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Enantioselective C–H Bond Addition of Pyridines to Alkenes Catalyzed by Chiral Half-Sandwich Rare-Earth Complexes

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Supporting Information

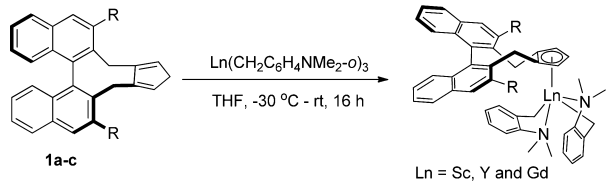
ABSTRACT: Cationic half-sandwich scandium alkyl complexes bearing monocyclopentadienyl ligands embedded in chiral binaphthyl backbones act as excellent catalysts for the enantioselective C–H bond addition of pyridines to various 1-alkenes, leading to formation of a variety of enantioenriched alkylated pyridine derivatives in high yields and excellent enantioselectivity (up to 98:2 er).

The enantioselective C–H bond addition of aromatic compounds to alkenes is the most atom-economical approach for the synthesis of enantioenriched alkylated arene derivatives.[1−3] Pyridine moieties are among the most important heterocyclic structural motifs, existing widely in a large number of natural products, pharmaceuticals, ligands, and functional materials.[4] Therefore, the enatioselective C–H addition of pyridines to alkenes is of great interest and importance. However, despite recent progress in the racemic C–H bond functionalization of pyridines,[5] the enatioselective C–H alkylation of pyridines has remained almost unexplored to date.[6] In 1994, Rodewald and Jordan reported the chiral-zirconocene-catalyzed asymmetric C–H bond addition of 2-picoline to 1-hexene, which afforded the corresponding alkylation product in 19% yield and 58% ee.[6] This is the only precedent of the asymmetric C–H addition of a pyridine compound to an alkene, as far as we are aware.

We recently reported that half-sandwich rare-earth alkyls[7] can serve as unique catalysts for the C–H bond addition of aromatic compounds such as pyridines[5l] and anisoles[8] to various 1-alkenes, which afforded the corresponding branched alkylation products with excellent selectivity. These results encouraged us to examine the asymmetric C–H bond addition to alkenes by chiral half-sandwich rare-earth complexes. In this paper, we report the synthesis of the first chiral half-sandwich rare earth alkyl complexes and their application to the catalytic enantioselective C–H addition of pyridines to alkenes. We found that the chiral half-sandwich scandium alkyl complexes can act as excellent catalysts for the enantioselective C–H addition of pyridines to various alkenes, which afforded the corresponding enantioenriched alkylated pyridine derivatives in high yields and high enantioselectivity.

The acid–base reaction between the rare-earth tris(aminobenzyl) compounds $Ln(CH_2C_6H_4NMe_2\text{-}o)_3$ (Ln = Sc, Y, Gd)[9] with one equimolar amount of binaphthyl-substituted cyclopentadienes **1a–c**[3f,10] in tetrahydrofuran (THF) gave straightforwardly the corresponding mono-Cp-ligated rare-earth bis(aminobenzyl) complexes **2a–c** in 65–81% isolated yields (Scheme 1).[11] The reaction is highly selective, and

Scheme 1. Synthesis of Chiral Half-Sandwich Rare-Earth Dialkyl Complexes



a: R = H
b: R = $OSiPh_2(^tBu)$
c: R = $OSi(^iPr)_3$

Ln = Sc, Y and Gd
2a-, 2b-, 2c-Sc, 74-81%
2c-Y, 65%
2c-Gd, 78%

formation of a bis(cyclopentadienyl)-coordinated rare-earth complex was not observed. Complexes **2a–c** are highly soluble in benzene, toluene, and THF. The scandium and yttrium complexes showed well resolved ^1H and ^{13}C NMR spectra (see Supporting Information (SI)), while the paramagnetic gadolinium complex did not give an informative NMR spectrum. To our knowledge, complexes **2a–c** represent the first examples of chiral half-sandwich rare-earth alkyl complexes.[12]

