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Rare-Earth-Metal-Catalyzed Synthesis of Azaindolines and Naphthyridines via C-H Cyclization of Functionalized Pyridines

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Abstract. We report herein a rare-earth-metal-catalyzed insertion of a 2-pyridine C(sp^2)-H bond into an intramolecular unactivated vinyl bond. This reaction provides streamlined access to a range of azaindolines in moderate to excellent yields. The salient features of this reaction include simple and mild reaction conditions, 100% atom efficiency, and wide substrate scope. This methodology is also used to construct other nitrogen-containing compounds such as naphthyridine derivatives. A plausible mechanism for the formation of azaindolines involving initial C-H bond activation by the lanthanide complex followed by C=C insertion into a Ln-C bond to form an alkyl lanthanide species that subsequently undergoes cyclization is proposed.

Keywords: rare-earth-metal catalysis; C-H cyclization; azaindolines; functionalized pyridine; naphthyridines

Introduction

Pyridine-fused heterocycles have received considerable interest because of their biological activity, interesting optical properties, and applications in organometallics that cannot be achieved by the pyridine skeleton alone.[1] Among numerous pyridine-fused hybrid scaffolds, azaindolines are of particular importance because of their prominence in natural products and drug discovery programs (see Figure 1 for representative examples).[2] Therefore, the synthesis of diverse azaindolines has been of long-standing interest in organic and medicinal chemistry. Compared with the multiple methods available for the synthesis of indolines,[3] classical strategies such as Fischer indole synthesis[4] and the Friedel–Crafts reaction[5] are usually unsuccessful when extended to azaindolines because of the subtle electronic perturbations of the pyridine ring.[6] Consequently, the development of methods to prepare azaindolines is important for medicinal chemistry and represents a worthwhile goal in organic synthesis.

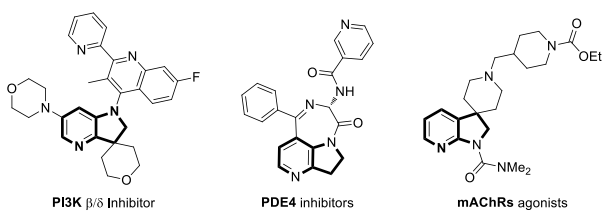
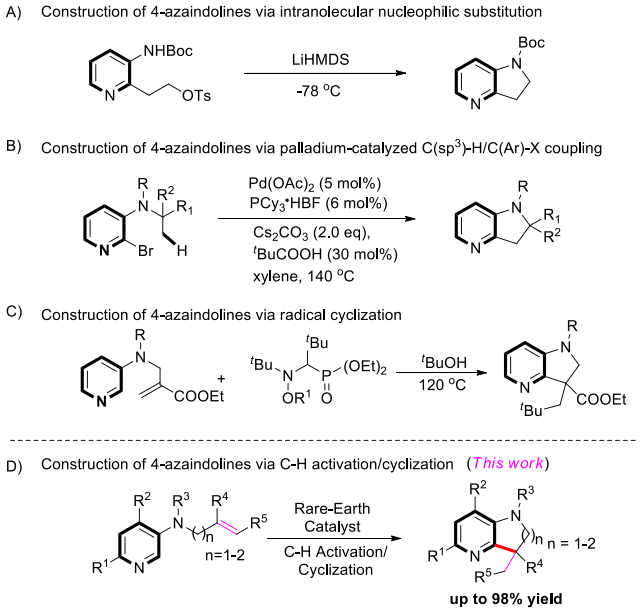


Figure 1. Azaindolines featured in various drug discovery programs.

