5-*endo* Heck-type cyclization of 2-(trifluoromethyl)allyl ketone oximes: synthesis of 4-difluoromethylene-substituted 1-pyrrolines

Junji Ichikawa,* Ryo Nadano and Naotaka Ito

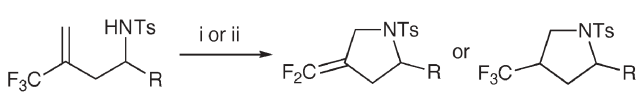
Received (in Cambridge, UK) 25th July 2006, Accepted 18th August 2006
First published as an Advance Article on the web 13th September 2006
DOI: 10.1039/b610690k

2-(Trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes undergo a palladium-catalyzed 5-*endo* mode of alkene insertion *via* oxidative addition of the N–O bond, followed by β-fluorine elimination to produce 4-difluoromethylene-1-pyrrolines.

Pyrrolidine derivatives with fluorinated one-carbon units (CF_3, CF_2H, CF_2= and CFH_2) have attracted much interest as mimics of naturally occurring five-membered heterocycles in medicinal and agricultural chemistry.[1] Nevertheless, their synthetic methods are limited and remain to be developed. Recently, we have reported a facile access to pyrrolidines with a difluoromethylene or trifluoromethyl group *via* S_N2'-type or addition reactions of *N*-[3-(trifluoromethyl)homoallyl]sulfonamides (Scheme 1).[2] This route was successfully accomplished by nucleophilic 5-*endo-trig* cyclization, although it has been considered an unfavorable process because of severe distortions required in the reaction geometry, according to Baldwin's rules.[3]

Employing imine nitrogen anions with an N–C double bond instead of amide nitrogen anions with an N–C single bond might provide pyrrolines, which present a possibly more challenging 5-*endo-trig* ring closure with an extra limitation in the bond rotation. This fact first prompted us to examine the nucleophilic cyclization of 3-trifluoromethyl-2,2-dimethyl-1-phenylbut-3-en-1-imine. Deprotonation of the NH moiety with NaH followed by heating at 90 °C gave only a small amount of 4-difluoromethyl-3*H*-pyrrole with accompanying double bond isomerization.[4] This result indicates that nucleophilic attack (S_N2'-type reaction) of an imine nitrogen anion on the (trifluoromethyl)vinyl group was not sufficiently favorable to give rise to the 5-*endo-trig* cyclization.

Our attention was next directed toward the cyclization promoted by a palladium catalyst, because C–N bond formation *via* an amino-Heck reaction of ketone oximes provides a powerful tool for the construction of nitrogen heterocycles.[5] In general, the intramolecular Heck reaction prefers *exo*-mode cyclization. Whereas 5-*endo* cyclization is far less likely to occur with few exceptions,[6–8] we have recently succeeded in palladium-catalyzed C–N bond formation in a 5-*endo-trig* fashion.[9] The reaction started from 1,1-difluoroallyl ketone *O*-pentafluorobenzoyloximes to afford the corresponding 5-fluoro-3*H*-pyrroles, where an electrostatic attraction between the difluorovinyl group and the N–Pd species presumably facilitated geometrically unfavorable cyclization. The Heck reactions of (trifluoromethyl)vinyl compounds with aryl halides so far reported resulted in selective arylation at the position β to the trifluoromethyl group,[10] which implies that the alkene insertion proceeded regioselectively. On the basis of these considerations, we expected that the geometrically disfavored 5-*endo* cyclization could be achieved with a palladium catalyst in 2-(trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes (Scheme 2).

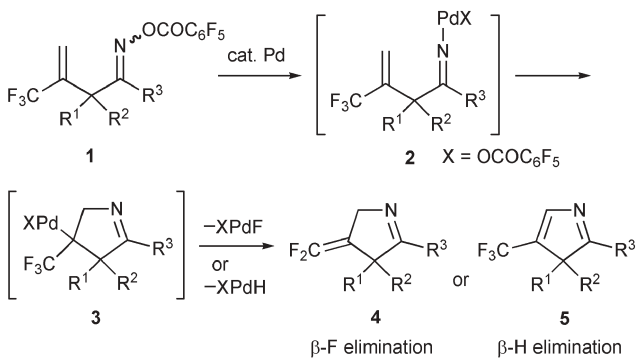


Scheme 1 Nucleophilic 5-*endo-trig* cyclization of amide nitrogen anions. *Reagents and conditions*: (i) NaH (1.3 eq), 120 °C, 2–4 h, DMF; (ii) KOH (5.0 eq), 130 °C, 10–20 h, $(CH_2OH)_2$.

Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan. E-mail: junji@chem.s.u-tokyo.ac.jp; Fax: +81-3-5841-4345; Tel: +81-3-5841-4345

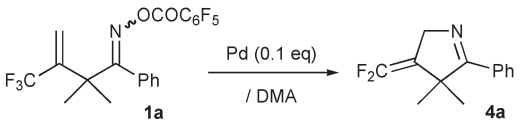
In the Heck reaction of alkenes bearing a heteroatom substituent, the competition of β-hydrogen elimination and β-heteroatom elimination is another issue of intense interest.[11] The previously reported intermolecular Heck reactions of (trifluoromethyl)vinyl compounds involved only β-hydrogen elimination to yield trifluoromethylated products.[10] Furthermore, a theoretical study by B3LYP level calculations suggested that elimination of a β-hydrogen is kinetically favored over that of a β-fluorine, whereas the β-H elimination product is thermodynamically less stable than the pre-eliminated species with a β-F to metal dative bond and the β-F elimination product.[11a] Our interest in such β-eliminations also led us to investigate the geometrically disfavored 5-*endo* Heck-type cyclization of N–Pd species bearing a (trifluoromethyl)vinyl moiety.

For the preparation of substrates, 2-(trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes, we employed two methods: (i) ring opening of oxiranes with 1-(trifluoromethyl)vinyllithium[12] and (ii) addition of 2-(trifluoromethyl)allylsilane to aldehydes,[13] both of which were followed by oxidation to provide 2-(trifluoromethyl)allyl ketones. The ketones thus obtained were



Scheme 2 5-*endo* Heck-type cyclization of aminopalladium species.

Table 1 Effect of additive and conditions on the Heck-type cyclization of **1a** (R^1 = R^2 = Me, R^3 = Ph)



Entry	Pd	Additive (eq)	Conditions	Yd./%
1	$Pd(PPh_3)_4$	Et_3N (5.0)	100 °C, 11 h	31
2	$Pd(PPh_3)_4$	$(CH_3)_2CHONa$ (2.0)	100 °C, 3 h	19
3	$Pd(PPh_3)_4$	PPh_3 (1.0)	100 °C, 1 h	60
4	$Pd(PPh_3)_4$	PPh_3 (1.0)	120 °C, 0.7 h	50
5	$Pd(OAc)_2$	PPh_3 (1.0)	100 °C, 1 h	8

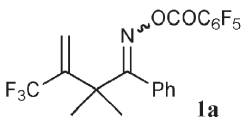
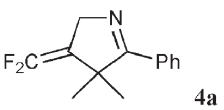
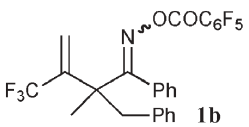
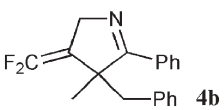
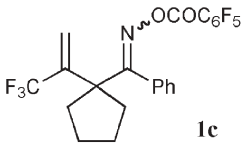
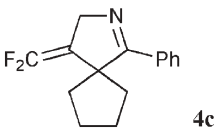
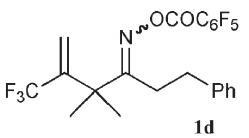
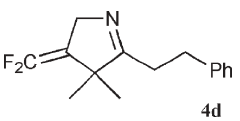
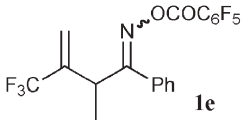
alkylated at the α-position, and then transformed into the desired *O*-pentafluorobenzoyloximes *via* oximation and subsequent pentafluorobenzoylation.

