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RESEARCH ARTICLE

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Ortho-C–H addition of 2-substituted pyridines with alkenes and imines enabled by mono(phosphinoamido)-rare earth complexes

Hailong Lin[1] | **Yongrui Li**[1] | **Jinyu Wang**[1] | **Mei Zhang**[1] | **Tao Jiang**[1] | **Jing Li**[2] | **Yanhui Chen**[1]

[1]College of Chemical Engineering and Materials Science, Tianjin University of Science and Technology (TUST), Tianjin, China

[2]College of Food Science and Engineering, Tianjin University of Science and Technology (TUST), Tianjin, China

Correspondence
Yanhui Chen, College of Chemical Engineering and Materials Science, Tianjin University of Science and Technology (TUST), 29 13th Avenue, TEDA, Tianjin, 300457 China.
Email: cyh@tust.edu.cn

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Abstract

We here reported a special catalytic performance of mono(phosphinoamido)-ligated rare earth complexes in *ortho*-C–H functionalization of pyridines with nonpolar alkenes and polar imines. Upon treatment with one equiv. of borate reagent $B(C_6F_5)_3$ or $[Ph_3C][B(C_6F_5)_4]$, complex **NP1-Sc** can act as an efficient catalyst for *ortho*-C–H alkylation of pyridines towards alkenes. In the presence of 1:1 mixed secondary amine of HN $(SiMe_3)_2$ and $HNBn_2$, complex **NP2-Gd** can catalyze *ortho*-C–H addition of pyridines towards imines, effectively. A wide range of substrates were subjected to the catalysis to render the one step synthesis of a variety of *ortho*-alkylated and *ortho*-aminoalkylated pyridine derivatives in good yields and an excellent regioselectivity and chemoselectivity.

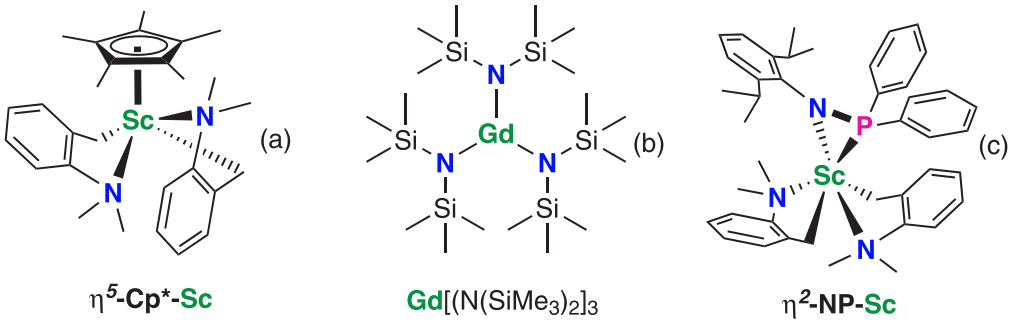
KEYWORDS

alkenes, C–H activation, imines, pyridine, rare earth

1 | INTRODUCTION

The elaboration of pyridine ring continues to be an active issue in synthetic chemistry, mainly due to the prevalence of pyridine in natural products, bioactive molecules, ligands, and functional materials.[1] Among the various synthetic strategies reported, the C–H functionality of pyridine mediated by organometallics is highly desirable in terms of its atom- and step-economy.[2] In particular, the catalytic C–H addition of pyridines towards unsaturated chemical bonds offers the most straightforward synthesis of alkylated pyridines with a 100% atom-efficiency.[3–9] Therefore, much effort has been devoted to this area. Late transition metal complexes, such as Rh,[3b,f,h] Co,[3i,k] Ni,[3c–e,l,n] Cr,[3m] and Ru,[3a,j] have been reported to catalyze C–H alkylation of pyridines with nonpolar alkene (or alkyne) to give *ortho*-, *meta*-, and *para*-substituted pyridines via a coupling of oxidative addition/reductive elimination. In addition, some alkyl zirconium and organo-rare earth complexes could also serve as efficient catalysts for *ortho*-C–H alkylation of pyridines with olefins through a σ-bond metathesis pathway.[5,6] In 1989, Jordan and co-workers pioneered the catalytic *ortho*-C–H addition of pyridine with propene by use of a zirconium bismetallocene under H_2 atmosphere.[5a] Subsequently, Teuben et al. found a metallocene yttrium complex, which can also be used as catalyst for the *ortho*-C–H alkylation of pyridine with ethylene at high reaction temperature and ethylene pressure.[6a] Recently, Hou and co-workers developed a combination of a half-sandwich scandium complex (Scheme 1a) and $B(C_6F_5)_3$, which indicates high catalytic activity for *ortho*-C–H functionalization of pyridines with various olefins including norbornene, styrene, allenes, and α-olefins.[6b–d]

In contrast to the numerous reports about the C–H functionalization of pyridine with nonpolar alkene and