Synthetic approaches to produce this class of compounds have hitherto relied on the derivatization of pre-existing pyridine frameworks to build the azaindoline skeleton. Many elegant general synthetic approaches to readily access all four isomers of azaindolines have been achieved.[7] Methods to prepare the 7-azaindoline motif include radical cyclization[8] and base- and metal-mediated annulations.[9] Synthetic methods to produce 6-azaindolines[10] and 5-azaindolines[11] have also been developed. Reports of 4-azaindolines are particularly scarce, with existing synthetic routes involving nucleophilic attack of nitrogen onto tosylate or alkenyl intermediates (Scheme 1A),[12] palladium-catalyzed C(sp^3)–H/C(Ar)–X coupling reactions (Scheme 1B),[13] and a radical cyclization pathway (Scheme 1C).[14] However, in many instances, the practicality of

the methods is offset by the low atom economy, narrow scope, special starting materials, and laborious workup needed to remove side products. Therefore, the development of convenient practical methods to construct azaindolines is still relevant.

Transition-metal-catalyzed C-H functionalization of pyridine has become a powerful strategy to synthesize pyridine derivatives in an energy-efficient and step-economic fashion.[15] In contrast to late transition-metal catalysts, lanthanides have played an important role in this type of transformation because of their high activity that is observed in the absence of complex additives and unprecedented types of reactivity.[16] Inspired by previous work, as part of our research on rare-earth-metal-catalyzed synthesis of *N*-containing heterocycles,[17] we envisioned that a variety of 4-azaindolines could be synthesized by C-H cyclization via a pyridine–lanthanide intermediate with a C=C bond generated in situ (Scheme 1D). Efficient one-step synthesis of 4-azaindoline skeletons with 100% atom economy has not been documented in the literature.

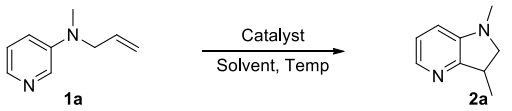


Scheme 1. Comparison of prior and current work.

Results and Discussion

With the above-described idea in mind, we initiated our investigation by attempting to synthesize 1,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (**2a**) from *N*-allyl-*N*-methylpyridin-3-amine (**1a**); the results are summarized in Table 1. First, five homoleptic bis(trimethylsilyl)amides of lanthanide metals were tested by performing the reaction at 80 °C for 24 h in toluene. $Y[N(SiMe_3)_2]_3$ was found to be the best catalyst tested, furnishing the target cyclized product **2a** in 75% NMR yield (Table 1, entries 1–5). A survey of solvents revealed that hexane was optimal to give a comparable yield of 70%, whereas the use of tetrahydrofuran (THF) and 1,2-dichloroethane (DCE) decreased the yield dramatically (Table 1, entries 6–8). To our delight, the NMR yield of **2a** increased to 95% when the reaction temperature was raised to 100 °C (Table 1, entries 9 and 10). Decreasing the reaction time and catalyst loading led to a drop of yield (Table 1, entries 11 and 12). The reaction did not work in the absence of $Y[N(SiMe_3)_2]_3$ (Table 1, entry 13).

Table 1. Optimization of the reaction conditions for formation of **2a** from **1a**.[a]



Entry	Catalyst (x mol%)	Solvent	Time (h)	Temp (°C)	Yield [b]
1	$La[N(TMS)_2]_3$ (10)	toluene	24	80	22%
2	$Sm[N(TMS)_2]_3$ (10)	toluene	24	80	56%
3	$Dy[N(TMS)_2]_3$ (10)	toluene	24	80	72%
4	$Lu[N(TMS)_2]_3$ (10)	toluene	24	80	32%
5	$Y[N(TMS)_2]_3$ (10)	toluene	24	80	75%
6	$Y[N(TMS)_2]_3$ (10)	THF	24	80	46%
7	$Y[N(TMS)_2]_3$ (10)	hexane	24	80	70%
8	$Y[N(TMS)_2]_3$ (10)	DCE	24	80	trace
9	$Y[N(TMS)_2]_3$ (10)	toluene	24	90	87%
10	**$Y[N(TMS)_2]_3$ (10)**	**toluene**	**24**	**100**	**>95% (94%)**[c]
11	$Y[N(TMS)_2]_3$ (5)	toluene	24	100	79%
12	$Y[N(TMS)_2]_3$ (10)	toluene	12	100	82%
13		toluene	24	100	NR
14	$Yb(OTf)_3$ (10)	toluene	24	100	NR
15	YCl_3 (10)	toluene	24	100	NR

