room temperature (25 °C). In the same reaction mode, the new and unexpected [3 + 2]-cycloaddition proceeded smoothly to provide the product in almost quantitative yield and good diastereoselectivity (Table 1, entry 1). After reaction temperature screenings, 45 °C was found to be optimal (Table 1, entry 2). Encouraged by those promising results, other bases were screened. 1,4-Diazabicyclo[2.2.2]octane (DABCO) gave better diastereoselectivity compared with DIPEA, DMAP, and $K_2CO_3$ (Table 1, entries 4−7) and was selected as the optimal base. Considering the lower solubility of the new 1,3-dipole in most organic solvents, solvent effects were then studied (Table 1, entries 8−13). Polarities of solvents slightly affected the yields but obviously changed the diastereoselectivities. $CHCl_3$ gave the best results and was selected as the optimal solvent (Table 1, entry 4). The diastereoselectivities significantly dropped in $CH_3CN$ and DMF (Table 1, entries 12 and 13). In particular, in toluene, the reaction became sluggish (Table 1, entry 10). When the base loading was reduced to 20 mol %, almost the same results were obtained (Table 1, entry 14). Higher loading of maleimide gave a better yield (Table 1, entry 15). Considering all of the active parameters, the optimal reaction conditions were established as 0.1 mmol of **1a** and 0.2 mmol of

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | base | solvent | temp (°C) | time (h) | yield[b] (%) | dr[c] |
|---|---|---|---|---|---|---|
| 1 | $Et_3N$ | $CHCl_3$ | 25 | 6 | 90 | 87:13 |
| 2 | $Et_3N$ | $CHCl_3$ | 45 | 2 | 95 | 89:11 |
| 3 | $Et_3N$ | $CHCl_3$ | 65 | 1 | 97 | 85:15 |
| 4 | DABCO | $CHCl_3$ | 45 | 3 | 88 | 93:7 |
| 5 | DIPEA | $CHCl_3$ | 45 | 10 | 98 | 81:19 |
| 6 | DMAP | $CHCl_3$ | 45 | 5 | 56 | 86:14 |
| 7 | $K_2CO_3$ | $CHCl_3$ | 45 | 4 | 84 | 90:10 |
| 8 | DABCO | $CH_2Cl_2$ | reflux | 1 | 98 | 86:14 |
| 9 | DABCO | DCE | 45 | 2 | 94 | 81:19 |
| 10 | DABCO | toluene | 45 | 20 | 98 | 90:10 |
| 11 | DABCO | THF | 45 | 2 | 97 | 83:17 |
| 12 | DABCO | MeCN | 45 | 2 | 99 | 72:28 |
| 13 | DABCO | DMF | 45 | 1 | 99 | 44:56 |
| 14[d] | DABCO | $CHCl_3$ | 45 | 10 | 82 | 93:7 |
| 15[d,e] | DABCO | $CHCl_3$ | 45 | 10 | 86 | 93:7 |

[a]Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and base (0.1 mmol) in 1 mL of solvent. [b]Yield of the diastereoisomeric mixture. [c]Determined by HPLC. [d]20 mol % loading of catalyst. [e]0.2 mmol of **2a** was used.