When *O*-pentafluorobenzoyloxime **1a** was treated with triethylamine and a catalytic amount of $Pd(PPh_3)_4$ in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 11 h, cyclized product **4a** with a difluoromethylene group was obtained in 31% yield (Table 1, entry 1) without accompanying ring-trifluoromethylated pyrrole **5**. This result indicates that the geometrically disfavored 5-*endo* cyclization was effected with a palladium catalyst, and that β-fluorine elimination was strongly preferred to β-hydrogen elimination in this 5-*endo* Heck-type cyclization, in contrast to the intermolecular examples so far reported in the literature.[10] The Pd(II) species generated by β-fluorine elimination should be reduced back to Pd(0) undergoing oxidative addition of the *O*-pentafluorobenzoyloxime moiety, which completes a catalytic cycle. Thus, we added sodium isopropoxide[14] or triphenylphosphine[15] for reduction, the latter improving the yield of **4a** to 60% (Table 1, entry 3).† After screening of reaction conditions, we found that the reaction performed with $Pd(PPh_3)_4$ and PPh_3 in DMA at 100 °C gave the best result.

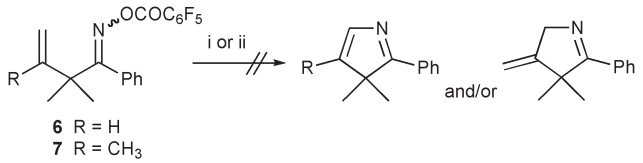
We tried other substrates **1** to synthesize difluoromethylene-substituted pyrrolines **4** under the reaction conditions above. The results are summarized in Table 2. Substrate **1b** bearing a benzyl group at the position α to the oxime group yielded the corresponding pyrroline **4b** in 71% yield (entry 2). The cyclization of substrate **1c** with a cyclopentane ring successfully afforded the spiro-type product **4c** (entry 3). The reaction of dialkyl ketone oxime **1d** proceeded, albeit in low yield (entry 4). When the reaction of α-monoalkylated substrate **1e** (R^2 = H) was examined to evaluate the effect of α-substituents, a mixture of many CF_3-containing compounds without cyclized products was obtained (entry 5). *gem*-Dialkyl substituents in **1** were required to promote the 5-*endo* Heck-type reaction, presumably because (i) an acidic proton at the α position of the oxime as well as the trifluoromethylvinyl moiety prevented the cyclization by protonation of aminopalladium intermediate **2** and/or (ii) the *gem*-dialkyl effect facilitated the unfavorable ring construction.[16]

To elucidate the role of the trifluoromethyl group, we examined the reaction of substrates **6** and **7** bearing a hydrogen atom or a methyl group instead of the trifluoromethyl substituent on the alkene moiety (Scheme 3). When **6** and **7** were subjected to reaction conditions similar to those described above, no cyclized products were observed. These results clearly show that the trifluoromethyl group plays a crucial role in the 5-*endo* Heck-type cyclization, where the trifluoromethyl substituent seems to

Table 2 Synthesis of 4-difluoromethylene-1-pyrrolines **4**[a]

Entry	Substrate	Product	Conditions	Yd./%
1	 **1a**	 **4a**	100 °C, 1 h	60
2	 **1b**	 **4b**	100 °C, 0.8 h	71
3	 **1c**	 **4c**	100 °C, 2.5 h	65
4	 **1d**	 **4d**	100 °C, 0.5 h	20[b]
5	 **1e**	—	80 °C, 2 h	—

[a] All the reactions were performed with $Pd(PPh_3)_4$ (0.1 eq) and PPh_3 (1.0 eq) in DMA. [b] Yield deduced from ^{19}F NMR spectrum relative to internal standard $(CF_3)_2C(C_6H_4$-*p*-$CH_3)_2$.



Scheme 3 Effect of vinylic substituents on the 5-*endo* Heck-type cyclization. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (0.1 eq), PPh_3 (1.0 eq), 140 °C, 2 h, DMF (for **6**), 100 °C, 1 h, DMA (for **7**); (ii) $Pd(PPh_3)_4$ (0.1 eq), PPh_3 (1.0 eq), Et_3N (2.0 eq), 140 °C, 1 h, DMF (for **6**).

contribute to the activation of the vinylic terminal carbon in **1** and the stabilization of the cyclized palladium intermediate **3**.

In summary, we have accomplished the Heck-type cyclization of 2-trifluoromethyl-1-alkenes bearing an *O*-acyloxime moiety, which represents a rare example of 5-*endo* mode alkene insertion into transition metal species. While there were two possible pathways, namely β-fluorine and β-hydrogen elimination after ring formation, the former elimination exclusively took place to construct an *exo*-difluoromethylene unit. This catalytic process provides facile access to 4-difluoromethylene-1-pyrrolines.