[a] *Reaction conditions:* **1a** (0.50 mmol), catalyst (x mol%), solvent (3 mL), N_2.
[b] Yield of the crude reaction mixture determined by ^1H NMR spectroscopy (internal standard: ferrocene).
[c] Isolated yield.

Replacement of $Y[N(SiMe_3)_2]_3$ with other rare-earth-metal sources, such as $Yb(OTf)_3$ or YCl_3, resulted in no reaction (Table 1, entries 14 and 15).

With these optimized conditions in hand, we subsequently explored the substrate scope and limitations of this rare-earth-metal-catalyzed intramolecular annulative insertion reaction by using various vinyl-substituted pyridin-3-amines as substrates for the synthesis of 4-azaindolines. First, the variation of the pyridine ring was investigated. The results showed that the electronic effect of the substituents dramatically affected the yield of this transformation under the standard conditions. For example, substrates bearing a methyl group afforded the cyclized products **2b** and **2c** in 86% and 91% yield, respectively (Table 2, entries 1 and 2). Electron-withdrawing groups such as fluoro, chloro, and bromo substituents at the 5-position on the pyridine ring were not well tolerated in this transformation, affording the desired 4-azaindolines **2d**–**2f** in low yield. In general, the presence of strongly coordinating atoms on the substrate had a negative influence on the lanthanide catalytic reaction because of their competing coordination with the highly Lewis-acidic Ln^{3+}. For example, the C-H cyclization reaction of **1g** gave inferior results to those for **1b** in the preparation of 4-azaindolines. However, when the *N*-benzyl-substituted

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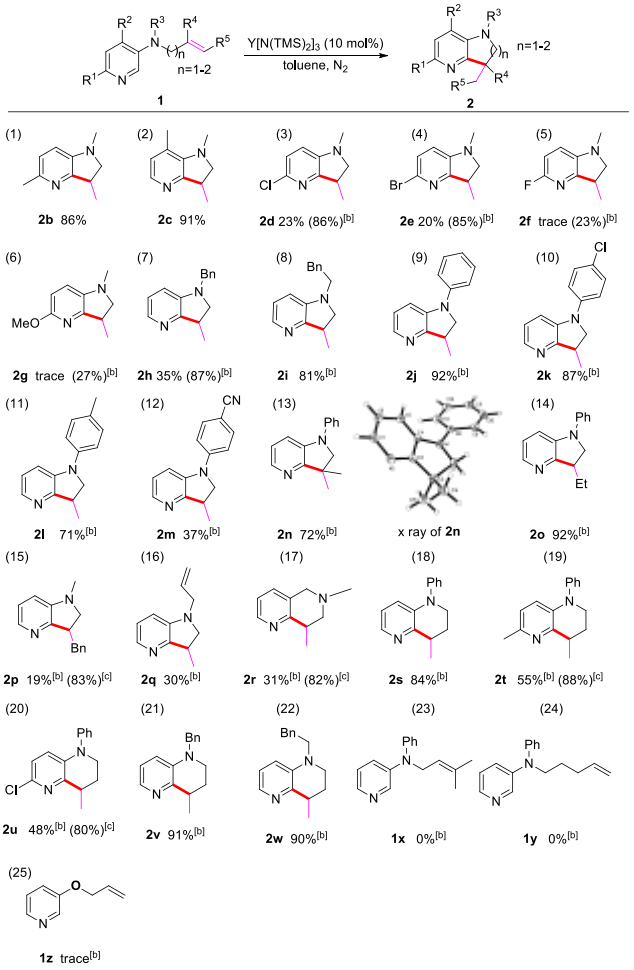
substrate **1h** was tested, this cyclization reaction could not proceed well under same conditions (Table 2, entry 7).

