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Lanthanide Triflate-Catalyzed Preparation of β,β-Difluorohomopropargyl Alcohols in Aqueous Media. Application to the Synthesis of 4,4-Difluoroisochromans

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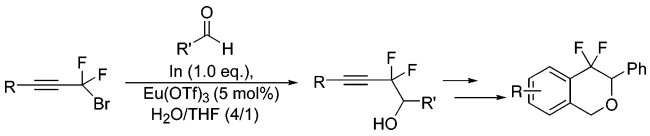

An indium-mediated Barbier-type reaction of difluoropropargyl bromide with several aldehydes in aqueous media was enhanced by a catalytic amount of a lanthanide triflate (5 mol %). The reaction gave the corresponding β,β-difluorohomopropargyl alcohols with high regioselectivity. The [2 + 2 + 2] alkyne cyclotrimerization of β,β-difluorohomopropargyl alcohols with monosubstituted acetylenes produced 4,4-difluoroisochromans in good yields with moderate regioselectivity.

Homopropargyl alcohols are versatile building blocks in organic synthesis.[1] In this regard, the placement of a *gem*-difluoromethylene carbon on a propargylic position can modify the stereoelectronic properties of the resulting alkyne, leading to regioselective carbon−carbon bond formation (i.e., propargyl allenyl) by judicious choice of reagents and conditions.[2a] Furthermore, the resulting alkyne or allene constitutes powerful cycloaddition partners, which, in the case of the difluoropropargyl system, could lead to practical syntheses of fluorinated cyclic or heterocyclic targets of biological interest. Currently, the synthesis of fluorinated heterocycles is done on a case-by-case basis. There are two possible fluorine locations around a triple bond: externally, capping the terminal acetylenic carbon using a CF_3 or Rf group (Scheme 1, top), or internally, bonded to the propargyl carbon (i.e., **2** or **3**) (Scheme 1, bottom). Externally substituted fluorinated acetylenes have been prepared from fluoroiodoolefins or trifluorobromopropene and have been used to make fluorinated isoquinolines[3a−c] and other medicinal targets such as panomifene.[3d] By comparison, there are fewer methodologies for the synthesis of **2** or **3**. The reason for this is the inherent difficulty of executing nucleophilic substitutions on a CF_2 group due to the electronic repulsion between the fluorine atoms and the incoming nucleophile, or the facile formation of carbenoid intermediates arising from α-elimination of fluoride in the presence of metals (Scheme 1, bottom). Our group has recently overcome the problem of nucleophilic substitution on a difluoromethylene carbon using a functionalized difluoroallene acting as a CF_2 cation equivalent.[2b] Both hard and soft nucleophiles produced **2** under mild conditions and good yields. Electrophilic substitution on **1** has also been accomplished using a Mg(0)-promoted reductive debromometalation without loss of fluorine to give *gem*-difluoropropargylsilanes or *gem*-difluoropropargylstannanes, which can then react with an electrophile to yield **3**.[2a] The latter approach was employed to synthesize homopropargyl alcohol **3ea** (R = R′ = Ph) in excellent yield; however, this reaction required stringent conditions and therefore it is not amenable for large-scale synthesis.

Another method to prepare homopropargyl alcohol **3** [E = −CH(OH)R′] uses zinc,[4] but this protocol requires anhydrous conditions. A green chemistry alternative is the indium-mediated Barbier-type reaction of **1** with aldehydes. We originally reported this approach using difluoropropargyl bromide[2c] but later found that this protocol could not be scaled up without decreasing the yield of the resulting homopropargyl alcohol **3** and reliable reproducibility; sonicating the reaction mixture shortened the reaction time, but it contributed to an increased amount of dimer **4**. We now wish to report a practical and scalable indium-mediated preparation of β,β-difluorohomopropargyl alcohol **3** using a lanthanide triflate as a Lewis acid catalyst in predominantly aqueous media. This alcohol was converted to 3,3-difluoro-1,7-diyne **6**, which in turn underwent a facile catalytic [2 + 2 + 2] alkyne cyclotrimerization that yielded fluorinated isochromans **8** and **9**.

