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Synthesis of fluorinated δ-lactams via cycloisomerization of *gem*-difluoropropargyl amides

Satoru Arimitsu[1] and Gerald B. Hammond[*2]

Full Research Paper

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Address:
[1]Department of Chemistry, Kyoto University, Kyoto, Japan and [2]Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States

Email:
Gerald B. Hammond[*] - gb.hammond@louisville.edu

* Corresponding author

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Abstract

gem-Difluoro-1,7-enyne amides are suitable building blocks for the synthesis of difluorodihydropyridinones via a ring-closing metathesis reaction, and of 4,4-difluoro-3-oxoisoquinolines through a ring-closing metathesis–enyne metathesis tandem reaction. These products, in turn, undergo a Diels–Alder reaction to yield heterotricyclic systems in moderate to good yields.

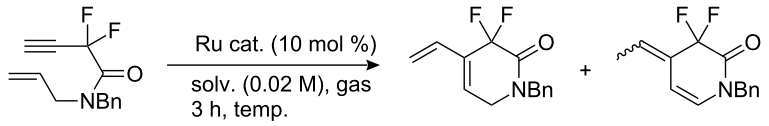
Introduction

It has been estimated that as many as 25% of all synthetic pharmaceutical drugs contain an amide bond [1]. Commonly, β- and γ-lactams are present in many natural products and pharmaceuticals, and the introduction of a *gem*-difluoromethylene moiety has been reported to improve their biological activities. For example, a *gem*-difluoro-γ-lactam can inhibit γ-lactamase, which is responsible for bacterial resistance to γ-lactam antibiotics [2-4]. Additionally, α,α-difluoro lactams are precursors of some biologically active compounds [5-8]. Our group's entry in this arena started as a collaboration with Professor Fustero and resulted in the syntheses of fluorinated β- and γ-lactams [9-13]. This sparked our interest in the synthesis of larger-ring lactams, with six to eight members, because nitrogen-containing medium-size heterocyclics are found in many natural products as part of fused cyclic structures. In their pioneering work on middle-range lactams bearing fluorine(s), Fustero et al. developed a ring-closing metathesis of α,α-difluoro-1,*n*-dienyl amides to furnish the corresponding α,α-difluorinated lactams [14]. The synthesis of medium-size heterocycles by a metathesis reaction is quite relevant, as demonstrated by its extensive application to multi-fused heterocyclics [15-19]. We postulated that functionalized fluorinated enyne amides could be used for the synthesis of a chemically diverse suite of δ-lactams because enynes are suitable partners in ring-closing metathesis reactions or cycloisomerizations. An additional benefit of using enynes in metathesis reactions is that the resulting diene product could be further elaborated using a Diels–Alder reaction to construct bi- or tricyclic ring systems [20].

Results and Discussion

Initially, we investigated the enyne metathesis reaction of fluorinated enyne **1a** with commercially available ruthenium carbene complexes, the Hoveyda–Grubbs second-generation catalyst being the most reactive (entries 1–3, Table 1). The reaction at 110 °C gave **2a-iso** as the major compound, probably through the isomerization of **2a** (entry 3, Table 1) [14]. The latter (**2a**) was isolated when the reaction was carried out at 70 °C in toluene (entry 4, Table 1). Other solvents did not give good yields or selectivities (entries 5 and 6, Table 1). From experimentation, it became clear that ethylene gas was crucial for driving this reaction forward (compare entry 4 with 7, Table 1) [21]. 2,6-Dichloro-1,4-benzoquinone, which has been reported to prevent isomerization [22], gave disappointing results (entry 8, Table 1). When our optimized conditions were applied to other fluorinated 1,7-enynes we isolated the desired lactams (entries 1–3, Table 2). Higher temperatures were required with internal alkynes (entries 2–5, Table 2), where isomerization occurs and the enyne ester **1d** did not yield satisfactory results. Interestingly, although enyne ketone **1e** gave a good ^{19}F NMR yield (97%) of the desired diene **2e**, we could only isolate the *ortho*-fluorophenol **3** in good yield after silica gel chromatography. This unexpected result could have positive synthetic repercussions, as *ortho*-fluorophenol is a moiety that has attracted attention because it is present in some bioactive compounds [23-25].

Table 1: Screening reaction conditions for the enyne metathesis of **1a**.

