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Metal-Free Directed Diastereoselective C2,C3-Cyclopropanation of Substituted Indoles with Diazoesters

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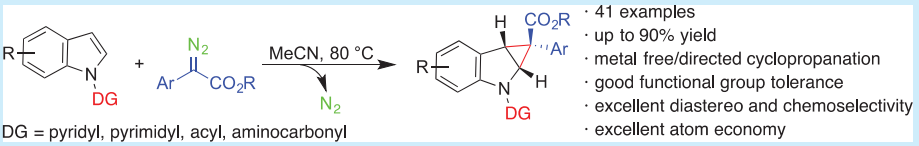
Supporting Information



ABSTRACT: A metal-free directed C2,C3-cyclopropanation of suitably substituted indoles with α-diazo esters has been accomplished for the diastereoselective synthesis of cyclopropane-fused indolines in good yield. This method works well with a wide range of differently substituted α-diazo esters as well as indole derivatives and shown excellent compatibility for diverse directing group like pyridyl, pyrimidyl, acyl, and urea derivatives. Furthermore, the preliminary mechanistic investigation revealed the importance of directing group for the developed transformation.

Cyclopropanes are ubiquitous subunits frequently encountered in various carbo- and heterocycles having wide biological activities.[1] In addition, the cyclopropane moiety has been utilized in the synthesis as key intermediates en route to accessing complicated structures, such as medium-sized rings or highly functionalized molecules via ring-opening and/or ring-expansion strategies.[2] Hence, number of strategies for the construction of cyclopropane has been described in the literature.[3] One of the well-known methods is the Simmons−Smith cyclopropanation reaction, where a methylene group is introduced to the olefin via cycloaddition on treatment of diiodomethane with the zinc−copper couple.[4] However, the most important and diversified cyclopropanation that found tremendous application is the transition-metal-catalyzed cyclopropanation of olefin with diazo compounds.[5]

On the other hand, substituted indole is one of the most widely spread heterocycles in natural products[6] and pharmaceuticals.[7] In particular, cyclopropane-fused indoles have exhibited appreciable toxicity toward B16 melanoma cells and also reverse multidrug resistance in vincristine-resistant KB cells.[8] Representative examples include lundurines A−D (Figure 1). The known method for the synthesis of 2,3-cyclopropane-fused indole skeleton is rather limited to transition-metal-catalyzed inter- or intramolecular coupling of indole with diazoesters.[9] For instance, Zhou, Zhu, and co-workers[9f] reported Cu(II)- or Fe(II)-catalyzed intramolecular cyclopropanation of indoles with high enantioselectivity using chiral spiro bisoxazolines as the chiral ligand (Scheme 1a).

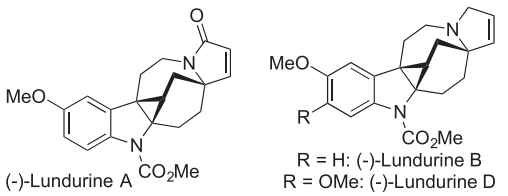
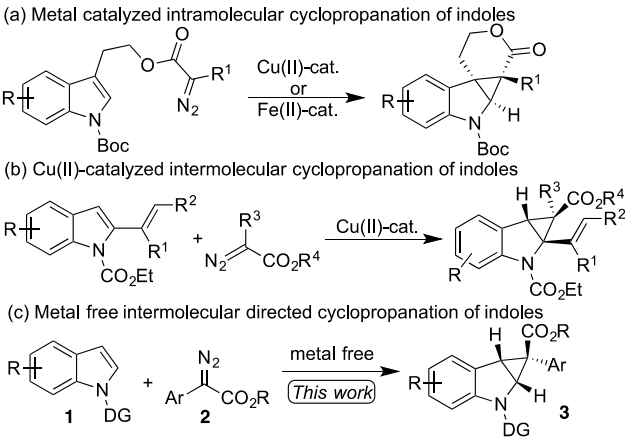


Figure 1. Natural products having 2,3-cyclopropanated indoles.