First, we revisited the reaction between difluoropropargyl bromide (**1a**) and benzaldehyde (**5a**) (Table 1) by examining the effect of the solvent on the yield of the product. Altering the ratio of THF and H_2O did not produce significant differences in the reaction results (Table 1, entries 1−4), but when anhydrous THF was employed, the reaction did not occur at all and only starting material **1a** was observed in the ^{19}F NMR spectrum (Table 1, entry 5). In anhydrous DMF, the reaction produced a complex mixture (Table 1, entry 6). Increasing the number of equivalents of aldehyde **5a** was not effective either (Table 1, entries 7 and 8). Because lanthanide triflates are known for their unique Lewis acid behavior and their tolerance to

(1) For recent examples, see: (a) Miranda, P. O.; Ramirez, M. A.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 1633−1636. (b) Miura, K.; Wang, D.; Matsumoto, Y.; Hosomi, A. *Org. Lett.* **2005**, *7*, 503−505. (c) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798−8807. (d) Trost, B. M.; Rhee, Y. H. *J. Am. Chem.* Soc. **2003**, *125*, 7482−7483.

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(3) (a) Konno, T.; Chae, J.; Miyabe, T.; Ishihara, T. *J. Org. Chem.* **2005**, *70*, 10172−10174. For other examples, see: (b) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 8258−8265. (c) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2004**, *60*, 11695−11700. (d) Konno, T.; Daitoh, T.; Noiri, A.; Chae, J.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2004**, *6*, 933−936.

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SCHEME 1. Synthetic Approaches to Externally and Internally Substituted Acetylenes

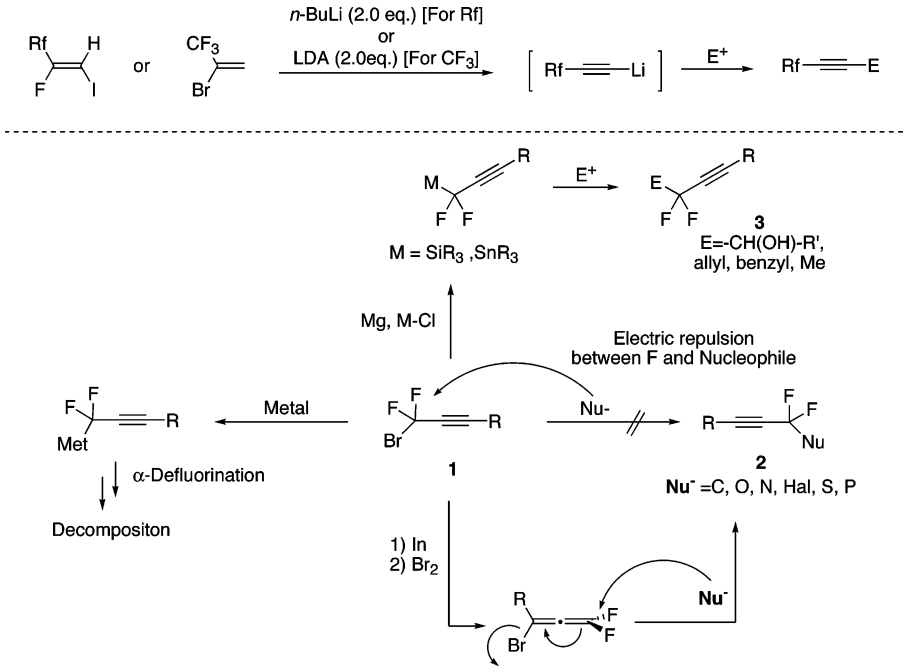
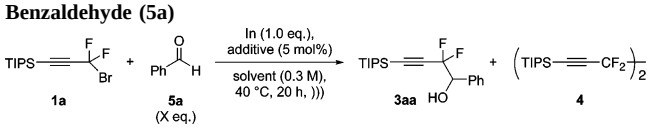


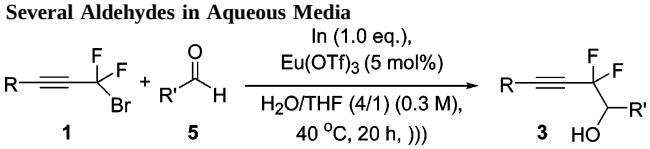
TABLE 1. Optimization of the Reaction between 1a and Benzaldehyde (5a)



entry	solvent	X (equiv of **5a**)	additive (5 mol %)	yield (%)[a] **3aa**:**4**
1	H_2O/THF (4/1)	1.1		20:6
2	H_2O/THF (1/1)	1.1		31:12
3	H_2O/THF (1/4)	1.1		25:7
4	*satd*NH_4Cl*aq*/THF (4/1)	1.1		20:4
5	THF	1.1		no reaction
6	DMF	1.1		complex mixture
7	H_2O/THF (4/1)	2.2		29:8
8	H_2O/THF (4/1)	3.3		36:4
9	H_2O/THF (1/1)	1.1	$Sc(OTf)_3$	42:4
10	H_2O/THF (4/1)	1.1	$Sc(OTf)_3$	68:7
11			$Er(OTf)_3$	64:7
12			$Eu(OTf)_3$	78:8
13			$Tb(OTg)_3$	76:10
14			$Sm(OTf)_3$	48:9
15			$Y(OTf)_3$	47:13
16			$Ce(OTf)_3$	77:8