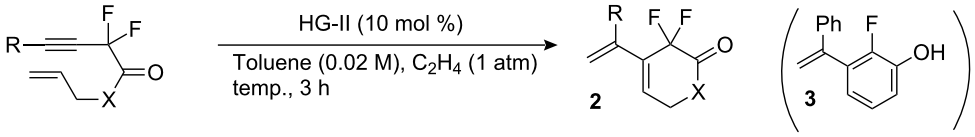


1a **2a** **2a-iso**

Entry	Solvent	Ru cat.	Gas	Temp. (°C)	Yield of products (%)[a] **1a/2a/2a-iso**
1	Toluene	G-I	C_2H_4	110	53/0/0
2	Toluene	G-II	C_2H_4	110	0/34/0
3	Toluene	HG-II	C_2H_4	110	0/6/66 (60)[b]
4	Toluene	HG-II	C_2H_4	70	0/85 (70)/0
5	1,2-DCE[c]	HG-II	C_2H_4	70	No rxn.
6	THF	HG-II	C_2H_4	70	30/25/0
7	Toluene	HG-II	Argon	70	28/34/0
8	Toluene	HG-II	C_2H_4[d]	110	0/20/11

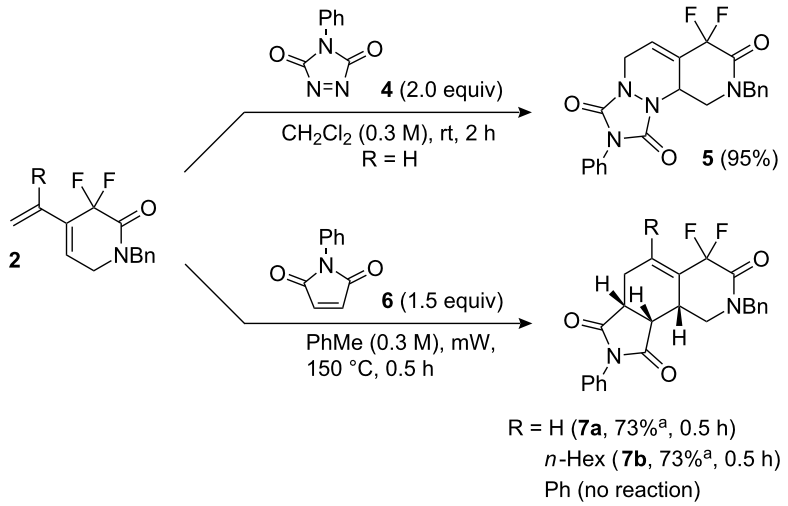
[a]Yield was determined by ^{19}F NMR and the value in parentheses is the isolated yield.
[b]**2a-iso** was isolated as an *E*/*Z* mixture (*E*/*Z* = 3/1).
[c]1,2-Dichloroethane.
[d]20 mol % of 2,6-dichloro-1,4-benzoquinone was used.

Table 2: Metathesis reaction of fluorinated 1,7-enyne carbonyl compounds.



Entry	X	R	Temp. (°C)	Yield of **2** (%)[a]
1	NBn	H (**1a**)	70	70 [85] (**2a**)
2	NBn	*n*-Hex (**1b**)	110	52 [78] (**2b**)
3	NBn	Ph (**1c**)	110	69 [95] (**2c**)
4	O	Ph (**1d**)	110	— [33][b] (**2d**)
5	C	Ph (**1e**)	110	— [97][c] (**2e**)

[a]The yields in brackets were determined by ^{19}F NMR.
[b]Isolation of **2d** was unsuccessful due to the complex mixture that had been formed.
[c]Compound **3** was isolated in 84% after silica gel chromatography.

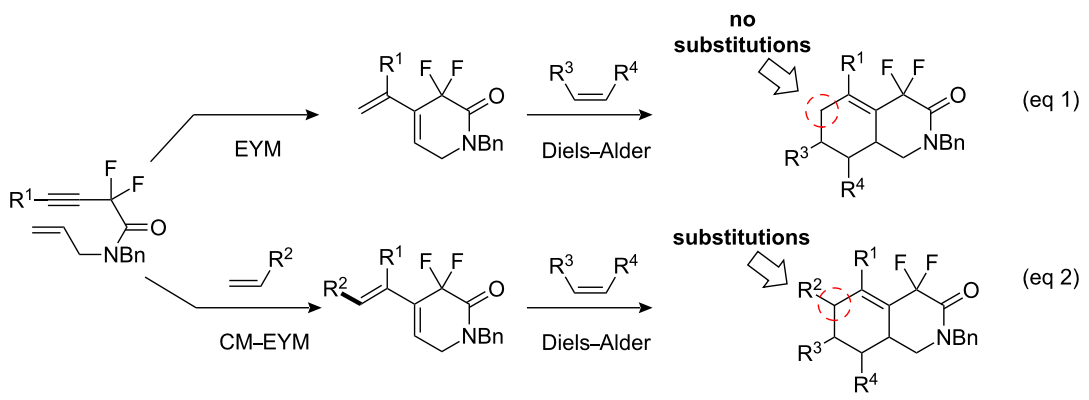


Scheme 1: Diels–Alder reaction of diene **2** with **4** and **6**. [a]The other isomers of **7a** and **7b** were isolated in 8% and 20% yield, respectively.

