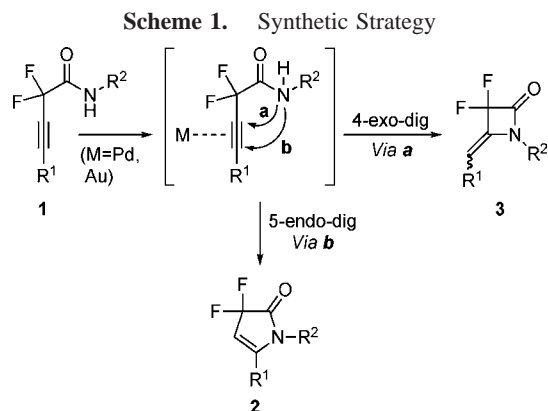


study the construction of these small heterocycles using difluoropropargyl bromides **4** as fluorinated building blocks. This synthon has been used for the preparation of several valuable intermediates, such as fluorinated allenes, fluoro-dienes, and other functionalized fluoroalkynes.⁵ We are now pleased 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 $-50\text{ }^{\circ}\text{C}$ (method A) or trimethyl aluminum in DCM at $0\text{ }^{\circ}\text{C}$ (method B) (Table 1).

Table 1. Preparation of Fluorinated Propargyl Amides **1**

entry	R ¹	R ²	method ^d	1 (yield %)
1	TIPS ^a	Bn	A	1a (80)
2	Ph	Bn	A	1b (75)
3	Ph	PMP ^b	B	1c (70)
4	Ph	Allyl	A	1d (85)
5	Ph	(<i>S</i>)-PhCH(Me)	B	1e (85)
6	3-thienyl	Bn	A	1f (70)
7	MMP ^c	Bn	A	1g (54)

^a TIPS = Triisopropylsilyl. ^b PMP = *p*-MeOC₆H₄. ^c MMP = 2-Me-4-MeO-C₆H₃. ^d **Method A**: NaH/R²NH₂/THF/ $-50\text{ }^{\circ}\text{C}$ /1–3 h. **Method B**: AlMe₃/R²NH₂/CH₂Cl₂/0 $^{\circ}\text{C}$ /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 Et₃N in THF, a

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

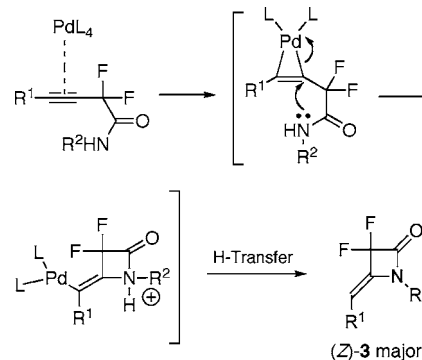
Table 2. Synthesis of β -Lactams **3** and **4**

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

^a Substrate **1a** was inert under the reaction conditions, probably due to steric hindrance 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



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

(5) (a) Hammond, G. B. *J. Fluorine Chem.* **2006**, *127*, 476. (b) Xu, B.; Mae, M.; Hong, J. A.; Li, Y.; Hammond, G. B. *Synthesis* **2006**, 803 and refs cited therein.

(6) Other sources of palladium were also tested, such as Pd(PPh₃)₄, PdCl₂(PPh₃)₂, and Pd₂(dba)₃·CHCl₃. The reaction was also performed with other bases (K₂CO₃), 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.

(8) (a) Jacobson, S.; Carty, A. J.; Mathew, M.; Palem, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 4330. (b) McGinnety, J. A. *J. Chem. Soc. Dalton Trans.* **1974**, 1038.

of the alkyne carbons increases through this interaction, thus resembling an sp^2 -like hybridization.

This pseudohybridization could favor both 4-*exo-dig* and 5-*endo-dig* modes of cyclization, but the presence of the *gem*-difluoro 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	1c	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	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

(9) (a) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (b) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007**, X, 121.

(10) For example, when substrates **1b** ($R^1 = \text{Ph}$) and **1h** ($R^1 = \text{H}$) were treated with AuCl₃ (10 mol %)/AcOH (3 equiv), the corresponding hemiaminal **6g** or ketone **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.

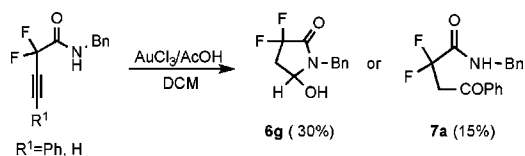


Table 4. Reaction of Compounds **2** with $R^3\text{OH}/\text{H}^+$

entry	substrate	R^3	acid	6, 7 (% yield)
1	2a	H	HCl 3 M	7a (94)
2	2b	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 ₂ SO ₄	6h (94)
9	2g	CF ₃ CH ₂ ^b	HB ₃ F ₄	6i (80)
10	2g	CH ₃ CO ^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** ($R^1 = \text{H}$) 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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