ChemPubSoc Europe

DOI: 10.1002/chem.201501121

CHEMISTRY
A European Journal
Communication

Synthetic Methods

Catalytic C–H Bond Addition of Pyridines to Allenes by a Rare-Earth Catalyst

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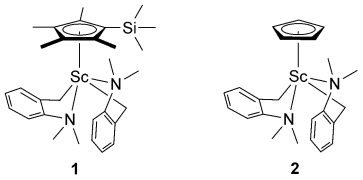
Abstract: The catalytic C–H addition of pyridines to allenes has been achieved for the first time by using a half-sandwich scandium catalyst, thus constituting a straightforward and atom-economical route for the synthesis of alkenylated pyridine derivatives. The reaction proceeded regio- and stereoselectively, affording a new family of alkenylated pyridine compounds which are otherwise difficult to synthesize. A cationic Sc-η^2-pyridyl species was isolated and confirmed to be a key catalyst species in this transformation.

Pyridine units are among the most important heterocyclic structural motifs, existing widely in many natural products, pharmaceuticals, ligands and functional materials.[1] The development of efficient protocols for the synthesis of pyridine derivatives has therefore received much current interest.[2,3] So far, extensive studies on the C–H alkylation of pyridines with alkenes have been carried out as the most atom-economical method for the synthesis of alkylated pyridine derivatives.[2] In contrast, studies on the synthesis of alkenylated pyridine derivatives by C–H functionalization of pyridines have remained very limited despite recent progress.[3] It was previously reported that the C–H addition of pyridines to alkynes catalyzed by late transition metal catalysts such as ruthenium[3a] and nickel[3b,c] could give the corresponding alkenylated pyridine derivatives, but this transformation suffered from poor regioselectivity when internal alkynes having two similar substituents were used as substrates. The palladium-catalyzed oxidative coupling of pyridines with alkenes was also reported to afford the alkenylated products,[3d] while this reaction is suitable only for alkenes having electron-withdrawing groups. The search for new protocols for the efficient, selective synthesis of alkenylated pyridine compounds is therefore of much interest and importance.

In principle, the catalytic C–H addition of pyridines to a C=C double bond of allenes[4] could serve as an efficient and atom-economical route for the synthesis of alkenylated pyridine derivatives. However, such catalytic C–H alkenylation of a pyridine compound with an allene unit has not been reported previously, although a large number of examples of allene insertion into aromatic C–H bonds are known.[5] The addition of a zirconium pyridyl species formed by pyridine C–H bond activation to 1,2-propadiene was reported previously, but the catalytic C–H alkenylation of a pyridine compound with an allene by a zirconium complex seemed difficult.[6] We recently found that cationic half-sandwich rare-earth alkyls could serve as efficient catalysts for the C–H alkylation of aromatic compounds such as pyridines[2f,j] and anisoles[7] with various alkenes. In most cases, the selectivity and functional group tolerance of the rare-earth catalysts are different from those of late transition metal catalysts. Encouraged by these results, we examined the use of rare-earth catalysts for pyridine C–H functionalization with allenes. Herein, we report, for the first time, the catalytic C–H addition of pyridines to allenes by a scandium catalyst. This transformation is highly regio- and stereoselective, leading to formation of a new family of alkenylated pyridine derivatives which are otherwise difficult to synthesize. A cationic Sc-η^2-pyridyl complex was confirmed to be the true active catalyst species, thus offering important information for understanding the reaction mechanism.

On the basis of the screening of several different rare-earth catalysts (see Supporting Information, Table S1), we chose the combination of the half-sandwich scandium **1** (Scheme 1) and $[Ph_3C][B(C_6F_5)_4]$ as a catalyst to examine the reactions of various pyridine derivatives (**3**) with cyclohexylallene (**4a**).



1 2

Scheme 1. Half-sandwich scandium dialkyl complexes with different cyclopentadienyl (Cp) ligands.