SCHEME 1 Rare earth complexes for *ortho*-C–H addition of pyridines towards olefins or imine

alkyne, the successful examples towards polarized π bonds are relatively scarce. Although a lot of work on catalytic C–H transformation of 2-arylpyridines into C = X (X = O, N) bonds has been extensively explored, in most cases, the C–H activation only occurs at arene ring rather than at the pyridine core.[7] In 2011, Shi et al. reported the nucleophilic addition of pyridines to aldehydes via a Ir-catalyzed *meta*-C–H activation of pyridine.[4b] Mindiola et al. demonstrated scandium-mediated *ortho*-C–H functionalization of pyridine with 2-isocyano-1,3-diisopropylbenzene.[8] Just recently, the first example for *ortho*-C–H addition of pyridines towards imines was also realized by Mashima and co-workers.[9a,b] Some amido-rare earth complexes, such as Gd[N $(SiMe_3)_2]_3$ (Scheme 1b), were found to be catalytically active for an insertion of nonactivated imines into the *ortho*-C–H bond of 2-substituted pyridines.[9a] Despite the fast-paced advances in C–H functionalization of pyridines towards various unsaturated bonds by a variety of catalysts, as far as we are aware, few organometallics have catalytic behavior for both nonpolar alkenes and polar imines in the *ortho*-C–H transformation of pyridines.

For many years, we have been drawing considerable attention in the synthesis and catalytic application of novel rare earth complexes. Intrigued by the special bidentate property of phosphinoamide ligand as well as its partial N–P multiple-bonding character,[10–12] we recently successfully prepared the first mono(phosphinoamido)-ligated rare earth dialkyl complexes and found that scandium complex (Scheme 1c) combined with one equiv. of $B(C_6F_5)_3$ could effectively catalyze cyclization/hydroarylation of 1,5-diene with pyridine, directly rendering the synthesis of pyridyl-functionalized *cis*-1,3-disubstituted cyclopentane derivatives with high diastereoselectivity.[13a] However, their catalytic application in C–H functionalization of pyridines with other π electrophiles has still remained unexplored. Herein, we decided to explore the feasibility of catalytic *ortho*-C–H addition of pyridines towards alkenes and imines by use of mono(phosphinoamido)-rare earth complexes. We found that the combination of scandium complex NP1-Sc and $B(C_6F_5)_3$ was highly efficient catalyst for *ortho*-C–H alkylation of 2-substituted pyridines towards higher olefins including norbornene, styrenes, α-olefins, and even α,ω-dienes. With an assist of 1:1 mixed secondary amine of HN $(SiMe_3)_2$ and $HNBn_2$, gadolinium complexes such as NP2-Gd are also highly effective for catalytic *ortho*-C–H aminomethylation of pyridines towards polar imines with formation of *ortho*-aminoalkylated pyridine derivatives. A wide range of substrates were tested, and good yields as well as excellent regioselectivity and chemoselectivity were obtained. In addition, the deuterium-labeling experiments were also conducted and the results indicated that the alkylation reaction of pyridines underwent a rare earth-mediated *ortho*-C–H activation.

2 | EXPERIMENTAL

2.1 | General procedures and materials

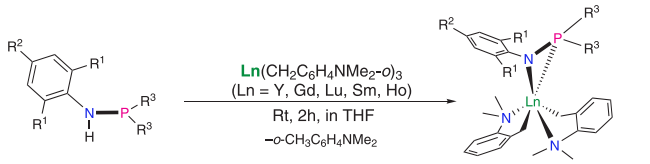
All manipulations were routinely carried out under a dry and oxygen free nitrogen atmosphere by using standard Schlenk-line techniques or using a glovebox. Samples (organo-rare earth complexes) for NMR spectroscopic measurements were prepared in the glovebox by use of J. Young valve NMR tubes. ^1H, ^{13}C, and ^{31}P spectra were recorded on a JEOL-AL400 or Ascend^{III}-400 (BRUKER) spectrometer. Elemental analyses were performed by a MICRO CORDER JM10. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra for alkylation pyridine products were recorded on Ascend^{III}-400 (BRUKER) spectrometer. Data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. GC/MS data were obtained on a GC/MS4000 (VARIAN). High-resolution MS were obtained on a LCMS-IT-TOF (SHIMADZU).

Gas chromatography analysis was performed on Agilent Technologies 7890A GC System.

All solvents used were dried and distilled over an appropriate drying agent under nitrogen. The secondary amines $NHBn_2$ and $NH(SiMe_3)_2$, pyridines (**1a**–**1m**), and olefins (**2a**–**2o**) were purchased from J&K® or TCI and dried over CaH_2, vacuum-transferred, degassed by two freeze-pump-thaw cycles and kept in a glovebox. Anhydrous rare earth chloride ($LnCl_3$) used were purchased from REO. $[Ph_3C][B(C_6F_5)_4]$ and $B(C_6F_5)_3$ were obtained from Tosoh Finechem Corporation and used without purification. Imines (**4a**–**4j**) were prepared according to the literature by the reaction of aldehydes and corresponding amines.[9] Phosphinoamines including **NHP1-NHP4**, Ln-$(CH_2C_6H_4NMe_2\text{-}o)_3$ (Ln = Sc, Y, Gd, Lu, Sm, Ho), and mono(phosphinoamido)-rare earth complexes **NP1-Ln** (**Ln** = **Sc**, **Y**, **Lu**), **NP2-Sc**, **NP3-Sc**, and **NP4-Sc** were prepared according to the literature.[13a,14,15]

