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Concise Preparation of 2,2-Difluorohomopropargyl Carbonyl Derivatives. Application to the Synthesis of 4,4-Difluoroisoquinolinone Congeners

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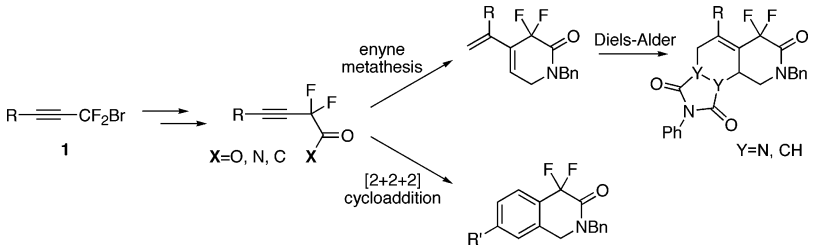

A scalable synthesis of 2,2-difluorohomopropargyl esters was achieved using a magnesium-promoted Barbier reaction of substituted difluoropropargyl bromides with alkyl chloroformates. These 2,2-difluorohomopropargyl esters were effective precursors in the synthesis of homopropargylic amides—by aminolysis using $AlMe_3$, as well as of ketones—through the reaction of the corresponding Weinreb amides with Grignard reagents. Ring closing metathesis using difluorinated 1,7-enyne carbonyl compounds furnished six-membered diene products, which were used as susbstrates in a Diels−Alder reaction to afford 4,4-difluoroisoquinolin-3-ones. The [2 + 2 + 2] cycloaddition of alkynes with fluorinated 1,7-diyne amides gave 4,4-difluoro-1,4-dihydro-3(2*H*)-isoquinolinone derivatives regioselectively.

Introduction

The coming of age of fluorine is unquestionable after decades of continuously impacting society. In particular, α,α-difluoromethylene carbonyl compounds have become increasingly important in medicinal chemistry.[1] Traditionally, fluorine has been installed in these systems by a selective fluorination of an α-ketocarbonyl group using diethylaminosulfur trifluoride (DAST) or a double fluorination of the active α-methylene protons of carbonyls; however, these fluorinating reagents are highly reactive and do not tolerate a variety of substituents or reaction conditions. The use of fluorine-containing unsaturated systems in biological structures has been disclosed by several groups;[2] similar efforts toward cyclic fluorinated structures are lacking. New synthetic options for the synthesis of α,α-difluoromethylene carbonyl compounds—especially cyclic derivatives—are needed. One possible approach would be the transition-metal-catalyzed cyclization of a suitably fluorinated carbonyl-containing unsaturated building block. In hydrocarbon chemistry, this has become an important synthetic tool in modern organic chemistry, because enables useful transformations employing less steps than traditional methodologies.[3] The fact that this strategy has not received the attention it deserves may be due

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(2) (a) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261−7267. (b) Audouard, C.; Barsukov, I.; Fawcett, J.; Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Chem. Commun.* **2004**, 1526−1527. (c) Hanzawa, Y.; Inazawa, K.; Kon, A.; Aoki, H.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 659−662.

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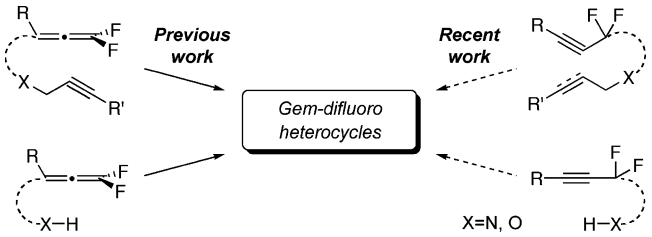
SCHEME 1. Complementary Synthetic Approaches toward *gem*-Difluoro Heterocycles



to limitations in the availability of starting materials bearing fluorinated carbons next to unsaturated bonds, especially triple bonds. A recent report by Bertozzi and co-workers[4] has highlighted the importance of cyclic *gem*-difluorodifluoropropargyl systems in the study of copper-free cellular click chemistry. Their paper also underscores the difficulty of preparing cyclic fluorinated derivatives, as it took the Bertozzi group 11 steps to synthesize their *gem*-difluorocyclooctyne target.

