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Published on Web 03/29/2003

Ruthenium-Mediated Regio- and Stereoselective Alkenylation of Pyridine

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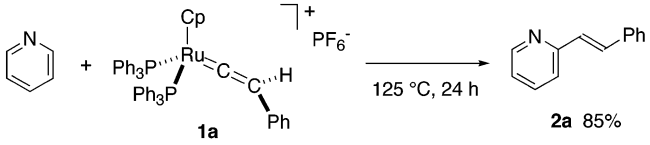
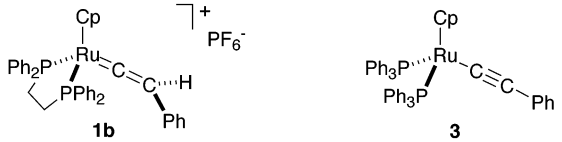
Direct introduction of a carbon side chain on an aromatic ring under mild conditions has been a challenging problem. Transition metals participate in a variety of reactions for this purpose through so-called C−H bond activation.[1] Pyridine derivatives constitute an important class of aromatic compounds because of their potent biological activities. For the synthesis of substituted pyridines, halopyridines are often used as the key starting materials.[2] Direct transformation of a pyridine core is more desirable, although the examples have been limited.[3] In this report, we describe a novel alkenylation reaction of pyridines which occurs in a regio- and stereoselective manner through mediation of ruthenium.[4]

Cationic ruthenium vinylidene complex **1a** (Cp = η^5-cyclopentadienyl) was heated in pyridine (20 equiv)[5] at 125 °C for 24 h. The cooled reaction mixture was filtered through a pad of florisil. Chromatographic isolation of the filtrate afforded 1-phenyl-2-pyridylethene **2a** in 85% yield. The *E* isomer was formed exclusively.



1a **2a** 85%

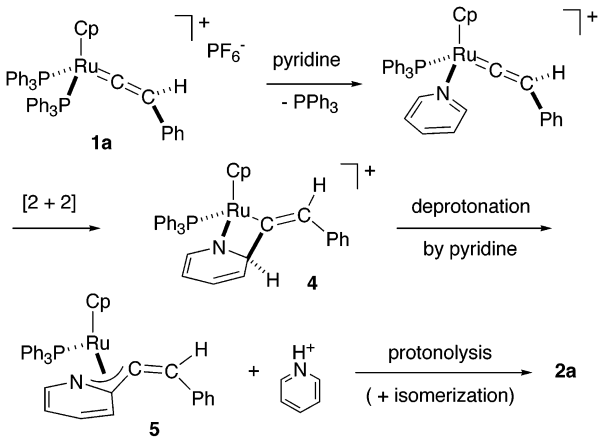
In contrast, ruthenium complex **1b** having a bidentate ligand dppe instead of the monodentate PPh_3 failed to react with pyridine. It is likely that dissociation of a phosphine ligand providing a coordination site for pyridine is an important step. No certain intemediate was observed when a stoichiometric reaction of **1a** with pyridine was carried out in an NMR tube. Neutral alkynyl complex **3**, which is possibly generated from **1a** by deprotonation,[6] failed to react with pyridine either.



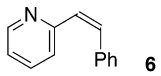
1b **3**

While vinylpyridine **2a** formally results from insertion of the vinylidene group of **1a** into the α C−H bond of pyridine, the precise mechanism of this transformation is unclear. Our working hypothesis, which is similar to the one we proposed for the alkene−alkyne coupling reaction,[7] is shown in Scheme 1. Initially, pyridine coordinates to ruthenium by displacement of one of the phosphine ligands of the vinylidene complex **1a**. Then, [2 + 2] heterocycloaddition occurs to form four-membered ruthenacyclic complex **4**. Deprotonation of the β-hydrogen[8] affords neutral π-azaallyl complex **5**. Protonolysis furnishes **2a**. As for the *E*-selectivity, we independently prepared 1-phenyl-2-pyridylethene, having *Z* geometry **6** by a literature procedure,[9] and heated it in pyridine at 125 °C in the presence of $CpRu(PPh_3)_2Cl$ and $NaPF_6$.[10] After 24 h, complete isomerization of **6** to the *E* isomer **2a** was observed.[11]

Scheme 1. Possible Mechanistic Scheme for the Formation of **2a**

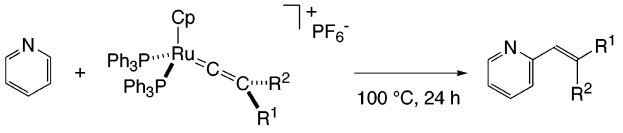


Therefore, it is also conceivable that the *Z* isomer **6** is initially formed either selectively or nonselectively and then isomerizes to **2a**, a thermodynamically more stable stereoisomer, under the reaction conditions.