2.2 | Synthesis of mono(phosphinoamido)-rare earth dialkyl complexes

As shown in Scheme 2, a THF (5 ml) solution of **NH-P2** ligand (0.45 g, 1.53 mmol) was added dropwise into a solution of Y $(CH_2C_6H_4NMe_2\text{-}o)_3$ (0.75 g, 1.53 mmol) in THF (10 ml), and the mixture was stirred for about 2 h at ambient temperature. After removing the solvent under reduced pressure, the residue was washed by hexane (5 ml × 2) to obtain a pale-yellow powder **NP2-Y** (0.86 g, 1.06 mmol, 87% yield). The crystals of **NP2-Y** suitable for X-ray analysis were obtained from toluene solution layered with hexane. According to the same procedure, complexes **NP1-Sm**, **NP1-Ho**, **NP1-Gd**, **NP2-Y**, **NP3-Y**, **NP4-Y**, **NP2-Lu**, and **NP2-Gd** were also obtained. These complexes are stable in solvent and fully characterized by spectroscopy and X-ray crystallography.[16,17]



SCHEME 2 Synthesis of mono(phosphinoamido)-rare earth dialkyl complex

2.3 | A typical procedure for *ortho*-C (sp^2)–H addition of 2-substituted pyridines with alkenes

A chlorobenzene solution (1.0 ml) of $B(C_6F_5)_3$ (20.4 mg, 0.04 mmol) was slowly dropped into a stirred chlorobenzene solution (1.0 ml) of **NP1-Sc** (27.0 mg, 0.04 mmol) in a 20-ml Schlenk tube. Then 2-substituted pyridine **1** (1.0 mmol), alkene **2** (4.0 mmol) was added in the reaction system. The Schlenk tube was sealed and taken out of the glovebox and headed at 100°C with magnetic stirring. The reaction was monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature and purified directly by silica gel column chromatography (hexane/EtOAc = 20/1) to afford alkylation pyridine **3**. The yield of **3** was calculated based on **1**.

2.4 | A typical procedure for *ortho*-C (sp^2)–H addition of 2-substituted pyridines with imines

To a solution of complex **NP2-Gd** (35.8 mg, 0.05 mmol, 10 mol%) in 2-ml toluene was added *N*,*N*-dibenzylamine (9.3 μl, 0.05 mmol, 10 mol%), 1,1,1,3,3,3-hexamethyldisilazane (11.4 μl, 0.05 mmol, 10 mol%), 2-substituted pyridine **1** (0.5 mmol), and imine **4** (1.0 mmol) in a 20-ml Schlenk tube. The Schlenk tube was sealed and heated at 100°C with magnetic stirring. The reaction was monitored with TLC. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with Et_2O (1.5 ml), and filtered through a short silica gel plug. The obtained solution was concentrated under reduced pressure at 100°C for at least 1 h to remove starting materials. The residue was purified by silica gel column chromatography (Hexane/EtOAc = 10/1) to give aminoalkylation pyridine **5**. The yield of **5** was calculated based on **1**.

3 | RESULTS AND DISCUSSION

3.1 | The typical solid structures of mono(phosphinoamido)-rare earth dialkyl complexes

The typical solid structures of yttrium complexes **NP2-Y** and **NP4-Y** are shown in Figure 1. A unique η^2–N–P coordination to yttrium center and σ–Y–N bond (**NP2-Y**: Y1-N1 2.302(2) Å, **NP4-Y**: Y1-N1 2.263(4) Å) are uncovered in the molecular structures. The relatively short N–P bond distance in these complexes (**NP2-Y**: 1.679(2) Å,

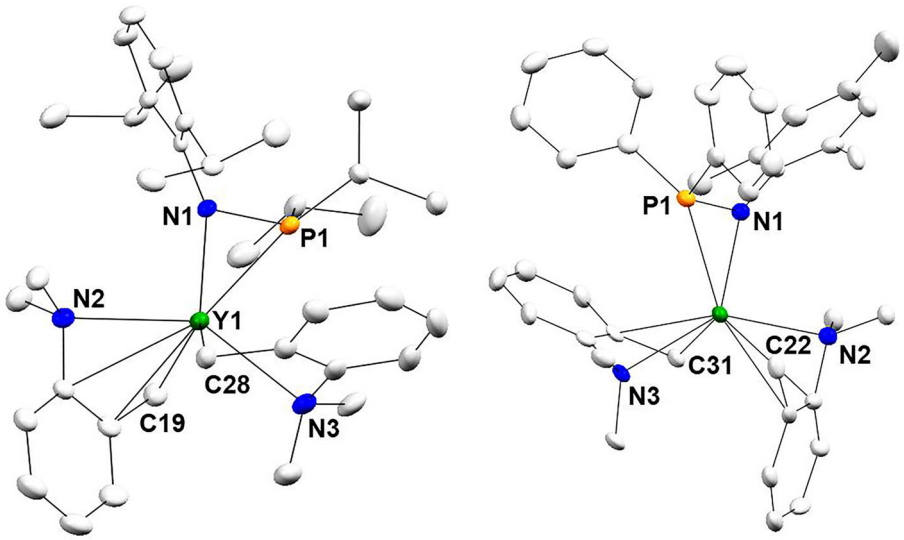


FIGURE 1 ORTEP drawings of **NP2-Y** (left) and **NP4-Y** (right) with 30% thermal ellipsoids. H atoms have been omitted for clarity. Selected bond lengths (Å) for **NP2-Y**: Y1-N1 2.302(2), Y1-C28 2.427(3), Y1-C19 2.449(3), Y1-N2 2.498 (2), Y1-N3 2.561(2), Y1-P1 2.7385(8), N1-P1 1.679(2). Selected bond lengths (Å) for **NP4-Y**: Y1-N1 2.263(4), Y1-C22 2.443(5), Y1-C33 2.427(5), Y1-N2 2.501 (4), Y1-N3 2.535(4), Y1-P1 2.8048(15), N1-P1 1.657(4)