**2a** with 20 mol % of DABCO as catalyst in 1 mL of $CHCl_3$ at 45 °C (Table 1, entry 15).

Under the optimized reaction conditions, the generality for different substrates was further investigated (Scheme 2). Generally, most isatin *N,N′*-cyclic azomethine imines **1** and maleimides **2** were well tolerated. For most *N*-aryl and aliphatic maleimides **2**, good yields and diastereoselectivities were smoothly obtained. The position of substituents on the aryl ring delivered significant influence on the yields and diastereoselectivities. The *ortho*-substituted maleimide **2b** gave 71% yield with 48:36:16 dr (**3ab**) (Scheme 2), and **2c** delivered the product in 72% yield and 53:25:22 dr (**3ac**) (Scheme 2), probably due to the axial chirality.[15] Differently, only two diastereoisomers were detected when *meta*- and *para*-substituted maleimides were used (**3ad−an**) (Scheme 2). The *meta*-substituted maleimides gave better diastereoselectivities compared with the *para*-substituted counterparts (**3ad−ai** vs **3aj−an**) (Scheme 2). The electronic characteristics of the substituents were also studied, while only a slight impact on yields and diastereoselectivities was observed, regardless of the substituted positions (**3ab−an**) (Scheme 2). Disappointedly, the aliphatic maleimides **2o** and **2p** gave only moderate yields and diastereoselectivities. The scope of **1** was also studied (**3ba−ia**) (Scheme 2). *N*-Allyl **1c** afforded the product with excellent results (94%, dr = 92:8), while *N*-H **1b** cannot work well, and only a trace amount of product was detected. The substitutions, whether electron-withdrawing or -donating on the aromatic ring in *N,N′*-cyclic azomethine imine, gave excellent yields (92−96%) and diastereoselectivities (dr = 91:9−95:5). However, when $R^4$ was changed to a methyl group instead of a hydrogen atom (**1i**), the reaction did not occur anymore, and no other reaction was observed. The absolute configuration of the reactant **1g** and the relative configuration



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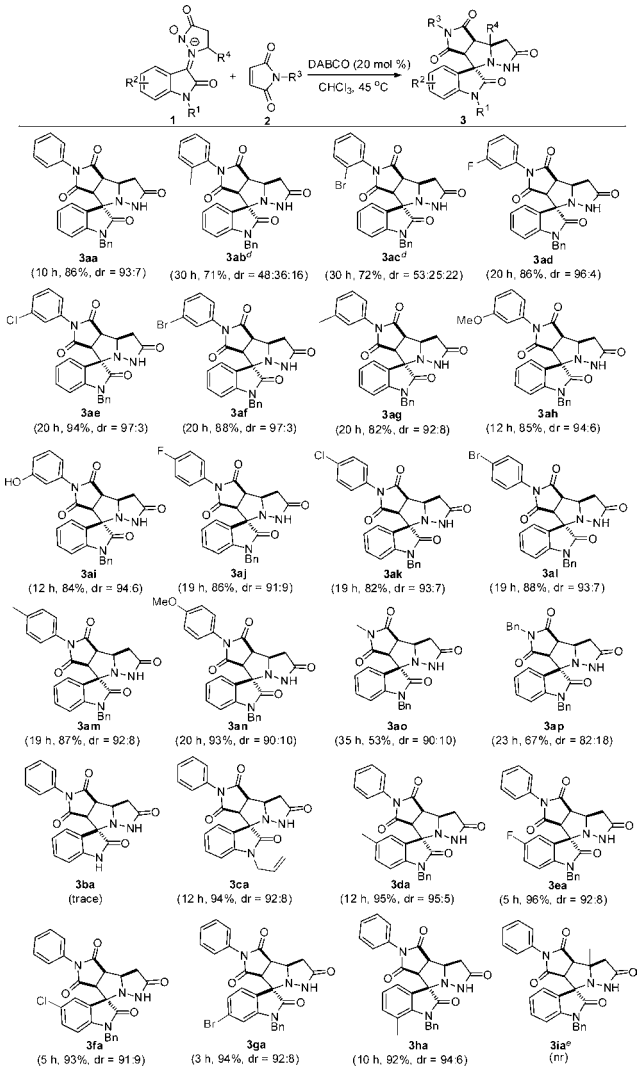
**Scheme 2. Generality of Substrate Scope**[a−c]




[a]Unless otherwise specified, all reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), and DABCO (0.02 mmol, 20 mol %) in 1 mL of $CHCl_3$ at 45 °C. [b]Yield of the diastereoisomeric mixture. [c]Determined by HPLC. [d]Determined by $^1H$ NMR of the crude reaction mixture. [e]No reaction.

of the product **3ef** were determined by X-ray crystallographic analysis (Figure 2).[16]

To understand the unexpected [3 + 2]-cycloaddition, we proposed a plausible catalytic mechanism as illustrated in Scheme 3. The reaction may be initiated by the resonance of **1a** to form **I**. After tautomerism in the presence of a base, the delocalized and more stable intermediate **II** was formed. Intermediate **II** reacted with maleimide **2a** to give the final product via [3 + 2]-cycloaddition.

