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Letter

Lanthanide Silylamide-Catalyzed Synthesis of Pyrano[2,3-*b*]indol-2-ones

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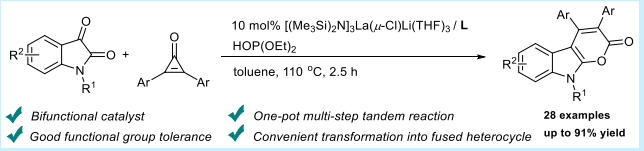
ABSTRACT: A lanthanide silylamide-catalyzed tandem reaction of isatins, diethyl phosphite, and 2,3-diarylcyclopropenones has been developed. A series of pyrano[2,3-*b*]indol-2-ones were synthesized in high yields. The cooperation of the Lewis acidity of the lanthanide center and the Bronsted basicity of the $N(SiMe_3)_2$ anion may be the key factor affecting the catalytic activity of lanthanide amides.



Fused heterocycles occupy a very important position in bioorganic and medicinal chemistry because of their numerous biological activities and extensive application as pharmaceuticals. Pyrano[2,3-*b*]indole, a heterocycle bearing both pyran and indole moieties, is one of the most important structural units in pharmaceutical chemistry, and its derivatives exhibit a range of therapeutic properties, including antimicrobial,[1] antimalarial,[2] antiproliferative,[2] and antitumor[3] activities. For example, hyrtimomine A,[4] a new alkaloid isolated from the Okinawan marine sponge *Hyrtios* sp., shows cytotoxicity against human epidermoid carcinoma KB cells and murine leukemia cells, and hyrtimomine B[5] is found to be an anticancer target of phosphoinositide-dependent kinase 1 (PDK1) (Figure 1). Accordingly, these findings have contributed to an increased demand for the development of synthetic routes to the pyrano[2,3-*b*]indole ring system.

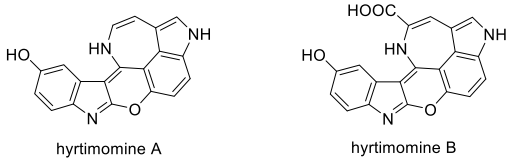
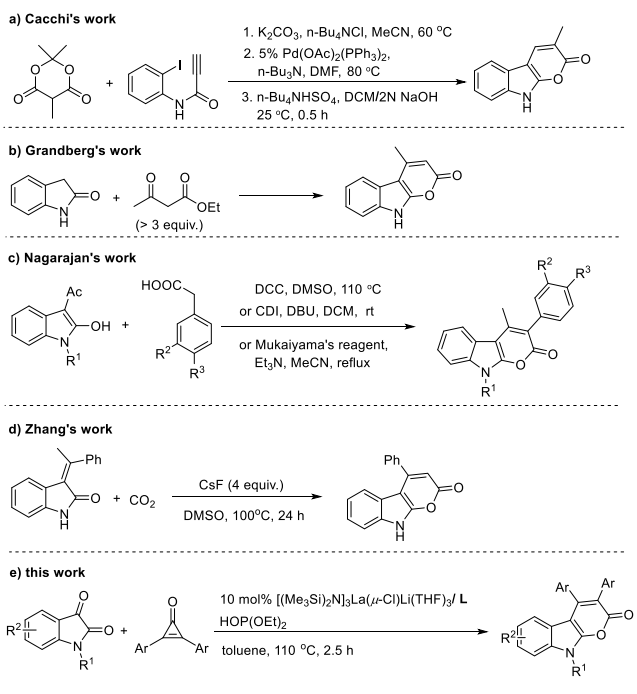


Figure 1. Representative biologically active compounds containing the pyrano[2,3-*b*]indole scaffold.