Some representative results are summarized in Table 1. In the presence of **1** (5 mol%) and $[Ph_3C][B(C_6F_5)_4]$ (5 mol%) in toluene at 70 °C, the reaction proceeded regio- and stereoselectively, affording the corresponding branched alkenylation product **5** through the addition of the pyridyl unit to the middle carbon atom and the addition of a hydrogen atom to the terminal carbon atom of the allene unit in an *E*-selective fashion.[8] A broad range of substituted pyridines such as 2-pi-

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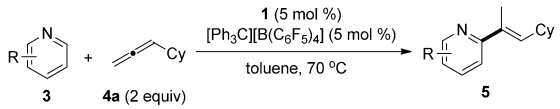
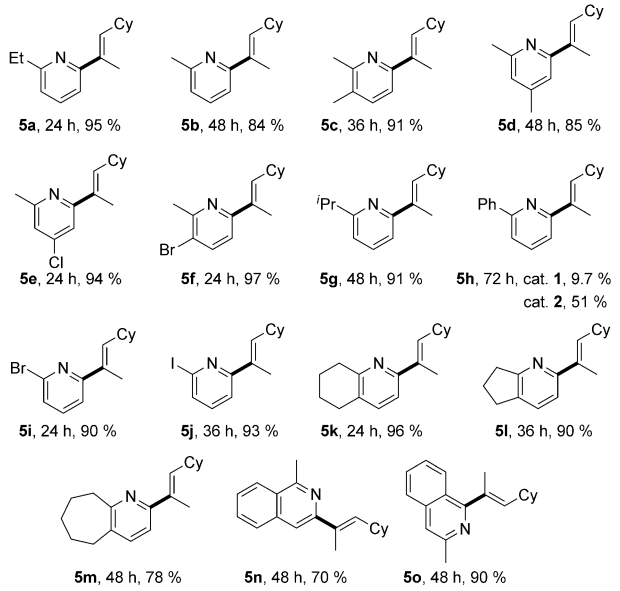
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501121.

coline, 2-isopropylpyridine, 2,3-lutidine, 2,4-lutidine, and ring-fused pyridine derivatives are suitable substrates for this catalytic transformation.[9] Remarkably, the chloro-, bromo- and iodo-substituents in the pyridine substrates survived the catalytic reaction conditions, leading to selective formation of the C–H alkenylation products without dehalogenation (**5e**, **5f**, **5i** and **5j**). 1-Methylisoquinoline and 3-methylisoquinoline were also alkenylated selectively to give the expected products **5n** and **5o**, respectively. In the case of 2-phenylpyridine, the sterically demanding $C_5Me_4(SiMe_3)$-ligated Sc catalyst **1** was less effective than the smaller C_5H_5-ligated analogue **2** for the formation of the expected product **5h**,[10] probably owning to the steric repulsion between the $C_5Me_4(SiMe_3)$ ligand in **1** and the phenyl ring in **4h**.[11]

Table 1. Catalytic C–H addition of various pyridines to cyclohexylallene.[a]

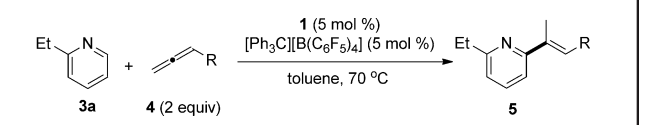


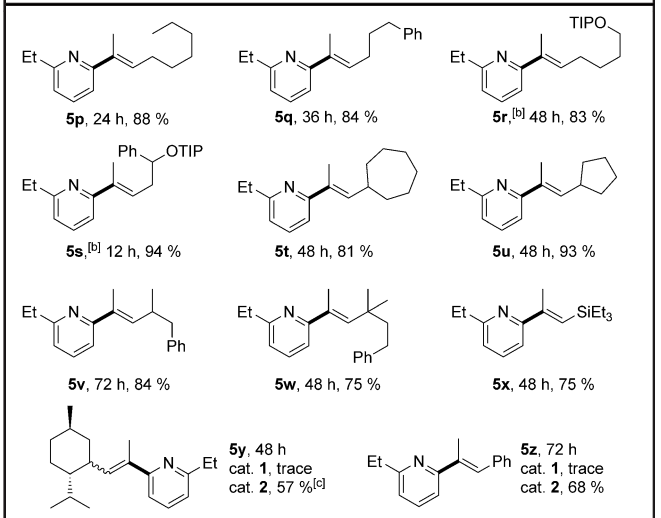


[a] General reaction conditions: **3** (0.4 mmol), **4a** (0.8 mmol, Cy = cyclohexyl), **1** (5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (5 mol %), toluene (2.0 mL), 70 °C, isolated yield. ^{1}H NMR spectra of the crude products indicated that only the *E* isomer was formed.

