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# Organocatalyzed [4 + 2] cycloaddition of $\alpha,\beta$ -unsaturated ketones and isatylidene malononitrile: accessing spiro[3-arylcyclohexanone]oxindole derivatives†

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Herein, we developed a series of compounds featuring spiro[3-arylcyclohexanone]oxindoles through Barbas [4 + 2] cycloaddition reactions between isatylidene malononitrile and  $\alpha,\beta$ -unsaturated ketones using L-proline as an organocatalyst. The reported methodology offers many advantages such as mild reaction conditions, diverse substrate scope with high yields, easy reaction setup, and use of easily synthesizable starting materials.

## Introduction

In the construction of complex organic molecules, cascade reactions are a potent tool that enable the creation of complex structures from relatively abundant small molecules.<sup>1</sup> The Barbas [4 + 2] cycloaddition reaction enables highly efficient C–C bond formation reactions, involving amino acid- or amine-catalyzed cycloaddition reactions between 2-aminobuta-1,3-diene and activated olefins.<sup>2</sup> The organocatalyzed cyclization of isatin derivatives has driven extraordinary progress in cascade or tandem reactions, facilitating the construction of diverse molecular frameworks, particularly spirooxindoles.<sup>3</sup> These motifs are found in natural products such as alkaloids, important pharmaceutical molecules, biologically active compounds, and even synthetic drugs that demonstrate a wide range of biological activities.<sup>4</sup> Notably, these spirooxindole structures hold great promise in drug development, exhibiting potential in areas such as anti-HIV, anti-cancer, and anti-tubercular applications.<sup>5</sup> Among spirooxindole derivatives, cyclohexaneoxindoles are the most important structural skeletons because they are found in a wide range of biologically active compounds, such as natural alkaloid gelsemine,<sup>6</sup> MDM2-p53 inhibitor,<sup>7</sup> NITD<sub>609</sub>, and exhibit promising therapeutic use

against malaria,<sup>8</sup> satavaptan,<sup>9</sup> nonsteroidal progesterone receptor modular,<sup>10</sup> spindomycine,<sup>11</sup> *etc.*

We have recently developed a novel organo-catalyzed one-pot strategy for the efficient synthesis of 3,3'-disubstituted oxindoles featuring an all-carbon quaternary center and spiro[2*H*-pyran-3,4'-indoline].<sup>12</sup> Later, we realized that the extension of the methodology also opened up opportunities for the synthesis of spiro[3-arylcyclohexanone]oxindole derivatives with potential biological significance (Fig. 1).

Substantial efforts have been made for the construction of spirocyclohexaneoxindole skeletons, such as through the double Michael addition reaction,<sup>13</sup> organocatalytic Michael/Michael/Aldol addition reaction,<sup>14</sup> Michael/Povarov reaction,<sup>15</sup> Michael/Aldol reaction,<sup>16</sup> and Barbas [4 + 2]cycloaddition reaction.<sup>2</sup>

L-Proline-catalyzed reactions have been successfully applied for the construction of C–C bond and C–heteroatom bonds.<sup>17</sup> However, to the best of our knowledge so far, the L-proline-

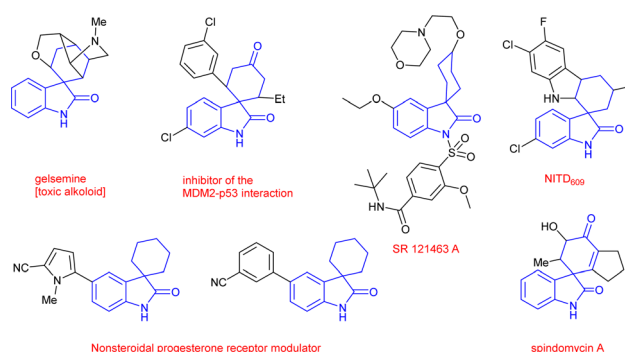


Fig. 1 Representative biologically active compounds with spirocyclohexaneoxindole skeletons.

