

Synthesis of Spiro Imines from Oximes by Palladium-Catalyzed Cascade Reaction

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Received 26 January 2001

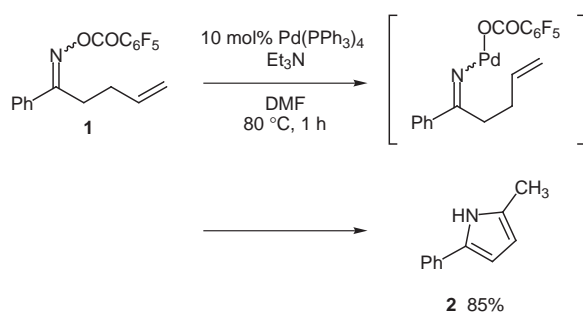
Dedicated to Professor Ryoji Noyori in recognition of his remarkable contribution to the modern synthetic organic chemistry.

Abstract: 1-Azaspiro[4.4]nonane system is constructed from dienyl ketone oximes by palladium-catalyzed cascade reaction.

Key words: cascade reaction, Heck-type reaction, oxime, palladium, spiro compound

Palladium-catalyzed coupling has been extensively studied in the past decade and has become one of the useful means of carbon–carbon bond formation,¹ while the application to carbon–nitrogen bond formation is less common. Buchwald and Hartwig, recently, have cultivated this area and have developed palladium-catalyzed C–N bond forming reactions directed toward the synthesis of aryl amines and heterocycles.²

Recently we found that oxime derivatives reacted with Pd(0) complex to generate alkylideneaminopalladium(II) species, which were used as intermediates of the Mizoroki-Heck-type cyclization of γ,δ -unsaturated ketone oxime derivatives to give pyrroles.³ For example, 4-methyl-1-phenylpyrrol (2) was prepared in 85% yield by the treatment of 1-phenyl-4-pentene-1-one *O*-pentafluorobenzoyloxime (1) with a catalytic amount of Pd(PPh₃)₄ and Et₃N in DMF at 80 °C. Thus, alkylideneaminopalladium(II) species can be generated from oximes and are useful intermediates for the formation of carbon–nitrogen bond. Therefore, we examined the synthesis of spiro imines by the cascade cyclization starting from dienyl ketone oxime derivatives.

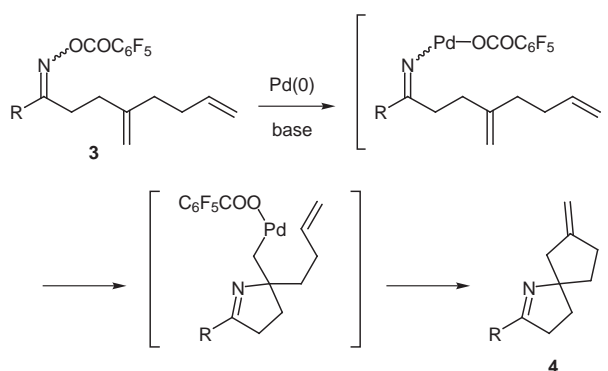


Equation 1

1-Azaspiro[4.4]nonane system is a unique structure and the core skeleton of cephalotaxines, whose analogue shows some pharmacological activity.⁴ Various synthetic

methods, therefore, have been developed toward the construction of azaspiro[4.4]nonane skeleton,⁵ such as acyloin condensation of 1,1-bis(methoxycarbonylmethyl)pyrrolidine,^{5a} cyclization from 1-formyl-1-(3-iodo-2-propenyl)pyrrolidine using stannyl anion,^{5b} aldol condensation of 1-carbonyl-1-acetylmethylpyrrolidine,^{5c} intramolecular S_N2' reaction of 1-(3-aminopropyl)-2-(1-hydroxyisopropyl)cyclopentene,^{5d} and lactam formation from 1-amino-1-(2-methoxycarbonyl)ethylcyclopentane.^{5e} In addition, Tietze et al. have recently reported the efficient metal-catalyzed formation of 1-azaspiro[4.4]nonane skeleton based on the Tsuji-Trost allylation.^{5f}

The outline of our strategy is depicted in Scheme, which is based on the cascade cyclization^{6,7} initiated by the generation of alkylideneaminopalladium(II) species from *O*-pentafluorobenzoyloxime having a dienyl moiety.



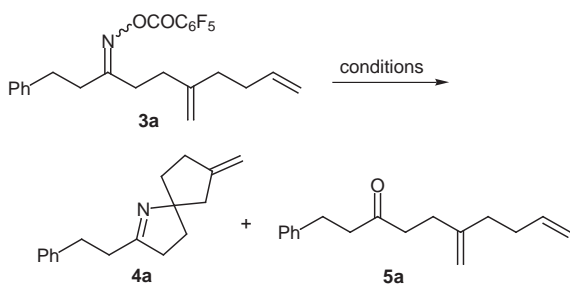
Scheme

As a model compound, oxime **3a** was chosen and the cascade reaction was examined in the presence of palladium catalysts and bases (Table 1). When the reaction was carried out at 80 °C with 10 mol% Pd(PPh₃)₄ and Et₃N in DMF, which are the optimal reaction conditions of the previous pyrrole synthesis,³ it took 11.5 h to consume **3a**, and the desired spiro imine **4a** was obtained in 60% yield accompanied with 34% yield of ketone **5a** (run 1). Although the use of Pd(dba)₂ and PPh₃ accelerated the reaction, yield of the cyclized product **4a** was not improved but a larger amount of the ketone was obtained (run 2). Palladium(II) complexes such as PdCl₂(PPh₃)₂ and PdCl₂(dppf) were not suitable for this coupling.