To probe the potential of the chiral half-sandwich rare-earth alkyl complexes as a catalyst for the C–H bond addition of pyridines to alkenes, we first examined the reaction of 2-picoline (**3a**) with a strained (reactive) bicyclic alkene, norbornene (**4a**).[3g] In the presence of $[Ph_3C][B(C_6F_5)_4]$ (5 mol %) in toluene at 25 °C, the scandium complex **2a-Sc** (5 mol %), which bears an unsubstituted binaphthylcyclopentadienyl ligand, afforded the C–H norbornylation product **5a** in 38% yield with an enantiomeric ratio (er) of 63:37 in 96 h (Table 1, entry 1). When **2c-Sc**, which possesses the $OSi(^iPr)_3$ substituents at the 3,3′-positions of the binaphthyl group in the Cp ligand, was used as a catalyst, the yield of **5a** increased to 92% and the er was improved to 89:11 under the similar conditions (Table 1, entry 3), suggesting that the activity and stereoselectivity of this reaction are significantly influenced by the steric hindrance of the ancillary ligands in the catalysts (see also Table 1, entries 2 and 3). Raising the reaction temperature from 25 to 50 °C slightly lowered the stereoselectivity but significantly accelerated the reaction (94% yield, in 36 h; 82:18 er) (Table 1, entry 4). No reaction was observed at 0 °C.

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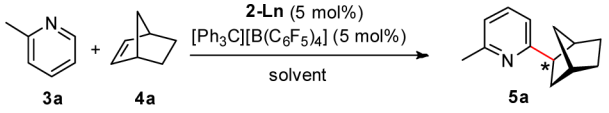
Table 1. Rare-Earth-Catalyzed Enantioselective C−H Addition of 2-Picoline to Norbornene[a]



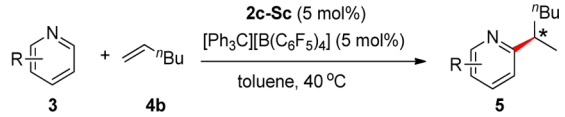
entry	[Ln]	time (h)	solvent	temp (°C)	yield (%)	er[b,c]
1	**2a-Sc**	96	toluene	25	38	63:37
2	**2b-Sc**	72	toluene	25	51	84:16
3	**2c-Sc**	72	toluene	25	92	89:11
4	**2c-Sc**	36	toluene	50	94	82:18
5	**2c-Sc**	72	toluene	0	0	
6	**2c-Sc**	72	chlorobenzene	25	89	86:14
7	**2c-Sc**	72	benzene	25	73	83:17
8	**2c-Y**	72	toluene	50	0	
9	**2c-Gd**	72	toluene	50	0	

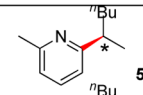
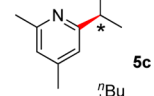
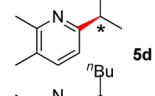
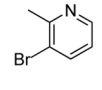
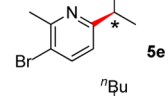
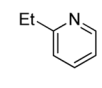
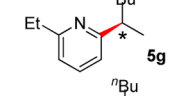
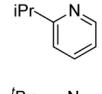
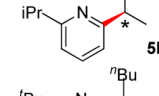
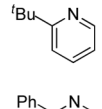
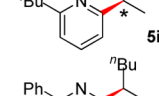
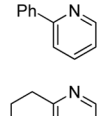
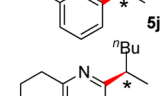
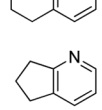
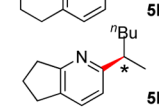
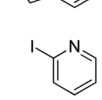
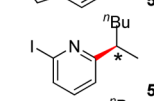
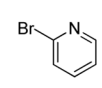
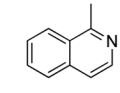
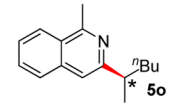
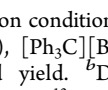
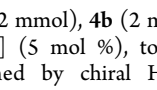
[a]Reaction conditions: **3a** (0.2 mmol), **4a** (0.3 mmol), [**Ln**] (5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (5 mol %), solvent (1.0 mL), isolated yield. [b]Determined by chiral HPLC. [c]The absolute configuration was confirmed by X-ray analysis of **5a-HPF$_6$** (see SI).

Changing the solvent from toluene to chlorobenzene or benzene showed little influence on the reaction (Table 1, entries 6 and 7). The analogous yttrium (**2c-Y**) and gadolinium (**2c-Gd**) complexes showed no activity under the similar conditions (Table 1, entries 8 and 9), in line with the metal influence observed previously in olefin polymerization.[13] The X-ray diffraction analyses of single crystals of the HPF_6 salt of **5a** revealed that the absolute configuration of **5a** is 1*R*, 2*R*, 4*S* (see SI).