Dienes **2a** and **2b** were used in Diels–Alder reactions with **4** and **6** to produce **5** and 4,4-difluoroisoquinolin-3-one derivatives **7**, respectively, in excellent yield and good stereoselectivity (Scheme 1). Phenyl-substituted diene **2c** gave no reaction, even after a longer reaction time. The stereochemistry of **7a** and **7b** was determined by COSY and NOESY experiments.

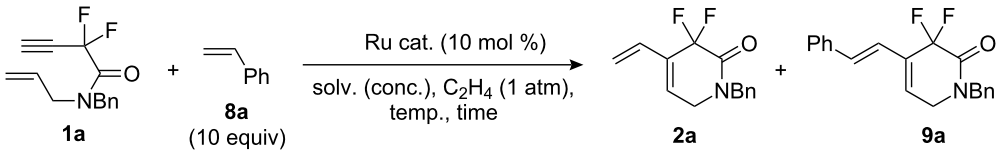
Recently, various tandem reactions with ruthenium complexes have become popular in organic chemistry because Ru(II) complexes are capable of catalyzing additional reactions [26,27]. Since our enyne metathesis reaction of fluorinated 1,7-enynes does not permit substitution at the 6-position of the resultant *gem*-difluoroisoquinolinone (eq 1, Scheme 2), we examined a potential cross metathesis–enyne metathesis tandem-type reaction (CM–EYM reaction). In theory, if the terminal vinyl group of diene **2** can be modified by a tandem metathesis reaction, this would permit the synthesis of multi-substituted *gem*-difluoroisoquinolinones through a subsequent Diels–Alder reaction (eq 2, Scheme 2) [28].

In this regard, we screened various ruthenium carbene complexes using 1,7-enyne amide **1a** and styrene **8a** as a model reaction and found that the Hoveyda–Grubbs second-generation catalyst gave the best mass balance of products **2a** and **9a** (entry 3, Table 3). We obtained better results when the reaction was carried out in a sealed pressure reaction vessel (compare entries 3 and 4, Table 3). More interestingly, the choice of solvent had a tremendous effect on the selectivity between **2a** (EYM product) and **9a** (CM–EYM product) (entries 4–8, Table 3). Methylene chloride was found to be the best solvent (entry 5, Table 3). Other reaction factors were also examined carefully; higher concentrations reduced the yield and selectivity slightly (entries 9 and 10, Table 3). Lower reaction temperature (50 °C) resulted in no conversion (entry 11,



Scheme 2: Synthetic concept toward multi-substituted *gem*-difluoroisoquinolinones.

Table 3: Screening of CM–EYM tandem reaction.



Entry	Ru cat.	Solvent	Conc. (M)	Temp. (°C)	Time[a] (h)	Yield of products **2a/3a** (%)[b]
1[c]	G-I	Toluene	0.02	110	1.5	Complex
2[c]	G-II	Toluene	0.02	110	1.5	23/17
3[c]	HG-II	Toluene	0.02	110	3	34/46
4	HG-II	Toluene	0.02	110	3	33/37
5	HG-II	CH_2Cl_2	0.02	110	24	0/68 (67)[d]
6	HG-II	1,2-DCE	0.02	110	24	26/24
7	HG-II	THF	0.02	110	24	4/28
8	HG-II	1,4-Dioxane	0.02	110	24	9/32
9	HG-II	CH_2Cl_2	0.05	110	24	0/56
10	HG-II	CH_2Cl_2	0.1	110	24	8/32
11	HG-II	CH_2Cl_2	0.02	50	24	No reaction
12[e]	HG-II	CH_2Cl_2	0.02	110	24	18/30

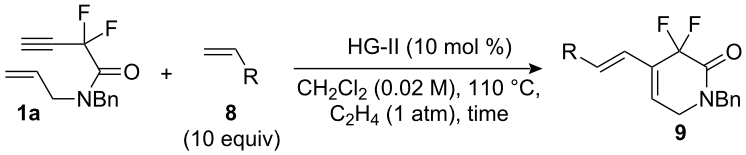
[a]Time was determined by TLC and/or GC–MS.
[b]The yield and ratio of products were determined by ^{19}F NMR.
[c]The reaction was carried out without a pressure vessel.
[d]The value in parentheses is the isolated yield.
[e]The reaction was carried out under argon.