We are grateful to Central Glass Co., Ltd. for financial support. We also thank Tosoh F-Tech, Inc. for a generous gift of 2-bromo-3,3,3-trifluoropropene.

Notes and references

† Representative procedure: To a solution of triphenylphosphine (145 mg, 0.55 mmol) and tetrakis(triphenylphosphine)palladium (64 mg, 0.055 mmol) in DMA (20 mL) was added 2,2-dimethyl-1-phenyl-3-(trifluoromethyl)but-3-en-1-one oxime *O*-pentafluorobenzoate **1a** (247 mg, 0.547 mmol). After the reaction mixture was stirred at 100 °C for 1 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was extracted with ether three times. The combined organic extracts were washed with water three times and brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography on silica gel (hexane–AcOEt 4 : 1) to give pyrroline **4a** (72 mg, 60%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (6H, s), 4.61 (2H, dd, J_{HF} = 3.6, 3.6 Hz), 7.37–7.42 (3H, m) and 7.69–7.73 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.6 (dd, J_{CF} = 3, 2 Hz), 51.6 (dd, J_{CF} = 4, 3 Hz), 57.8 (dd, J_{CF} = 3, 2 Hz), 97.5 (dd, J_{CF} = 21, 15 Hz), 127.9, 128.2, 129.7, 133.7 (dd, J_{CF} = 2, 2 Hz), 149.3 (dd, J_{CF} = 287, 282 Hz) and 178.5. ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) δ 68.5 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 4 Hz) and 76.3 (1F, dt, J_{FF} = 64 Hz, J_{FH} = 4 Hz). IR (neat) ν 2978, 1765, 1466, 1267, 1223, 1132, 1047, 1014, 775, 694 and 598 cm^{-1}. HRMS (FAB) calcd for $C_{13}H_{14}F_2N$ ($[M + H]^+$) 222.1094, found 222.1091.

1 For recent examples of trifluoromethyl-substituted pyrrolidines, see: (*a*) A. Covarrubias-Zúñiga, *Heterocycles*, 2004, **63**, 2071; (*b*) X.-L. Qiu and F.-L. Qing, *J. Org. Chem.*, 2003, **68**, 3614; (*c*) X.-L. Qiu and F.-L. Qing, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2052; (*d*) J. R. Del Valle and M. Goodman, *Angew. Chem., Int. Ed.*, 2002, **41**, 1600; (*e*) P.-H. Liang, L.-W. Hsin and C.-Y. Cheng, *Bioorg. Med. Chem.*, 2002, **10**, 3267.For recent examples of difluoromethyl-substituted pyrrolidines, see: (*f*) X.-L. Qiu and F.-L. Qing, *J. Org. Chem.*, 2005, **70**, 3826; (*g*) X.-L. Qiu and F.-L. Qing, *Synthesis*, 2004, 334. For recent examples of difluoromethylene-substituted pyrrolidines, see: (*h*) A. Kamal, P. S. M. M. Reddy, D. R. Reddy, E. Laxman and Y. L. N. Murthy, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5699; (*i*) X.-L. Qiu and F.-L. Qing, *J. Org. Chem.*, 2002, **67**, 7162. For recent examples of monofluoromethyl-substituted pyrrolidines, see: (*j*) X.-L. Qiu and F.-L. Qing, *Bioorg. Med. Chem.*, 2005, **13**, 277; (*k*) X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 5201; (*l*) P. Van der Veken, K. Senten, I. Kertèsz, A. Haemers and K. Augustyns, *Tetrahedron Lett.*, 2003, **44**, 969.

2 J. Ichikawa, T. Mori and Y. Iwai, *Chem. Lett.*, 2004, **33**, 1354.

3 (*a*) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734; (*b*) J. E. Baldwin, J. Cutting, W. Dupont, L. I. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736; (*c*) J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.*, 1977, **42**, 3846.

4 The reaction was conducted on treatment of 3-trifluoromethyl-2,2-dimethyl-1-phenylbut-3-en-1-imine with 1.3 equivalents of NaH in *N*,*N*-dimethylformamide (DMF). The reaction mixture was stirred at 0 °C for 20 min and then heated at 90 °C for 1.5 h to give 4-difluoromethyl-3,3-dimethyl-2-phenyl-3*H*-pyrrole (9%) with decomposition of the starting imine.

