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Intramolecular Hydroamination of Difluoropropargyl Amides: Regioselective Synthesis of Fluorinated β - and γ -Lactams^{||}

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ABSTRACT

$$F = \begin{bmatrix} F & O \\ N & R^2 \end{bmatrix}$$

$$R^2 = \begin{bmatrix} Pd(OAc)_2 \\ 4-exo-dig \end{bmatrix}$$

$$R^1 = \begin{bmatrix} Pd(OAc)_2 \\ R^1 \end{bmatrix}$$

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$$F$$

R¹= H, TIPS, Ph, 3-thienyl, 2-Me-4-MeO-C₆H₃ R²= Bn, PMP, Allyl, (S)-PhCH(Me)

Functionalized *gem*-difluoro β - and γ -lactams were synthesized through a novel intramolecular hydroamination reaction of difluoropropargyl amides. β -Lactams were obtained via a Baldwin disfavored 4-exo-digonal cyclization using palladium acetate as the catalyst, whereas γ -lactams were produced under basic conditions. Acid hydration of γ -lactams produced ketoamides or hemiaminals selectively.

Catalytic hydroamination of multiple carbon—carbon bonds constitutes one of the most efficient methodologies to create carbon—nitrogen bonds. The intramolecular version of this process is an attractive method to generate nitrogen heterocycles, converting starting materials into desired products in a single operation, without the formation of side products

(1) For reviews of hydroamination, see: (a) Hong, S.; Marks, T. J. Acc. Chem. Res. 2004, 37, 673. (b) Nakamura, I.; Yamamoto, Y. Chem. Rev. 2004, 104, 2127. (c) Alonso, F.; Beletskaya, I.; Yus, M. Chem. Rev. 2004, 104, 3079. (d) Bytschkov, I.; Doye, S. Eur. J. Org. Chem. 2003, 935. (e) Pohlki, F.; Doye, S. Chem. Soc. Rev. 2003, 32, 104. (f) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. Synlett 2002, 1579. (g) Seayad, J.; Thiel, A.; Hartung, C. G.; Beller, M. Adv. Synth. Catal. 2002, 344, 795. (h) Cacchi, S. J. Organomet. Chem. 1999, 576, 42. (i) Müller, T.; Beller, M. Chem. Rev. 1998, 98, 675.

and with high atom efficiency. To overcome the high activation energy required for the direct addition of amines or their derivatives across multiple carbon—carbon bonds, a variety of catalytic and noncatalytic methods have appeared in the literature.² The synthesis of *gem*-difluoromethylene-containing compounds has witnessed a growing interest because of their interesting biological activities.³ Very recently, we described the regioselective synthesis of sixto eight-membered ring fluorinated lactams through a tandem ring-closing metathesis—isomerization protocol.⁴ However, this methodology is not amenable for the synthesis of fourand five-membered ring difluoro lactams. We decided to

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Dedicated to Prof. Kenji Uneyama on the occasion of his 65th birthday.

⁽²⁾ Chianese, A. R.; Lee, S. J.; Gagné, M. R. Angew. Chem., Int. Ed. 2007, 46, 4042 and refs cited therein.

⁽³⁾ Mae, M.; Hong, J. A.; Hammond, G. B.; Uneyama, K. *Tetrahedron Lett.* 2005, 46, 1787 and refs cited therein.

⁽⁴⁾ Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706.

study the construction of these small heterocycles using difluoropropargyl bromides **4** as fluorinated building blocks. This synthon has been used for the preparation of several valuable intermediates, such as fluorinated allenes, fluorodienes, and other functionalized fluoroalkynes.⁵ We are now pleased to report that base treatment of amide **1**—obtained from **4**—led to the formation of γ -lactams **2** via a nucleophilically driven 5-endo-digonal cyclization mode (Scheme 1, Via b), while the use of a palladium catalyst afforded the

unexpected β -lactams 3, via a 4-exo-digonal cyclization mode (Scheme 1, $Via\ a$).

Amides 1 were efficiently prepared using a Grignard derivative of 4 that was treated with methyl chloroformate followed by reaction with an amine in the presence of either sodium hydride in THF at -50 °C (method A) or trimethyl aluminum in DCM at 0 °C (method B) (Table 1).

