Heck-type 5-*endo-trig* cyclization promoted by vinylic fluorines: synthesis of 5-fluoro-3*H*-pyrroles

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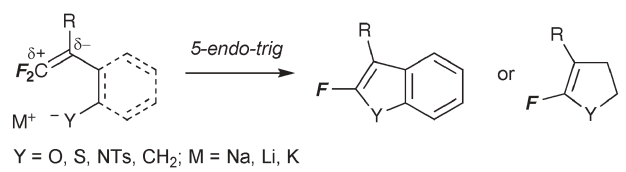
A 5-*endo-trig* alkene insertion proceeds under palladium catalysis *via* aminopalladium species starting from 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes, providing a facile access to 5-fluoro-3*H*-pyrroles.

The Heck reaction is one of the most valuable reactions of transition metals in contemporary organic synthesis.[1] Intramolecular Heck reactions have been widely used to construct a variety of ring systems. Normally, *exo*-mode cyclization is the favored path, and *endo* cyclization is less likely for the formation of smaller rings.[2] Especially, 5-*endo-trig* cyclizations in the Heck reaction are limited. All reports on such palladium-catalyzed 5-*endo-trig* ring closure are confined to the reaction of *N*-vinyl-2-haloarylamines or *N*-vinyl-2-haloalkenylamines,[3] to the best of our knowledge, with one exception of an efficient carbonylative cyclopentenone formation starting from 1-halo-1,3-dienes.[4–6] The reactions of these vinylamine (enamine-type) substrates can be, however, interpreted in terms of a mechanism other than a 5-*endo-trig* fashion: (i) oxidative addition of the aryl halides to Pd(0), (ii) 6-membered palladacycle formation through nucleophilic substitution with the enamine at the Pd and (iii) subsequent reductive elimination, which leads to the 5-*endo-trig* type products.[3m]

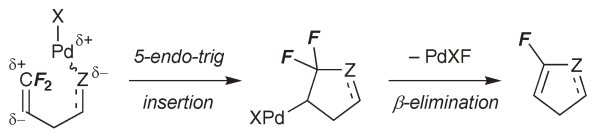
In general, the 5-*endo-trig* cyclization has long been considered, according to Baldwin's rules,[7] to be a disfavored process for the construction of five-membered rings, which is due to the severe distortions required in the reaction geometry. In our recent publications, we have reported nucleophilic 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes with an *N*, *O* or a *C*-nucleophile, providing five-membered ring-fluorinated hetero- and carbocycles, such as indoles, 2-pyrrolines, benzo[*b*]furans, 2,3-dihydrofurans, indenes and cyclopentenes (Scheme 1).[8] Their remarkable reactivity toward nucleophilic 5-*endo-trig* cyclizations is probably due to (i) the polarization of the carbon–carbon double bond caused by the two fluorines,[9] which exerts electrostatic attraction for an intramolecular nucleophile to overcome the difficulty of the initial ring formation and (ii) the leaving group ability of the fluoride ions, which suppresses the reverse ring opening.



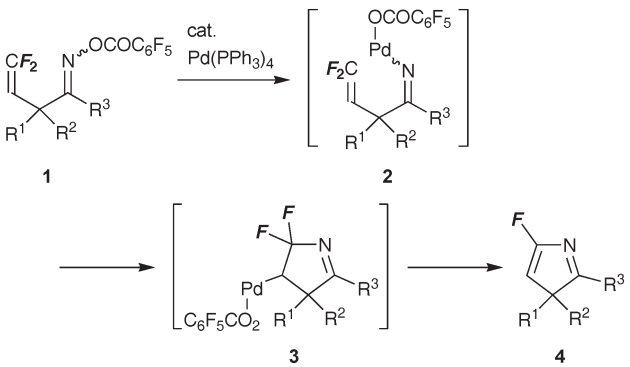
Scheme 1 Nucleophilic 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes.

In these 5-*endo-trig* cyclizations, typical metal species such as lithium, sodium, and potassium compounds were employed as intramolecular nucleophiles (Scheme 1). Thus, we turned our attention to organotransition metal chemistry to broaden the scope of the 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes. There is only one example describing the Heck-type reaction of a 1,1-difluoro-1-alkene.[10] Heitz reported that arylpalladium species replaced the fluorine atom of 1,1-difluoroethene to afford α-fluorostyrenes *via* alkene insertion and subsequent β-fluorine elimination.[11] We expected that the electrostatic attraction between the polarized double bond of the difluoroalkenes and palladium species would allow the 5-*endo-trig* cyclization, even though this pathway is sterically hindered (Scheme 2).