[a] Yield was determined by ^{19}F NMR.

TABLE 2. Indium-Mediated Barbier-Type Reaction of 1 with Several Aldehydes in Aqueous Media



entry	R	R′	yield (%)[a]
1	TIPS (**1a**)	Ph (**5a**)	68 (**3aa**) [9.8][d]
2	TES (**1b**)[b]	Ph (**5a**)	72 (**3ba**) [17.3][d]
3	TMS (**1c**)[c]	Ph (**5a**)	41 (**3ca**) [26.5][d]
4	*n*-hex (**1d**)[b]	Ph (**5a**)	55 (**3da**)
5	Ph (**1e**)[b]	Ph (**5a**)	35 (**3ea**)
6	TES (**1b**)[b]	4-Me-C_6H_4 (**5b**)	65 (**3bb**)
7		4-MeO-C_6H_4 (**5c**)	61 (**3bc**)
8		3-MeO-C_6H_4 (**5d**)	60 (**3bd**)
9		2,4-$(MeO)_2$-C_6H_3 (**5e**)	73 (**3be**)
10		4-OH-C_6H_4 (**5f**)	62 (**3bf**)
11		3,5-$(CH_3O)_2$-4-OH-C_6H_2 (**5g**)	61 (**3bg**)
12		4-Cl-C_6H_4 (**5h**)	71 (**3bh**)
13		2-F-C_6H_4 (**5i**)	65 (**3bi**)
14		4-NO_2-C_6H_4 (**5j**)	no reaction
15		Et (**5k**)	52 (**3bk**)
16		$(CH_3)_2CH$ (**5l**)	69 (**3bl**)
17		$BzOCH_2$ (**5m**)	65 (**3bm**)

[a] Isolated yield [b] The reaction was sonicated for 12 h. [c] The reaction was sonicated for 6 h. [d] The value in the parentheses is the yield ratio of **3** and dimer **4** calculated by ^{19}F NMR.

aqueous media,[5] we decided to screen various triflates (Table 1, entries 9−16), all of which showed an increase in the yield of the alcohol. $Eu(OTf)_3$ was found to give the best results (Table 1, entry 12), and therefore it was chosen for subsequent studies.

Next, the effect of R in the reaction of **1** with benzaldehyde (**5a**) (Table 2, entries 1−5) was investigated. The nature of this substituent had a pronounced effect on the product yield: alkyl and aryl substituents were less efficient than silyl groups, the only exception being TMS. Triethylsilyl (TES) and triisopropylsilyl (TIPS) substituents were selected for further studies because these functionalities could serve as convenient synthetic handles for future transformations. The majority of aldehyde substrates tested produced β,β-difluorohomopropargyl alcohols **3** in good to very good yields (Table 2, entries 6−17). Notably, aldehydes bearing free hydroxyl groups could be used without protection (Table 2, entries 10 and 11), but the reaction with reactive 4-nitroaldehyde **5j** did not give the expected product, and only starting material **1b** was recovered (Table 2, entry 14). We never observed the formation of allenyl alcohols during these experiments. This is in marked contrast with similar reactions employing nonfluorinated alkynes, where the size of the substituent influences the allenyl-to-propargyl ratio.

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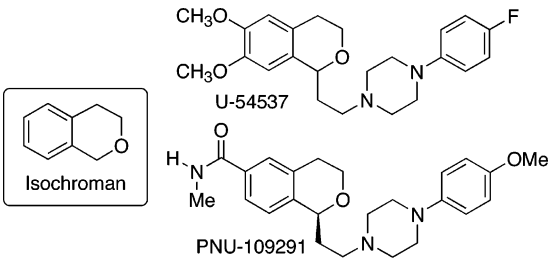


FIGURE 1. Examples of biologically active isochroman derivatives.

