

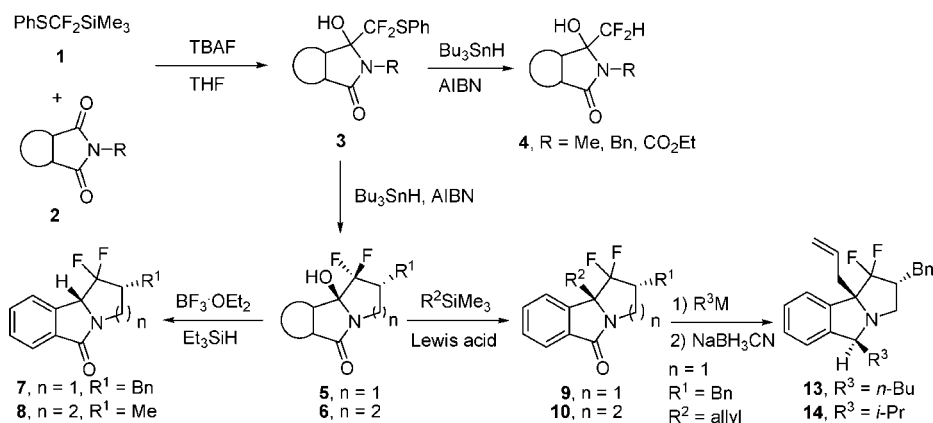
Fluoride-Catalyzed Addition of PhSCF₂SiMe₃ to *N*-Substituted Cyclic Imides Followed by Radical Cyclization: General Synthetic Strategy of *gem*-Difluoromethylenated 1-Azabicyclic Compounds

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PhSCF₂SiMe₃ (**1**) was found, for the first time, to undergo fluoride-catalyzed nucleophilic difluoro-(phenylsulfanyl)methylation reaction to cyclic imides **2**, affording the corresponding adducts **3** in moderate to good yields. Reductive cleavage of the phenylsulfanyl group of *N*-alkylated adducts **3** with Bu₃SnH/AIBN yielded *gem*-difluoromethylated products **4**. Under the same reduction conditions, *N*-alkenylated and *N*-alkynylated adducts **3** afforded the corresponding *gem*-difluoromethylenated 1-azabicyclic compounds **5** and **6** with *trans* stereoselectivity. These compounds were employed as precursors for preparing substituted *gem*-difluoromethylenated pyrrolizidinones and indolizidinones **7** and **8** by treatment with Et₃SiH/BF₃·OEt₂, and compounds **9** and **10** by nucleophilic displacement of the hydroxyl group, using organosilanes in the presence of BF₃·OEt₂. The synthesis of highly substituted *gem*-difluoromethylenated pyrrolizidines **13** and **14** was also demonstrated.

Introduction

gem-Difluoromethylene moiety has been incorporated into bioactive compounds due to its properties as an isopolar and isosteric substituent for an oxygen.¹ The presence of the *gem*-difluoromethylene group can enhance the biological properties

of drug molecules.² Therefore, syntheses of *gem*-difluoromethylenated analogs of natural products have been extensively investigated.³ Few general synthetic methods for constructing

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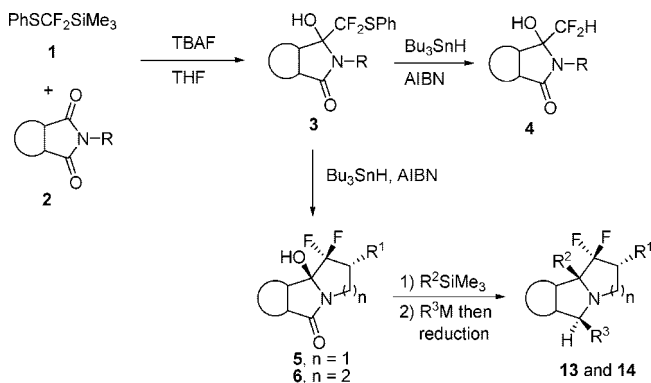
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gem-difluoromethylenated compounds were previously reported.⁴ It is still desirable to develop new flexible and facile strategies for the preparation of these compounds. Recently, PhSCF₂SiMe₃ (**1**) has been demonstrated as a useful gem-difluoromethylene building block.⁵ Compound **1** reacts extensively with carbonyl derivatives,⁶ γ -ketoesters,⁷ imines,⁸ and alkyl bromides,⁹ providing convenient routes for the preparation of the corresponding gem-difluoromethylated alcohols, γ -lactones, amines, and alkanes, respectively. Furthermore, the stereoselective difluoromethylation of chiral imines using PhSCF₂SiMe₃ (**1**) and the synthesis of chiral disubstituted gem-difluoromethylenated pyrrolidines have been recently reported.^{10a} In addition, alternative new entries to assemble various fluorinated *S*-, *O*-, and *N*-heterocycles have also been developed.^{10b–d}