Moreover, Narasaka and co-workers recently showed that homoallyl ketone *O*-pentafluorobenzoyloximes underwent oxidative addition to Pd(0) to generate alkylideneaminopalladium species, which afforded nitrogen heterocycles *via* insertion of an alkene moiety in a 5-*exo* fashion.[12] These facts prompted us to investigate the reaction of the alkylideneaminopalladium with an intramolecular difluoroalkene moiety, which might open up the 5-*endo-trig* pathway. Herein we report the Heck-type 5-*endo-trig* cyclization promoted by vinylic fluorines, which provides an approach to ring-fluorinated 3*H*-pyrrole derivatives (Scheme 3).



Scheme 2 Heck-type 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes.



Scheme 3 Heck-type 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes with N–Pd species.

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

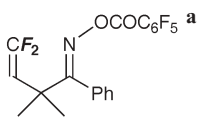
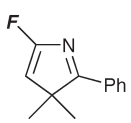
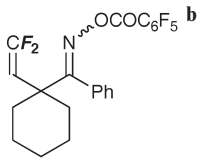
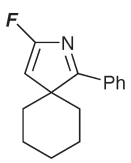
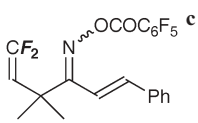
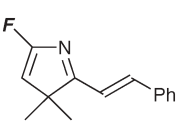
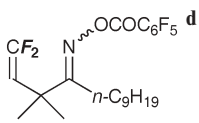
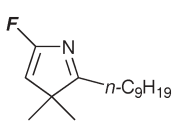
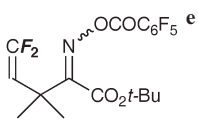
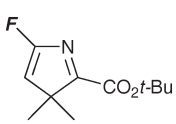
Entry	$Pd(PPh_3)_4$ (eq)	Additive (eq)	Solvent	Conditions	Yield/%
1	0.3	none	DMF	80 °C, 1 h	71
2	0.1	none	DMF	80 °C, 2 h then 110 °C, 2 h	19
3	0.1	Et_3N (5.0)	DMF	80 °C, 2 h then 110 °C, 9 h	< 30
4	0.1	PPh_3 (1.0)	DMF	100 °C, 4 h	57
5	0.1	PPh_3 (1.0)	DMA	110 °C, 8 h	71

For the synthesis of substrates, 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes **1**, we employed acylation of enamines, derived from aldehydes, with acid chlorides to prepare β-ketoaldehyde intermediates. Their selective Wittig-type difluoromethylenation[13] gave difluoroallyl ketones, which were in turn transformed into *O*-pentafluorobenzoyloximes **1** *via* oximation and subsequent pentafluorobenzoylation.

Having obtained 3,3-difluoroallyl ketone oxime **1a** ($R^1 = R^2 = Me$, $R^3 = Ph$; *Z*-form[14]), we investigated their Heck-type cyclization (Scheme 3, Table 1). The catalytic reaction gave the desired compound, 5-fluoro-3*H*-pyrrole **4a**, albeit in only 19% yield (entry 2). Then, we examined the reagents for reduction of the *in-situ* generated palladium(II) species to Pd(0). On treatment with $Pd(PPh_3)_4$ and Et_3N,[10] **4a** was obtained in low yield (entry 3). After screening of reductants, we found that a stoichiometric amount of PPh_3 was effective to reduce $C_6F_5CO_2Pd(II)F$ to Pd(0), which allowed the cyclization to proceed under palladium catalysis[15] with generation of $Ph_3P{=}O$. When the reaction was conducted in *N*,*N*-dimethylacetoamide (DMA) at a higher temperature (110 °C), the yield of **4a** was improved up to 71% (entry 5).[16]†

We tried to synthesize other fluoropyrroles **4** under the optimized conditions (Table 2). The cyclization of substrate **1b** with a cyclohexane ring successfully afforded the spiro-type product **4b** (entry 2). Substrate **1c** bearing a conjugated alkene moiety on the oxime carbon readily underwent cyclization to give the corresponding pyrrole **4c** (entry 3). The reactions of substrates **1d**,**e** bearing a primary alkyl or an acyl group as R^3 resulted in poor yield (entries 4 and 5). Furthermore, the construction of a fused tricyclic system of 4,5-dihydro-3a*H*-benzo[*g*]indole **4f**, where the transition state would be more strained, was achieved by this method (Scheme 4).