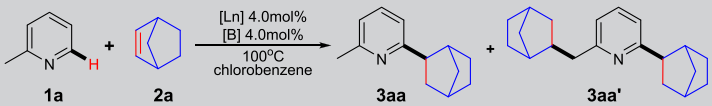


TABLE 1 Optimization of the reaction conditions[a]

Entry	[Ln]	[B]	t/h	Yield [%]	
				3aa	**3aa′**
1	**NP1-Sc**	-	24	-	-
2	-	$B(C_6F_5)_3$	24	-	-
3	**NP1-Sc**	$B(C_6F_5)_3$	1	98	-
4	**NP1-Sc**	$[Ph_3C][B(C_6F_5)_4]$	0.5	90	5
5	**NP1-Sc**	$[Ph_3C][B(C_6F_5)_4]$	6	-	99
6	**NP2-Sc**	$B(C_6F_5)_3$	1	97	-
7	**NP3-Sc**	$B(C_6F_5)_3$	1	97	-
8	**NP4-Sc**	$B(C_6F_5)_3$	1	34	-
9	**NP1-Y**	$B(C_6F_5)_3$	24	12	-
10	**NP1-Lu**	$B(C_6F_5)_3$	24	24	-
11	**NP1-Sm**	$B(C_6F_5)_3$	24	12	-
12	**NP1-Ho**	$B(C_6F_5)_3$	24	20	-
13	**NP1-Gd**	$B(C_6F_5)_3$	24	14	-
14[b]	**NP1-Sc**	$B(C_6F_5)_3$	2	97	-
15[c]	**NP1-Sc**	$B(C_6F_5)_3$	2	95	-
16	***η*** **^{5}-Cp*-Sc**	$B(C_6F_5)_3$	4	99	-
17	$Y[N(SiMe_3)_2]_3$	$B(C_6F_5)_3$	24	-	-
18	$Sc[N(SiMe_3)_2]_3$	$B(C_6F_5)_3$	24	-	-

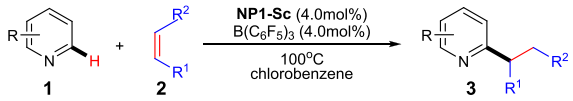
[a]Reaction conditions: [Ln] = mono(phosphinoamido)-rare earth complex (0.04 mmol), [B] = borate reagent (0.04 mmol), **1a** (1.0 mmol), **2a** (4.0 mmol, 4.0 equiv), chlorobenzene (2 ml), yields of **3aa** and **3aa′** were determined by GC with mesitylene as an internal standard.
[b]Toluene as solvent (2 ml).
[c]Benzene as solvent (2 ml).

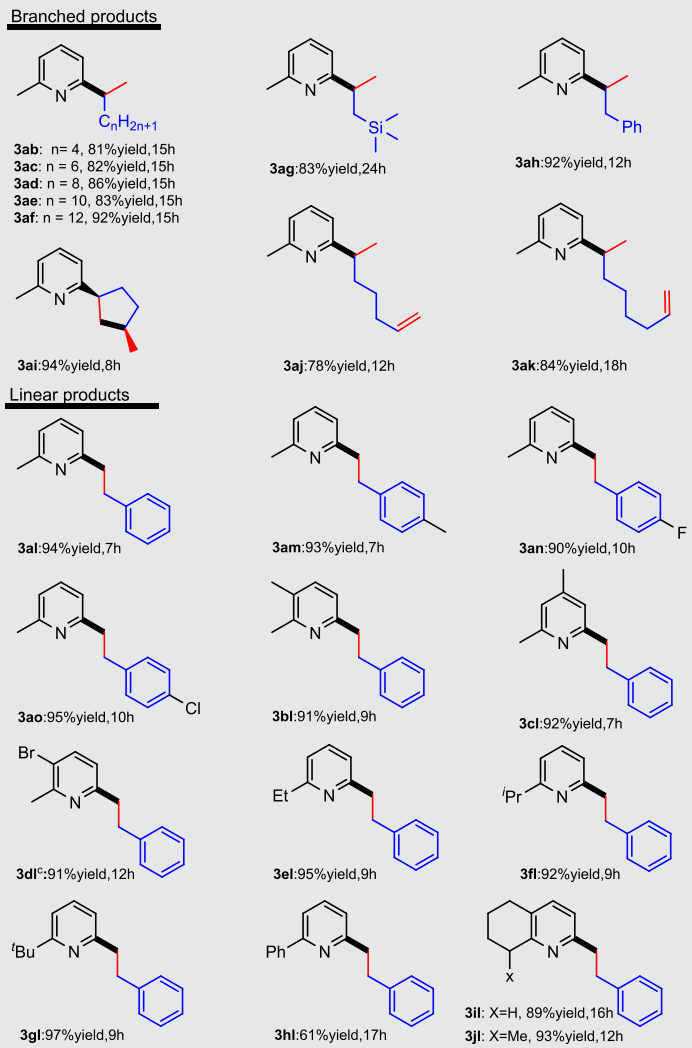
NP4-Y: 1.657(2) Å) suggests partial N–P multiple-bonding character.[13a,18]