To achieve an asymmetric version of the present reaction, a series of organocatalysts, such as cinchonas, bifunctional cinchona thioureas, primary amines, and chiral phase-transfer catalysts, were screened. Unfortunately, no positive results were obtained. Only in the presence of phase-transfer catalyst **4** and $K_2CO_3$ was a good yield (80%) with excellent diastereoselectivity but poor enantioselectivity (ee = 24%) obtained (Scheme 4).

In summary, a new isatin *N,N′*-cyclic azomethine imine synthon was devised and an unexpected abnormal [3 + 2]-cycloaddition with maleimides catalyzed by DABCO has been disclosed. A variety of tricyclic spiropyrrolidine oxindoles bearing dinitrogen heterocycles and succinimide scaffolds were obtained in excellent yields (up to 96%) and diastereoselectivities (up to 97:3) under mild conditions, and a series of *N,N′*-cyclic azomethine imines and maleimides are compatible with this protocol. Further studies on the potential of this reaction and catalytic applications of the new isatin *N,N′*-cyclic azomethine imine 1,3-dipole with other substrates are currently underway in our laboratory.

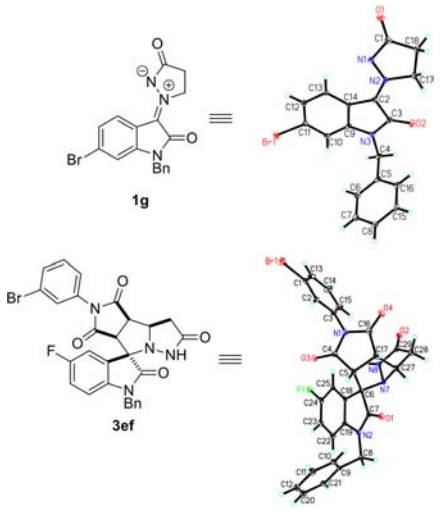
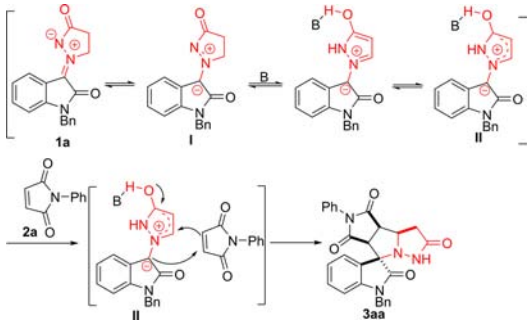
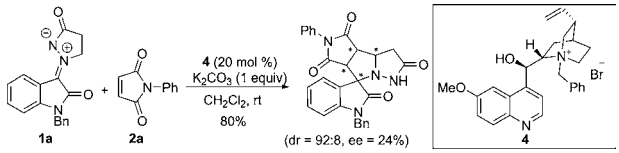



**Figure 2.** Representative X-ray crystallographic structure of reactant **1g** and cycloadduct **3ef**.

**Scheme 3. Proposed Reaction Pathway**




**Scheme 4. Catalytic Enantioselective Variant**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03815.

X-ray crystal details for **1g** (CIF)
X-ray crystal details for **3ef** (CIF)
Experimental procedures and detailed characterization data of all compounds (PDF)



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### Notes

The authors declare no competing financial interest.

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(15) The minor isomer could be isolated and characterized by $^{1}$H NMR. The other two axial isomers was not able to be isolated but could be assigned from $^{1}$H NMR data.

(16) CCDC 1521084 (**1g**) and CCDC 1521083 (**3ef**) contain the supplementary crystallographic data for this paper. Those 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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