We have recently begun to utilize the fluorinated triple bond scaffold in cyclizations. As shown in Scheme 1, our group possesses two complementary fluorinated starting materials. One is equipped with a *gem*-difluorinated allenyl moiety, whereas the other is fitted with a *gem*-difluorinated propargyl moiety. The activation of X−H (X = N, O) usually requires stoichiometric amounts of base (Scheme 1),[5] but when we investigated the use of catalytic amounts of transition metal for the efficient activation of these fluorinated unsaturated bonds we obtained unique *gem*-difluorocyclic structures.[6]

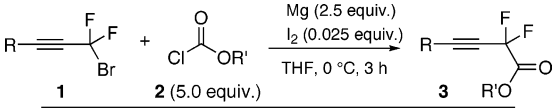
In this paper, we are pleased to report the concise and scalable synthesis of 2,2-difluorohomopropargyl compounds (esters, amides and ketones) and their useful role of cyclization partners, as demonstrated by novel syntheses of 4,4-difluoroisoquinolinone congeners.

Results and Discussion

Kobayashi has reported two procedures to prepare 2,2-difluorohomopropargyl esters: the fluorination of homopropargyl ketoester by DAST[7] and the reaction of iododifluoroacetate-copper with alkynyl iodide.[8] However, both methods have limitations on the scale-up and yields. To address these shortcomings, we first examined the synthesis of 2,2-difluorohomopropargylic esters because esters can be readily converted into other carbonyl analogs like amides and ketones.[9] Optimized reaction conditions[10] were applied to the reaction of substituted difluoropropargyl bromides **1** and alkyl chloroformates **2** (Table 1, entries 1−8). These reactions were easily performed at a molar fraction scale, and products were isolable by distillation. Next, the transformation of methyl 2,2-difluoropropargyl esters **3b**−**e** to the corresponding amides **5** were explored (Table 2). The reactions were successfully carried out with aminoaluminum reagents generated from $AlMe_3$ and either primary amines (entries 1−4, Table 2), secondary amines (entries 5−8, Table 2), or MeONHMe·HCl salt (entries 9 and 10, Table 2), in moderate to good yields.

The reaction of Weinreb amides and Grignard reagents gave the best results in the preparation of 2,2-difluorohomopropargyl ketones **7** (Table 3).[11] Various Grignard reagents containing

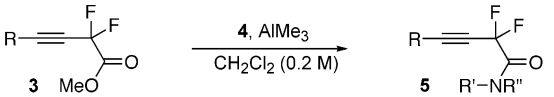
TABLE 1. Synthesis of 2,2-Difluorohomopropargyl Esters 3



1 **2** (5.0 equiv.) **3**

Entry	R	R'	Isolated yields of **3** (%)
1	TES (**1a**)	Me (**2a**)	42 (**3a**)
2	TIPS (**1b**)		73 (**3b**)
3	*n*-Hex (**1c**)		67 (**3c**)
4	Ph (**1d**)		62 (**3d**)
5	*o*-Me-C_6H_4 (**1e**)		51 (**3e**)
6	*p*-Me-C_6H_4 (**1f**)		62 (**3f**)
7	Ph (**1d**)	(**2b**)	62 (**3g**)
8	*p*-Me-C_6H_4 (**1f**)		62 (**3h**)
9	TIPS (**1b**)	(**2c**)	No Rxn.

TABLE 2. Aminolysis of Esters 3 with Amines and $AlMe_3$



3 MeO **5** R'−NR"

Entry	R	R'NR"	*T*	Isolated yields of **5** (%)
1	TIPS (**3b**)	(**4a**)[a]	rt	87 (**5a**)
2	*n*-Hex (**3c**)			61 (**5b**)
3	Ph (**3d**)			80 (**5c**)
4	*o*-Me-C_6H_4 (**3e**)			70 (**5d**)
5	TIPS (**3b**)	(**4b**)[a]	refl.	61 (**5e**)
6	*n*-Hex (**3c**)			52 (**5f**)
7	Ph (**3d**)			90 (**5g**)
8	TIPS (**3b**)	(**4c**)[a]	refl.	72 (**5h**)
9	TIPS (**3b**)	(**4d**)[b]	0 °C	65 (**5i**)
10	Ph (**3d**)			59 (**5j**)

[a] 2.0 equiv of amine and $AlMe_3$ were used; the reaction time was 20 h. [b] 1.05 equiv of **4d** and $AlMe_3$ were used; the reaction time was 1 h.

(4) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci. U.S.A.* **2007**, *104*, 16793−16797.

(5) (a) Lan, Y.; Hammond, G. B. *Org. Lett.* **2002**, *4*, 2437−2439. (b) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552. (c) Sham, H. L.; Betebenner, D. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1134−1135.

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(7) Hanazawa, Y.; Kawagoe, K.; Inazawa, K.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5665−5666.