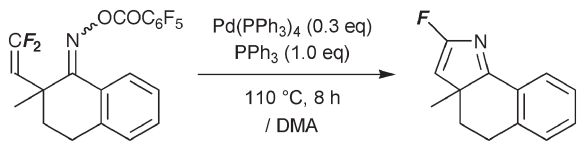
Table 2 Synthesis of 5-fluoro-3*H*-pyrroles **4** from difluoroalkenes **1**[a]

Entry	Substrate **1**[b]	Product **4**	Time/h	Yield/%
1	 **a**		8	71
2	 **b**		8	78
3	 **c**		1	76
4	 **d**		8	29
5	 **e**		12	14

[a] All the reactions were performed with $Pd(PPh_3)_4$ (0.1 eq) and PPh_3 (1.0 eq) in DMA at 110 °C. [b] Each of substrates **1** was a single isomer, while the stereochemistry of **1b–e** was not determined.

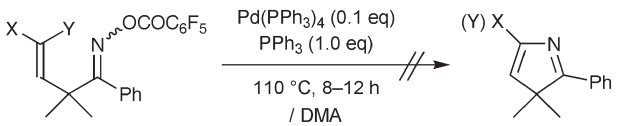
In order to elucidate the role of the vinylic fluorines, we examined the reaction of substrates that have atoms other than fluorine at the vinylic positions, such as the corresponding monofluoroalkene **5**, fluorine-free alkene **6**, dichloroalkene **7** and dibromoalkene **8** (Scheme 5).[17] When **5–8** were subjected to the same reaction conditions as above, no cyclized products were observed; instead, the corresponding ketones generated *via* hydrolysis of the oxime moiety were obtained. These results clearly show that two vinylic fluorines play an important role in this Heck-type 5-*endo-trig* cyclization.

In summary, we have accomplished a 5-*endo-trig* alkene insertion in the Heck-type cyclization of 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes by taking advantage of the polarized



1f (1:2 *E*/*Z* mixture) **4f** 47%

Scheme 4 Construction of a fused tricyclic system *via* the Heck-type 5-*endo-trig* cyclization.



5: X = H, Y = ***F***
6–8: X = Y = H, Cl, Br

Scheme 5 Effect of vinylic substituents on the Heck-type 5-*endo-trig* cyclization.

double bond of 1,1-difluoro-1-alkenes. This catalytic process provides a facile access to 5-fluoro-3*H*-pyrroles.[18,19]

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Notes and references

† Representative procedure: Pentafluorobenzoyloxime **1a** (72 mg, 0.17 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and PPh_3 (49 mg, 0.17 mmol) were dissolved in DMA (7 ml) and heated to 110 °C for 8 h under argon. After the mixture was cooled to room temperature, the reaction was quenched with phosphate buffer (pH 7). The organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin-layer chromatography on silica gel (benzene–hexane 1 : 1) to give 3*H*-pyrrole **4a** (23 mg, 71%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (6H, d, J = 1.2 Hz), 5.32 (1H, d, J_{HF} = 6.6 Hz), 7.44–7.48 (2H, m), 7.99–8.01 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1 (d, J_{CF} = 3 Hz), 55.0, 106.4 (d, J_{CF} = 88 Hz), 128.1, 128.6, 130.8, 132.0 (d, J_{CF} = 1 Hz), 161.8 (d, J_{CF} = 345 Hz), 183.5 (d, J_{CF} = 11 Hz). ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) 47.8 (d, J_{FH} = 6 Hz) ppm. IR (neat) ν 3097, 3060, 2972, 1633, 1460, 1279, 1254, 1132, 1012, 945, 783, 702 cm^{-1}. HRMS: calcd for $C_{12}H_{12}NF$ (M^+) 189.0954, found 189.0960.

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14 The *E*/*Z* stereochemistry of **1a** was confirmed by X-ray crystallography of the corresponding free oxime. **Crystal data.** $C_{12}H_{13}F_2NO$, M = 225.23, monoclinic, a = 7.5652(18), b = 6.3060(15), c = 23.707(6) Å, U = 1121.4(5) Å^3, T = 120(2) K, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 0.107 mm^{-1}, 6907 reflections measured, 2186 unique (R_{int} = 0.0158) which were used in all calculations. The final $wR(F^2)$ was 0.3643 (all data). The largest residual electron density hole was −1.338 e.Å^{-3}. CCDC 278998. See http://dx.doi.org/10.1039/b510039a for crystallographic data in CIF or other electronic format.

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