Table 1. Preparation of Fluorinated Propargyl Amides 1

eı	ntry	\mathbb{R}^1	\mathbb{R}^2	$method^d$	1 (yield %)
	1	TIPS^a	Bn	A	1a (80)
	2	Ph	Bn	A	1b (75)
	3	Ph	PMP^b	В	1c (70)
	4	Ph	Allyl	A	1d (85)
	5	Ph	(S)-PhCH(Me)	\mathbf{B}	1e (85)
	6	3-thienyl	Bn	\mathbf{A}	1f(70)
	7	MMP^c	Bn	\mathbf{A}	1g (54)

 a TIPS = Triisopropylsilyl. b PMP = $p\text{-MeOC}_6H_4$. c MMP = 2-Me-4-MeO-C_6H_3 . d Method A: NaH/R²NH2/THF/-50 °C/1-3 h. Method B: AlMe3/R²NH2/CH2Cl2/0 °C/2-4 h.

Our initial intramolecular hydroamination studies were carried out with alkyne 1b using several palladium catalysts. With palladium acetate in the presence of Et_3N in THF, a

diastereomeric mixture of (Z)-3 \mathbf{a} and (E)-3 \mathbf{a} was obtained in 63% yield (13:1) (Table 2, entry 1).^{6,7} The extension of

Table 2. Synthesis of β -Lactams 3 and 4

entry	$\mathrm{substrate}^a$	(Z)-3 + (E) -3 (yield %)	Z/E^b
1	1b	(Z)-3 a + (E) -3 a (63)	13:1
2	1c	(Z)-3 b + (E) -3 b (54)	>50:1
3	1d	(Z)-3 c + (E) -3 c (33)	14:1
4	1e	(Z)-3d + (E) -3d (40)	10:1
5	1f	(Z)-3 e + (E) -3 e (34)	10:1
6	1g	(Z)-3f $+ (E)$ -3f (34)	10:1

^a Substrate 1a was inert under the reaction conditions, probably due to steric hyndrance of the TIPS group. ^b Diastereoisomeric ratios were determined by ¹⁹F NMR.

this protocol to other amides, **1**, led to the formation of the corresponding β -lactams (*Z*)-**3** and (*E*)-**3** in moderate yields and good selectivities (Table 2). β -Lactams **3** were relatively unstable in solution; for example, when a CH₂Cl₂ solution of **3a** was stirred at rt for one week, it evolved into ketone **7a** (see Table 4, entry 1).

Scheme 2. Possible Pd-Catalyzed 4-exo-dig Cyclization

$$\begin{bmatrix}
F & O \\
Pd & N-R^2 \\
R^1 & H
\end{bmatrix}$$
H-Transfer
$$F & N \\
R^2 \\
R^1 \\
(Z)-3 \text{ major}$$

A possible mechanism (Scheme 2) may involve initial alkyne activation through coordination of the triple bond with palladium(0). Literature reports suggest⁸ that the p character

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⁽⁶⁾ Other sources of paladium were also tested, such us $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3$ ·CHCl $_3$. The reaction was also performed with other bases (K_2CO_3), solvents (DMF, DCM), temperatures, and reaction times. In all cases tested, less satisfactory results were obtained.

⁽⁷⁾ The stereochemistry of the β -lactams was determined by NOESY experiments over the diastereomeric mixture of compounds (*Z*)-3b + (*E*)-3b that were unseparable by flash chromatography.

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of the alkyne carbons increases through this interaction, thus resembling an sp²-like hybridization.

This pseudohybridization could favor both 4-exo-dig and 5-endo-dig modes of cyclization, but the presence of the gemdifluoro moiety should predispose the α -position for intramolecular nucleophilic attack by the amidic nitrogen, thus favoring a 4-exo-dig cyclization mode.