At a higher temperature (110 °C), the reaction with 10 mol% Pd(PPh₃)₄ proceeded smoothly and the spiro compound **4a** was obtained in 70% yield, though the ketone **5a** was still formed considerably (run 3). Although K₂CO₃ was also efficient as a base like triethylamine, the reproducibility was low (run 4). The reaction worked well in polar solvents, especially DMF was found to be the best choice (run 3, 5, 6).

Addition of molecular sieve 4 Å was efficient to decrease the formation of ketone **5a**, and the yield of **4a** was improved to 77% (run 7). The role of molecular sieve is considered to trap a trace amount of water and acidic substances to prevent the decomposition of alkylideneaminopalladium(II) intermediate to imine, which is then transformed to ketone **5a**.

Table 1 Palladium-Catalyzed Cyclization of *O*-Pentafluorobenzoate **3a**



run	Pd cat. (10 mol%)	base (5 eq)	solv.	T / °C	time / h	Yield / % ^a	
						4a	5a
1	Pd(PPh ₃) ₄	Et ₃ N	DMF	80	11.5	60	34
2	Pd(dba) ₂ + n PPh ₃ ^b	Et ₃ N	DMF	80	1-8	17-53	78-42
3	Pd(PPh ₃) ₄	Et ₃ N	DMF	110	2	70	22
4	Pd(PPh ₃) ₄	K ₂ CO ₃	DMF	110	1	60-82	20-5
5	Pd(PPh ₃) ₄	Et ₃ N	DMPU ^c	110	0.5	58	3
6	Pd(PPh ₃) ₄	Et ₃ N	toluene	110	2	43	44
7 ^d	Pd(PPh ₃) ₄	Et ₃ N	DMF	110	0.5	77	trace

^aIsolated yield.

^bn = 2, 4 or 6.

^cDMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

^dIn the presence of MS 4 Å.

The present method exhibits a wide generality as shown in Table 2. Aromatic ketone oxime derivative **3b** cyclized to give **4b** in 82% yield (run 1). Tricyclic compound **4c** was obtained in a moderate yield as a 1:1 diastereomer mixture (run 2). Compared with **3c**, 1-tetalone oxime derivative **3d** was converted to tetracyclic imine **4d** (diastereomer ratio = 1:1) in a good yield (run 3). Cyclic imine having ethoxy carbonyl group **4e**, which is possible to be utilized as an intermediate for the synthesis of cephalotaxines by removal of the ethoxy carbonyl moiety,^{8,9} was also obtained from the oxime derivative of α -keto ester **3e** (run 4).

Table 2 Cyclization of Various *O*-Pentafluorobenzoxyloximes

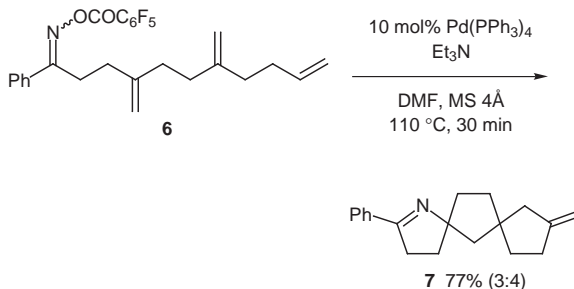
oxime		product		Yield / % ^a
run	oxime	product		
1	3b	4b		82
2 ^b	3c	4c		64 (1 : 1) ^c
3	3d	4d		80 (1 : 1) ^c
4	3e	4e		76

^aIsolated yield.

^bThe reaction carried out for 1 h.

^cDetermined by ¹H NMR.

In a similar manner, triple cyclization occurred smoothly in the presence of molecular sieve 4 Å to give the bis-spiro compound **7** as a two diastereomer mixture.¹⁰

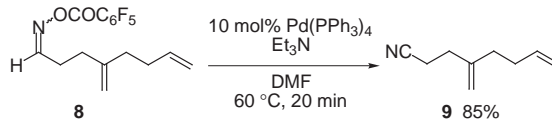


Equation 2

As described above, spiro imines were synthesized from oxime derivatives having dienyl and trienyl moieties by the palladium-catalyzed cascade reaction.

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- (7) For a review about Heck reaction including cascade mode, see: (a) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Brase, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
- (8) Although the core skeleton of cephalotaxines is expected to be prepared from aldoxime derivative **8**, which readily suffer the Beckmann fragmentation to give corresponding nitrile **9**.



Equation 3

- (9) Bender, M. L., *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971, p. 169.
- (10) The stereochemistry of **7** is not determined.

Article Identifier:
1437-2096,E;2001,0,SI,0974,0976,ftx,en;Y03001ST.pdf