As a part of our ongoing research interest in developing methodologies for the preparation of 1-azabicyclic derivatives,¹¹ we sought for a general method to synthesize gem-difluoromethylenated 1-azabicyclic analogs, employing **1** as a gem-difluoromethylene building block. It has been demonstrated that cyclic imides can undergo fluoride-catalyzed trifluoromethylation, using (trifluoromethyl)trimethylsilane (CF₃SiMe₃).¹² Hence, it is anticipated that fluoride-catalyzed nucleophilic difluoro-

SCHEME 1. Fluoride-Catalyzed Nucleophilic Difluoro(phenylsulfanyl)methylation of **1** with Imides **2** and Synthetic Conversion of the Resulting Adducts **3** into Compounds **4**, **5**, and **6** and Subsequently to Compounds **13** and **14**



(phenylsulfanyl)methylation of **1** to cyclic imides **2** would generate the corresponding adducts **3**. When R groups of adducts **3** are allylic and homoallylic, reductive cleavage of the corresponding phenylsulfanyl moiety could afford radical intermediate that should then undergo intramolecular radical cyclization, providing gem-difluoromethylenated 1-azabicyclic compounds **5** and **6**, respectively (Scheme 1). Furthermore, nucleophilic displacement of the hydroxyl group and subsequent organometallic addition to carbonyl group followed by reduction would lead to highly substituted difluoromethylenated 1-azabicyclic compounds **13** and **14**. The proposed synthetic operations are summarized in Scheme 1.

Results and Discussion

The initial investigation involved fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation of imide **2a** with PhSCF₂SiMe₃ (**1**). The expected adduct **3a** was obtained in 95% yield when the reaction was carried out using 10 mol % of anhydrous tetrabutylammonium fluoride (TBAF) in dry THF at -78 °C to room temperature overnight followed by acidic workup (2 M HCl; Table 1, entry 1). To demonstrate the generality of the reaction, the reactions of **1** with *N*-substituted phthalimide and succinimide derivatives, which were prepared by base-catalyzed *N*-alkylation of imides¹³ with alkylating agents (Table 1, entries 1–6, 8, 10–13, 15 and 17), Mitsunobu reaction of imides with alcohols¹⁴ (Table 1, entries 7, 14 and 16), and cross-olefin metathesis¹⁵ of *N*-alkenylated imides with alkenes (Table 1, entries 9 and 18), were investigated. The results are summarized in Table 1. Except for some cases, the reactions of **1** with imide derivatives conducted under the standard conditions as for **3a** readily gave the corresponding adducts; yields range from moderate to good (Table 1). In case of imide **2i**, under the standard conditions, adduct with double bond transposition was obtained as a major product (33% yield). Gratifyingly, the reaction employing tetrabutylammonium triphenyldifluorosilicate (TBAT) in place of TBAF gave adduct **3i** in moderate yield

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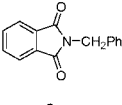
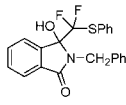
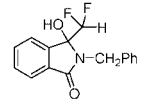
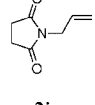
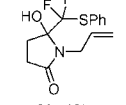
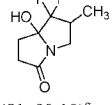
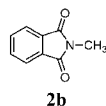