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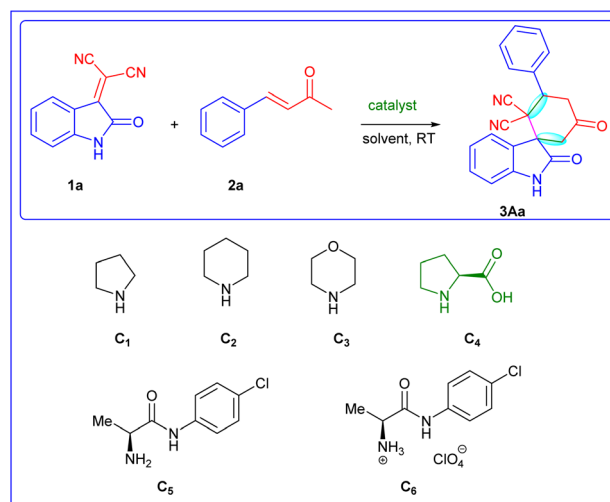
catalyzed Barbas [4 + 2] cycloaddition reaction has not been reported in the literature, especially for the synthesis of spiro[3-arylcylohexanone] oxindoles. Therefore, we herein report the synthesis of spiro[3-arylcylohexanone]oxindole derivatives from the L-proline-catalyzed Barbas [4 + 2] cycloaddition of  $\alpha,\beta$ -unsaturated ketones and isatylidene malononitrile using ethanol as a green solvent.

## Result and discussion

We initiated our preliminary investigation by employing isatylidene malononitrile (**1a**) as an appropriate Michael acceptor and benzylideneacetone (**2a**) as a model starting material. From our previous experience for the L-proline-catalyzed one-pot synthesis of 3,3-disubstituted oxindole in ethanol solvent, our optimization initiative commenced by using ethanol as the solvent. We started our reaction with various amine catalysts by visualizing the formation of an enamine (Michael donor) from benzylideneacetone (**2a**).

Under the catalyst-free condition, the formation of the product (**3Aa**) was not observed (Table 1; entry 1). Then, we used pyrrolidine (**C<sub>1</sub>**) as the catalyst and observed that the reaction was slower with a low yield of 35% (Table 1; entry 2). In case of piperidine (**C<sub>2</sub>**) as the catalyst, the reaction worked better than for pyrrolidine and the yield was improved to 63% (Table 1; entry 3). Furthermore, when we examined the reaction using morpholine (**C<sub>3</sub>**) as the catalyst, the rate of reaction was again slower and the product yield also decreased (Table 1; entry 4). Then, we tried the reaction with piperidine (**C<sub>2</sub>**) and the monochloroacetic acid additive and observed that the additive had no effect on the yield (Table 1; entry 5). Then, we moved toward the use of amino acids as the catalyst, and we first tried the reaction with L-proline as the catalyst and we obtained a 76% yield in 10 h with a diastereomeric ratio of 1 : 2 (Table 1; entry 6). Then, to improve the dr of product **3**, we tried a bulky amino acid amide<sup>18</sup> (**C<sub>5</sub>**) as the catalyst and observed that the reaction required a longer time and the yield was low. Moreover, no improvement in dr was observed (Table 1; entry 7). Finally, we tried the reaction with an amino acid amide ionic liquid (**C<sub>6</sub>**) and found that the reaction proceeded very slow with a very poor yield, as well as no improvement in dr (Table 1; entry 8). From the screening of all the above catalysts, we found that L-proline was an effective catalyst for this reaction. With the best catalyst in hand, we next aimed to optimize the catalyst loading for the reaction. We lowered the catalyst loading to 15 and 10 mol%; however, the reaction took a longer time compared to the optimized catalyst loading of 20 mol% with a low yield (Table 1; entries 9 and 10). With the optimized catalyst loading, we next checked the effect of ketone **2a** on the reaction and the use of 1.5 equiv. of **2a** we obtained an excellent yield within 8 h (Table 1; entry 11). Further, we added 2 equiv. of **2a**, but we obtained the same result (Table 1; entry 12). Next, various solvents, such as methanol (MeOH), dichloromethane (DCM), acetonitrile (ACN), dichloroethane (DCE), tetrahydrofuran (THF), dimethylformamide (DMF), 1,4-dioxane (dioxane), dimethyl sulfoxide (DMSO), and toluene were examined with an aim to improve the dr of the product, but unfortunately there