3.2 | Rare earth-catalyzed *ortho*-C–H addition of pyridines with alkenes

The C–H alkylation of pyridine with alkenes provides a most straightforward and 100% atom-efficient route for the synthesis of alkylated pyridine derivatives. The special η^2-chelating mode and partial N–P multiple-bonding character in the mono(phosphinoamido)-rare earth complex partly resemble to the η^5-fashion of Cp ligand in half-sandwich rare earth catalyst, which intensively encouraged us to explore its catalytic feasibility in *ortho*-C–H addition of pyridines towards olefins. As shown in Table 1, the *ortho*-C–H alkylation of 2-picoline with norbornene was chosen as a model reaction for

TABLE 2 Scope of pyridines and olefins[a,b]





[a]Reaction conditions: **NP1-Sc** (0.04 mmol), $B(C_6F_5)_3$ (0.04 mmol), **1** (1.0 mmol), **2** (4.0 mmol), and chlorobenzene (2 ml).
[b]Isolated yields.
[c]**NP1-Sc** (0.06 mmol), $B(C_6F_5)_3$ (0.06 mmol).

testing. The reaction was carried out in chlorobenzene at 100°C with 4.0 mol% catalyst loading. Neither the natural scandium complex **NP1-Sc** nor $B(C_6F_5)_3$ used alone was ineffective, while the combination of **NP1-Sc**/$B(C_6F_5)_3$ was highly efficient, and the catalytic reaction was accomplished in only 1 h with the formation of the alkylation product **3aa** in 98% yield (entries 1–3). These results suggest the cationic scandium alkyl species, generated in situ from the reaction of **NP1-Sc** with borate reagent, is essential for this transformation.[6b–d,13a] Upon replacing $B(C_6F_5)_3$ with $[Ph_3C][B(C_6F_5)_4]$, a higher catalytic efficiency was achieved. The alkylation product **3aa** was obtained in 90% yield accompanied with a little amount of product **3aa′** in 0.5 h. The formation of bialkylation product **3aa′** indicated that the 2-pyridymethyl C(sp^3)–H of 2-picoline was also alkylated by this catalysis. Notably, when the reaction time was extended to 6 h, the bialkylation product **3aa′** was yielded quantitatively (entries 4–5). Further experiments disclosed that the substituents on the phosphorus atom of the phosphinoamide anion had a much lower influence on the catalyst activity than those on nitrogen atom (entries 3 and 6–8). As a contrast, analogous yttrium complex **NP1-Y**, lutetium complex **NP1-Lu**, samarium complex **NP1-Sm**, holmium complex **NP1-Ho**, and gadolinium complex **NP1-Gd** are less effective (entries 9–13). The reaction in toluene or benzene could also proceed well (entries 14 and 15). Employing **η^5-Cp*-Sc**/$B(C_6F_5)_3$ as catalyst under the same conditions, the reaction was completed in 4 h with the quantitative yield of **3aa** (entry 16). Triamido-rare earth complexes, such as Sc[N $(SiMe_3)_2]_3$ and Y [N $(SiMe_3)_2]_3$, were unactive, which implied that the σ–Ln–C bond plays an important role for C–H alkylation of pyridine towards olefins (entries 17 and 18).

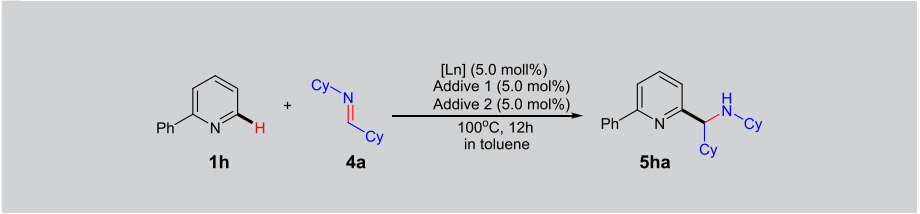
With the optimal reaction conditions in hand, we next examined the scopes of pyridines and olefins with the combination of NP1-Sc/$B(C_6F_5)_3$ as catalyst. As indicated in Table 2, a series of olefins was first tested with 2-picoline as C–H partner. Besides norbornene, linear α-alkenes with a formula of $CH_2 = CH_2C_nH_{2n+1}$ ($n = 4$, 6, 8, 10, and 12) were also compatible with this catalytic protocol, and the branched alkylation pyridine products **3ab**–**3af** were obtained in 81–92% yields in 15 h. The formation of branched addition products **3ab**–**3af** suggests that a 2,1-insertion of Ln–C bond into α-olefins occurs in the catalytic cycle,[6b,13a] which contrasted with the linear adductive products by late-transition metal catalyst in a 1,2-insertion fashion.[3b,d,i,l] Allyltrimethylsillane (2g) and allylbenzene (2h) were effective substrates (See **3ag** in 83% yield and **3ah** in 92% yield). α,ω-Dienes were also suitable for this catalytic protocol. 1,5-Hexadienes (**2i**) was converted into the cyclic product **3ai** as a single *cis*-isomer in 94% yield via a cascade 2,1-insertion of alkene sequence.[13] In the cases of 1,6-heptadiene (**2j**) and 1,7-octadiene (**2k**), acyclic adducts were formed as main products so that a free C=C double bond remained (see **3aj** in 78% yield and **3ak** in 84% yield).[19] Similar to the cationic half-sandwich scandium catalyst, the *ortho*-C–H alkylation of pyridine towards styrene furnished a linear alkylation product **3al** in 94% yield. This should be attributed to the 1,2-insertion of Sc–C into styrene.[6b] As a contrast, late-transition metal catalysts usually produce a branched additive product via a 2,1-insertion mode.[3d,i,k,m] Under the same conditions, substituted styrenes such as 4-methyl- and 4-halogen styrenes were all well tolerated (see **3am**–**3ao** in 90–95% yields). Subsequently, we examined the scope of pyridines with styrene as partner. 2,3-Dimethyl-, 2,4-dimethyl-, 3-bromo-2-methyl-, 2-ethyl-, 2-isopropyl-, 2-*tert*-butyl-, and 2-phenyl-substituted pyridines were all alkylated by styrene to generate linear alkylation products **3bl**–**3hl** in high yields. It is noteworthy that the C–H alkylation of 2-phenylpyridine only took place at the ortho-position of the pyridine unit rather than on the phenyl ring. The *ortho*-C–H alkylation of 5,6,7,8-tetrahydroquinoline (**1i**) and 8-methyl-5,6,7,8-tetrahydroquinoline (**1j**) towards styrene could also proceed well. Unfortunately, simple pyridine as well as quinoline was ineffective for this catalysis. All of these experimental results indicated that the catalytic performance of current mono(phosphinoamido)-scandium catalyst is comparable with that of half-sandwich scandium catalyst reported.[6b–d]