6

Other ruthenium vinylidene complexes **1c**−**h** also underwent an analogous reaction with pyridine to afford alkenylated pyridines **2c**−**h** in moderate to good yields. *E* isomers were obtained selectively except the case of trisubstituted alkene **2h**. Disubstituted vinylidene complexes **1g** and **1h**, with which the rearrangement to an η^1 alkynyl or η^2 alkyne complex is difficult, did react in an analogous way, being supportive that the vinylidene complex directly reacts with pyridine. On the other hand, ruthenium complex **1i** having a bulky tertiary butyl group failed to react with pyridine, probably due to steric conditions.

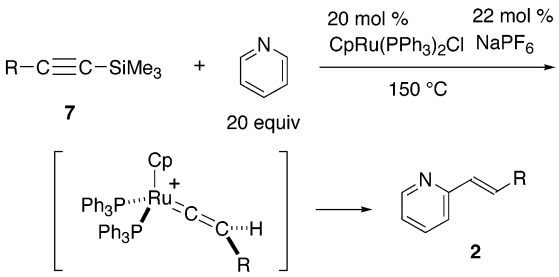


1c R^1 = *p*-F-C_6H_4 R^2 = H	**2c** 56%
1d R^1 = *p*-Me-C_6H_4 R^2 = H	**2d** 82%
1e R^1 = *p*-MeO-C_6H_4 R^2 = H	**2e** 54%
1f R^1 = *n*-C_5H_{11} R^2 = H	**2f** 76%
1g R^1 = Ph R^2 = Me	**2g** 88%
1h R^1 = *n*-C_6H_{13} R^2 = Me	**2h** 56% (*E* : *Z* = 2 : 1)
1i R^1 = *t*-C_4H_9 R^2 = H	— 0%

Apart from its precise mechanism, the reaction described above is of great synthetic interest since an alkenyl group is directly

10.1021/ja029829z CCC: $25.00

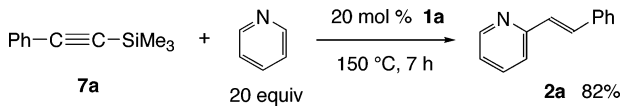
Table 1. Alkenylation of Pyridine with (Alkyn-1-yl)silanes



entry	R of **7**	time / h	product	yield / %
1	Ph (**7a**)	7	**2a**	87
2	*p*-Me-C_6H_4 (**7b**)	9	**2d**	92
3	*n*-C_5H_{11} (**7c**)	6	**2f**	90
4	1-cyclohexenyl (**7d**)	11	**2i**	75

introduced on pyridine in a regio- and stereoselective way. With the knowledge that vinylidene complexes are readily generated from 1-alkyne or from (alkyn-1-yl)trimethylsilane,[12] we next attempted the reaction of pyridine with these alkyne substrates in the presence of catalytic amount of **1a**. Although simple 1-alkynes underwent self-dimerization rather than the desired alkenylation reaction, (alkyn-1-yl)trimethylsilanes were converted into alkenylpyridine derivatives under catalytic conditions. Thus, treatment of (2-phenylethyn-1-yl)trimethylsilane **7a** with pyridine (20 equiv) in the presence of **1a** (0.20 equiv) at 150 °C for 7 h stereoselectively afforded **2a** in 82% yield. Complex **1a** initially alkenylates pyridine, and the product **2a** is liberated from **5** by protonolysis, as depicted in Scheme 1. The resulting cationic ruthenium species then reacts with **7a** to regenerate **1a**, completing the catalytic cycle. This process was accompanied by protiodesilylation[13] due to the presence of water in the reaction medium.

More conveniently, $CpRu(PPh_3)_2Cl$ (20 mol %) and $NaPF_6$ (22 mol %) could be used as the source of cationic ruthenium species.[10]



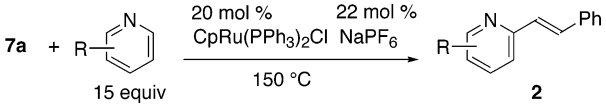
Thus, pyridine was alkenylated by (alkyn-1-yl)trimethylsilanes **7a**−**d** to afford 2-alkenylpyridines in good yield (Table 1).[14] Both aromatic and aliphatic alkynes could be employed.