A six-membered transition state in which the indium complex coordinates with the carbonyl oxygen of aldehydes has been invoked to explain the allenyl-propargyl regiocontrol in nonfluorinated systems.[6] If our reaction had followed a similar six-membered transition state pathway, then we should have observed a difluoroallenyl alcohol. The fact that we did not observe such a byproduct led us to ponder whether a radical pathway was in effect, in which case, water would play a crucial role in the generation of radical species.[7] Further studies to probe the reaction mechanism of this unusual regioselectivity are needed.

Despite that fact that isochromans are biologically interesting compounds (Figure 1),[8] to our knowledge, there have been no reports on the preparation of partially fluorinated isochromans.

We decided to investigate the synthesis of 4,4-difluoroisochromans **8** or **9** using a rhodium-catalyzed [2 + 2 + 2] cyclotrimerization of 3,3-difluoro-1,7-diene **6** with monosubstituted acetylenes. The starting material **6** was easily prepared in two steps from propargyl alcohol **3aa** (eq 1).

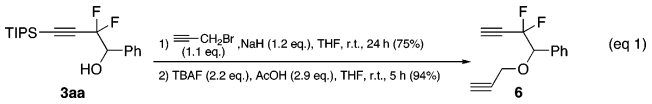
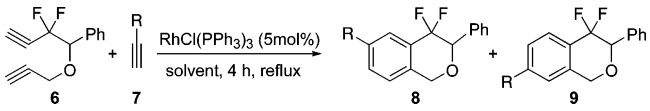


Table 3 shows the optimization and scope of this methodology. Of the solvents screened, benzene furnished the best ratio of **8a**-to-**9a** (Table 3, entry 5), and thus it was selected for the cyclotrimerization of **6** with other alkynes **7**. With the exception of **7c** (Table 3, entry 7), this cyclization yielded a mixture of regioisomers **8** and **9** in moderate-to-good yields. When the substituent R contained an electron-withdrawing group, the mass balance of products **8** and **9** diminished (Table 3, entries 9−11), possibly due to the formation of complex fluorinated byproducts, visible in the ^{19}F NMR spectrum of the reaction mixture. In all cases examined, the dominant product was the regioisomer **9**, even though both alkyne groups in **6** are terminal; these results

TABLE 3. Synthesis of Difluoroisochromanes via $RhCl(PPh_3)_3$ Catalyzed [2 + 2 + 2] Cyclization



entry	R	solvent	yield (%)[a] **8**:**9**
1	CH_2OH (**7a**)	toluene	31:59
2		EtOH	48:47
3		CH_2Cl_2	42:47
4[b]		THF	41:50
5		benzene	29:69
6	*n*-hex (**7b**)		39:55
7	TMS (**7c**)		0:0
8	Ph (**7d**)		15:68
9	*p*-F-C_6H_4 (**7e**)		14:47
10	*p*-CF_3-C_6H_4 (**7b**)		19:20
11	C_6F_5 (**7g**)		0:15

[a] Yield was determined by ^{19}F NMR. [b] Recovered starting material (8%).

may imply that the regiochemistry of the reaction is controlled by electronic rather than steric effects.

On the basis of the widely accepted mechanism of [2 + 2 + 2] alkyne cyclotrimerizations,[9] we proposed the pathway outlined in Scheme 2 to explain the regioselectivity found in our experiments.

Initially, two triple bonds coordinate to the metal to give metallacyclopentadiene **Int-I** through an oxidative coupling, followed by a third triple bond insertion to the intermediate metallacyclopentadiene, and a final reductive elimination to yield products **8** and **9**. The rationale for this regioselectivity can be traced to the steric hindrance that exists between the metal ligands and the substituent R of the third acetylene, and the electronic density differences between C-**a** and C-**b** (see **TS-A** and **TS-B** in Scheme 2). The electronic deficiency in C-**a** may be due to the strong electron-withdrawing effect of fluorine, and therefore the insertion of the third acetylene to the metallacyclopentadiene would take place from the C-**b** side.[10]

In summary, we have investigated an environmentally friendly and reliable synthesis of difluorohomopropargyl alcohols utilizing indium and a catalytic amount of $Eu(OTf)_3$. 3,3-Difluoro-1,7-diene, prepared in two steps from β,β-difluorohomopropargyl alcohol, reacted with monosubstituted acetylenes in the presence of $RhCl(PPh_3)_3$ to produce the hitherto unknown 4,4-difluoroisochromans in moderate-to-good yields and regioselectivities.