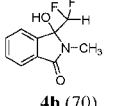
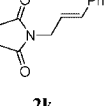
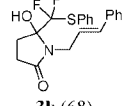
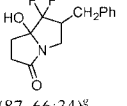
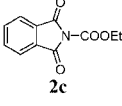
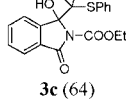
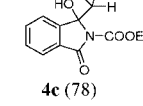
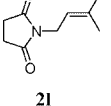
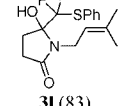
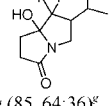
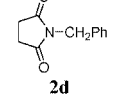
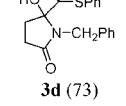
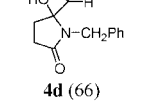
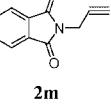
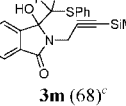
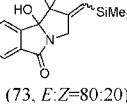
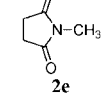
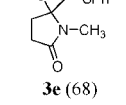
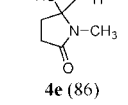
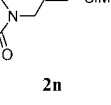
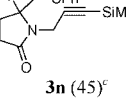
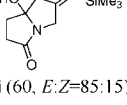
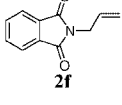
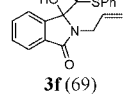
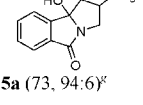
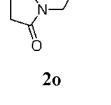
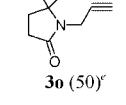
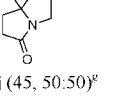
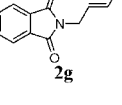
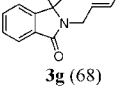
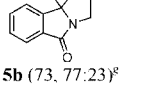
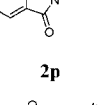
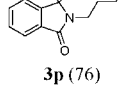
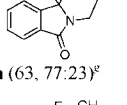
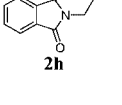
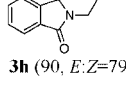
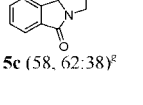
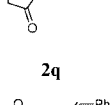
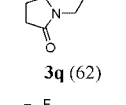
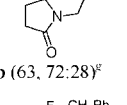
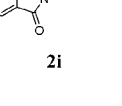
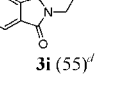
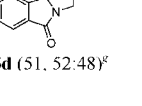
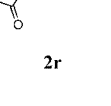
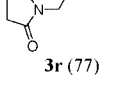
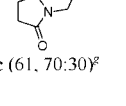
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TABLE 1. Preparation of Adducts **3**, *gem*-Difluoromethylated Lactams **4**, and *gem*-Difluoromethylated 1-Azabicyclic Compounds **5** or **6**

entry	imides 2	3 (% yield) ^{a,b}	4, 5 or 6 (% yield) ^{a,c} , <i>trans</i> : <i>cis</i>)	entry	imides 2	3 (% yield) ^{a,b}	4, 5 or 6 (% yield) ^{a,c} , <i>trans</i> : <i>cis</i>)
1				10			
	2a	3a (95)	4a (80)		2j	3j (62)	5e (81, 90:10) ^e
2				11			
	2b	3b (70)	4b (70)		2k	3k (68)	5f (87, 66:34) ^e
3				12			
	2c	3c (64)	4c (78)		2l	3l (83)	5g (85, 64:36) ^e
4				13			
	2d	3d (73)	4d (66)		2m	3m (68) ^c	5h (73, <i>E</i> : <i>Z</i> =80:20) ^f
5				14			
	2e	3e (68)	4e (86)		2n	3n (45) ^e	5i (60, <i>E</i> : <i>Z</i> =85:15) ^f
6				15			
	2f	3f (69)	5a (73, 94:6) ^e		2o	3o (50) ^e	5j (45, 50:50) ^e
7				16			
	2g	3g (68)	5b (73, 77:23) ^e		2p	3p (76)	6a (63, 77:23) ^e
8				17			
	2h	3h (90, <i>E</i> : <i>Z</i> =79:21) ^f	5c (58, 62:38) ^e		2q	3q (62)	6b (63, 72:28) ^e
9				18			
	2i	3i (55) ^f	5d (51, 52:48) ^e		2r	3r (77)	6c (61, 70:30) ^e