As the most important pyrano[2,3-*b*]indole derivatives, pyrano[2,3-*b*]indol-2-ones have garnered considerable research attention. However, to the best of our knowledge, there are very few reported methods for the efficient construction of pyrano[2,3-*b*]indol-2-one scaffolds. As rare examples, in 1993, Cacchi[6] achieved the first synthesis of pyrano[2,3-*b*]indol-2-one using Meldrum's acid and *N*-(2-iodophenyl)propiolamide as substrates through a multistep process (Scheme 1a); in 2006, Grandberg[7] reported that the condensation of oxindole with a 3-fold excess of acetoacetic ester at high temperature affords pyrano[2,3-*b*]indol-2-one in 18% yield (Scheme 1b),

Scheme 1. Currently Reported Synthetic Routes to Pyrano[2,3-*b*]indol-2-ones



and Nagarajan[8] developed three metal-free synthetic routes to pyrano[2,3-*b*]indol-2-ones (Scheme 1c). More recently,

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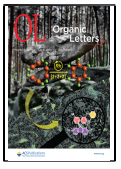

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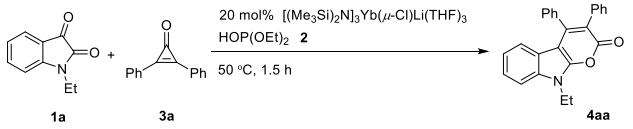
Zhang[9] reported the preparation of a pyrano[2,3-*b*]indol-2-one by cesium fluoride-promoted carboxylative cyclization of 3-(1-phenylethylidene)indolin-2-one via γ-carboxylation using carbon dioxide (Scheme 1d). In most of these studies, only one pyrano[2,3-*b*]indol-2-one product was prepared and unsatisfactory yields were reported. Thus, the development of novel and highly efficient processes for the synthesis of pyrano[2,3-*b*]indol-2-ones is of great value.

Lanthanide silylamides are bifunctional compounds that exhibit both the Lewis acidity of the lanthanide center and the Bronsted basicity of the silylamino group. They have been found to be efficient catalysts for a series of valuable transformations.[10] On the other hand, as amphiphilic microcyclic molecules with large ring strain, cyclopropenones have often been used as building blocks for the construction of larger molecules.[11] Accordingly, in the course of our development of efficient strategies for building cyclic compounds,[12] we conceived the idea of establishing a method for the synthesis of pyrano[2,3-*b*]indol-2-ones using a lanthanide silylamide as the catalyst and cyclopropenone as the starting material.

We first investigated the reaction of *N*-ethyl isatin (**1a**), diethyl phosphite (**2**), and 2,3-diphenylcyclopropenone (**3a**) catalyzed by $[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$ (Table 1). First,

Table 1. Solvent Screening[a]



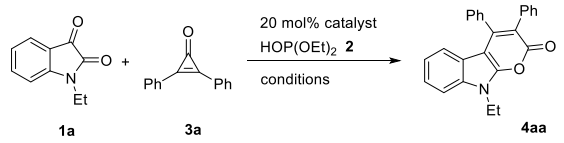
entry	solvent	yield (%)
1	THF	60
2	DMF	19
3	DMSO	43
4	MeCN	36
5	1,4-dioxane	53
6	DME	54
7	DCE	51
8	PhCl	69
9	*n*-hexane	57
10	toluene	78

[a]Reaction conditions: 0.29 mmol of **1a**, 0.29 mmol of **2**, 0.24 mmol of **3a**, 20 mol % $[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$ (relative to **3a**), 50 °C, 1.5 h, 1.0 mL of solvent. Isolated yields are reported.

1a and diethyl phosphite were mixed in the presence of 20 mol % $[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$ for 30 min, and then **3a** and THF were added. The mixture was stirred for a further 1.5 h at 50 °C. After workup, the major product was isolated and identified as the expected product pyrano[2,3-*b*]indol-2-one. The yield was 60%. Encouraged by this preliminary result, we investigated a series of reaction conditions. The results of solvent screening (Table 1) showed that high-polarity solvents, such as DMF, DMSO, and MeCN, do not favor the formation of the product (entries 2−4, respectively), while ethers, halohydrocarbons, and *n*-hexane provide only moderate yields (entries 5−9). Toluene was found to be the best solvent among those screened, achieving a 78% yield (entry 10).