(8) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103−6106.

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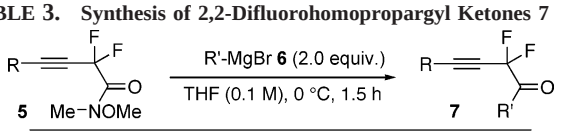
(10) Other solvents (Et_2O and DMF) and temperatures (rt, −20 °C and −78 °C) did not give satisfactory results.

(11) Other synthetic protocols attempted included (i) the reaction of **1** with acyl chloride in the presence of Mg and (ii) the reaction of **3** with Grignard reagents. Both procedures resulted in no reaction or complex mixtures.

TABLE 3. Synthesis of 2,2-Difluorohomopropargyl Ketones 7



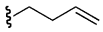
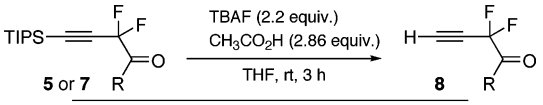
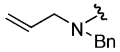
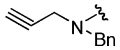
Entry	R	R'	Isolated yields of **7** (%)
1	TIPS (**5i**)	Ph (**6a**)	86 (**7a**)
2	Ph (**5j**)	Ph (**6a**)	88 (**7b**)
3	Ph (**5j**)	4-F-C_6H_4 (**6b**)	71 (**7c**)
4	Ph (**5j**)	4-MeO-C_6H_4 (**6c**)	87 (**7d**)
5	Ph (**5j**)	2-MeO-C_6H_4 (**6d**)	94 (**7e**)
6	Ph (**5j**)	 (**6e**)	72 (**7f**)

TABLE 4. Desilylation of TIPS



Entry	R		Isolated yields of **8** (%)
1	Ph	(**7a**)	71 (**8a**)
2		(**5a**)	>99 (**8b**)
3		(**5e**)	98 (**8c**)
4		(**5h**)	98 (**8d**)

aromatic substituents bearing electron-withdrawing (entry 3, Table 3) and electron-donating groups (entries 4 and 5, Table 3), as well as an aliphatic substituent (entry 6, Table 3), gave the desired ketones **7** in good yields.

The triisopropylsilyl (TIPS) substituent serves not only as a useful synthetic handle but it is also a protective group on reactive triple bonds.[12] We found that desilylation could be accomplished smoothly using TBAF and CH_3CO_2H without any noticeable degradation (Table 4). These newly synthesized 2,2-difluorohomopropargyl carbonyl derivatives are versatile molecular building blocks for the synthesis of *gem*-difluoro heterocyclic compounds. For example, we recently reported the use of amides **5c** in the selective synthesis of β-lactams—using $Pd(OAc)_2$ as a Lewis acid—and γ-lactams—with TBAF as a base.[13]

The *gem*-difluorocarbonyl substrates described above can be used in the synthesis of heterobicyclic and -tricyclic systems. First, we investigated the ring closing metathesis reaction of **8** with ruthenium carbene complexes, as the resulting diene product could be elaborated further using a Diels—Alder reaction (Scheme 3).[14] During the course of screening this reaction, we found the Hoveyda—Grubbs second-generation catalyst to be the most reactive among other ruthenium carbene complexes (Scheme 2, Table 5), but the reaction at 110 °C gave **9a-iso** as

SCHEME 2. Ruthenium Carbene Metathesis Complexes

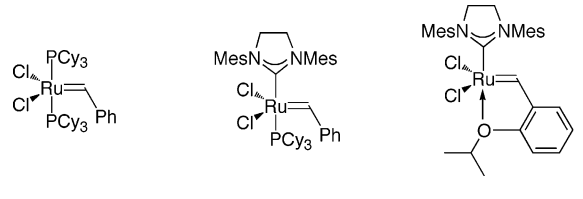
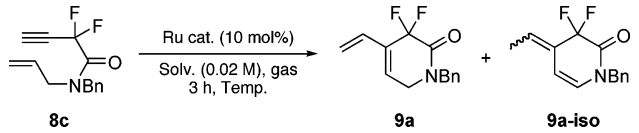