Scheme 1. Cyclopropanation of Indole with Diazoester



Pirovano and co-workers reported[9h] the diastereo- and enantioselective synthesis of 2-vinylcyclopropa[b]indolines through intermolecular reaction of 2-vinylindoles with diazo compounds in the presence of $Cu(OTf)_2$·Tol as catalyst and pyridine-containing macrocycles as ligands (Scheme 1b). However, all of these methods require a significant amount of transition-metal catalyst for the successful cyclopropanation of indoles. Thus, the development of a general and efficient diastereoselective metal-free[10] cyclopropanation of indole is highly desirable and significant. In continuation of our interest

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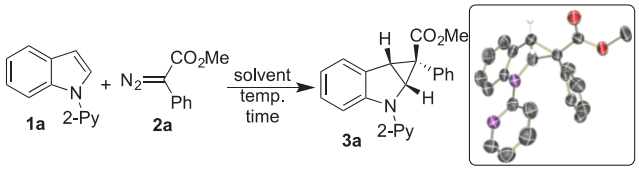
Org. Lett. XXXX, XXX, XXX−XXX

in functionalization of diazo compounds,[11] we herein disclose the first metal-free directed cyclopropanation of indole with diazoester for the synthesis of cyclopropane-fused indolines (Scheme 1c).

At the start, 1-(pyridin-2-yl)-1*H*-indole **1a** and methyl 2-diazo-2-phenylacetate **2a** were chosen as model substrates for the directed C2,C3-cyclopropanation of indole. Gratifyingly, reaction of 1 equiv of **1a** with 1.2 equiv of **2a** in toluene at 80 °C gave the expected product **3a** in 47% yield as single diastereomer (Table 1, entry 1). The structure and relative

Table 1. Cyclopropanation of 1a with 2a: Optimization[a]



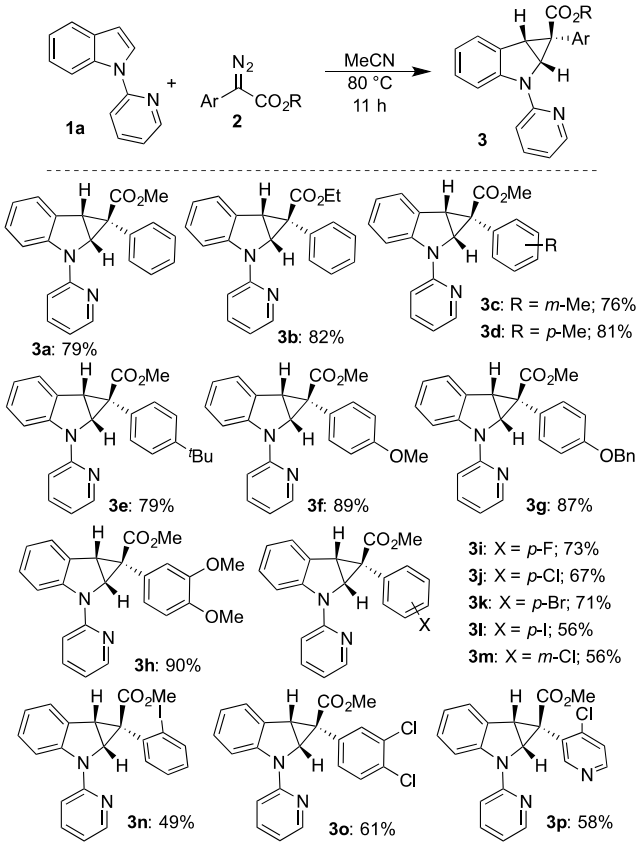
entry	solvent	temp (°C)	time (h)	yield[b] (%)
1	toluene	80	11	47
2	DCE	80	11	27
3	MeCN	80	11	79 (70)[c]
4	PhCN	80	11	69
5	dioxane	80	11	48
6	PhCl	80	11	43
7	DMF	80	11	52
8	$MeNO_2$	80	11	65
9	MeCN	70	18	62
10	MeCN	90	10	75