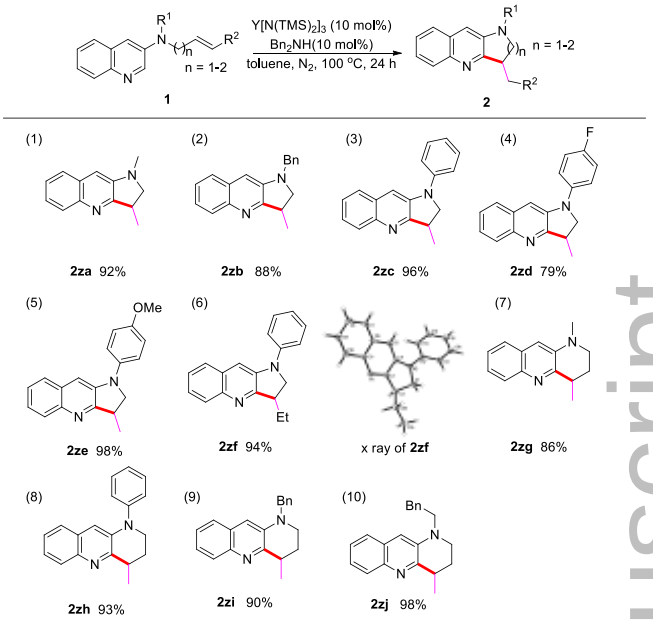
To improve the catalytic efficiency of this reaction, we next investigated various amine additives[18] (see the Supporting Information) and found that when 10 mol% of Bn_2NH was added, the yield of **2h** increased to 87%. Next, we examined the reaction of **1d**–**1g** with Bn_2NH as additive and found that the transformation afforded the desired products in higher yields, ranging from 23% to 86%, with the remaining starting material recovered. Other alkyl groups such as 2-phenylethyl were compatible with the transformation, affording **2i** in 81% yield (Table 2, entry 8). We also examined *N*-aryl substrates; the results demonstrated that the electronic properties of the substituents affected the yield to some extent. In general, electron-donating substituents (e.g., methyl-containing substrates) provided a low yield (Table 2, entries 9–11). A cyano-containing substrate was also compatible with this cyclization protocol, affording the desired product in 37% yield, with remaining **1m** recovered (Table 2, entry 12). Next, we examined the R^4 and R^5 groups at the vinyl substituent. The results demonstrated that both the steric

Table 2. Substrate scope of vinyl-substituted pyridin-3-amines.[a]



[a] Reaction conditions: **1** (0.5 mmol), $Y[N(TMS)_2]_3$ (10 mol%), toluene (3 mL), sealed Schlenk tube equipped with a Teflon cap under N_2, 100 °C, 24 h, isolated yield. [b] Bn_2NH (10 mol%) was added. [c] Bn_2NH (10 mol%), 120 °C, 48 h.

Table 3. Substrate scope of vinyl-substituted quinoline-3-amines.[a]



Reaction conditions: **1** (0.5 mmol), $Y[N(TMS)_2]_3$ (10 mol%), toluene (3 mL), Bn_2NH (10 mol%), sealed Schlenk tube equipped with a Teflon cap under N_2, 100 °C, 24 h, isolated yield.

and electronic effects of the substituent influenced the reaction. For example, when a substrate bearing a methyl group attached to the proximal carbon of the vinyl substituent was examined, **2n** was obtained in a lower yield of 72% compared to that of **2j** (Table 2, entry 13). A substrate bearing an electron-withdrawing phenyl group attached to the terminal carbon of the linker only afforded **2p** in 19% yield under same conditions, which was much lower than the yields of **2o** and **2a** (Table 2, entries 14 and 15). Use of *N*,*N*-diallylpyridin-3-amine resulted in a lower yield (Table 2, entry 16).