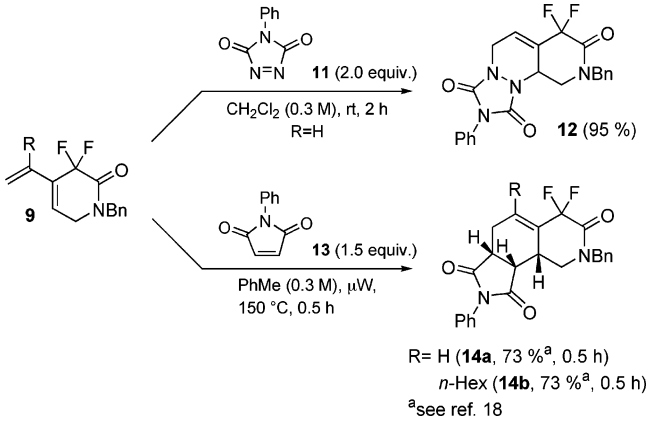
TABLE 5. Screening Reaction Conditions for the Enyne Metathesis of 8c



entry	solvent	Ru cat.	gas	*T* (°C)	yields of product[a] (%) **8c**/**9a**/**9a-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-dichloroethane	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[c]	110	0/20/11

[a] Yield was determined by ^{19}F NMR, and the value in parentheses is the isolated yield. [b] **9a-iso** was isolated as an *E*/*Z* mixture (*E*/*Z* = 3/1). [c] 20 mol % of 2,6-dichloro-1,4-benzoquinone was used.

SCHEME 3. Diels—Alder Reaction of Diene 9 with 11 and 13



the major compound, probably through the isomerization of **9a**[15] (entry 3, Table 5). The latter was obtained when the reaction was carried out at 70 °C in toluene (entry 4, Table 5). Other solvents (e.g., 1,2-dichloroethane or THF) gave neither good yields nor selectivities (entries 5 and 6, Table 5). From experimentation, it became clear that ethylene gas was crucial to make this reaction proceed forward (compare entry 4 with 7, Table 5).[16a] 2,6-Dichloro-1,4-benzoquinone, which has been reported to prevent isomerization,[16b] gave disappointing results

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(15) For tandem RCM-isomerization reactions, see: Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706−2714 and literature cited therein.

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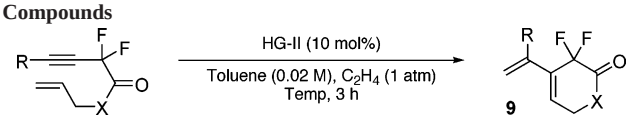
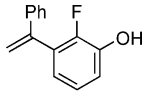
TABLE 6. Metathesis Reaction of Fluorinated 1,7-Enyne Carbonyl Compounds



entry	X	R	*T* (°C)	yields of **9**[a] (%)
1	NBn	H (**8c**)	70	70 [85] (**9a**)
2	NBn	*n*-Hex (**5f**)	110	52 [78] (**9b**)
3	NBn	Ph (**5g**)	110	69 [95] (**9c**)
4	O	Ph (**3h**)	110	[33][b] (**9d**)
5	C	Ph (**7f**)	110	[97][c] (**9e**)

[a] The yields in brackets were determined by ^{19}F NMR. [b] Isolation of **9d** was unsuccessful due to the complex mixture formed. [c] Compound **10** was isolated in 84 % after silica gel chromatography.



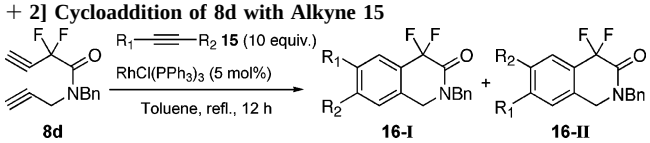
10

(entry 8, Table 5). When our optimized conditions were applied to other fluorinated 1,7-enynes, we only could isolate the corresponding lactams (entries 1−3, Table 6). Higher temperatures were required when internal alkynes were employed (entries 2−5, Table 6), but the enyne ester **3h** did not give satisfactory results. Interestingly, although enyne ketone **7f** gave a good ^{19}F NMR yield of the desired diene **9e** [97%, δ: −103.99 ppm (s, 2F)], after workup and silica gel chromatography we only obtained, in good yield, the *o*-fluorophenol **10**. This unexpected result could have positive synthetic repercusions as the *o*-fluorophenol is a moiety that has attracted attention elsewhere.[17]

With an efficient access to conjugated dienes **9**, we were in the position to prepare bi- or tricyclic systems, as demonstrated in Scheme 3. Accordingly, dienes **9a** and **9b** were used in Diels−Alder reactions with **11** and **13** to give **12** and 4,4-difluoroisoquinolin-3-one derivatives **14**, respectively, in excellent yield and good stereoselectivity.[18]