The reactions with substituted pyridines were also examined (Table 2). Although 2-methylpyridine failed to react with **7a** probably due to steric reasons (entry 1), 3-methyl- and 4-methylpyridines were alkenylated with **7a** (entries 2 and 3). In the case of 3-methylpyridine, the 6-position on the less hindered side was regioselectively alkenylated.

In conclusion, we have developed the *direct* alkenylation reaction of pyridines.[15] The ruthenium vinylidene intermediate, which originates from (alkyn-1-yl)trimethylsilane, regio- and stereoselectively inserts the vinylidene group into the α C−H bond of a pyridine core. Application to other heterocyclic systems is the subject of further investigation.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Table 2. Ruthenium-Catalyzed Alkenylation of Substituted Pyridines



entry	R–	time / h	product	yield / %
1	2-methyl	24	–	0
2	3-methyl	15	**2j**	68
3	4-methyl	10	**2k**	76
4	4-ethyl	11	**2l**	66
5	4-methoxy	11	**2m**	74

Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79.
(2) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, 2000; Chapter 4 and references therein.
(3) (a) Moore, E., J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888−5890. (b) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778−779. (c) Grigg, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 5737−5740.
(4) Leading references for the ruthenium-catalyzed C−C bond-forming reactions: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660. (b) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311−323. (c) Puerta, M. C.; Valerga, P. *Coord. Chem. Rev.* **1999**, *193*−*195*, 977−1025. (d) Yi, C. S.; Liu, N. *Synlett* **1999**, 281−287. (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (g) Rüba, E.; Mereiter, K.; Schmid, R.; Sapunov, V. N.; Kirchner, K.; Schottenberger, H.; Calhorda, M. J.; Veiros, L. F. *Chem. Eur. J.* **2002**, *8*, 3948−3961.
(5) A large excess of pyridine was needed for the success of the reaction. It probably favors displacement of PPh_3 with the weaker ligand, pyridine.
(6) Bruce, M. I.; Wallis, R. C. *J. Organomet. Chem.* **1978**, *161*, C1−C4.
(7) (a) Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361−7362. (b) Murakami, M.; Ubukata, M.; Ito, Y. *Chem. Lett.* **2002**, 294−295.
(8) Slugovc, C.; Mereiter, K.; Schmid, R.; Kirchner, K. *Eur. J. Inorg. Chem.* **1999**, *16*, 1141−1149.
(9) Konakahara, T.; Takagi, Y. *Synthesis* **1979**, 192−194.
(10) Blackmore, T.; Bruce, M. I.; Stone, F. G. A. *J. Chem. Soc. (A)* **1971**, 2376−2382.
(11) No isomerization was observed in the absence of the ruthenium catalyst.
(12) (a) Schneider, D.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 700−702. (b) Katayama, H.; Ozawa, F. *Organometallics* **1998**, *17*, 5190−5196 and references therein.
(13) Protiodesilylation is often observed during the formation of vinylidene complexes: (a) Bruce, M. I.; Koutsantonis, G. A. *Aust. J. Chem.* **1991**, *44*, 207−217. (b) Bianchini, C.; Marchi, A.; Marvelli, L.; Peruzzini, M.; Romerosa, A.; Rossi, R. *Organometallics* **1996**, *15*, 3804−3816. (c) Kawata, Y.; Sato, M. *Organometallics* **1997**, *16*, 1093−1096. This lability might be in conjunction with the relatively high acidity of *H*C═C═M.
(14) A representative experimental procedure: A mixture of (2-phenylethyn-1-yl)trimethylsilane (**7a**, 52.3 mg, 0.30 mmol), pyridine (485 μL, 6.0 mmol), $CpRu(PPh_3)_2Cl$ (43.6 mg, 60 μmol), and $NaPF_6$ (11.1 mg, 66 μmol) was heated at 150 °C for 7 h. The cooled reaction mixture was filtered through a pad of florisil, and the filtrate was purified by preparative thin-layer chromatography on silica gel (hexane/AcOEt = 3/1) to afford **2a** (47.3 mg, 87%) as white crystals. The yield of **2a** decreased to 24% when 10 mol % of $CpRu(PPh_3)_2Cl$ and 12 mol % of $NaPF_6$ were used as the catalyst precursors.
(15) Direct propargylation of aromatic compounds using a ruthenium complex has recently been reported: Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846−11847.

JA029829Z