Table 2 summarizes the reactions of 2-ethylpyridine with various allenes.[12] The allene substrates having linear, branched and cyclic substituents all afforded the corresponding alkenylation products in a highly regio- and stereoselective fashion. Siloxy groups such as $OSi(iPr)_3$ (**5r** and **5s**) are compatible with the catalyst system.[13] The reaction of 2-ethylpyridine with triethylsilylallene also took place regio- and stereoselectively, affording the corresponding silylalkenylation product **5x** in 75% yield. In the case of allenes having a sterically demanding substituent, such as menthylallene and phenylallene, the smaller

Table 2. Catalytic C–H addition of 2-ethylpyridine to various allenes.[a]



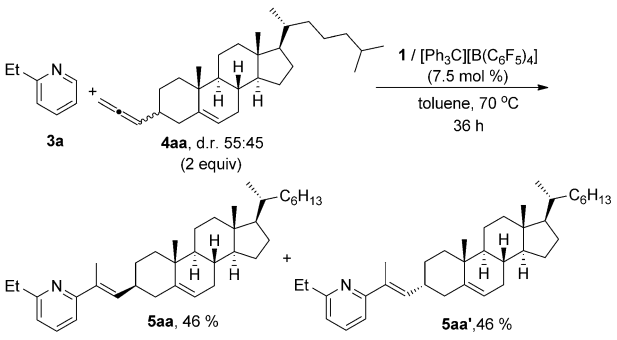


[a] General reaction conditions: **3a** (0.4 mmol), **4** (0.8 mmol), **1** (5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (5 mol %), toluene (2.0 mL), 70 °C, isolated yield. [b] TIP = triisopropylsilyl. [c] **4y**: diastereomeric ratio (d.r.) = 60:40; **5y**: d.r. = 54:46.

catalyst **2** showed much better performance than **1** for the formation of the expected alkenylation products (**5y** and **5z**).[11]

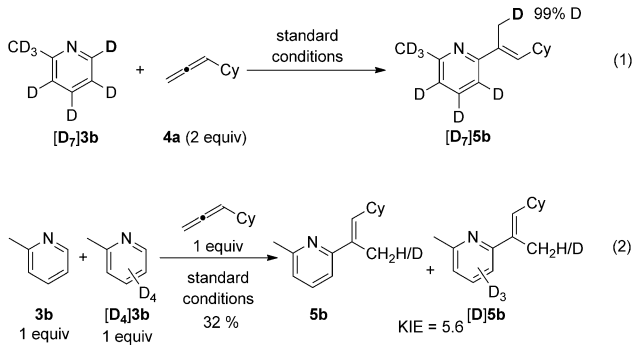
The treatment of 2-ethylpyridine with a cholesteryl-substituted allene **4aa** (d.r. = 55:45) afforded the corresponding 2-pyridylvinyl steroid compound in 92% yield in a highly regio- and stereoselective manner (Scheme 2),[14] demonstrating that the present C–H alkenylation reaction could be applied to the synthesis of pyridine derivatives bearing naturally occurring structures.

The reaction of $[D_7]$2-methylpyridine ($[\mathbf{D_7}]\mathbf{3b}$) and cyclohexylallene afforded the C–D addition product $[\mathbf{D_7}]\mathbf{5b}$, in which 99% deuterium was incorporated at the methyl position [Eq. (1)]. The reaction of a 1:1 mixture of 2-methylpyridine (**3b**)

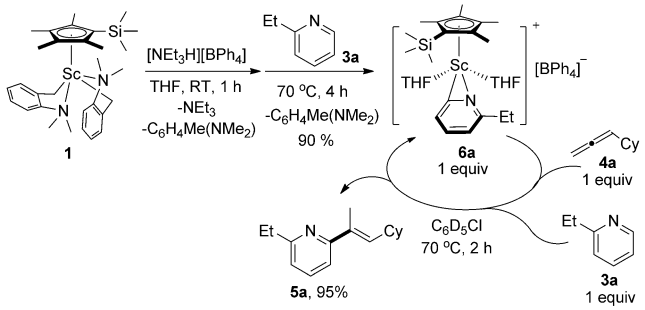


Scheme 2. The C–H addition of 2-ethylpyridine to cholesteryl allene. The relative stereochemistry of **5aa** was confirmed by an X-ray crystallographic analysis (see the Supporting Information).