Further study of the lanthanide center of the catalyst was then conducted. $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ with different metal centers from La to Yb was evaluated, and all of the reactions afforded the product in high yields (Table 2, entries

Table 2. Optimization of Reaction Conditions[a]



entry	catalyst	temp (°C)	time (h)	yield (%)
1	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	50	1.5	82
2	$[(Me_3Si)_2N]_3Nd(\mu\text{-Cl})Li(THF)_3$	50	1.5	79
3	$[(Me_3Si)_2N]_3Sm(\mu\text{-Cl})Li(THF)_3$	50	1.5	73
4	$[(Me_3Si)_2N]_3Er(\mu\text{-Cl})Li(THF)_3$	50	1.5	79
5	$[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$	50	1.5	78
6	–	50	1.5	0
7	$LaCl_3$	50	1.5	trace
8[b]	$NaN(SiMe_3)_2$	50	1.5	14
9	$La[N(SiMe_3)_2]_3$	50	1.5	43
10	LiCl	50	1.5	0
11	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	rt	1.5	72
12	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	80	1.5	82
13	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	110	1.5	90
14	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	110	1	84
15	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	110	3	86
16	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	110	6	87

[a]Reaction conditions: 0.29 mmol of **1a**, 0.29 mmol of **2**, 0.24 mmol of **3a**, 20 mol % catalyst (relative to **3a**), 1.0 mL of toluene. Isolated yields are reported. [b]With 60 mol % $NaN(SiMe_3)_2$.

1−5), while no reaction was observed in the absence of a catalyst (entry 6). $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ was found to be slightly more active than the other catalysts.

Owing to the bifunctionality of lanthanide silylamides, several comparative experiments were conducted to explore the origin of their catalytic activity in this reaction. Reactions with $LaCl_3$ and $NaN(SiMe_3)_2$ as the catalyst afforded very little product, indicating that a Lewis acid or Brønsted base alone cannot catalyze the reaction (entries 7 and 8). $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ may be considered as chloride-bridged "ate" complexes derived from homoleptic lanthanide silylamides $\{Ln[N(SiMe_3)_2]_3\}$. Accordingly, each individual component of the catalyst was evaluated (entries 9 and 10). However, the reaction with homoleptic $La[N(SiMe_3)_2]_3$ gave a yield of only 43%, while LiCl was found to be inactive in this reaction, indicating that the way $La[N(SiMe_3)_2]_3$ bonds to LiCl has a remarkable influence on activity in this system. The reaction temperature and time were also optimized (entries 11−16). The final yield obtained from the reaction in toluene under reflux for 1.5 h was 90%.

As a means to optimize catalyst loading, ligands were added to the reaction system. A series of ligands were investigated with a 10 mol % loading of $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ (Table 3). In the absence of a ligand, the product was obtained in 50% yield (entry 1). Phenols with bulkier substituents, such as 4-(*tert*-butyl)phenol, 2-(*tert*-butyl)phenol, and 2,6-di(*tert*-butyl)-4-methylphenol, did not improve the reactivity significantly, nor did quinolin-8-ol ($\mathbf{L_1}$) (entries 2−7). Salens ($\mathbf{L_2}$ and $\mathbf{L_3}$) and *N*-phenyl-1-(pyrrol-2-yl)methanimines ($\mathbf{L_4}$ and $\mathbf{L_5}$) also led to unsatisfactory results (entries 8−13). When β-diketimines derived from pentane-2,4-dione ($\mathbf{L_6}$ and $\mathbf{L_7}$) were evaluated (entries 14−17), better results were obtained and it was found that more sterically hindered ligands lead to higher reaction yields. Therefore, β-diketimines derived from

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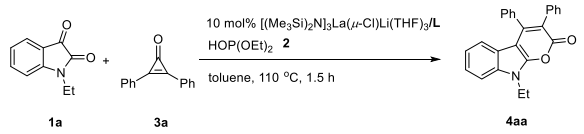
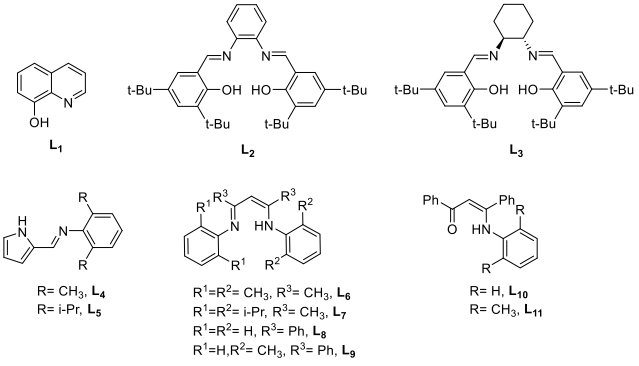
Table 3. Ligand Screening[a]