The **2c-Sc**/$[Ph_3C][B(C_6F_5)_4]$ combination was then chosen as a catalyst to examine the reaction of various pyridine derivatives with an unstrained alkene, 1-hexene (**4b**). Some representative results are summarized in Table 2. The C−H bond addition of 2-picoline to 1-hexene took place selectively at 40 °C, affording the corresponding branched asymmetric alkylation product **5b** in high yield (90%) and high enantioselectivity (94:6 er) (Table 2, entry 1). These results are in contrast with those of the zirconium-catalyzed reaction reported previously.[6] The bromo and chloro substituents in the picoline substrates are compatible with the catalyst, giving exclusively the corresponding chiral C−H alkylation products (Table 2, entries 4 and 5). The asymmetric alkylation of 2-ethyl-, 2-isopropyl-, 2-*tert*-butyl-, and 2-phenyl-substituted pyridines could also be achieved with analogously high yields (83−94%) and high enantioselectivity (88:12.−92:8 er) (Table 2, entries 6−9). It is also worth noting that, in the case of 2-phenylpyridine, the C−H activation reaction occurred selectively at the pyridine unit rather than at the phenyl group, in contrast with the reactions catalyzed by late transition metal catalysts.[14] Tetrahydroquinoline and 2,3-cyclopentenopyridine are also suitable substrates for the asymmetric C−H alkylation with 1-hexene (Table 2, entries 10 and 11). In the case of 2-iodo- and 2-bromopyridines, the alkylation took place exclusively at the C−H position rather than the C−I or C−Br bond (Table 2, entries 12 and 13). 1-Methylisoquinoline is also applicable, affording the alkylation product **5o** in 81% isolated yield with excellent enatioselectivity (97:3 er) (Table 2, entry 14). The alkylation reaction was not observed in the case of unsubstituted pyridine or quinoline, probably because their coordination to the metal center is too strong, which could hamper the access of 1-hexene to the metal center.

Table 2. Scandium-Catalyzed Enantioselective Addition of Pyridines to 1-Hexene[a]



entry	substrate	time (h)	product	yield (%)	er[b]
1		72	 **5b**	90	94:6
2		72	 **5c**	93	98:2
3		48	 **5d**	95	95:5
4		24 48[d]	 **5e**	95 94	87:13 95:5
5		48	 **5f**	91	96:4
6		72	 **5g**	93	92:8
7		72	 **5h**	94	88:12[c]
8		24[d] 72[e]	 **5i**	98 83	78:22[c] 92:8[c]
9		72	 **5j**	94	92:8[c]
10		72	 **5k**	93	92:8[c]
11		96	 **5l**	63	93:7
12		72	 **5m**	87	94:6[c]
13		48	 **5n**	85	94:6[c]
14		72	 **5o**	81	97:3

[a]Reaction conditions: **3** (0.2 mmol), **4b** (2 mmol, 10 equiv), **2c-Sc** (5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (5 mol %), toluene (1.0 mL), 40 °C, isolated yield. [b]Determined by chiral HPLC. [c]Determined by quantitative ^{13}C NMR in the presence of Mosher's acid. [d]The reaction was conducted at 25 °C. [e]The reaction was conducted at 15 °C.

Table 3 shows the reactions of 2-picoline with various 1-alkenes. Similar to 1-hexene, 1-heptene and 1-octene also gave the expected branched products in high yields (92%) and high enantioselectivity (93:7 er) (Table 3, entries 1 and 2). 4-Methyl-1-pentene, allylcyclohexane, and allyltrimethylsilane,

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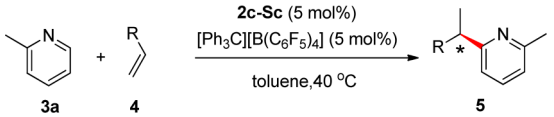
Table 3. Asymmetric Alkylation of 2-Picoline with Various Olefins[a]

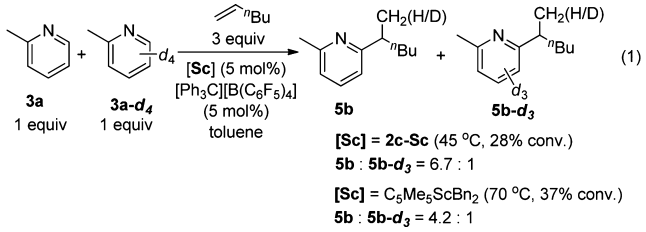


entry	substrate	time (h)	product	yield (%)	er[b]
1	$^{n}C_5H_{11}$	48	**5p**	92	93:7
2	$^{n}C_6H_{13}$	72	**5q**	92	93:7
3		96	**5r**	95	90:10
4		72	**5s**	94	91:9
5		72	**5t**	80	86:14

[a]Reaction conditions: **3a** (0.2 mmol), **4** (2 mmol, 10 equiv), **2c-Sc** (5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (5 mol %), toluene (1.0 mL), 40 °C, isolated yield. [b]Determined by chiral HPLC.

which contain bulky substituents in close proximity to the C−C double bond, could also serve as good alkylation agents in a similar fashion (Table 3, entries 3−5).