and [D_4]2-methylpyridine ([**D$_4$**]**3b**) with cyclohexylallene catalyzed by **1**/[Ph_3C][$B(C_6F_5)_4$] yielded a mixture of the C–H and C–D alkenylation products **5b** and [**D**]**5b** with a KIE (kinetic isotope effect) value of 5.6 [Eq. (2)], suggesting that C–H bond activation may be involved in the rate-determining step.[2j]



To gain more information on the active catalyst species and mechanistic details, the stoichiometric reaction of 2-ethylpyridine with a 1:1 reaction mixture of **1** and [Et_3NH][BPh_4] was conducted in THF at 70 °C (Scheme 3).



Scheme 3. Isolation and transformation of a cationic Sc-η^2-pyridyl complex **6a**.

A cationic half-sandwich Sc-η^2-pyridyl complex **6a** was isolated in 90% yield, which after recrystallization from THF/hexane afforded single crystals suitable for X-ray diffraction studies. It was revealed that complex **6a** is a separated ion-pair complex, in which the Sc atom is bonded to one $C_5Me_4SiMe_3$, one pyridyl and two THF ligands, without direct bonding interaction between the Sc atom and the borate anion $[BPh_4]^-$ (Figure 1).

The pyridyl unit is bonded to the Sc atom in an η^2-(N,C) fashion.[15] Kinetic studies on the transformation of **1** to **6a** revealed the activation parameters of $\Delta H^{\neq} = 22.85$ kcal mol^{-1} and $\Delta S^{\neq} = -7.1$ eu (see the Supporting Information). The relatively small entropy of activation is in agreement with an intramolecular process. The stoichiometric reactions of **1**/[Et_3NH][BPh_4] with **3b** and [**D$_7$**]**3b** gave a KIE value of 7.9 [Eq. (3)], suggesting again that C–H activation is involved in the rate-determining step while the coordination of a pyridine unit to scandium should be quick. Addition of 1 equiv of cyclohexylallene (**4a**)

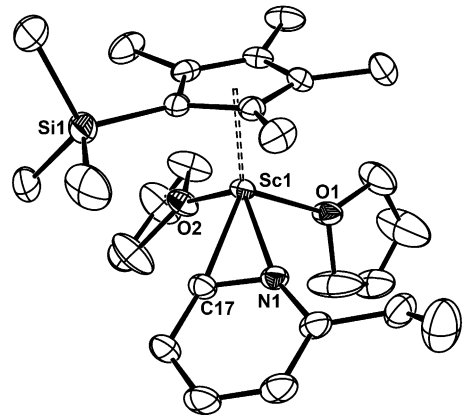
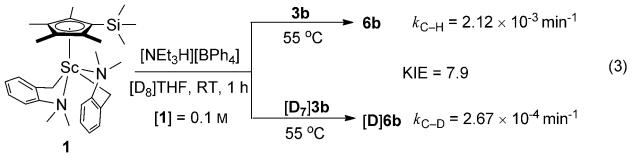
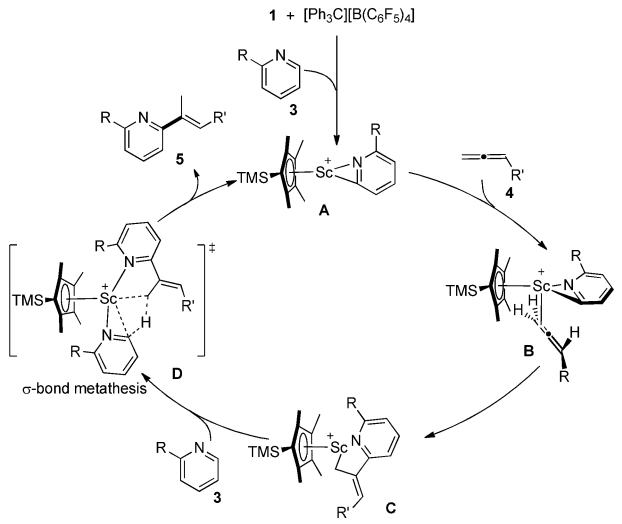