Table 1 Optimization of the reaction conditions<sup>a</sup>



Entry	Catalyst (mol%)	Solvent (1 ml)	Time (h)	dr <sup>f</sup>	Yield <sup>b</sup> (%)
1	—	EtOH	48	—	N.R.
2	<b>C<sub>1</sub></b> (20)	EtOH	24	1 : 1	35
3	<b>C<sub>2</sub></b> (20)	EtOH	10	1 : 1	63
4	<b>C<sub>3</sub></b> (20)	EtOH	16	1 : 1	50
5 <sup>c</sup>	<b>C<sub>2</sub></b> (20)	EtOH	9	1 : 1	61
6	<b>C<sub>4</sub></b> (20)	EtOH	10	1 : 2	76
7	<b>C<sub>5</sub></b> (20)	EtOH	150	1 : 2	50
8	<b>C<sub>6</sub></b> (20)	EtOH	170	1 : 2	20
9	<b>C<sub>4</sub></b> (10)	EtOH	14	1 : 2	61
10	<b>C<sub>4</sub></b> (15)	EtOH	10.5	1 : 2	69
11 <sup>d</sup>	<b>C<sub>4</sub></b> (20)	<b>EtOH</b>	<b>8</b>	<b>1 : 2</b>	<b>92</b>
12 <sup>e</sup>	<b>C<sub>4</sub></b> (20)	EtOH	8	1 : 2	92
13	<b>C<sub>4</sub></b> (20)	MeOH	35	1 : 2	82
14	<b>C<sub>4</sub></b> (20)	DCM	48	1 : 1.5	68
15	<b>C<sub>4</sub></b> (20)	ACN	48	1 : 1	20
16	<b>C<sub>4</sub></b> (20)	DCE	130	1 : 1.5	76
17	<b>C<sub>4</sub></b> (20)	THF	52	1 : 1	58
18	<b>C<sub>4</sub></b> (20)	DMF	50	1 : 2	<30
19	<b>C<sub>4</sub></b> (20)	1,4-Dioxane	42	1 : 1.8	40
20	<b>C<sub>4</sub></b> (20)	DMSO	53	1 : 2	55
21	<b>C<sub>4</sub></b> (20)	Toluene	130	1 : 1	75
22 <sup>g</sup>	<b>C<sub>4</sub></b> (20)	EtOH	36	1 : 2	90
23 <sup>h</sup>	<b>C<sub>4</sub></b> (20)	EtOH	6	1 : 2	42

<sup>a</sup> Unless otherwise noted, all the reactions were performed with **1** (0.5 mmol, 1 equiv.), **2** (0.55 mmol, 1.1 equiv.) and the catalyst (20 mol%) in the mentioned solvent (1 ml). <sup>b</sup> Isolated yield of two diastereomers. <sup>c</sup> Added monochloroacetic acid (40 mol%). <sup>d</sup> **2** (0.75 mmol, 1.5 equiv.). <sup>e</sup> **2** (1 mmol, 2 equiv.). <sup>f</sup> dr of the product calculated by <sup>1</sup>H NMR of the crude product. <sup>g</sup> Reaction at 0 °C. <sup>h</sup> Reflux reaction at 80 °C.

was no improvement in yield as well as dr (Table 1; entries 13 to 21). Finally, we performed the reaction at different temperatures to check the effect of temperature on the reaction. At 0 °C, the reaction rate was slower with no improvement in dr (Table 1; entry 22), and at reflux conditions at 80 °C, we observed a lower yield with some decomposition (Table 1; entry 23).