Fluorinated diynes are useful building blocks,[19] as shown in our reported synthesis of 3,3-difluoroisochroman derivatives using [2 + 2 + 2] cycloaddition.[20] To extend our methodology further, we used 1,7-diyne amide **8d** (see entry 4, Table 4) to synthesize 4,4-difluoro-1,4-dihydro-3(*2H*)-isoquinolinones, which could be expected to have interesting bioactivities and/or become useful intermediates.[21] The reaction proceeded effectively with several alkynes **15** and catalytic amount of $RhCl(PPh_3)_3$ (5 mol %) (Table 7). It is worth mentioning the interesting regioselectivity of products **16-I**/**16-II** observed when terminal alkynes **15a**−**f** (entry 1−6, Table 7) were utilized. The product **16-II** was obtained as the major isomer in all cases regardless of the substrate on the terminal alkyne **15**. It is known that the regioselectivity of [2 + 2 + 2] cycloaddition is often controlled by steric interactions between the substituents in diynes and alkynes. However, both triple bonds in diyne **8d** are terminal; therefore, the observed regioselectivity could be explained by cooperative effects between electron-withdrawing effects of fluorine and steric interactions between ligand and substrate on alkyne **15** in its transition state.[22]

TABLE 7. Synthesis of 4,4-Difluoro-1,4-dihydro-3(2*H*)-isoquinolinone Derivatives by [2 + 2 + 2] Cycloaddition of 8d with Alkyne 15



entry	R_1	R_2	yields of product (%) [**16-I**:**16-II**][a]
1	CH_2OH	H (**15a**)	92 [1:4] (**16a**)
2	TMS	H (**15b**)	85 [1:3] (**16b**)
3	C_6H_5	H (**15c**)	85 [1:6] (**16c**)
4	*o*-$NO_2C_6H_4$	H (**15d**)	37 [1:1.5] (**16d**)
5	OEt	H (**15e**)	55 [1:2.5] (**16e**)
6	CO_2Me	H (**15f**)	40 [1:2] (**16f**)
7	CH_2OH	CH_2OH (**15g**)	52 (**16g**)
8	CO_2Et	CO_2Et (**15h**)	45 (**16h**)

[a] The isomer ratio was determined by ^{19}FNMR.

In conclusion, the Barbier reaction of substituted difluoropropargyl bromides **1** with Mg and alkyl chloroformates provides 2,2-difluorohomopropargyl esters **3**, and the aminolysis of methyl 2,2-difluorohomopropargyl esters furnished the corresponding amides **5**. 2,2-Difluorohomopropargyl ketones **7** were successfully obtained by the reaction of its Weinreb amide precursor with a Grignard reagent. These 2,2-difluorohomopropargyl carbonyl compounds proved to be good cycloaddition partners. The enyne metathesis of fluorinated 1,7-enyne carbonyl compounds using Hoveyda−Grubbs second generation catalyst furnished the six-membered diene ring **9**, which proved to be an efficient diene in a Diels−Alder reaction to afford 4,4-difluoroisoquinolin-3-one. Additionally, a fluorinated 1,7-diyne amide was used in the regioselective synthesis of 4,4-difluoro-1,4-dihydro-3(2*H*)-isoquinolinones using a [2 + 2 + 2] cycloaddition protocol with $RhCl(PPh_3)_3$.

Experimental Section

Synthesis of Methyl 2,2-Difluoro-4-(triisopropylsilyl)-3-butynoate (3b). A suspension of Mg (0.25 mol) and I_2 (2.5 mmol) in dry THF (400 mL) was stirred under argon for 30 min at room temperature until the solution become cloudy. Then a solution of the corresponding difluoropropargyl bromide **1b** (0.1 mol) and methyl chloroformate **2a** (0.5 mol) was slowly added at 0 °C, rinsing with dry THF (100 mL). The reaction mixture was stirred for 3 h and quenched with aqueous 10% HCl (30 mL) in ice. The organic solvent was removed by rotary evaporation, the reaction mixture

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was extracted with Et_2O (3 × 30 mL) and washed by aqueous saturated sodium bisulfite and brine, and the combined organic layers were dried over Na_2SO_4. After removal of the solvent, **3b** was isolated by distillation in 73% yield (21.2 g). ^1H NMR ($CDCl_3$) δ: 1.10−1.16 (bs, 21H), 3.94 (s, 1H); ^{19}F NMR ($CDCl_3$) δ: −90.50 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 11.0, 18.5, 54.2, 95.2 (t, J = 36.5 Hz), 95.3 (t, J = 5.0 Hz), 103.7 (t, J = 242.1 Hz), 162.2 (t, J = 34.6 Hz). IR (neat) cm^{-1}: 2947, 2870, 2185, 1772, 1471. MS *m*/*z*: 271 (100), 107 (55), 79 (38). HRMS (EI): calcd for $C_{14}H_{24}F_2O_2Si$ (M^+) 290.1513, found 290.1511.