5 M. Kitamura and K. Narasaka, *Chem. Rec.*, 2002, **2**, 268.

6 Most of the studies on Heck cyclizations in a 5-*endo* fashion dealt with substrates bearing an enamine (or its equivalent) moiety, which can be interpreted in terms of a mechanism other than a 5-*endo* cyclization, involving: (i) the oxidative addition of aryl or alkenyl halides to Pd(0), (ii) the formation of six-membered palladacycles through nucleophilic substitution with the enamine on the palladium and (iii) a subsequent reductive elimination, which leads to the 5-*endo* type products. For recent examples, see: (*a*) L. Ackermann, L. T. Kaspar and C. J. Gschrei, *Chem. Commun.*, 2004, 2824; (*b*) T. Watanabe, S. Arai and A. Nishida, *Synlett*, 2004, 907; (*c*) G. Kim, J. H. Kim, W. Kim and Y. A. Kim, *Tetrahedron Lett.*, 2003, **44**, 8207; (*d*) K. Yamazaki and Y. Kondo, *Chem. Commun.*, 2002, 210; (*e*) A. García, D. Rodoríguez, L. Castedo, C. Saá and D. Domínguez, *Tetrahedron Lett.*, 2001, **42**, 1903; (*f*) R. Grigg and V. Savic, *Chem. Commun.*, 2000, 873.

7 5-*endo* Cyclizations of aryl- and alkenylpalladiums are less efficient. (*a*) P. Wiedenau, B. Monse and S. Blechert, *Tetrahedron*, 1995, **51**, 1167; (*b*) J.-M. Gaudin, *Tetrahedron Lett.*, 1991, **32**, 6113; (*c*) B. O'Connor, Y. Zhang and E. Negishi, *Tetrahedron Lett.*, 1988, **29**, 3903.

8 5-*endo* Cyclizations of acylpalladiums are originally reported by Negishi and modified by Larock. (*a*) S. V. Gagnier and R. C. Larock, *J. Am. Chem. Soc.*, 2003, **125**, 4804; (*b*) E. Negishi, C. Copéret, S. Ma, T. Mita, T. Sugihara and J. M. Tour, *J. Am. Chem. Soc.*, 1996, **118**, 5904.

9 (*a*) K. Sakoda, J. Mihara and J. Ichikawa, *Chem. Commun.*, 2005, 4684; (*b*) J. Ichikawa, K. Sakoda, J. Mihara and N. Ito, *J. Fluorine Chem.*, 2006, **127**, 489.

10 (*a*) Y. Gong, K. Kato and H. Kimoto, *J. Fluorine Chem.*, 2000, **105**, 169; (*b*) S. Peng, F.-L. Qing and Y. Guo, *Synlett*, 1998, 859; (*c*) G.-Q. Shi, X.-H. Huang and F. Hong, *J. Chem. Soc., Perkin Trans. 1*, 1996, 763; (*d*) T. Fuchikami, M. Yatabe and I. Ojima, *Synthesis*, 1981, 365. Regiochemistry in intermolecular Heck reaction of 3,3,3-trifluoropropene was explained by DFT calculations, see: (*e*) R. J. Deeth, A. Smith and J. M. Brown, *J. Am. Chem. Soc.*, 2004, **126**, 7144.

11 For recent reports on β-heteroatom elimination, see: (*a*) H. Zhao, A. Ariafard and Z. Lin, *Organometallics*, 2006, **25**, 812 and references therein; (*b*) V. G. Zaitsev and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 4156; (*c*) Z. Zhang, X. Lu, Z. Xu, Q. Zhang and X. Han, *Organometallics*, 2001, **20**, 3724.

12 R. Nadano and J. Ichikawa, *Synthesis*, 2006, 128.

13 T. Yamazaki and N. Ishikawa, *Chem. Lett.*, 1984, 521.

14 X. Bei, A. Hagemeyer, A. Volpe, R. Saxton, H. Turner and A. S. Guram, *J. Org. Chem.*, 2004, **69**, 8626.

15 V. V. Grushin, *Chem.–Eur. J.*, 2002, **8**, 1006.

16 For a recent review on the *gem*-dialkyl effect, see: M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735.