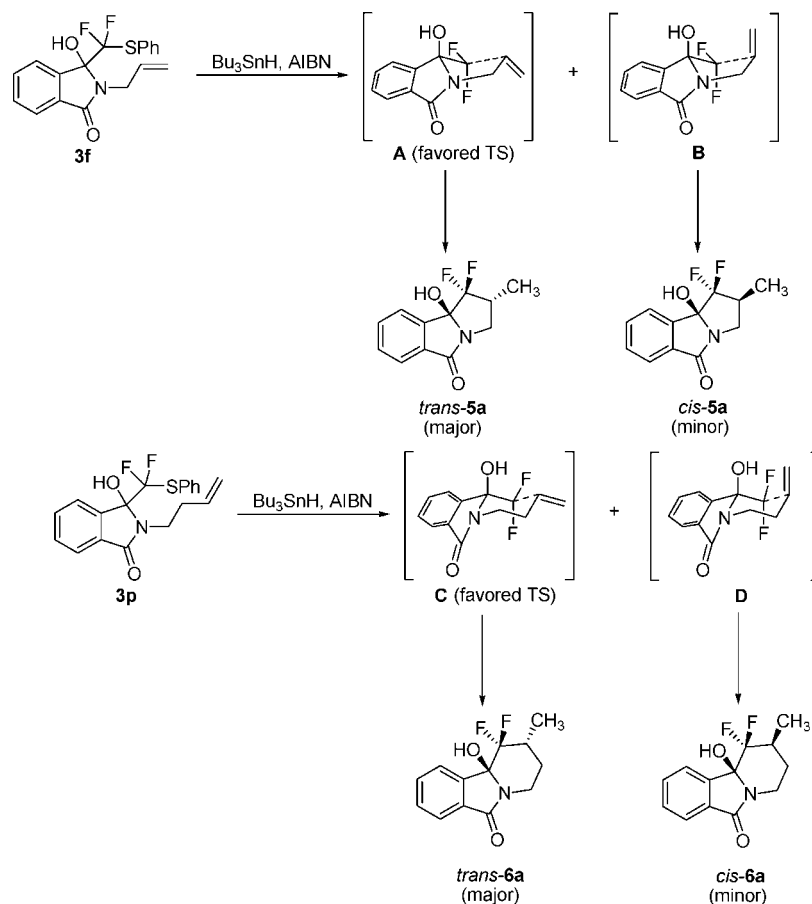
^a Isolated yields. ^b Unless otherwise noted, all reactions were carried out employing 10 mol % TBAF/THF, -78 °C to rt. ^c By using 10 mol % TBAT/DMF, -78 °C to rt. ^d By using 10 mol % TBAT/THF, -78 to 15 °C, 5 h. ^e By using 10 mol % TBAT/THF, -78 °C to rt. ^f Ratio of *E*- and *Z*-isomers was determined by ^1H NMR integration of the crude product. ^g Ratios of isomers (*trans/cis*) were determined by ^1H NMR integration of the crude products.

(55%) and the double bond transposition adduct was not observed (Table 1, entry 9). It is also worth mentioning that the reaction of **1** with *N*-trimethylsilylpropargyl succinimide **2n** under the standard conditions furnished the expected product **3n** in only 2% yield, but the desilylated adduct **3o** was obtained as a major product (30% yield). However, the reaction employing 10 mol % of TBAT in dry DMF at -78 °C to room temperature gave the desired product **3n** in 45% yield together with **3o** (10% yield; Table 1, entry 14). Similar results, that is, **3n** (40% yield) and **3o** (8% yield) were obtained when the

reaction was carried out using THF as the solvent. Interestingly, treatment of **1** with *N*-propargylphthalimide **2m** employing 10 mol % TBAT in DMF at -78 °C to room temperature unexpectedly provided trimethylsilylated derivative **3m** in 68% yield (Table 1, entry 13).

The reductive desulfenylation of adducts **3a–e** was achieved by treating with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene. The *gem*-difluoromethylated products **4a–e** were obtained in moderate to good yields (66–86%; Table 1,

SCHEME 2. Proposed Transition States for the Radical Cyclization



entries 1–5).^{6b,16} The *gem*-difluoromethyl radical intermediate, generated by CF₂–SPh bond cleavage of the adducts **3** containing the *N*-unsaturated substituents, could be trapped intramolecularly by an unsaturated functional moiety,¹⁷ affording *gem*-difluoromethylenated 1-azabicyclic compounds **5**. Thus, under similar radical conditions, intramolecular radical cyclization of **3f** readily proceeded to provide **5a** in 73% yield as a 94:6 mixture of *trans*- to *cis*-isomers together with a small amount of the corresponding reduced product. A single *trans*-**5a** was obtained in pure form after purification by either preparative thin-layer chromatography on silica gel or crystallization. Its relative stereochemistry was established by X-ray crystallography (see Supporting Information).

To demonstrate the efficiency and viability of our methodology, series of *gem*-difluoromethylenated pyrrolizidine derivatives **5b–g**, as mixtures of isomers, were synthesized, in moderate to good yields, by treatment of adducts **3g–l** under standard radical conditions (Table 1, entries 7–12). Based on the X-ray crystallographic data of the major *trans*-isomer of **5a**, we

