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Intramolecular Hydroamination of Difluoropropargyl Amides: Regioselective Synthesis of Fluorinated β- and γ-Lactams[||]

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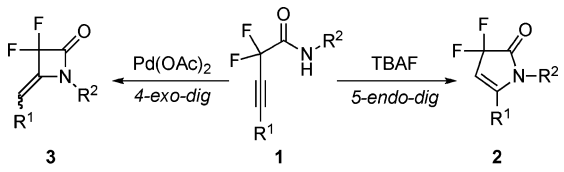
ABSTRACT



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.[1] 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 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 six- to eight-membered ring fluorinated lactams through a tandem ring-closing metathesis−isomerization protocol.[4] However, this methodology is not amenable for the synthesis of four- and five-membered ring difluoro lactams. We decided to

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

(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.; Tillack, 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.

(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.

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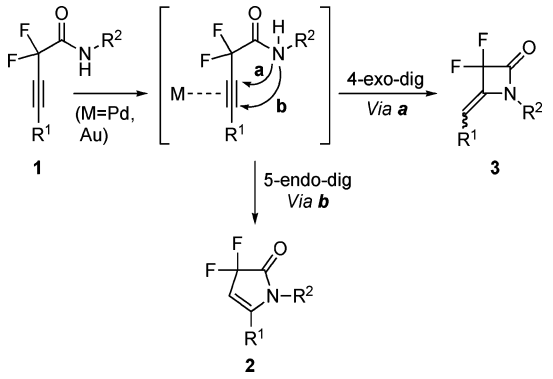
study the construction of these small heterocycles using difluoropropargyl bromides **4** as fluorinated building blocks. This synthon has been used for the preparation of several valuable intermediates, such as fluorinated allenes, fluorodienes, and other functionalized fluoroalkynes.[5] We are now 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

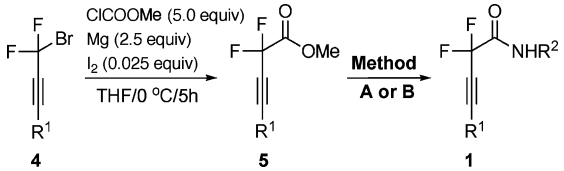
Scheme 1. Synthetic Strategy



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**

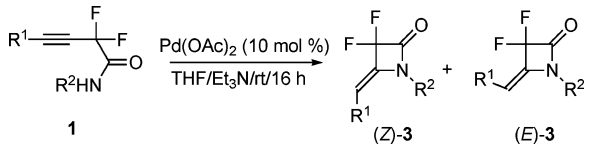


entry	R^1	R^2	method[d]	**1** (yield %)
1	TIPS[a]	Bn	**A**	**1a** (80)
2	Ph	Bn	**A**	**1b** (75)
3	Ph	PMP[b]	**B**	**1c** (70)
4	Ph	Allyl	**A**	**1d** (85)
5	Ph	(*S*)-PhCH(Me)	**B**	**1e** (85)
6	3-thienyl	Bn	**A**	**1f** (70)
7	MMP[c]	Bn	**A**	**1g** (54)

[a] TIPS = Triisopropylsilyl. [b] PMP = *p*-MeOC$_6$H$_4$. [c] MMP = 2-Me-4-MeO−C$_6$H$_3$. [d] **Method A**: NaH/R^2NH_2/THF/−50 °C/1−3 h. **Method B**: $AlMe_3$/R^2NH_2/CH_2Cl_2/0 °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*)-**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**

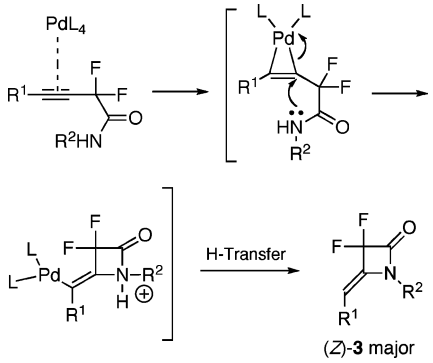


entry	substrate[a]	(*Z*)-**3** + (*E*)-**3** (yield %)	*Z*/*E*[b]
1	**1b**	(*Z*)-**3a** + (*E*)-**3a** (63)	13:1
2	**1c**	(*Z*)-**3b** + (*E*)-**3b** (54)	>50:1
3	**1d**	(*Z*)-**3c** + (*E*)-**3c** (33)	14:1
4	**1e**	(*Z*)-**3d** + (*E*)-**3d** (40)	10:1
5	**1f**	(*Z*)-**3e** + (*E*)-**3e** (34)	10:1
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 ^{19}F 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 CH_2Cl_2 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 suggest[8] 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 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.

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

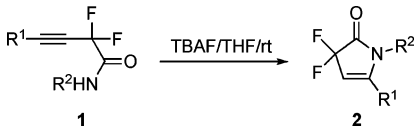
of the alkyne carbons increases through this interaction, thus resembling an sp^2-like hybridization.

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 $AgSbF_6$, $AuCl_3$, $Au(PPh_3)OTf$]. 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*-Pr_2NEt, $LiN(TMS)_2$, 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



1 **2**

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 = Ph) and **1h** (R^1 = H) were treated with $AuCl_3$ (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.

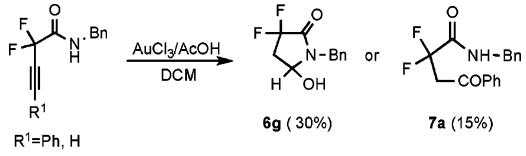
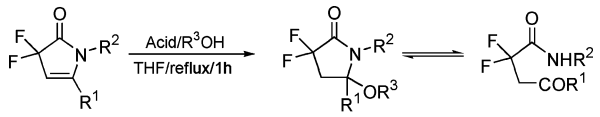


Table 4. Reaction of Compounds **2** with R^3OH/H^+



2 **6** **7**

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_2SO_4	**6h** (94)
9	**2g**	CF_3CH_2[b]	HBF_4	**6i** (80)
10	**2g**	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** (R^1 = 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 HBF_4 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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