Table 3), and the reaction produced a mixture of **2a** and **9a** in lower yield in the absence of ethylene gas (entry 12, Table 3).

These optimized reaction conditions were applied to other vinyl compounds **8** (Table 4). After 4-substituted aryl alkenes gave the desired product **9** in moderate yields with excellent selectivity (*E*-major) (entries 3 and 4, Table 4), it then became clear that steric hindrance and the electronic deficiency of alkenes **8** decrease the efficiency of the tandem reaction; the non-tandem product **2a** being formed instead (entries 2 and 6, Table 4). Allyl acetate **8f** gave the desired product only when toluene was employed as solvent (entry 6, Table 4).

The stereochemistry of the terminal double bond of **9** was determined by comparing coupling constants of vinyl protons of compound **2a**. The coupling constants of *trans*-protons (Ha–Hc)

Table 4: CM–EYM tandem reaction with fluorinated 1,7-enyne **1a** and alkene **8**.



Entry	R	Time (h)[a]	Isolated yields of **9** [*E*/*Z*][b] + **2a** (%)
1	Ph (**8a**)	24	67 [1/0] (**9a**) + 0
2	3-MeO-C_6H_4 (**8b**)	24	36 [1/0] (**9b**) + 15
3	4-MeO-C_6H_4 (**8c**)	24	33 [1/0] (**9c**) + trace
4	4-Cl-C_6H_4 (**8d**)	24	43 [1/0] (**9d**) + trace
5	4-F-C_6H_4 (**8e**)	27	33 [1/0] (**9e**) + 19
6[c]	CH_2OAc (**8f**)	3	31 [1/0] (**9f**) + 31

[a]Time was determined by TLC and/or GC–MS.
[b]The ratio of products was determined by ^1H and/or ^{19}F NMR.
[c]Toluene was used instead of CH_2Cl_2.

and *cis*-protons (Ha–Hb) on a double bond are J = 17.5 Hz and J = 11.0 Hz, respectively (Figure 1).

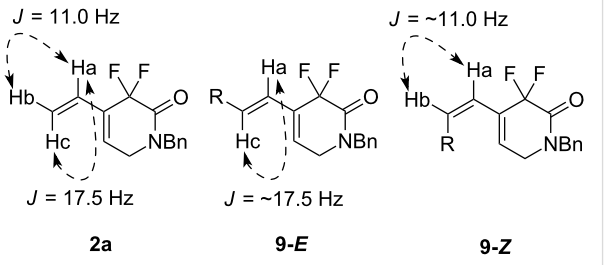
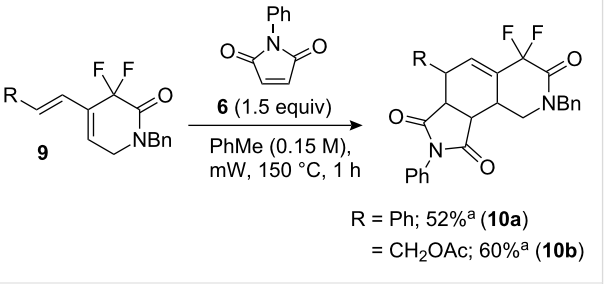


Figure 1: Comparison of coupling constant of vinyl protons.

As expected, the Diels–Alder reaction with *N*-phenylmaleimide **6** gave 6-substituted *gem*-difluoroisoquinolinones efficiently with slight stereoselectivity (Scheme 3).



Scheme 3: Diels–Alder reaction with **9** and **6**. [a]Combined yield of two isomers.

In summary, *gem*-difluoro-1,7-enyne carbonyl derivatives are useful reaction partners in enyne metathesis cycloisomerization and CM–EYM tandem reactions catalyzed by ruthenium carbene complexes. The resulting diene products can be elaborated further using a Diels–Alder reaction.