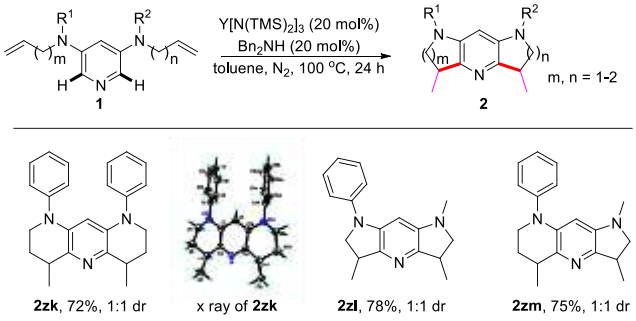
This rare-earth-metal catalyzed C-H cyclization reaction can also proceed smoothly to afford naphthyridine derivatives under modified conditions. Either a methyl or chloro group at the 5-position of the pyridine ring decreased the cyclization efficiency to the naphthyridine skeleton (Table 2, entries 17–22), possibly because Ln^{3+} favored the coordinated configuration of intramolecular γ C=C over δ C=C for five-membered ring construction. In addition to 1,1-disubstituted alkenes, compound **1x** did not undergo the transformation under current conditions. This was possibly because steric hindrance inhibited the insertion of Ln-pyridine into the C=C bond (Table 2, entry 23). Finally, the precursor for seven-membered pyridine-fused cycle **1y** was tried as a substrate but the

desired product was not obtained (Table 2, entry 24). The sluggishness of this reaction likely resulted from the poor steric orientation of the pyridine-Ln species coordinated with remote ε C-C double bonds. Replacing the nitrogen atom in the linker with another heteroatom such as oxygen did not provide the corresponding C-H cyclization product (Table 2, entry 25). The structure of **2n** was confirmed by X-ray crystallographic analysis.[19]

We next set out to investigate vinyl-substituted quinoline-3-amines. Compared with the pyridine analogues, these substrates showed better catalytic efficiency. Both *N*-alkyl- and *N*-aryl-substituted quinoline-3-amines were efficient substrates, affording the corresponding products **2za**–**2zj** in 79%–98% yield (Table 3, entries 1–10). The structure of **2zf** was confirmed by X-ray crystallographic analysis.[19]

Further demonstrating the synthetic practicality of this bicyclization process, the treatment of diverse symmetrical or asymmetrical 3,5-diaminoalkenyl functionalities attached to pyridine substrates were next investigated, giving the double-insertion products **2zk**–**2zm** as a 1:1 mixture of diastereomers in 72%–78% yield. The structure of **2zk** was confirmed by X-ray crystallographic analysis.[19]

Table 4. Bicyclization of vinyl-substituted pyridine-3-amines.[a]



Reaction conditions: **1** (0.5 mmol), $Y[N(TMS)_2]_3$ (20 mol%), toluene (3 mL), Bn_2NH (20 mol%), sealed Schlenk tube equipped with a Teflon cap under N_2, 100 °C, 24 h, isolated yield.

To gain some insight into the mechanism of this rare-earth-metal-catalyzed C-H bond activation/cyclization process, a set of control experiments were conducted. First, ^1H NMR monitoring revealed that the addition of $Y[N(TMS)_2]_3$ (10 mol%) to **1a** in toluene-d_8 at 100 °C led to the complete liberation of the $(Me_3Si)_2N$ ligand (a new peak at 0.08 ppm) from the catalyst[17a] and **1a** was cleanly converted into **2a** (Figure 2).