3.3 | Rare earth-catalyzed *ortho*-C–H addition of pyridines towards imines

Recently, triamido-rare earth complexes, such as Gd [N $(SiMe_3)_2]_3$ (Scheme 1b), were demonstrated to be catalytically active for *ortho*-C–H addition of 2-substituted pyridines towards imines with the formation of *ortho*-aminomethylation pyridine derivatives. In this catalytic process, the σ-amido-rare earth bond undoubtedly plays an important role. Considering the σ-amido-rare earth bond in these mono(phosphinoamido)-rare earth complexes,[9a,b] we next decide to explore the probability of catalytic *ortho*-C–H addition of pyridine into polar C=N double bond of imines by use of mono(phosphinoamido)-rare earth complexes.

As shown in Table 3, the *ortho*-C–H addition reaction of pyridine **1h** with *N*,1-dicyclohexylmethanimine (**4a**) was chosen as model reaction for checking, and the reaction was conducted in toluene at 100°C for 12 h. We first explored the influence of second amine on the reaction in the presence of 5.0 mol% of **NP1-Y**. No conversion took place without addition of any second amine

TABLE 3 Optimization of the reaction conditions[a]



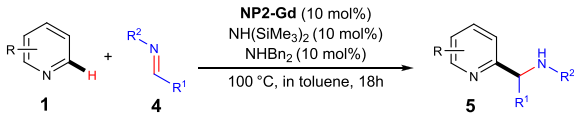
Entry	[Ln]	Additive 1	Additive 2	Yield **5ha** (%)
1	**NP1-Y**	-	-	-
2	**NP1-Y**	NH $(SiMe_3)_2$	NH $(SiMe_3)_2$	31
3	**NP1-Y**	$NHBn_2$	$NHBn_2$	23
4	**NP1-Y**	NH $(SiMe_3)_2$	$NHBn_2$	36
5	**NP2-Y**	NH $(SiMe_3)_2$	$NHBn_2$	42
6	**NP3-Y**	NH $(SiMe_3)_2$	$NHBn_2$	35
7	**NP4-Y**	NH $(SiMe_3)_2$	$NHBn_2$	34
8	**NP2-Sc**	NH $(SiMe_3)_2$	$NHBn_2$	trace
9	**NP2-Lu**	NH $(SiMe_3)_2$	$NHBn_2$	20
10	**NP2-Gd**	NH $(SiMe_3)_2$	$NHBn_2$	88
11[b]	**NP2-Gd**	NH $(SiMe_3)_2$	$HNBn_2$	97(93)[c]
12[d]	$Gd[N(SiMe_3)_2]_3$	-	$HNBn_2$	90[c]
13	**η^5-Cp*-Y**	NH $(SiMe_3)_2$	$HNBn_2$	-