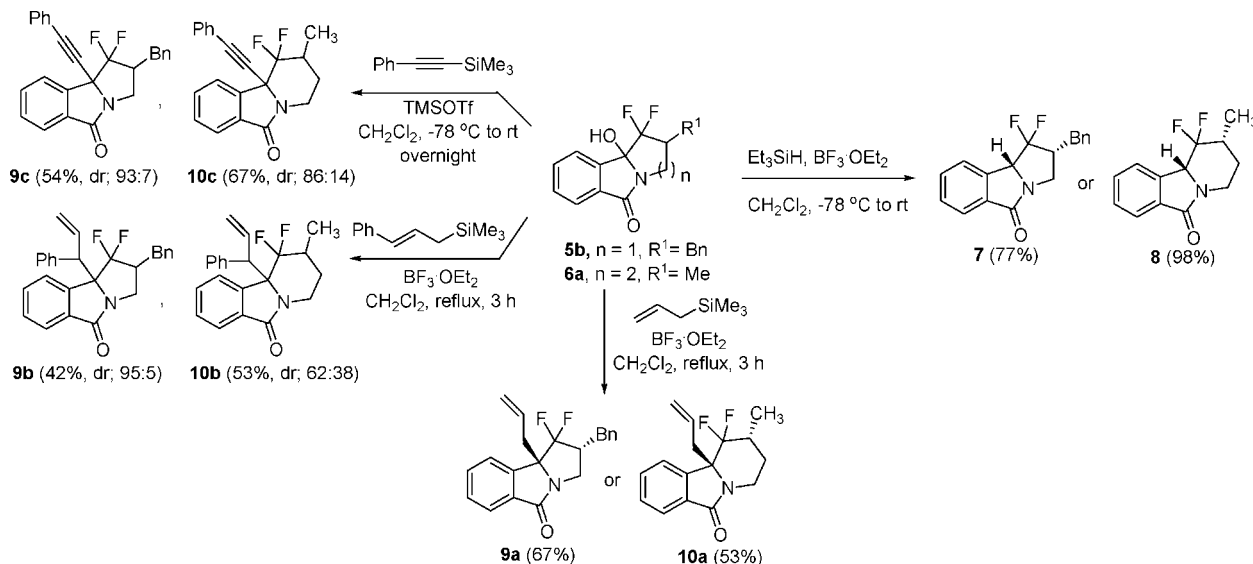
assumed that the *trans*-isomers of **5b–g** were the major isomers. Notably, similar radical cyclization of *N*-propargyl substituted adducts proceeded smoothly, providing the cyclized products in moderate yields (Table 1, entries 13–15). Cyclization of silylated alkynyl derivatives **3m** and **3n** afforded compounds **5h** and **5i** as a mixture of *E*- and *Z*-isomers. The *E*-isomer was obtained as a major isomer, of which the stereochemistry was established by NOE experiments (see Supporting Information). Irradiation of the olefinic proton of **5h** or **5i** led to no enhancement of the allylic protons. The formation of tributylstannylated product **5j** (Table 1, entry 15) presumably resulted from consecutive addition of the tributylstannyl group to the triple bond followed by *gem*-difluoromethyl radical addition to the resulting vinylstannane derivative.¹⁸ The presence of the exocyclic methylene moiety in compounds of types **5h** and **5i** should be valuable for further synthetic modification.

Having established an efficient access to *gem*-difluoromethylenated pyrrolizidine derivatives **5**, we further demonstrated that our method could be used as a general route for the synthesis of *gem*-difluoromethylenated indolizidine derivatives **6**. Thus, *N*-homoallylated adducts **3p–r** were treated with Bu₃SnH/AIBN in refluxing toluene, yielding the corresponding *gem*-difluoromethylenated indolizidines **6a–c** as a mixture of *trans*- and *cis*-isomers (Table 1, entries 16–18). The relative stereochemistry of the major *trans*-**6a** was confirmed by X-ray crystallography (see Supporting Information).

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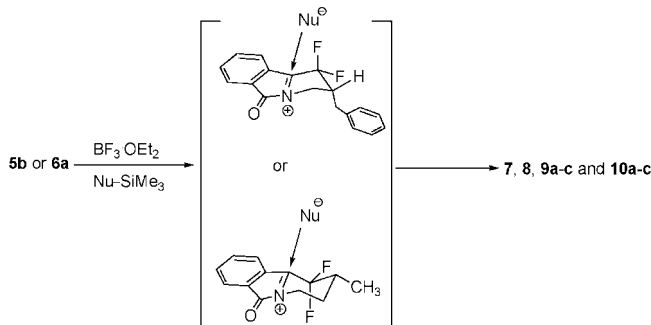
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SCHEME 3. Lewis Acid-Catalyzed Nucleophilic Substitution of the Hydroxyl Group of Compounds **5b** and **6a**

The stereochemical outcomes of compounds **5** and **6** can be rationalized as shown in Scheme 2. The radical mediated cyclization was proposed to proceed via 5-*exo* or 6-*exo* cyclization mode.¹⁹ Transition states **A** and **C** are energetically more favorable due to minimized steric interaction between the pseudoaxial hydroxyl group and the vinylic double bond, resulting in the formation of thermodynamically more stable *trans*-isomer of pyrrolidine or piperidine heterocycles.