Synthesis of *N*-Allyl-*N*-benzyl-2,2-difluoro-4-(triisopropylsilyl)-3-butynamide (5e). To a solution of *N*-allyl-*N*-benzylamine **4b** (40 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under argon was added dropwise $AlMe_3$ (40 mmol, 20 mL of 2.0 M solution in hexanes). The ice bath was removed, and the light yellow solution was allowed to stir at room temperature for 1 h, after which it was recooled to 0 °C. Then a solution of **3b** (20 mmol) in CH_2Cl_2 (25 mL) was added, followed by CH_2Cl_2 (25 mL) used to aid in the rinsing. The reaction mixture was allowed to warm to room temperature and then heated to reflux temperature. After the mixture was heated for 20 h, the consumption of **3b** was confirmed by GC. The reaction was quenched by aqueous 10% HCl (100 mL) in ice and then extracted by EtOAc (3 × 30 mL), and the organic layer was washed with brine and dried over Na_2SO_4. Pure compound **5e** was obtained in 61% yield (4.95 g) after silica gel chromatography using hexane/EtOAc (30/1) as eluent. ^1H NMR ($CDCl_3$) δ: 0.97−1.02 (m, 21H), 3.84 (d, J = 8.0 Hz, 1H), 3.98 (d, J = 6.0 Hz, 1H), 4.556 (s) and 4.68 (s) for 2H, 5.03 (d, J = 17.5 Hz) and 5.14 (d, J = 17.5 Hz) for 1H, 5.13 (d, J = 10.0 Hz) and 5.22 (d, J = 10.0 Hz) for 1H, 5.61−5.75 (m, 1H), 7.14−7.30 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: −85.20 (s) and −86.20 (s) for 2F. ^{13}C NMR ($CDCl_3$) δ: 10.8, 18.3, 47.6, 47.9, 49.2, 50.4, 95.1 (t, J = 36.0 Hz), 96.6, 95.8, 95.9 (t, J = 36.5 Hz), 105.0, (t, J = 241.8 Hz), 105.1 (t, J = 241.9 Hz), 118.3, 119.3, 127.4, 127.6, 127.9, 128.0, 128.7, 128.8, 131.0, 132.3, 135.3, 135.8, 161.0 (t, J = 29.2 Hz), 161.3 (t, J = 30.2 Hz). IR (neat) cm^{-1}: 2945, 2867, 2359, 1689. MS *m*/*z*: 405 (3, M^+), 92 (80).

Synthesis of *N*-Methoxy-*N*-methyl-2,2-difluoro-4-(triisopropylsilyl)-3-butynamide (5i). To a suspension of MeONHMe·HCl **4d** (1.05 mmol) in dry CH_2Cl_2 (2.5 mL) at 0 °C under argon was added dropwise $AlMe_3$ (1.05 mmol, 0.52 mL of 2.0 M solution in hexanes). The ice bath was removed, and the solution was allowed to stir at room temperature for 1 h. After recooling to 0 °C, a solution of **3b** (1.0 mmol) in CH_2Cl_2 (1.5 mL) was added, followed by CH_2Cl_2 (1.0 mL) used to the aid in the rinsing. The reaction mixture was kept at 0 °C for 1 h, after which it was quenched with aqueous 10% HCl (10 mL) in ice and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine and dried over Na_2SO_4. Pure compound **5i** was obtained in 65% (208 mg) after silica gel chromatography using hexane/EtOAc (40/1) as eluent. ^1H NMR ($CDCl_3$) δ: 1.06−1.14 (bs, 21H), 3.23 (bs, 3H), 3.76 (s, 3H). ^{19}F NMR ($CDCl_3$) δ: −88.78 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 10.7, 18.6, 33.0, 61.5, 93.4, 95.7 (t, J = 35.2 Hz), 104.5 (t, J = 240.9 Hz), 161.0 (t, J = 29.8 Hz); IR (neat) cm^{-1}: 3419, 2945, 2867, 1700, 1174. MS *m*/*z*: 239 (6, M^+), 116 (18), 93 (11). HRMS (FAB): calcd for $C_{15}H_{27}F_2NO_2Si$ (M^+) 319.1779, found 320.1857 (M^++H)