entry	ligand	catalyst:L	yield (%)
1	–		50
2	4-(*tert*-butyl)phenol	1:3	48
3	2-(*tert*-butyl)phenol	1:3	59
4	2,6-di(*tert*-butyl)-4-methylphenol	1:1	59
5		1:3	67
6	L_1	1:1	54
7		1:3	56
8	L_2	1:1	62
9	L_3	1:1	54
10	L_4	1:1	45
11		1:3	42
12	L_5	1:1	58
13		1:3	45
14[b]	L_6	1:1	55
15[b]		1:3	57
16[b]	L_7	1:1	69
17[b]		1:3	72
18[b]	L_8	1:1	85
19[b]		1:3	84
20[b]	L_9	1:1	88
21[b]		1:3	85
22[b]	L_{10}	1:1	58
23[b]		1:3	67
24[b]	L_{11}	1:1	67
25[b]		1:3	65

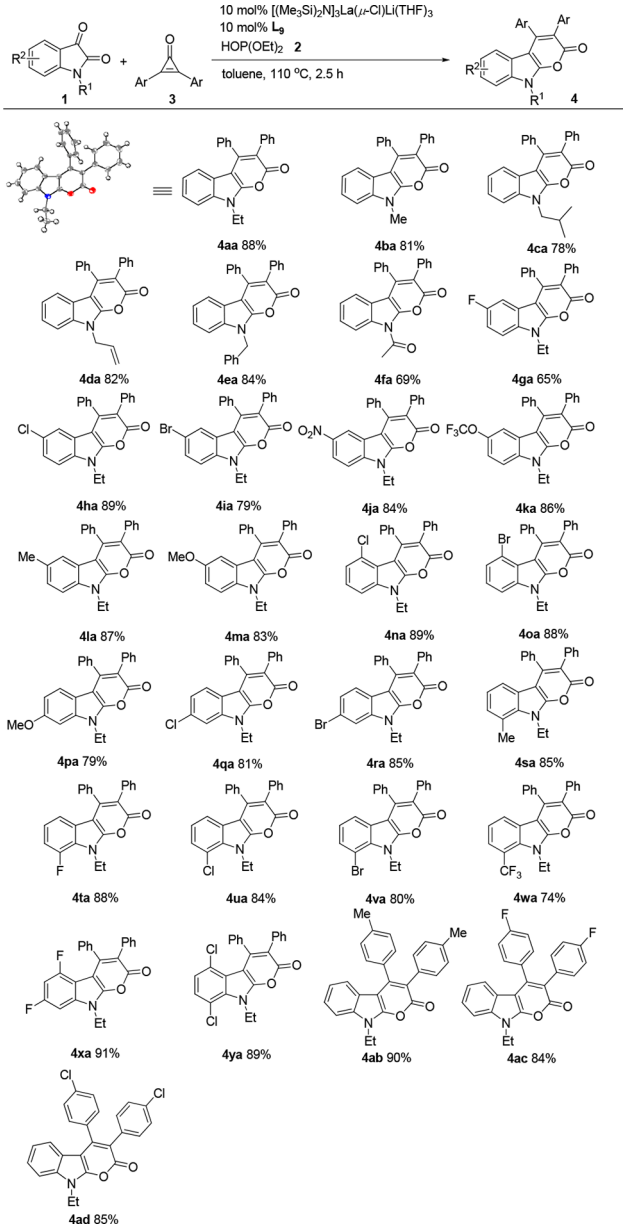


[a]Reaction conditions: 0.29 mmol of **1a**, 0.29 mmol of **2**, 0.24 mmol of **3a**, 10 mol % $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ (relative to **3a**), 110 °C, 1.5 h, 1.0 mL of toluene. Isolated yields are reported. [b]Reaction time of 2.5 h.