To determine whether C-H activation is the rate-determining step, a kinetic isotope effect (KIE) was measured using parallel experiments. The initial rate of cyclization of the deuterated *N*-allyl-*N*-methylquinolin-3-amine (**1za**-*d*) was determined. Less than 5% of the deuterated C-H cyclization product **2za**-*d* was detected (Scheme 2a). The high KIE value of 19 observed for the reaction between **1za**/**1za**-*d* is consistent with a turnover-limiting C-H activation step (Scheme 2b). The yield of deuterated **2za**-*d* obviously increased when 20 mol% of $Y[N(TMS)_2]_3$ was used as the catalyst (Scheme 2c). These results provided evidence that C-H activation is the rate-determining step in the catalytic cycle.

To further investigate the electronic preference of the reaction, competitive cyclization of **1b** and **1d** with different electronic characters was performed. The C-H cyclization was favored by the more electron-rich substrate **1b** (Scheme 2d). To obtain further information about the mechanism of the reactions involving Bn_2NH, a series of control experiments were carried out. The catalytic performance of this in situ mixture prompted us to isolate triaminoyttrium complex **Y-1** according to a reported procedure[18c] (Scheme 2e). The catalytic activity of **Y-1** was found to be higher than that observed for $Y[N(TMS)_2]$ in some cases (Scheme 2f and g). These results showed that the $HNBn_2$ additive possibly induced the generation of activated triaminoyttrium species **Y-1**, which underwent the C-H cyclization reaction.

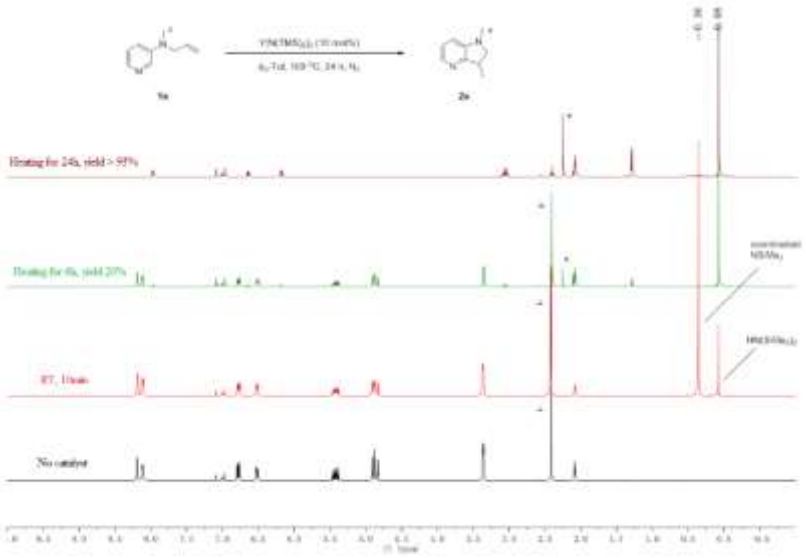
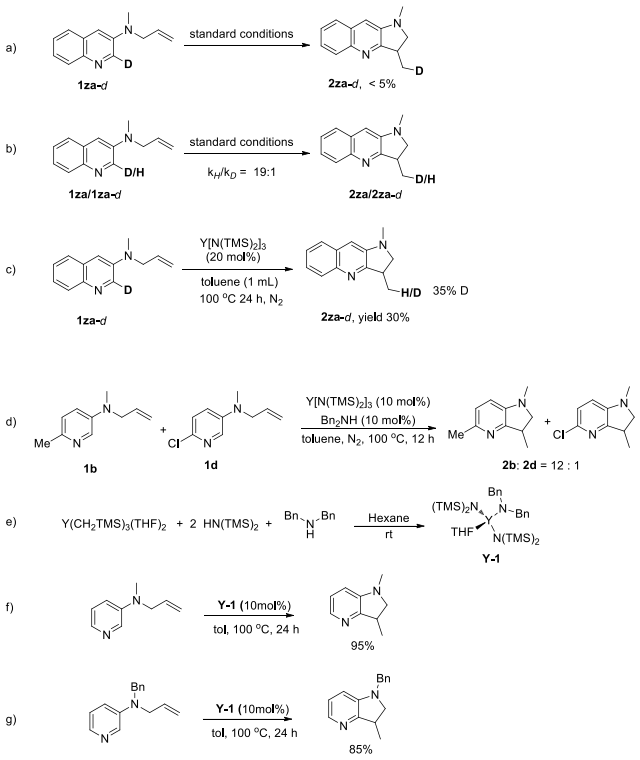
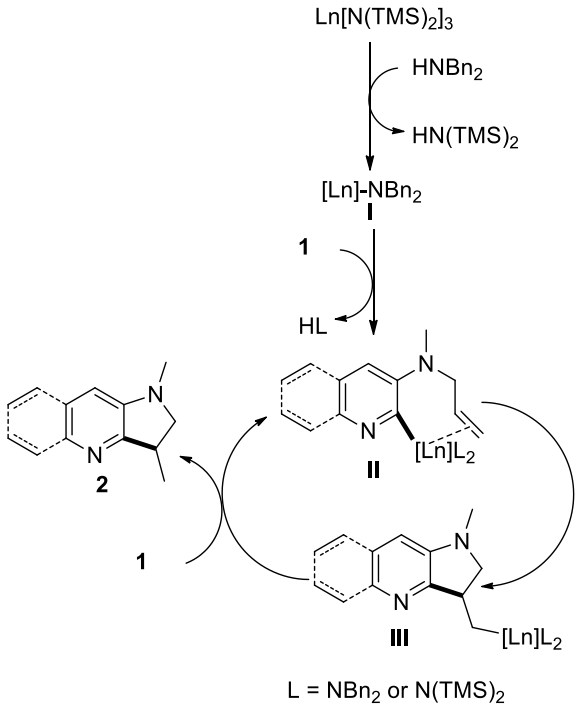