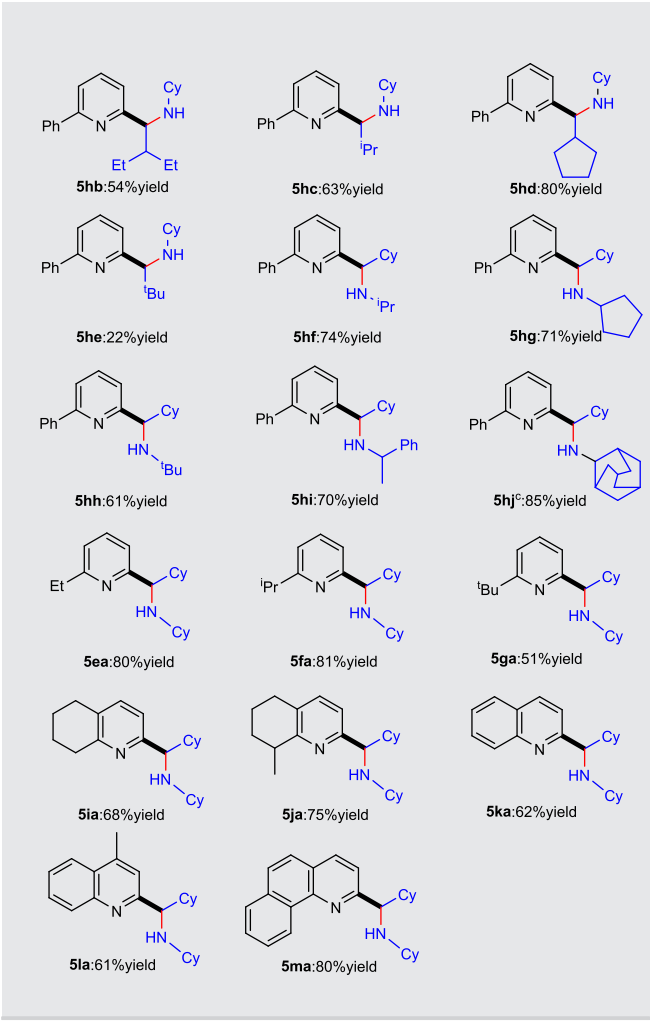
[a]Reaction conditions: [Ln] = organo-rare earth complex (0.025 mmol), additive 1 (0.025 mmol), additive 2 (0.025 mmol), **1 h** (0.5 mmol), **4a** (0.75 mmol, 1.5 equiv.), 100°C, 12 h, toluene (2 ml). The yields of **5ha** was determined by GC with mesitylene as an internal standard.
[b]**4a**(1.0 mmol).
[c]Isolated yield.
[d]$Gd[N(SiMe_3)_2]_3$ (10.0% mol), $HNBn_2$ (10.0%mol), 24 h (See Nagae et al.[9a]).

(entry 1). A small amount of alkylation product **5ha** was detected when 10 mol% NH $(SiMe_3)_2$ or $NHBN_2$ was added into the reaction system (entries 2–3). In the presence of a mixture of secondary amines NH $(SiMe_3)_2$ (5 mol%) and $NHBN_2$ (5 mol%), the yield of **5ha** was increased up to 36% (entry 4). Then, a series of various mono(phosphinoamido)-yttrium complexes were tested and found no increment in yield (entries 4–7). The analogous scandium and lutetium were also less catalytically efficient (entries 8–9). To our delight, when analogous gadolinium complex **NP2-Gd** was employed under the same reaction conditions, the yield of **5ha** was rocketed to 88% (entry 10). Remarkably, upon employing 2.0 equiv. amount of **4a**, **5ha** was obtained in 97% yield (entry 11). As contrast, the reported combination of Gd $[N(SiMe_3)_2]_3$ (10 mol%)/$HnBn_2$ (10 mol%) gave a 90% yield of **5ha** in 24 h[9a] (entry 12). The half-sandwich rare earth complexes η^5–Cp*–Y was less effective under the same conditions (entry 13). Loading 10 mol% of complex **NP2-Gd** accompanied with equimolar amount of NH $(SiMe_3)_2$ and $NHBN_2$, we next scrutinized various pyridines and imines, as showed in Table 4. With 1h as C–H partner, we first checked the scope of imines. The imine with an isopropyl, pentan-3-yl, or cyclopentyl group at the imine carbon atom reacted with 1 h to give the corresponding aminomethylation products **5hb–5hd** in a good yield. When the more hindered *tert*-butyl unit was introduced onto imine carbon atom, the aminomethylation reaction gave low conversion (see **5he** in 22% yield). This is presumably due to the steric hindrance that impedes the insertion of Gd–C bond into C=N double bond of imine to some extent. In contrast, the imines anchoring a *tert*-butyl group at nitrogen atom led to a good yield (see **5hh** in 61% yield). In a similar manner, substituents at nitrogen atom of imine, such as isopropyl, cyclopentane, 1-phenylethyl, and even 2-adamantyl, are all well tolerated, and the addition products were obtained in good yield (see **5hf**, **5hg**, **5hi**, and **5hj**). Unfortunately, when a primary alkyl was attached to the carbon or nitrogen atom of imine, the related catalysis is less efficient, probably because of the stronger interaction between the formed aminomethylation product and metal center.[9a,b]

With imine **4a** as model substrate, a series of 2-substituted pyridines were evaluated in this catalysis. The aminomethylation reaction of 2-ethyl-(**1e**),