Having a general route to synthesize derivatives **5** and **6**, we subsequently focused on the synthetic utilities of these adducts as precursors for the preparation of substituted *gem*-difluoromethylene pyrrolidines and indolizidines. It is anticipated that the presence of hydroxyl group in adducts **5** and **6** should provide a convenient access to an iminium intermediate,^{20,21} which, in principle, can be trapped by an appropriate nucleophile. The results are summarized in Scheme 3. The adducts **5b** (*trans/cis*; 77:23) and **6a** (*trans/cis*; 88:12) were reduced with $\text{BF}_3\cdot\text{OEt}_2$ and Et_3SiH ²² in CH_2Cl_2 at -78°C to room temperature, generating the corresponding lactams **7** (77% yield) and **8** (98% yield) as a single isomer, as confirmed by the NOE experiments (see Supporting Information). Alkylation of **5b** with Grignard reagents (MeMgBr or *i*- PrMgCl in THF in the presence of $\text{BF}_3\cdot\text{OEt}_2$ at 0°C to rt, overnight) or organocoppers (*n*- Bu_2CuLi or *n*- $\text{Bu}_2\text{Cu}(\text{CN})\text{Li}_2$ in THF in the presence of $\text{BF}_3\cdot\text{OEt}_2$ at -30°C to rt overnight) was unsuccessful, and only

SCHEME 4. Proposed Transition States for the Formation of *trans*-Isomers of Products **7–10**

starting material was recovered. However, allylation reaction of **5b**, employing allyltrimethylsilane with $\text{BF}_3\cdot\text{OEt}_2$ in CH_2Cl_2 at -78°C to rt overnight, led to **9a** in low yield (10% yield) together with recovery of **5b**. Gratifyingly, when the reaction was performed under refluxing conditions for 3 h, **9a** was obtained in moderate yield (67% yield). Similarly, under the same conditions, **10a** was synthesized in 53% yield from the corresponding compound **6a**. Both compounds **9a** and **10a** were obtained as a single isomer (see Supporting Information). Similarly, treatment of **5b** and **6a** with cinnamyltrimethylsilane afforded adducts **9b** and **10b**, respectively, as a mixture of diastereomers, as shown in Scheme 3. The reactions of **5b** and **6a** with phenyltrimethylsilylacetylene employing trimethylsilyl triflate (TMSOTf) as the Lewis acid at -78°C to rt overnight provided the respective adducts **9c** (54% yield as a 93:7 mixture of isomers) and **10c** (67% yield as a 86:14 mixture of isomers). The use of $\text{BF}_3\cdot\text{OEt}_2$, SnCl_4 , and TiCl_4 did not furnish the desired products but led to the recovery of the starting material **5b** and phenylacetylene. This result may be due to extensive decomposition of phenyltrimethylsilylacetylene to phenylacetylene prior to its addition to iminium ion intermediate. The relative *trans* stereochemistries of adducts **7** and **9** could be rationalized based on the fact that the nucleophiles (hydride or organosilanes) attack the initially formed iminium ion intermediate from the face opposite to the benzyl group to avoid steric interaction (Scheme 4). In addition, attack of nucleophiles to the iminium ion derived from **6a** from the pseudoaxial direction

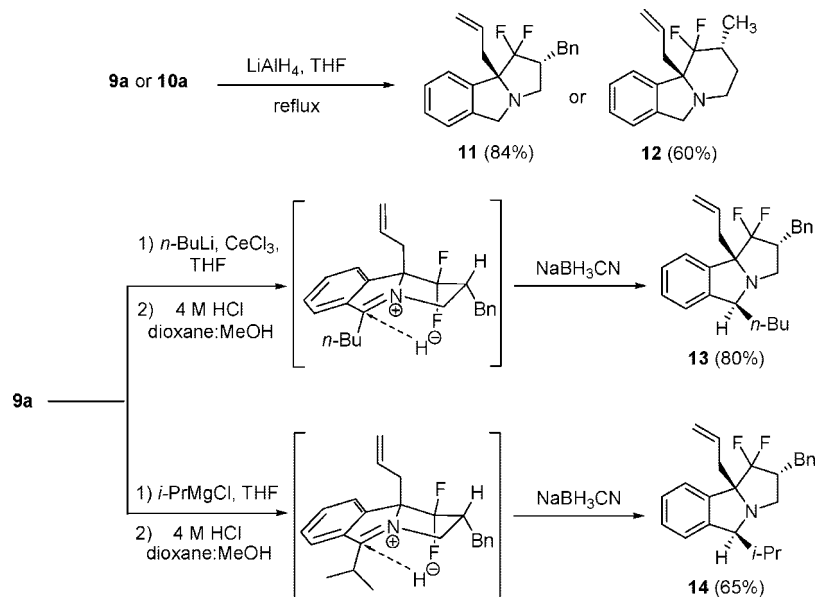
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(22) For an example, see Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651–1657.