1,3-diphenylpropane-1,3-dione (L_8 and L_9) were synthesized and added to the reaction mixtures (entries 18−21), resulting in remarkably enhanced yields. Monoimines derived from 1,3-diphenylpropane-1,3-dione (L_{10} and L_{11}) did not exhibit behaviors similar to those of *β*-diketimines (entries 22−25). Accordingly, L_9 at a catalyst:ligand ratio of 1:1 was chosen for further reaction.

With the optimum reaction conditions in hand, the generality of our method for the synthesis of pyrano[2,3-*b*]indol-2-ones was investigated using structurally varied isatins and cyclopropenones. The results are summarized in Scheme 2. Isatins with different substituents connected to the nitrogen atom (**1a**−**1e**) all reacted well, except for the *N*-acetyl-

Scheme 2. Synthesis of Pyrano[2,3-*b*]indol-2-ones[a]



[a]Reaction conditions: 0.29 mmol of **1**, 0.29 mmol of **2**, 0.24 mmol of **3**, 10 mol % $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ (relative to **3**), 10 mol % L_9, 110 °C, 2.5 h, 1.0 mL of toluene. Isolated yields are reported.

substituted isatin. The latter gave a lower yield of 69% (**4fa**). The reaction system was also found to be applicable to isatins with substituents at each position of the benzene ring (**1g**−**1y**). Cyclopropenones bearing different aryl groups at positions 2 and 3 (**3b**−**3d**) were tried, and satisfactory yields were obtained.

A scale-up experiment was performed to show the practicability of this reaction system (Scheme 3), and product **4aa** was obtained in 76% yield.

Considering the unique properties of lanthanide silylamides, a plausible mechanism for this reaction is proposed (Scheme 4). First, diethyl phosphite goes through a rapid deprotonation initiated by the lanthanide silylamide, generating catalytically active species **A**. The central lanthanide ion of **A** then coordinates to the ketone carbonyl moiety of the isatin, and a

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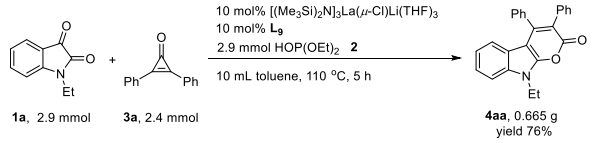
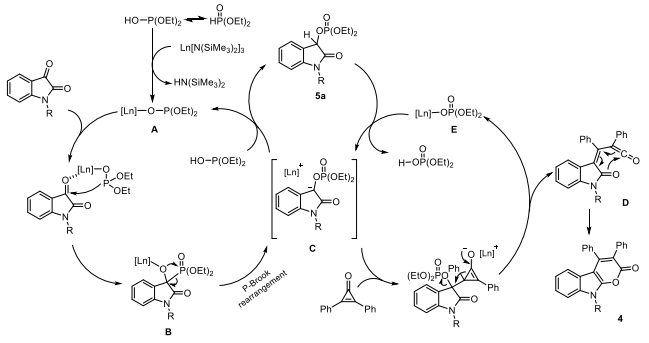
Scheme 3. Scale-up Experiment