Considering the increased importance of gold catalysis in hydroamination reactions,⁹ we also explored the behavior of amides 1 in the presence of gold salts [i.e., AuCl, AuCl/AgOTf or AgSbF₆, AuCl₃, Au(PPh₃)OTf]. All cyclization attempts were unsuccessful, and either complex mixtures or, when identified, no hydroamination products were obtained.¹⁰

We decided then to seek the base-mediated activation of the amidic nitrogen to produce γ -lactams **2**. Of all bases tried (DBU, NaH, i-Pr₂NEt, LiN(TMS)₂, KOH, t-BuOK, TBAF), the best results were obtained using 1.1 equiv of TBAF at rt (Table 3). In this case, the triple bond is electron deficient,

Table 3. Hydroamination Mediated by TBAF

entry	substrate	time (h)	2 (yield %)
1	1b	1.5	2a (61)
2	1 c	2	2b (60)
3	1d	3	2c (64)
4	1e	0.5	2d (62)
5	1f	1	2e (66)
6	1g	3	2f(67)
7	$\mathbf{1h}^a$	3	2g(78)

^a Substrate **1h** was obtained in 98% yield from **1a** by treatment with TBAF/AcOH (see Supporting Information).

so a base-promoted nucleophilic addition occurs. Since a 5-endo-digonal cyclization is favored, the formation of γ -lactam 2 is expected.

When **2a** was heated for 1 h in the presence of a catalytic amount of HCl (3 N), ketone **7a** was obtained in almost quantitative yield (Table 4, entry 1). The same conditions applied to substrates **2b**-**f** afforded the corresponding

Table 4. Reaction of Compounds 2 with R³OH/H⁺

$$F \xrightarrow{N^{-}R^{2}} \xrightarrow{Acid/R^{3}OH} \xrightarrow{F} \xrightarrow{N^{-}R^{2}} \xrightarrow{F} \xrightarrow{N^{+}R^{2}} \xrightarrow{F} \xrightarrow{N^{+}R^{2}}$$
2
6
7

entry	substrate	\mathbb{R}^3	acid	6 , 7 (% yield)
1	2a	Н	HCl 3 M	7a (94)
2	2 b	H	HCl 3 M	7b (66)
3	2c	H	HCl 3 M	7c (62)
4	2d	H	HCl 3 M	7d (66)
5	2e	H	HCl 3 M	7e (60)
6	2f	H	HCl 3 M	7f (62)
7	2g	H	HCl 3 M	6g (98)
8	2g	Me^a	H_2SO_4	6h (94)
9	2g	$\mathrm{CF_3CH_2}^b$	${ m HBF_4}$	6i (80)
10	2g	$\mathrm{CH_3CO}^c$	_	6j (63)

^a MeOH was used as solvent with a catalytic amount of 98% sulfuric acid. ^b Trifluoroethanol was used as solvent with a catalytic amount of tetrafluoroboric acid. ^c The reaction was performed in refluxing acetic acid.

ketones **7** in good yields (Table 4, entries 2–6). With 2g (R¹ = H) the product was isolated as the corresponding hemiaminal 6g (Table 4, entry 7). Using the same strategy, it was also possible to introduce alkoxy groups instead of the hydroxyl functionality. With sulfuric acid as the catalyst, compound 2g reacts with methanol in very good yield (Table 4, entry 8). The best results with trifluoroethanol were obtained when HBF₄ was the acid of choice (Table 4, entry 9). Finally, when the reaction was performed in refluxing acetic acid, the corresponding acetate was isolated in good yield (Table 4, entry 10).

In conclusion, we have described the regioselective preparation of fluorinated β - and γ -lactams through an intramolecular hydroamination reaction of difluoropropargyl amides. Under palladium catalysis, the reaction takes place in a 4-*exo-digonal* cyclization mode, in sharp contrast with other palladium-catalyzed hydroaminations, that showed a strong preference for the formation of a five-membered ring. The activation of the amidic nitrogen with TBAF led to the formation of γ -lactams.

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Supporting Information Available: Experimental procedures and NMR spectra for 1–7. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁰⁾ For example, when substrates ${\bf 1b}$ (${\bf R}^1={\bf Ph}$) and ${\bf 1h}$ (${\bf R}^1={\bf H}$) were treated with ${\bf AuCl}_3$ (10 mol %)/AcOH (3 equiv), the corresponding hemiaminal ${\bf 6g}$ or ketone ${\bf 7a}$ was obtained as the only identifiable product. That can be explained assuming activation of the triple bond by the metal, and final gold displacement from the water, indicating that the amidic nitrogen is not nucleophilic enough to perform the cyclization.