SCHEME 5. Preparation of Alkyl-Substituted gem-Difluoromethylenated Pyrrolizidines 11, 13, and 14 and Indolizidine 12



could be further explained by stereoelectronic principle, leading preferably to the *trans*-isomers of adducts **8** and **10**.

The conversions of compounds **9a** and **10a** to alkyl-substituted *gem*-difluoromethylenated pyrrolizidines and indolizidines proceeded smoothly (Scheme 5). Reduction of compounds **9a** and **10a** using LiAlH_4 in refluxing THF provided the corresponding *gem*-difluoromethylenated pyrrolizidine **11** (84% yield) and indolizidine **12** (60% yield), respectively (Scheme 5). The reaction of **9a** with *n*-BuLi/ CeCl_3 in THF²³ followed by acidification generating in situ iminium ion intermediate, which was subsequently reduced by sodium cyanoborohydride (NaBH_3CN) to afford butyl-substituted *gem*-difluoromethylenated pyrrolizidine **13** in 80% yield as a single diastereomer. Similarly, a single diastereomer of isopropyl-substituted *gem*-difluoromethylenated pyrrolizidine **14** was produced in 65% yield. The relative stereochemistries of compounds **11**–**14** were established by NOE experiments (see Supporting Information). The observed stereochemical outcomes of the reactions can be explained that the addition of organometallic reagents followed by acidification afforded iminium ions which were preferably reduced from the less sterically hindered face opposite to the allyl substituent (Scheme 5). It is worth mentioning that compound **10a** did not react with either *n*-BuLi/ CeCl_3 or *i*-PrMgCl in THF under the same conditions as for **9a**.

Conclusion

In conclusion, we have successfully developed for the novel fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation reactions of $\text{PhSCF}_2\text{SiMe}_3$ to succinic and phthalimide derivatives. The resulting adducts were employed as useful precursors for the preparation of *gem*-difluoromethylenated pyrrolizidines and indolizidines. The synthetic operation involves sequential intramolecular radical cyclization, nucleophilic displacement of the hydroxyl functionality using Lewis acid/allyltrimethylsilanes or trimethylsilylacetylenes, organometallic addition employing *n*-BuLi/ CeCl_3 and *i*-PrMgCl onto the

carbonyl group of the γ -lactam moiety, followed by reduction of the resulting adducts with NaBH_3CN . The synthetic application of our method for preparation of *gem*-difluoromethylenated analogs of some polyhydroxylated natural products is currently being investigated.

Experimental Section

General Procedure for the Preparation of Compounds 3. **2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-isoidolin-1-one (3a).** To a mixture of compound **1** (0.928 g, 4 mmol) and 2-benzylisoidolin-1,3-dione (**2a**; 0.470 g, 2 mmol) in THF (5 mL), was added 10 mol % TBAF (0.4 mL, 0.4 mmol, 1 M solution in THF). The reaction mixture was stirred at -78°C followed by slowly warming up to room temperature overnight. The solution was quenched with 1 M HCl (3 mL) and extracted with EtOAc (3 \times 25 mL). The organic phase was washed successively with water and brine and dried over anhydrous Na_2SO_4 . After solvent removal, the crude product was purified by radial chromatography (SiO_2 , 10–20% EtOAc in hexanes) to give a white crystal of **3a** (0.753 g, 95% yield, mp = 142–144 $^\circ\text{C}$). ^1H NMR (300 MHz, CDCl_3): δ 7.86–7.83 (m, 1H, ArH), 7.72–7.68 (m, 1H, ArH), 7.60–7.58 (m, 2H, ArH), 7.35–7.25 (m, 3H, ArH), 7.20–7.10 (m, 7H, ArH), 4.95 (d, J = 15.6 Hz, 1H, CHH), 4.45 (d, J = 15.6 Hz, 1H, CHH), 3.85 (br s, 1H, OH). ^{13}C NMR (125 MHz, CDCl_3): δ 168.3 (C=O), 141.9 (C), 137.5 (2 \times C), 136.7 (2 \times CH), 132.8 (CH), 131.5 (C), 131.0 (2 \times CH), 130.1 (CH), 129.24 (t, J = 187.5 Hz, CF_2), 129.0 (2 \times CH), 128.5 (3 \times CH), 127.4 (CH), 124.2 (CH), 123.8 (CH), 91.2 (t, J = 25.0 Hz, C), 43.5 (CH_2). ^{19}F NMR (470 MHz, CDCl_3): δ -80.48 (d, J = 211.0 Hz, 1F), -81.57 (d, J = 211.0 Hz, 1F). IR (nujol): ν_{max} 3207br, 1682s, 1612s, 1612m, 1497m, 1471s, 1456s, 1455s, 1427m, 1397s, 1361s, 1163s, 1137m, 1108m, 1073m, 1061s, 1027m, 1012m, 974m, 945m, 907m, 897m, 886m, 845m, 823m, 770s, 752s, 709s, 700s, 690s cm^{-1} . MS: m/z (%) relative intensity 398 (M^+ , 10), 380 (7), 250 (6), 238 (47), 161 (11), 160 (100), 91 (20), 65 (7). HRMS (ESI-TOF) Calcd for $\text{C}_{22}\text{H}_{17}\text{F}_2\text{NO}_2\text{SNa}$ [$\text{M} + \text{Na}$] $^+$, 420.0846; found, 420.0851.