Experimental Section

Synthesis of 2,2-Difluoro-1-phenyl-4-triethylsilylbut-3-yn-1-ol (3ba). To a flask were added indium powder (2.0 mmol, 1.0 equiv) and $Eu(OTf)_3$ (0.1 mmol, 5 mol %), then triethylsilyl difluoropropargyl bromide (**1b**) (2.0 mmol) and benzaldehyde (**5a**) (2.2 mmol, 1.1 equiv) with rinsing by THF/H_2O solution (1/4) (6.6 mL, 0.3 M). The reaction was sonicated at 40 °C for 12 h. The reaction was quenched with 10% HCl (10 mL) and extracted by

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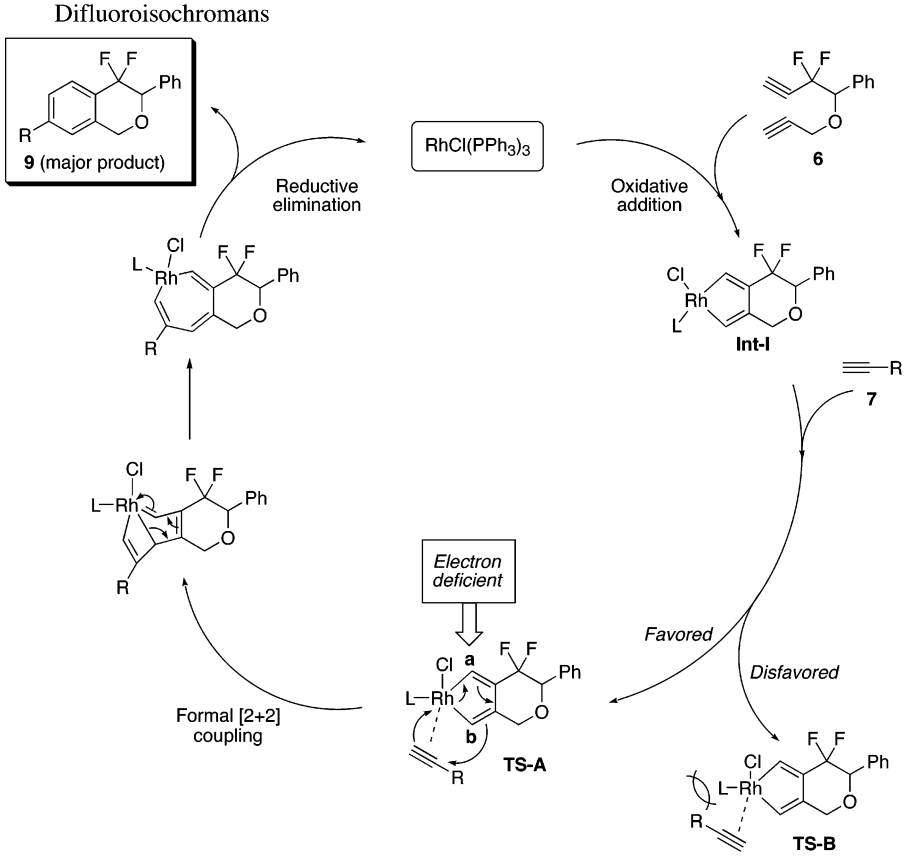
SCHEME 2. Plausible Reaction Mechanism for [2 + 2 + 2] Cyclization Leading to Difluoroisochromans



ethyl acetate (10 mL × 3), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel with EtOAc/hexane (1/40) to afford **3ba** (388 mg, 72%). ^{1}H NMR ($CDCl_3$) δ: 0.62 (q, J = 8.0 Hz, 6H), 0.96 (t, J = 8.0 Hz, 9H), 2.60 (d-like, 1H), 4.93−4.97 (m, 1H), 7.37−7.39 (m, 3H), 7.50−7.52 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: −93.50 (dd, J = 267.7, 6.6 Hz, 1F), −95.23 (dd, J = 274.4, 9.9 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ: 4.0, 7.5, 76.6 (t, J = 29.3 Hz), 95.1, 95.6 (t, J = 37.7 Hz), 113.3 (t, J = 238.5 Hz), 128.1, 128.4, 129.3, 135.4; IR (neat) cm^{-1}: 3446, 2958, 2877, 2360, 2187, 1716; MS *m*/*z* (%): 243 (14), 187 (11), 109 (12), 91 (15), 81 (100); Anal. Calcd: C, 64.83; H, 7.48. Found: C, 64.93; H, 7.57.