With the optimized reaction conditions in hand, our focus next was to check the efficiency of the methodology across



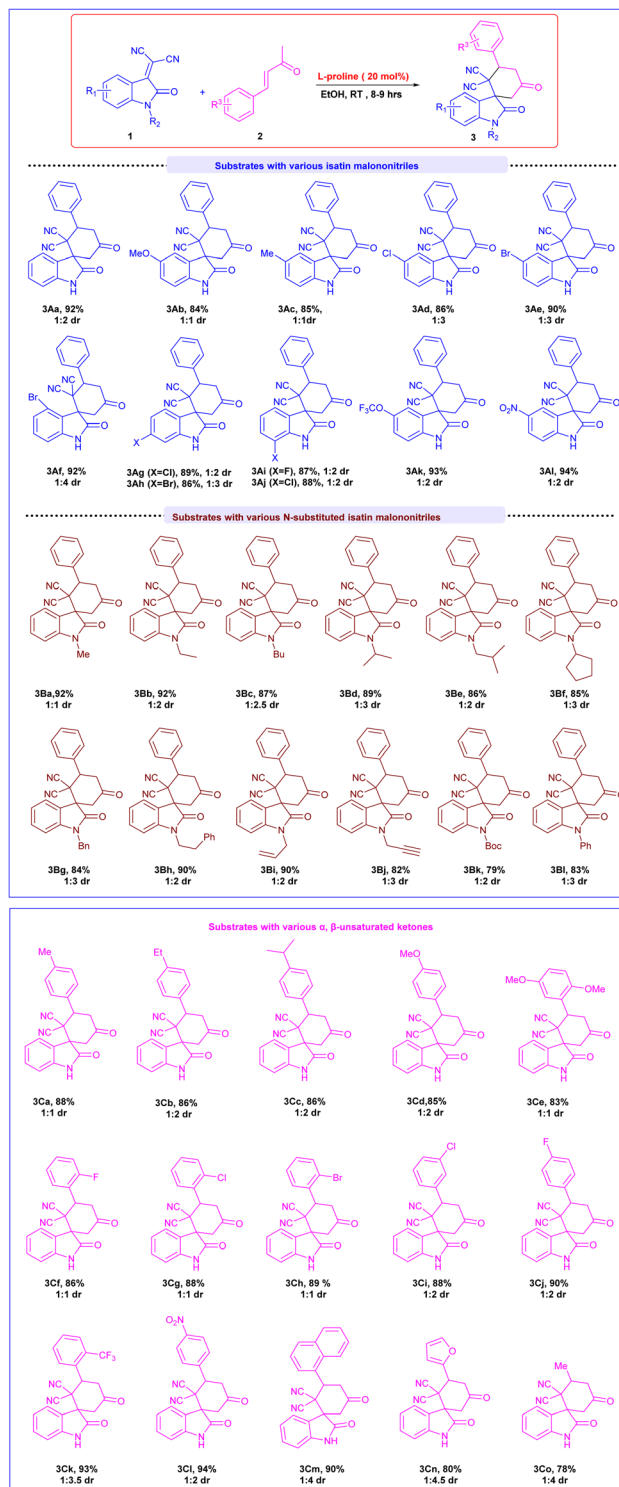
a more extensive substrate scope. Initially we checked isatylidene malononitriles with the electron-donating groups 5-Me and 5-OMe, which gave the corresponding product in good yields but with a poor dr up to 1:2 (**3Ab**, **3Ac**). Isatylidene malononitriles with a halogen substitute at different positions (5-Cl, 5-Br, 4-Br, 6-Cl, 6-Br, 7-F, and 7-Cl) were next studied and showed excellent yields up to 85–90% with dr up to 1:3 (**3Ad–3Aj**). Further we checked isatylidene malononitriles with electron-withdrawing groups such as 5-OCF<sub>3</sub> (**3Ak** 93% yield, 1:2 dr) and 5-NO<sub>2</sub> (**3Al** 94% yield, 1:2 dr), and the reaction worked smoothly. When comparing the reaction rate of the substrates with electron-withdrawing groups and electron-donating groups, it was observed that the rate of reaction was faster with electron-withdrawing groups (Scheme 1).