Supporting Information

Supporting Information File 1

Synthesis of fluorinated δ-lactams via cycloisomerization of *gem*-difluoropropargyl amides
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-48-S1.pdf]

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References

1. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999,** *1,* 55–68. doi:10.1021/cc9800071
2. Wakselman, M.; Joyeau, R.; Kobaiter, R.; Boggetto, N.; Vergely, I.; Maillard, J.; Okochi, V.; Montagne, J.-J.; Reboud-Ravaux, M. *FEBS Lett.* **1991,** *282,* 377–381. doi:10.1016/0014-5793(91)80517-7
3. Maillard, J.-L.; Favreau, C.; Reboud-Ravaux, M.; Kobaiter, R.; Joyeau, R.; Wakselman, M. *Eur. J. Cell Biol.* **1990,** *52,* 213–218.
4. Joyeau, R.; Molines, H.; Labia, R.; Wakselman, M. *J. Med. Chem.* **1988,** *31,* 370–374. doi:10.1021/jm00397a018
5. Angelastro, M. R.; Bey, P.; Mehdi, S.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1992,** *2,* 1235–1238. doi:10.1016/S0960-894X(00)80220-6
6. Evans, G. B.; Furneaux, R. H.; Lewandowicz, A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003,** *46,* 3412–3423. doi:10.1021/jm030145r
7. Inagaki, H.; Miyauchi, S.; Miyauchi, R. N.; Kawato, H. C.; Ohki, H.; Matsuhashi, N.; Kawakami, K.; Takahashi, H.; Takemura, M. *J. Med. Chem.* **2003,** *46,* 1005–1015. doi:10.1021/jm020328y
8. Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986,** *29,* 2080–2087. doi:10.1021/jm00160a048
9. Fustero, S.; Bello, P.; Fernández, B.; del Pozo, C.; Hammond, G. B. *J. Org. Chem.* **2009,** *74,* 7690–7696. doi:10.1021/jo9013436
10. Hammond, G. B.; Arimitsu, S. Synthesis of *gem*-difluorinated heterocycles using a difluoropropargyl building block. In *Fluorinated Heterocycles;* Gakh, A. A.; Kirk, K. L., Eds.; ACS Symposium Series 1003; American Chemical Society: Washington, DC, 2009; pp 135–164.
11. Arimitsu, S.; Bottom, R. L.; Hammond, G. B. *J. Fluorine Chem.* **2008,** *129,* 1047–1051. doi:10.1016/j.jfluchem.2008.05.010
12. Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008,** *73,* 2656–2661. doi:10.1021/jo7025965
13. Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007,** *9,* 4251–4253. doi:10.1021/ol701811z
14. Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006,** *71,* 2706–2714. doi:10.1021/jo0525635
15. Deiters, A.; Martin, S. F. *Chem. Rev.* **2004,** *104,* 2199–2238. doi:10.1021/cr0200872 (see for a review).
16. Cheng, Z.-L.; Chen, Q.-Y. *J. Fluorine Chem.* **2006,** *127,* 894–900. doi:10.1016/j.jfluchem.2006.03.020
17. Wang, R.-W.; Qing, F.-L. *Org. Lett.* **2005,** *7,* 2189–2192. doi:10.1021/ol050558h
18. Pan, Y.; Holmes, C. P.; Tumelty, D. *J. Org. Chem.* **2005,** *70,* 4897–4900. doi:10.1021/jo050599r
19. Beeler, A. B.; Gadepalli, R. S. V. S.; Steyn, S.; Castagnoli, N., Jr.; Rimoldi, J. M. *Bioorg. Med. Chem.* **2003,** *11,* 5229–5234. doi:10.1016/j.bmc.2003.08.002
20. Poulsen, C. S.; Madsen, R. *Synthesis* **2003,** 1–18. doi:10.1055/s-2003-36243
21. Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998,** *63,* 6082–6083. doi:10.1021/jo980896e
22. Hong, S. K.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005,** *127,* 17160–17161. doi:10.1021/ja052939w
23. Dabideen, D. R.; Cheng, K. F.; Aljabari, B.; Miller, E. J.; Pavlov, V. A.; Al-Abed, Y. *J. Med. Chem.* **2007,** *50,* 1993–1997. doi:10.1021/jm061477+

24. Mewshaw, R. E.; Bowen, S. M.; Harris, H. A.; Xu, Z. B.; Manas, E. S.; Cohn, S. T. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 902–906. doi:10.1016/j.bmcl.2006.11.066
25. Mewshaw, R. E.; Edsall, R. J., Jr.; Yang, C.; Manas, E. S.; Xu, Z. B.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2005,** *48,* 3953–3979. doi:10.1021/jm058173s
26. Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001,** *101,* 2067–2096. doi:10.1021/cr000666b
27. Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998,** *98,* 2599–2660. doi:10.1021/cr9403695
28. Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003,** *5,* 3439–3442. doi:10.1021/ol035194c
(a similar approach with non-fluorinated building blocks has been reported).

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