[a]Reaction conditions: **1a** (0.25 mmol, 1 equiv), **2a** (0.31 mmol, 1.2 equiv), solvent (1.5 mL), temp, time. [b]all are isolated yields. [c]yield of gram scale reaction.

stereochemistry of **3a** were unambiguously confirmed by X-ray analysis. Changing the solvent to a chlorinated solvent like DCE decreased the yield of **3a** (27%) (Table 1, entry 2). On the other hand, using acetonitrile, more polar coordinating solvent afforded the product **3a** in 79% yield after 11 h (Table 1, entry 3), but benzonitrile gave a comparatively low yield (69%) (Table 1, entry 4). Using other solvents like dioxane, chlorobenzene, DMF, and nitromethane did not increase the yield of **3a** (Table 1, entries 5−8). Decreasing the temperature to 70 °C gave a negative influence and reduced the yield to 62% (Table 1, entry 9). Furthermore, increasing the temperature did not have a significant effect and gave the product in 75% yield (Table 1, entry 10). Thus, 1 equiv of **1**, 1.2 equiv of **2**, acetonitrile as solvent, and 80 °C were chosen as the optimal reaction conditions for the directed cyclopropanation.

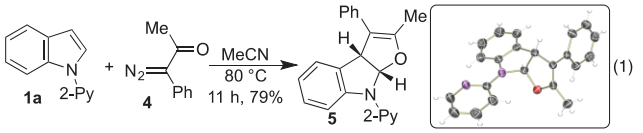
Having the optimized reaction conditions in hand, the generality of various substituted diazoesters was examined (Scheme 2). Both methyl and ethyl 2-diazophenylacetate gave the corresponding C2,C3-cyclopropanated products **3a** and **3b** in 79 and 82% yield, respectively. Diazoesters having various substitutions on the benzene ring also provided the expected product in good yield. *m*- and *p*-tolyl diazoesters provided the corresponding products **3c** and **3d** in 76 and 81% yield, respectively. A *p*-*tert*-butyl-substituted diazoester led to the formation of the product **3e** in 79% yield. Electron-donating substitutions like *p*-OMe and *p*-OBn on the phenyl ring had positive influence on the reaction and afforded the corresponding cyclopropane-fused indolines **3f** and **3g** in 89 and 87% yield, respectively. Additionally, *m*,*p*-dimethoxy

Scheme 2. Scope of Diazoesters



substituted diazoester also led the product **3h** in 90% yield. The formation of readily functionalizable halogen substituted derivatives **3i**−**l** was also achieved in good yields. Most interestingly, *o*-iodo-, *m*-chloro-, and *m*,*p*-dichloro-substituted diazo esters also gave the products **3n**, **3m**, and **3o** in 49, 56, and 61% yield, respectively. Furthermore, diazoester derived from pyridine derivative also underwent a smooth reaction to furnish the corresponding product **3p** in 58% yield. However, strongly electron-withdrawing nitro- and cyano-substituted diazo esters did not afford the expected cyclopropanated product.

Next, relatively electron-deficient the diazo ketone **4** derived from α-phenylacetone was utilized in place of diazo esters. The reaction of **1a** with **4** under the optimized conditions did not afford the expected cyclopropanated product; instead, formation of bicyclic product **5** was observed in 79% yield, which was confirmed by single-crystal X-ray analysis (eq 1).



The formation of **5** can be rationalized through the initial nucleophilic attack of C3-position of indole to carbene carbon followed by intramolecular trapping of resultant iminium ion.