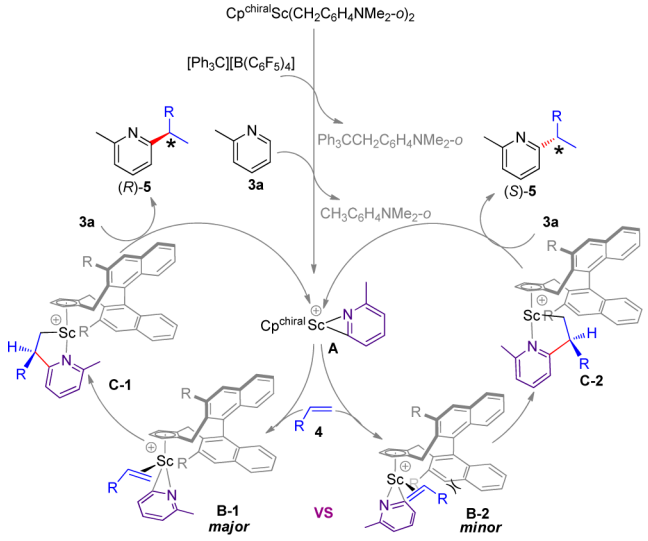
The reaction of a 1:1 mixture of 2-picoline (**3a**) and 2-methylpyridine-d_4 (**3a-d_4**) with 1-hexene catalyzed by **2c-Sc**/$[Ph_3C][B(C_6F_5)_4]$ gave a mixture of **5b** and **5b-d_3** (eq 1). In



this reaction, the protonation and deuteration were observed in the alkylation products of both **3a** and **3a-d_4**. The kinetic isotope effect (KIE = **5b**: **5b-d_3**) was found to be 6.7 after 28% conversion. For comparison, the reaction catalyzed by a nonchiral catalyst $(C_5Me_5)Sc(CH_2C_6H_4NMe_2\text{-}o)_2$ was also examined, which yielded a similar deuterated/hydrogenated product mixture and gave a KIE value of 4.2 under the similar conditions (70 °C, 37% conversion).

A possible reaction mechanism for the present asymmetric C−H alkylation is proposed in Scheme 2. A cationic chiral Sc-η^2-pyridyl species such as **A** could be formed by the deprotonation of 2-picoline (**3a**) at the C6 position with a cationic Sc benzyl species $[Cp^{chiral}Sc(CH_2C_6H_4NMe_2\text{-}o)]^+$ which was generated by the reaction of **2c-Sc** with an equimolar amount of $[Ph_3C][B(C_6F_5)_4]$.[5l,11,15] The diastereoselective coordination of a 1-alkene (**4**) to the metal center in **A** could afford **B-1** preferably to avoid steric repulsion between the R substituent in the alkene and the Cp^{chiral} moiety of the catalyst.[5l,16] The subsequent 2,1-addition of the Sc−pyridyl bond to the coordinated alkene in **B-1** would give **C-1**, which

Scheme 2. Possible Reaction Pathway



on reaction with 2-picoline (**3a**) (C−H deprotonation) should release the alkylation product (*R*)-**5** and regenerate **A**. This scenario is consistent with the experimental observation of the norbornylation product **5a** having the (1*R*, 2*R*, 4*S*) absolute configuration (see SI).

In summary, we have developed a new family of half-sandwich rare-earth dialkyl complexes that bear chiral mono(cyclopentadienyl) ligands. In combination with $[Ph_3C][B(C_6F_5)_4]$, the chiral scandium complexes such as **2c-Sc** can serve as excellent catalysts for the enantioselective C−H bond addition of pyridines to various α-olefins (including unconstrained simple alkenes), leading to formation of a variety of enantioenriched alkylated pyridine derivatives. This protocol features high yields, excellent stereoselectivity, and good functional group compatibility. Explorations of the potential of chiral half-sandwich rare-earth catalysts for other transformations are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures, characterization data for all new compounds, HPLC traces of the alkylated pyridines, and crystallographic data (CIF) for **5a-HPF$_6$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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