Figure 2. ^{1}H NMR spectra monitoring the progress of the model reaction.



Scheme 2. Mechanistic Studies.



Scheme 3. Proposed Mechanism.

A plausible mechanism for the rare-earth-metal-catalyzed C-H cyclization reaction is shown in Scheme 3. Initial deprotonation of $HNBn_2$ by $Ln[N(TMS)_2]_3$ provides lanthanide amide **I**. Activation of the vinyl-substituted pyridin-3-amine leads to the formation of lanthanide-pyridine complex **II** with the liberation of $HN(SiMe_3)_2$ or $HNBn_2$. Coordination and sequential insertion of C=C into the Ln-pyridine bond of **II** gives intermediate **III**, which could undergo intermolecular protonation with **1** to afford product **2** and regenerate lanthanide species **II**.

Conclusion

We developed a new approach to synthesize 4-azaindolines through the rare-earth-metal-catalyzed C-H bond activation/cyclization reaction of functionalized pyridine. In addition, the protocol was successfully applied to the synthesis of naphthyridine derivatives. This rare-earth-metal-catalyzed process represents an important supplement toward late-transition-metal-catalyzed approach to obtain 4-azaindolines with 100% atom efficiency under mild reaction conditions. Further studies on lanthanide-catalyzed tandem insertion/cyclization reactions to construct other useful *N*-heterocycles are underway in our laboratory.

Experimental Section

General Procedure for the Synthesis of 4-Azaindolines

In a glove box, $Y[N(SiMe_3)_2]_3$ (28.5 mg, 0.05 mmol, 10 mol%) was added to a Schlenk tube equipped with a magnetic stirring bar and Teflon cap. Then, a mixture of functionalized pyridine derivative (0.50 mmol) and amine (0.05 mmol, 10 mol%) in toluene (3 mL) were added. The sealed tube was taken out from the glove box and then stirred at 100 °C for 24 h. After completion of the reaction, the crude product was purified by flash column chromatography on silica gel with ethyl acetate/hexane as the eluent.

Acknowledgements

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[19] CCDC 1950730 (**2n**), 1950731 (**2zf**) and 1962443 (**2zk**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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FULL PAPER

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