The influence of substitutions on the indole moiety and on the directing group was investigated (Scheme 3). 5-Methyl- and 5-phenyl-substituted indoles gave the cyclopropanated products **3q** and **3r** in 66 and 82% yield, respectively. Electron-donating methoxy-substituted indole derivative furnished the

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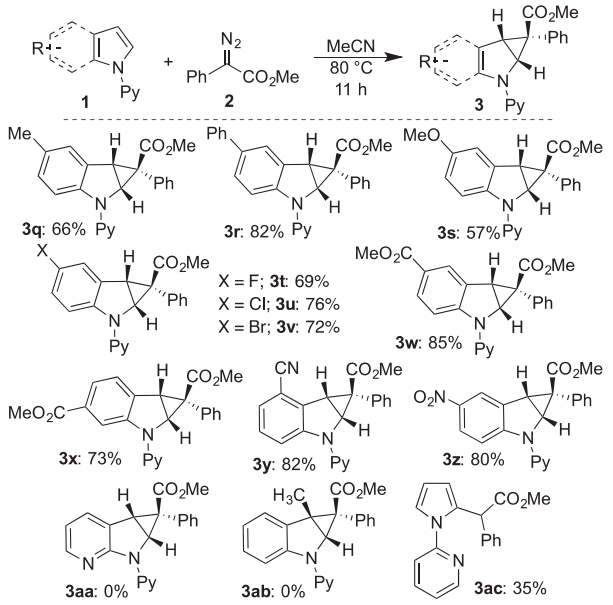
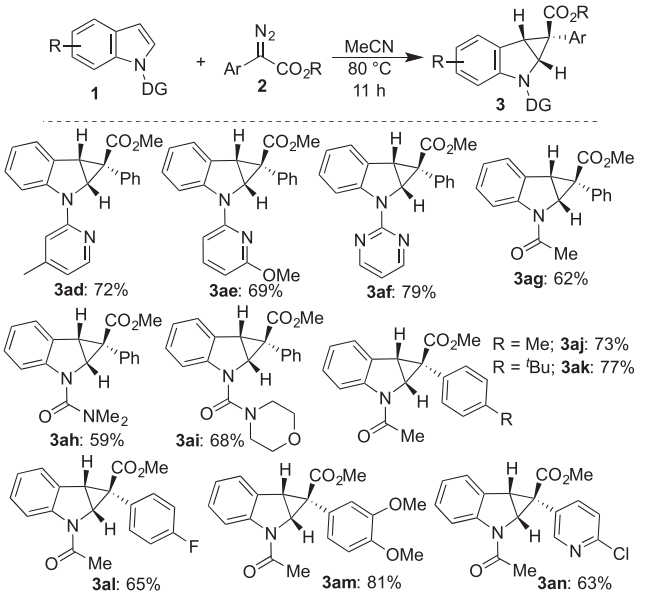
Scheme 3. Scope of Indole Derivatives



Scheme 4. Scope of Directing Group

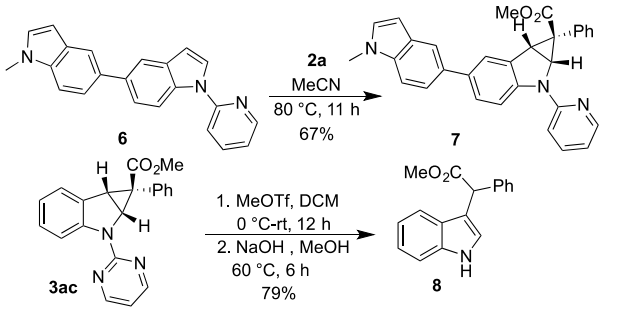


product **3s** in 57% yield. Importantly, 5-halo-substituted indoles led to the formation of products **3t**–**v** in good yield. Electron-withdrawing substituents such as methoxycarbonyl, cyano, and nitro groups at different positions showed good tolerance under the optimized conditions and gave the products **3w**, **3x**, **3y**, and **3z** in 85, 73, 82, and 80% yield, respectively. On the other hand, reaction of 3-methylindole and 7-azaindole derivatives under the optimized conditions did not afford the expected cyclopropanated products (**3aa** and **3ab**), and most of the starting material was recovered. This indicated that the present successful cyclopropanation reaction requires electron-rich and C2,C3-unsubstituted indole derivatives. Unlike *N*-pyridylindole, *N*-pyridylpyrrole did not afforded the cyclopropanated product but rather gave the C2-alkylated product **3ac** in 35% yield.