Then, we tried the reaction with various *N*-alkyl-substituted isatylidene malononitrile-like derivatives, such as *N*-methyl, *N*-ethyl, *N*-butyl, *N*-isopropyl, *N*-isobutyl, *N*-cyclopentyl, *N*-benzyl, and *N*-ethyl phenyl, and all worked well with high to excellent yields and dr of up to 1:3 (**3Ba–3Bh**, yields from 82–92%, 1:1–1:3 dr). Isatylidene malononitriles with *N*-allyl and *N*-propargyl substrates reacted slowly to give high yields (**3Bi** and **3Bj**). In case of *N*-Boc isatylidene malononitriles, the reaction worked well with a high yield (**3Bk**, yield 79%, 1:2 dr). The optimized reaction conditions also worked for *N*-phenyl isatylidene malononitrile to give a high yield and 1:3 dr (**3Bl**). For more confirmation of the products, we performed single-crystal X-ray analysis for compounds **3Ac** and **3Bd**, as shown in Fig. 2.

Finally, we explored the reaction with various  $\alpha,\beta$ -unsaturated acetones, and all worked smoothly under the optimized reaction conditions. We started from the  $\beta$ -phenyl group with alkyl substitutions, like *p*-methyl, *p*-ethyl, *p*-isopropyl  $\alpha,\beta$ -unsaturated acetone, which all gave high yields and dr up to 1:3 (**3Ca–3Cc**). Further, we checked the  $\beta$ -phenyl group with electron-donating groups on the phenyl ring, like *p*-OMe and *o,m'*-DiOMe, and we got the corresponding product with high yields (**3Cd** and **3Ce**, yields 85% and 83%, dr up to 1:2). Then, we checked the efficiency of the methodology with halogen substitute  $\beta$ -phenyl groups, like *o*-F, *o*-Cl, *o*-Br, *m*-Cl, and *p*-F, and all gave the corresponding product with high to excellent yields (**3Cf–3Cj**, yields from 86–90%, dr up to 1:2). With electron-withdrawing groups on the  $\beta$ -phenyl group like *o*-CF<sub>3</sub> and *p*-NO<sub>2</sub>, the reaction gave excellent yields with dr up to 1:3.5 (**3Ck** and **3Cl**).

After conducting the reaction with various  $\alpha,\beta$ -unsaturated acetones, we observed that the  $\beta$ -phenyl group (electron-withdrawing groups) reacted faster than the case with electron-donating or halo-substituted  $\beta$ -phenyl groups. Further, we checked the reaction with a  $\beta$ -naphthyl group, affording the corresponding product with a 90% yield and with dr 1:4 (**3Cm**). A  $\beta$ -heteroaryl group like furan also worked under the optimized reaction conditions and gave an 80% yield and dr of 1:4.5 (**3Cn**). Ultimately, we checked the efficiency of the methodology with a  $\beta$ -methyl group and it worked well and gave a 78% yield with dr of 1:4 (**3Co**).

On the basis of the previously reported related mechanistic research,<sup>2a,b</sup> we propose a plausible mechanism based on the Barbas [4 + 2] cycloaddition reaction, as illustrated in Fig. 3.



**Scheme 1** Substrate scope for the synthesis of spiro[3-arylcylohexanone] oxindoles. Reaction condition: all the reactions were performed in reaction tubes with **1** (0.5 mmol, 1 equiv.), **2** (0.75 mmol, 1.5 equiv.), and L-proline (20 mol%) in ethanol (1 ml) at rt. Yields given here are for the addition of two diastereomers. dr values mentioned above were calculated by <sup>1</sup>H NMR of the crude product. Yields shown above are the combined yields of two diastereomers. We separated the two diastereomers by silica gel column chromatography and the ESI characterizations provided are for the major diastereomer only.