Preparation of 3,3-Difluoro-4-phenyl-4-(2-propynyloxy)-1-butyne (6). To a suspension of NaH (5.75 mmol, 1.15 equiv) in THF (50 mL, 0.1 M) was slowly added 2,2-difluoro-1-phenyl-4-triisopropylsilylbut-3-yn-1-ol (**3aa**) (5.0 mmol, 1.0 equiv) at 0 °C for 30 min, then the propargyl bromide (5.5 mmol, 1.1 equiv) was added into the reaction mixture at 0 °C, and the reaction mixture was stirred at room temperature for 24 h. After the reaction mixture was quenched by 10% HCl and extracted with Et_2O, the product was obtained in 75% by simple short silica gel column purification. Desilylation was performed by the following procedure. First, a solution of AcOH (2.2 equiv) and TBAF (2.86 equiv) in THF (12 mL) was mixed together at room temperature for 30 min, then the THF solution (12 mL) of the prepared starting material was added at room temperature, and the mixture was stirred at room temperature for 5 h. The reaction was quenched and extracted by the same method described above. The final product **6** (776 mg, 94%) was isolated by silica gel column chromatography with EtOAc/hexane (1/40). ^{1}H NMR ($CDCl_3$) δ: 2.48 (1H), 2.81 (t, J = 5.0 Hz, 1H), 4.10 (dd, J = 16.0, 2.0 Hz, 1H), 4.38 (dd, J = 16.0, 2.0 Hz, 1H), 4.90 (t, J = 9.3 Hz, 1H), 7.41−7.42 (m, 3H), 7.48−7.49 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: −91.89 (d, J = 277.2 Hz, 1F), −94.39 (d, J = 280.5 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ: 56.8, 74.5 (t, J = 38.9 Hz), 75.8, 77.5, 78.1, 80.9 (t, J = 29.2 Hz), 112.1 (t, J = 238.5 Hz), 128.4, 128.8, 129.5, 132.5; IR (neat) cm^{-1}: 3293, 3066, 3035, 2900, 2358, 2134, 1961, 1456, 1338, 1176, 1076; MS *m*/*z* (%): 165 (13), 145 (100), 115 (34), 105 (92), 92 (3); Anal. Calcd: C, 70.90; H, 4.58. Found: C, 70.35; H, 4.35

Synthesis of 4,4-Difluoroisochromans 8a and 9a. Into a flask were added $RhCl(PPh_3)_3$ (0.025 mmol, 5.0 mol %), the starting material (**6**) (0.5 mmol, 1.0 equiv), and also propargyl alcohol (**7a**) (2.5 mmol, 5.0 equiv) in benzene (0.01 M), and the reaction mixture was heated to reflux for 6 h. After the consumption of starting material (**6**) (as monitored by TLC or GC−MS), the solvent was removed by rotary evaporation, and the corresponding products **8a** (30 mg, 22%) and **9a** (82 mg, 60%) were isolated by the silica gel chromatography with EtOAc/hexane (1/4).

4,4-Difluoro-7-hydroxylmethyl-3-phenylisochroman (9a). ^{1}H NMR ($CDCl_3$) δ: 1.73 (1H), 4.68 (2H), 4.79 (dd, J = 20.0, 2.0 Hz, 1H), 4.92 (dd, J = 15.0, 4.0 Hz, 1H), 5.00 (dd, J = 15.5, 1.0 Hz, 1H), 7.12 (1H), 7.31−7.37 (m, 4H), 7.46 (d, J = 7.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ: −94.23 (dd, J = 271.1, 23.1 Hz, 1F), −107.90 (d, J = 272.5 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ: 64.9, 68.8, 80.0 (dd, J = 29.1, 26.0 Hz), 114.2 (dd, J = 247.6, 239.9 Hz), 121.9, 126.18, 126.22, 128.1, 128.4, 129.0, 129.7 (t, J = 25.7 Hz), 133.7, 136.4, 143.7; MS *m*/*z* (%): 255 (4), 198 (6), 170 (100), 141 (7), 122 (5), 105 (9).

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Supporting Information Available: Analytical and spectroscopic data for **3ca**, **3da**, **3bb**−**3bm**, **8a**, **8b**, **8d**−**8f**, and **9b**, **9d**−**9g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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