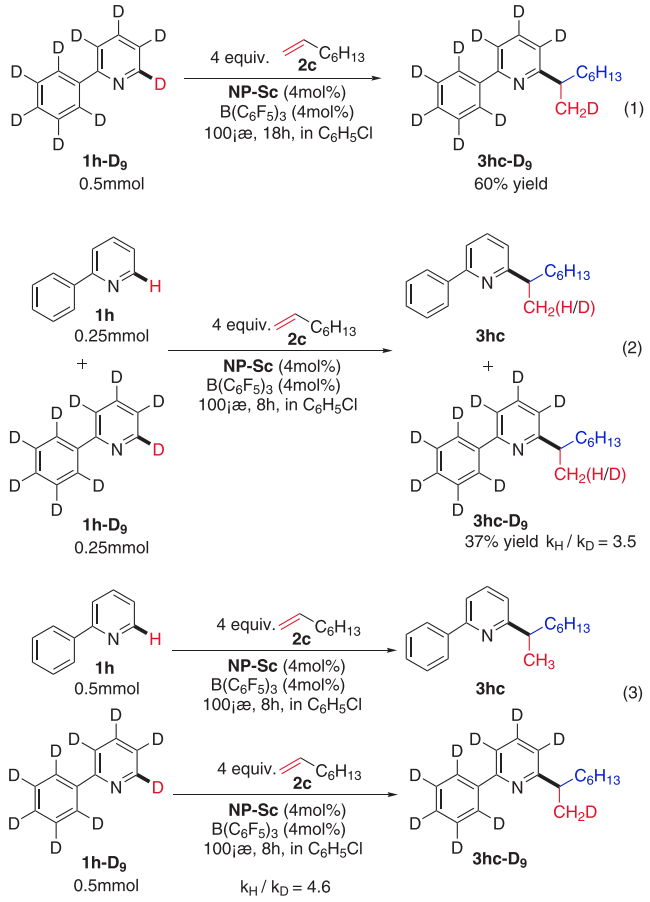
TABLE 4 Scope of pyridines and imines[a,b]





[a]Reaction conditions: **NP2-Gd** (0.05 mmol), NH $(SiMe_3)_2$ (0.05 mmol), $NHBn_2$ (0.05 mmol), **1** (0.5 mmol), **4** (1.0 mmol), 100°C, toluene (2 ml).
[b]Isolated yields.
[c]20 mol% catalyst loading.

2-isopropyl-(**1f**), and 2-*tert*-butyl-(**1g**) pyridines could be readily aminomethylated with moderate to good yields of isolation product (see **5ea**, **5fa**, and **5ga**, 51–81% yields). The ring-fused 5,6,7,8-tetrahydroquinoline and 8-methyl-5,6,7,8-tetrahydroquinoline are also effective substrates (see **5ia** and **5ja**). Notably, the aminomethylation of quinolines could also proceed efficiently by this catalysis with the formation of quinoline derivatives **5ka** and **5la** in 62% and 61% yields, respectively. It is noteworthy that the C–H alkylation of quinolines selectively occurred at 2-position of quinoline ring without modifying C–H in 8-position. Benzo[*h*]quinoline (**1m**) could also be aminomethylated, effectively (see **5ma** in 80% yield).



SCHEME 3 Deuterium-labeling experiments

3.4 | Deuterium-labeling experiments

In order to get some mechanistic insight into this C–H transformation by rare earth catalyst, deuterium-labeling experiments were carried out under the standard conditions. As shown in Scheme 3, the reaction of **1h**-D_9 with 1-octene (**2c**) indicated that the *ortho*-deuterium atom of pyridine **1h**-D_9 was transferred to the expected methyl unit of alkylation product **3hc**-D_9, which implied a pyridine *ortho*-C–H cleavage process in the catalysis cycle (Equation 1).The competitive and parallel reactions of **1h** and **1h**-D_9 with 1-octene gave a kinetic isotope effect (KIE) value of $k_H/k_D = 3.5$ and 4.6, respectively, suggesting that the C–H bond activation (deprotonation) should be involved in the rate determining steps for the current catalysis (Equations 2 and 3).

4 | CONCLUSIONS

In summary, we have demonstrated for the first time that mono(phosphinoamido)-rare earth complexes, such as **NP1-Sc** and **NP2-Gd**, can serve as efficient catalyst precursors for *ortho*-C–H addition of pyridines with nonpolar alkenes and polar imines with an excellent regioselectivity and chemoselectivity. A broad range of substrates were subjected to the current catalysis, directly rendering the synthesis of a variety of *ortho*-alkylation and *ortho*-aminoalkylated pyridine derivatives in moderate to excellent yields and with a 100% atom-efficiency. The behaviors of current catalyst are comparable to those of half-sandwich rare earth catalyst along with amido-rare earth catalyst reported previously. The key to the success of mono(phosphinoamido)-rare earth complexes may be attributed to its special η^2-coordiantion of **N-P** to rare earth site as well as its unique σ-amido-rare earth bond. Further research on the catalytic applications of the mono(phosphinoamido)-rare earth complexes in other chemical transformations are now in progress.

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AUTHOR CONTRIBUTIONS

Hailong Lin: Data curation. **Yongrui Li:** Methodology. **Jinyu Wang:** Investigation. **Mei Zhang:** Formal analysis. **Tao Jiang:** Funding acquisition; supervision. **YanHui Chen:** Funding acquisition; supervision.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article.

ORCID

Hailong Lin https://orcid.org/0000-0002-3454-0246
Yongrui Li https://orcid.org/0000-0002-1522-044X
Jinyu Wang https://orcid.org/0000-0002-3714-8733
Mei Zhang https://orcid.org/0000-0002-5767-7421
Tao Jiang https://orcid.org/0000-0002-9854-7228
Jing Li https://orcid.org/0000-0003-3338-0284
Yanhui Chen https://orcid.org/0000-0002-6293-535X

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[19] In the case of 1,6-heptadiens, a small amount of carbocyclic product **3aj'** (ca. 20% yield) was also produced as an inseparable byproduct.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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