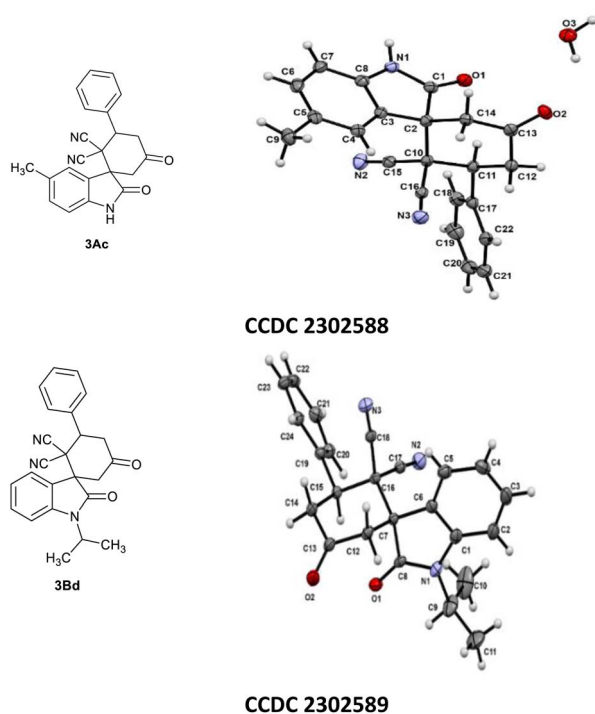


Fig. 2 ORTEP diagrams for compounds **3Ac** and **3Bd**.

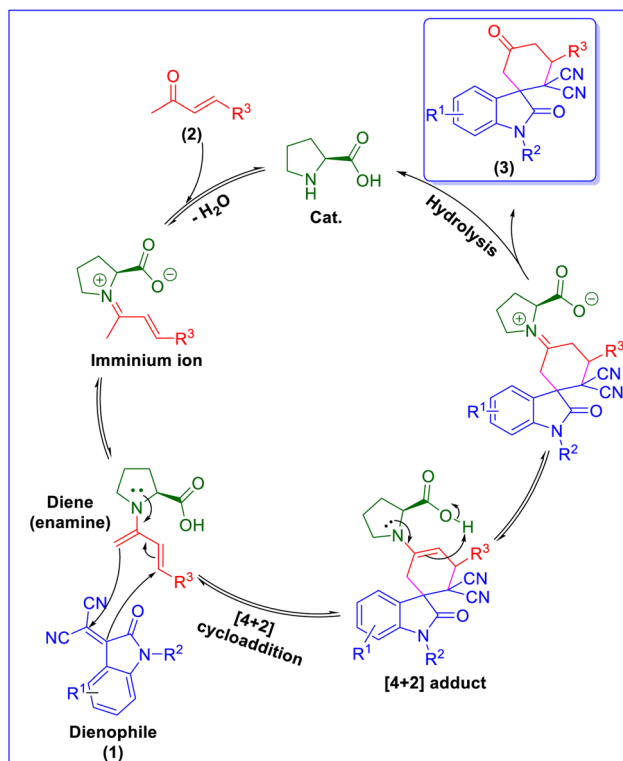


Fig. 3 Plausible reaction mechanism.

Here, initially, L-proline (**Cat.**) reacts with benzylideneacetone (**2a**), leading to the formation of enamine *via* carbinolamine and iminium-ion intermediates. This enamine functions as 2-

aminobuta-1,3-diene (**Diene**). Simultaneously, isatylidene malononitrile acts as a dienophile in the [4 + 2] cycloaddition, affording a [4 + 2] adduct. With the formal [4 + 2] cycloaddition it offers, subsequent hydrolysis of the adduct yields spiro[3-arylcyclohexanone]oxindoles, with the regeneration of L-proline for the next catalyst cycle.

## Conclusion

In summary, we developed an efficient methodology for the construction of spiro[3-arylcyclohexanone]oxindoles derivative *via* a Barbas [4 + 2] cycloaddition reaction of isatylidene malononitrile and  $\alpha,\beta$ -unsaturated ketones using L-proline as a catalyst. The presented synthetic protocol offers many advantages, including the use of easily synthesizable starting materials from cheaply available materials, operational simplicity with an easy reaction setup, and the final product achieved in high to excellent yields with poor to moderate diastereoselectivity. Research for asymmetric expansion of this methodology is ongoing in our laboratory.

## Author contributions

B. R. P. Perform the experiment and developed the method. S. S. C. expanded the substrate scope. B. R. P. and C. B. N. wrote main manuscript, ESI† and analyzed data, A. K. K. directed the project. G. R. K. performed the single-crystal X-ray data analysis.

## Conflicts of interest

The authors declare no competing financial interest.

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