Figure 1. ORTEP drawing of the cationic part of **6a** with thermal ellipsoids set at the 30% probability level. Hydrogen atoms and the counter-anion part [BPh_4] were omitted for clarity. Selected bond lengths [Å] and angles [°]: Sc1–N1 2.142(2), Sc1–C17 2.174(3); N1-Sc1-C17 36.38(9), N(1)-Sc(1)-O(1) 89.77(8), C(17)-Sc(1)-O(2) 96.10(10).

to a C_6D_5Cl solution of the pyridyl complex **6a** at either room or higher temperatures (70 °C) did not give an isolable pure product. Nevertheless, heating **6a** with a 1:1 mixture of 2-ethylpyridine (**3a**) and cyclohexylallene (**4a**) at 70 °C in C_6D_5Cl afforded almost quantitatively the alkenylation product **5a**, with **6a** remaining unchanged (Scheme 3). The transformation of **3a** and **4a** to **5a** could be achieved catalytically in the presence of **6a** (5 mol%, 48 h, 70 °C; 75% yield), demonstrating that the isolated cationic Sc pyridyl complex **6a** could serve as a catalyst for the present transformation despite the presence of two coordinating THF ligands.[16]



On the basis of the experimental results described above, a possible reaction mechanism for the present catalytic C–H alkenylation of pyridines with allenes is proposed as shown in Scheme 4. The sequential reaction of **1** with [Ph_3C][$B(C_6F_5)_4$] and a pyridine compound **3** should generate a cationic scandium pyridyl species such as **A**. The approach of an allene compound **4** to **A** could take place through coordination of the terminal C=C double bond to the Sc atom to afford **B**, in which the substituent R′ in the allene unit should be directed away from the pyridyl group to avoid steric repulsion. The addition of the pyridyl unit to the coordinated C=C double bond would yield **C**, which on reaction with another molecule of a pyridine compound **3** (C–H deprotonation, **D**) could give the alkenylated pyridine derivative **5** and regenerate **A**. Obviously, the regio- and stereochemistry of the alkenylation product **5** should be governed by the coordination of the allene unit to the metal center and the subsequent intramolecular migration of the pyridyl group in **B**.



Scheme 4. A possible catalytic cycle.

In summary, we have demonstrated that cationic half-sandwich scandium alkyl species can serve as an excellent catalyst for the C–H addition of pyridines to various terminal allenes in a regio- and stereoselective fashion, thus constituting the first example of the catalytic C–H addition of pyridines to allenes as well as an atom-economical route for the synthesis of alkenylated pyridine derivatives. Functional groups such as halogens and siloxy units and some naturally occurring moieties are compatible with this catalyst system. This protocol can yield a new family of alkenylated pyridine compounds which were difficult to prepare previously. The isolation and reactivity investigation of the cationic pyridyl complex **6a** together with related kinetic studies have offered important information for understanding the mechanistic details.

Acknowledgements

Financial support by a grant-in-aid for scientific research (S) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 26220802) is gratefully acknowledged. G.S. thanks RIKEN for a FPR fellowship.

Keywords: alkenylation · allenes · C–H addition · pyridines · scandium

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[9] In the case of unsubstituted pyridine, the alkenylation reaction did not occur probably because the coordination of pyridine (with less steric hindrance) to the scandium ion is too strong to allow access of the allene (**4**) to the metal center, as observed previously. See also refs. [2f] and [2j].

[10] It is also noteworthy that the product **5h** formed by C–H alkenylation at the pyridine unit is the only detectable product. This is in contrast with late transition-metal-catalyzed reactions of 2-phenylpyridine, in which C–H bond activation usually took place at the phenyl ring rather than at the pyridine group. For reviews, see: a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651.

[11] The catalyst species (a cationic half-sandwich scandium alkyl or pyridyl species) bearing a bulkier Cp ligand may show higher stability and have a longer lifetime, thus giving a higher product yield when the reaction substrates do not have much steric hindrance. However, in the case of more sterically demanding substrates, a catalyst having a smaller Cp ligand could show higher activity and give a higher yield because of less steric repulsion between the catalyst and the substrate, even if it has a shorter lifetime.

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Received: March 23, 2015
Published online on April 21, 2015