After successful demonstration of the diazoesters and indole derivatives, the efficiency of various directing groups was examined (Scheme 4). At first, the effect of substitution on the directing pyridine group was studied. Methyl- and methoxy-substituted pyridines afforded the corresponding products **3ad** and **3ae** in 72 and 69% yield, respectively. Similar to pyridine, pyrimidine was also highly effective as a directing group and led to the formation of **3af** in 79% yield. Next, the nitrogen-based directing group was replaced with an oxygen-based directing group. Interestingly, *N*-acetylindole on reaction with diazoester **2a** under the optimized conditions afforded the cyclopropaned product **3ag** in 62% yield, which demonstrates the wide applicability of the present transformation. Inspired by the result, next, *N*,*N*-dimethyl-1*H*-indole-1-carboxamide and (1*H*-indol-1-yl)(morpholino)methanone were synthesized and subjected under the optimized reaction conditions, which led to the corresponding products **3ah** and **3ai** in 59 and 68% yield, respectively. Subsequently, applicability of *N*-acetylindole with other diazoesters was also tested under the developed conditions. *p*-Methyl and *p*-*tert*-butyl diazoester on reaction with *N*-acetylindole afforded the products **3aj** and **3ak** in good yield. Biologically important fluorine containing diazoester underwent smooth reaction and gave the product **3al** in 65% yield. Highly electron rich *m*,*p*-dimethoxy-substituted and pyridine-containing diazoester also furnished the products **3am** and **3an** in good yield.

Subsequently, focus was directed toward the synthetic utility of the developed transformation. Bisindole **6** having pyridyl at one nitrogen and methyl at other was subjected to demonstrate the chemoselectivity of the present transformation. Gratifyingly, reaction of **6** under the optimized conditions gave exclusively the product **7** in 67% yield (Scheme 5), which was

Scheme 5. Synthetic Application



confirmed by 2D NMR. This demonstrates that the reaction occur in an intramolecular fashion and only at the indole having directing group. On the other hand, the reaction of compound **3af** with MeOTf in DCM followed by treatment with aqueous NaOH in methanol at 60 °C did not afford the expected deprotected product; instead, 3-alkylated indole **8** was observed in 79% yield. The formation of **8** could be rationalized via the initial deprotection of pyrimidine to form sodium amide, which led to subsequent cyclopropane ring opening and aromatization (Scheme 5).

In order to understand the insight into the reaction mechanism, few control experiments were carried out. In order to obtain information about the influence of the directing group, the reaction was performed with *N*-phenylindole **9a** as the substrate (Scheme 6a). Reaction of **9a** with **2a** did not afford the expected cyclopropanated product. Similarly, replacement of a 2-pyridyl group with 3-pyridyl or 4-pyridyl as the directing group also did not furnish the cyclopropanated

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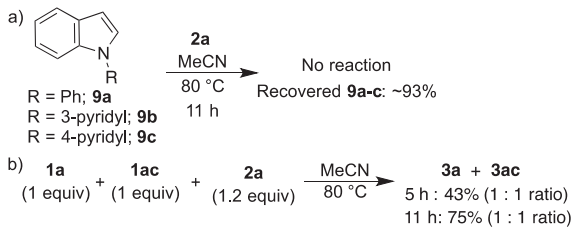
Scheme 6. Control Experiments