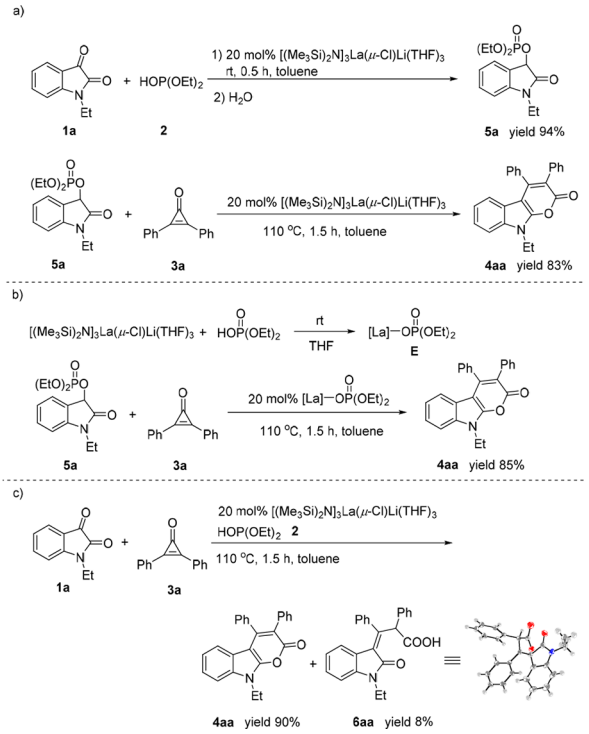
Scheme 4. Proposed Reaction Mechanism



Pudovik reaction[13] occurs to form intermediate **B**, which undergoes rapid [1,2]-phospha-Brook rearrangement[14] to generate intermediate **C**. As the key intermediate of the cycle, **C** abstracts the proton of the diethyl phosphite to produce phosphate **5a** and regenerate active species **A** to accomplish the first catalytic cycle. Furthermore, **C** can attack 2,3-diphenylcyclopropenone through 1,4-addition followed by a ring-opening process to generate intermediate **D**. Upon the formation of **D**, another possible active species **E** may be created. The proton exchange between **5a** and **E** then releases intermediate **C** again. Target product **4** can be obtained by intramolecular cyclization of **D**. For further insight into the role of ligand $\mathbf{L_9}$ in improving the catalytic activity, the $\mathbf{L_9}$–La complex was synthesized by the treatment of $\mathbf{L_9}$ with $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ in a molar ratio of 1:1 at 50 °C in THF. After evaporation of the solvent, a powder was obtained and characterized by ^{1}H NMR spectroscopy (see the Supporting Information). The spectrum showed that the central La atom bonds to two silylamides and one ligand, and two tetrahydrofuran molecules are also coordinated to the central metal. Due to the variation of the coordination environment around the lanthanide metal center, the sterically more crowded [La]–$N(SiMe_3)_2$ complex may undergo the metathesis reaction with $HOP(OEt)_2$ more rapidly to form species **A**.

To confirm this mechanism, several further experiments were conducted. First, the reaction of *N*-ethyl isatin and diethyl phosphite[15] catalyzed by $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ was carried out at room temperature for 0.5 h followed by the addition of water (Scheme 5a). The expected product, diethyl (1-ethyl-2-oxoindolin-3-yl)phosphate (**5a**), was obtained in 94% yield, indicating the generation of intermediate **C**. When **5a** was mixed with 2,3-diphenylcyclopropenone in the presence of 20 mol % $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ under typical reaction conditions, **4aa** was obtained in 83% yield. **E** was proposed as an active species formed during the catalytic process. Accordingly, an *in situ*-formed **E**-catalyzed reaction starting with **5a** was conducted. Lanthanum phosphate **E** was prepared by the metathesis reaction of $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ and diethyl phosphate, the structure of which was confirmed by ^{1}H NMR detection.

Scheme 5. Mechanistic Investigation Experiments



Then, 20 mol % **E** was added to the mixture of **5a** and diphenylcyclopropenone, and the reaction was carried out under standard conditions (Scheme 5b). After workup, product **4aa** was obtained in 85% yield, confirming the role of **E** in the process. In addition, 3-(1-ethyl-2-oxoindolin-3-ylidene)-2,3-diphenylproanoic acid (**6aa**) was isolated in 8% yield in addition to **4aa** after a typical reaction process (Scheme 5c), indicating the existence of intermediate **D**, which serves as the precursor of **4aa**. The structure of **6aa** was confirmed by X-ray crystallography.

In conclusion, we have developed a lanthanide silylamide-catalyzed tandem reaction of isatins, diethyl phosphite, and 2,3-diarylcyclopropenones that provides a variety of pyrano-[2,3-*b*]indol-2-ones in high yields. The high efficiency of the lanthanide amide in catalyzing the reaction is the result of the cooperation between the lanthanide metal center and the $N(SiMe_3)_2$ anion. *β*-Diketimines derived from 1,3-diphenyl-propane-1,3-dione were found to be valuable ligands for the reaction. This method provides a simple and efficient synthetic tool for the construction of pyrano[2,3-*b*]indole scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01506.

Experimental procedures, characterization data, NMR spectra, and X-ray data for compounds **4aa** and **6aa** (PDF)

Accession Codes

CCDC 2041573 and 2044799 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

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Notes

The authors declare no competing financial interest.

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