Synthesis of 3,3-Difluoro-1-phenyloct-7-en-1-yn-4-one (7f). To a solution of **5j** (4.7 mmol) in dry THF (47 mL) at 0 °C under argon was added dropwise 3-butenylmagnesium bromide **6e** (9.4 mmol, 18.8 mL of 0.5 M solution in THF). The reaction mixture was stirred at 0 °C for 1.5 h, quenched with aqueous 10% HCl (30 mL) in ice, and extracted with Et_2O (3 × 20 mL). The organic layer was then washed with brine and dried over Na_2SO_4. Pure compound **7f** was obtained in 72% (793 mg) after silica gel chromatography using hexane/EtOAc (15/1) as eluent. ^1H NMR ($CDCl_3$) δ: 2.47 (apparent q, J = 7.0 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 5.06 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.81−5.89 (m, 1H), 7.39−7.56 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: −94.18 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 26.8, 35.0, 78.0 (t, J = 38.6 Hz), 91.3 (t, J = 6.5 Hz), 107.8 (t, J = 244.5 Hz), 116.0, 119.2, 128.6, 130.6, 132.3, 135.8, 195.0 (t, J = 31.2 Hz). IR (neat) cm^{-1}: 3082, 2923, 2234, 1755. MS *m*/*z*: 234 (17, M^+), 213 (19), 151 (100), 105 (67). HRMS (FAB): calcd for $C_{14}H_{12}F_2O$ (M^+) 234.0856, found 235.0925 (M^+ + H).

Synthesis of *N*-Allyl-*N*-benzyl-2,2-difluoro-3-butynamide (8c). A solution of AcOH (37.2 mmol) and TBAF (28.6 mmol, 28.6 mL of 1.0 M solution in THF) in wet THF (100 mL) was stirred at room temperature for 30 min, and then a THF solution (30 mL) of **5e** (13.0 mmol) was added slowly at room temperature and the mixture stirred at room temperature for 3 h. After this time, it was quenched with water and extracted with EtOAc (3 × 40 mL). The organic layer was washed with brine and dried over Na_2SO_4. The final product **8c** was isolated in 98% (3.18 g) after silica gel column chromatography using hexane/EtOAc (20/1) as eluent. ^1H NMR ($CDCl_3$) δ: 3.04 (t, J = 5.5 Hz) and 3.07 (t, J = 5.5 Hz) for 1H, 3.92 (d, J = 6.0 Hz) and 4.04 (d, J = 5.5 Hz) for 2H, 4.63 (s) and 4.74 (s) for 2H, 5.11 (d, J = 17.0 Hz) and 5.23 (d, J = 17.5 Hz) for 1H, 5.22 (d, J = 10.0 Hz) and 5.31 (d, J = 10.5 Hz) for 1H, 5.70−5.83 (m, 1H), 7.23−7.34 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: −86.36 (s) and −87.00 (s) for 2F. ^{13}C NMR ($CDCl_3$) δ: 47.9, 48.2, 49.0, 50.1, 73.8 (t, J = 37.5 Hz), 73.9 (t, J = 37.5 Hz), 79.5 (t, J = 6.3 Hz), 79.7 (t, J = 6.2 Hz), 105.9 (t, J = 243.8 Hz), 118.4, 119.4, 127.3, 127.7, 127.9, 128.1, 128.71, 128.73, 130.8, 131.9, 135.0, 135.7, 160.3 (t, J = 29.3 Hz), 160.6 (t, J = 29.8 Hz). IR (neat) cm^{-1}: 3225, 3087, 3031, 2933, 2125, 1681, 1445. MS *m*/*z*: 249 (13, M^+), 161 (17), 134 (4), 92 (8). Anal. Calcd: C, 67.46; H, 5.26. Found: C, 66.99; H, 5.26.