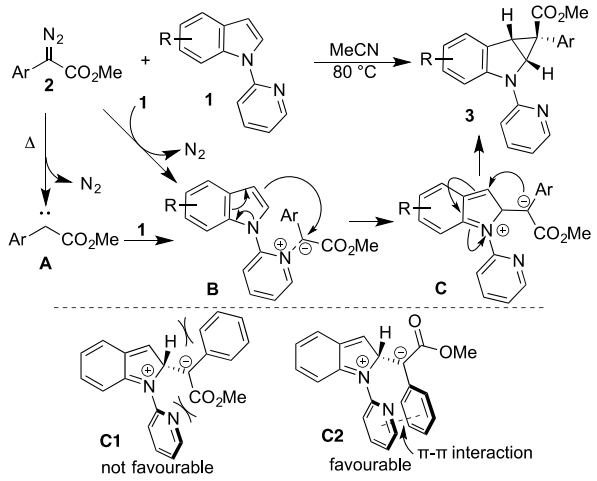


product. These experiments revealed that (1) the directing group is highly essential for the successful cyclopropanation, (2) the directing group must be at the *ortho* position, and (3) directed cyclopropanation is an intramolecular transformation.

Another experiment was carried out to understand the influence of the directing group. The same equimolar mixture of **1a** and **1af**, having pyridyl (one directing site) and pyrimidyl (two directing site) directing groups, was treated with 1.2 equiv of **2a** under standard reaction conditions (Scheme 6b). Analysis of the reaction mixture after 5 h afforded the ∼1:1 ratio of the corresponding cyclopropanated products **3a** and **3af** in 43% overall yield. Similar results were observed even after 11 h with complete reaction. This experiment implies that the number of co-ordination sites does not significantly alter the rate of the reaction. Next, variable-temperature ^{1}H NMR was recorded for the mixture of **1a** and **2a**. Interestingly, a significant amount of downfield shift for the C6-proton of pyridine was observed (see the Supporting Information), which further enforced the potential interaction of pyridine nitrogen with diazo compound.

Based on these preliminary investigations, a plausible mechanism was proposed for the developed reaction (Scheme 7). At first, the diazo compound **2** would undergo thermal-assisted nitrogen extrusion to form the carbene **A**, which might coordinate with directing group of indole derivative **1** to give the ylide intermediate **B**. Alternatively, direct displacement of molecular nitrogen in the diazo compound **1** by the directing group in **2** would also generate the ylide intermediate **B**.

Scheme 7. Plausible Reaction Pathway



Intramolecular attack with the assistance of pyrrolic nitrogen would generate the zwitterion **C**. Formation of cyclopropanate product **3** from **C** could be readily visualized through the intramolecular cyclization, where the cyclization affords the exclusively single diastereomer. The observed diastereoselectivity could be rationalized from the stability of two possible orientations of intermediate **C** that affords the cyclized product. As shown in Scheme 7, orientation **C2** is relatively favored compared to the orientation **C1**, which is possibly due to the presence of significant steric hindrance in the **C1** orientation (the phenyl group and hydrogen as well as the ester moiety and pyridyl group face each other) and absence of similar steric problem and presence of favorable $\pi-\pi$ interaction in **C2** orientation. Thus, cyclization from C2 orientation would afford the observed diastereomer as the sole product. On the other hand, amide- and aminocarbonyl-directed cyclopropanation also could proceed through the generation of oxygen-based ylide followed by cyclization.

In conclusion, we have successfully developed a metal-free-directed C2,C3-cyclopropanation method of indole with diazoesters for the synthesis of cyclopropane-fused indoline skeleton. The method was well accepted for a wide range of differently substituted diazoesters as well as indole derivatives, which results in expected cyclopropanated products in good yield. Moreover, the method has shown excellent compatibility for a significant variety of directing groups like pyridyl, pyrimidyl, acyl, and urea derivatives. A synthetic application of the method the directing group was removed, but during the process the cyclopropane ring opened up and 3-alkylated indole derivative was formed. Additionally, on the basis of preliminary mechanistic investigation, a plausible reaction mechanism was proposed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01197.

Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra of isolated compounds (PDF)

Accession Codes

CCDC 1888375 and 1908121 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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