Synthesis of 1-Benzyl-3,3-difluoro-4-vinyl-3,6-dihydropyridin-2-one (9a). To a suspension of Hoveyda−Grubbs second-generation catalyst (0.38 mmol) in toluene (170 mL) was added **8c** (3.8 mmol) with the aid of toluene (20 mL) at room temperature under argon. The argon gas was replaced with ethylene gas, and the mixture was stirred at 70 °C for 3 h. The reaction was quenched with water and extracted with EtOAc (3 × 20 mL), and the organic layer was washed with brine and dried over Na_2SO_4. The final product **9a** was isolated in 70% (663 mg) after silica gel column chromatography using hexane/EtOAc (4/1) as eluent. ^1H NMR ($CDCl_3$) δ: 3.88−3.91 (m, 2H), 4.63 (s, 2H), 5.26 (d, J = 11.0 Hz, 1H), 5.63 (d, J = 17.5 Hz, 1H), 6.08 (s, 1H), 6.19 (dd, J = 18.0, 11.5 Hz, 1H), 7.18−7.28 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: −95.83 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 46.7, 49.8, 107.6 (t, J = 237.1 Hz), 118.9, 127.0, 128.1, 128.2, 128.9, 129.1, 131.0 (t, J = 24.2 Hz), 135.0, 160.2 (t, J = 29.8 Hz). IR (CCl_4) cm^{-1}: 3032, 2940, 1674. MS *m*/*z*: 249 (13, M^+), 230 (45), 91 (100). HRMS (FAB): calcd for $C_{14}H_{12}F_2O$ (M^+) 249.0965, found 250.1033.

Synthesis of Diels−Alder Adduct 12. To a solution of **11** (0.48 mmol) in CH_2Cl_2 (0.2 mL) was added **9a** (0.32 mmol) with the aid of CH_2Cl_2 (0.8 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3 × 15 mL), and the organic layer was washed with brine and dried over Na_2SO_4. The final product **12** was isolated in 95% yield (194 mg) after silica gel column chromatography using CH_2Cl_2/EtOAc (100/1) as eluent. ^1H NMR ($CDCl_3$) δ: 3.30 (dt, J = 2.5, 10.8 Hz, 1H), 4.06 (dd, J = 6.0, 11.0 Hz, 1H), 4.26−4.32 (m, 2H), 4.50 (d, J = 14.5 Hz, 1H), 4.87 (d, J = 14.5 Hz, 1H), 4.94 (bs, 1H), 6.64 (bs, 1H), 7.28−7.49 (m, 10H). ^{19}F NMR ($CDCl_3$) δ: −88.27 (d, J = 287.6 Hz, 1F), −119.01 (d, J = 287.6 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ: 42.7, 48.0, 49.2, 51.2, 108.0 (dd, J = 249.4, 250.1 Hz), 121.6 (t, J = 11.3 Hz), 125.2, 127.5 (t, J = 22.8 Hz), 128.37, 128.43, 128.6, 129.1, 129.3, 130.4, 134.6, 151.76, 151.83, 160.2 (t, J = 30.4 Hz). IR (CCl_4) cm^{-1}: 3064, 2948, 2890, 1727, 1677. HRMS (FAB): calcd for $C_{22}H_{18}F_2N_4O_3$ (M^+) 424.1347, found 424.1354.

General Synthesis of 4,4-Difluoro-1,4-dihydro-3(2*H*)-isoquinolinone Derivatives (16). To a solution of the amide **8d** (0.4 mmol) in dry toluene (4 mL) at room temperature were slowly added

acetylene **15a** (4.0 mmol) and $RhCl(PPh_3)_3$ (0.02 mmol). The reaction mixture was heated at reflux during 12 h. After the reaction was complete, the solvent was removed under reduced pressure and the residue was purified by repeated silica gel column chromatography using EtOAc/hexane (1/10) and then (1/2) as eluents to afford **16a** as a white solid in 92% yield (112 mg) forming a mixture of regioisomers, **16a-I**/**16-II** = 1/4. Major isomer **16a-II**. Mp = 58−60 °C. ^{1}H NMR ($CDCl_3$) δ: 4.47 (s, 2H), 4.74 (s, 2H), 4.82 (s, 2H), 7.22 (s, 1H), 7.29−7.36 (m, 5H), 7.42 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ: −95.7 (s, 2F). ^{13}C NMR ($CDCl_3$) δ: 47.7, 49.4, 63.2, 106.8 (t, J = 189.9 Hz), 122.3, 124.6, 125.5, 127.1, 127.9, 131.4, 134.1, 143.3, 160.4 (t, J = 24.5 Hz). HRMS (EI) calcd for $C_{17}H_{15}F_2NO_2$ (M^+) 303.1070, found 303.1076.

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Supporting Information Available: Analytical and spectroscopic data for **3c**−**h**, **5a**−**d**,**f**−**h**,**j**, **7a**−**e**, **8a**,**b**,**d**, **9a-iso**, **9b**,**c**, **10**, **14a**,**b**, and **16b-II**−**16i-II**. This material is available free of charge via the Internet at http://pubs.acs.org.

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