General Procedure for the Reductive Cyclization of Compounds 3 to Compounds 5. **Preparation of 1,1-Difluoro-9b-hydroxy-2-methyl-2,3-dihydro-1H-pyrrolo[2,1-a]isoidol-5(9bH)-one (5a).** Argon was bubbled through a solution of **3f** (0.374 g, 1 mmol) in toluene (2 mL) for 30 min, and a mixture of Bu_3SnH (0.47 mL, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in toluene

(23) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398–404.

(8 mL) was added dropwise at reflux over a 1 h period followed by refluxing for an additional 4 h. Volatiles were evaporated and the tin byproduct were removed by column chromatography (SiO₂, CH₂Cl₂ then EtOAc) to give a crude product, which was purified by column chromatography (SiO₂, 20% EtOAc in hexanes) to afford white crystals of **5a** (0.191 g, 73% yield, mp = 122–125 °C) as a 94:6 mixture of *trans*- and *cis*-isomers. ¹H NMR (500 MHz, CDCl₃, *cis*-isomer marked*): δ 7.68–7.64 (m, 6H, ArH of *trans*- and *cis*-isomers), 7.57–7.55 (m, 2H, ArH of *trans*- and *cis*-isomers), 4.12* (dd, *J* = 12.0, 9.3 Hz, 1H, CHH), 3.72 (br s, 2H, OH of *trans*- and *cis*-isomers), 3.68–3.63 (m, 1H, CHH), 3.39–3.27 (m, 3H, CHH of the *trans*-isomer and CH of *trans*- and *cis*-isomers), 3.13* (dd, *J* = 12.0, 4.9 Hz, 1H, CHH), 1.50* (d, *J* = 7.5 Hz, 3H, CH₃), 1.19 (d, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 170.7 (C=O), 141.4 (C), 133.2 (CH), 132.9 (C), 130.9 (CH), 123.9 (CH), 123.2 (CH), 122.9 (t, *J* = 258.2 Hz, CF₂), 93.1 (t, *J* = 25.1 Hz, C), 46.4 (d, *J* = 7.4 Hz, CH₂), 39.3 (t, *J* = 22.7 Hz, CH), 9.5 (d, *J* = 7.1 Hz, CH₃). ¹⁹F NMR (470 MHz, CDCl₃, *cis*-isomer marked*): δ -101.16* (dd, *J* = 232.2, 23.5 Hz, 1F), -126.86* (d, *J* = 232.2 Hz, 1F), -127.82 (dd, *J* = 220.9, 24.9 Hz, 1F), -129.60 (dd, *J* = 220.9, 6.8 Hz, 1F). IR (nujol): ν_{max} 3237br, 1681s, 1616s, 1469s, 1378m, 1239m, 1147m, 1123m, 1958m, 1003m, 759s, 709m, 701m, 604m cm⁻¹. MS: *m/z* (%) relative intensity 239 (M⁺, 33), 203 (22), 201 (62), 200 (100), 188 (66), 172 (23), 161 (34), 160 (42), 145 (27), 133 (48), 132 (22), 125 (25), 117 (59), 91 (28), 77 (41). HRMS (ESI-TOF) Calcd for C₁₂H₁₁F₂NO₂Na [M + Na]⁺, 262.0656; found, 262.0634.

General Procedure for the Preparation of Compounds 9 and 10. **Preparation of (2R*,9bR*)-9b-Allyl-2-benzyl-1,1-difluoro-2,3-dihydro-1H-pyrrolo[2,1-*a*]isoindol-5(9bH)-one (9a).** BF₃·OEt₂ (0.6 mL, 4.93 mmol) and allyltrimethylsilane (2.6 mL, 16.5 mmol) were added to a stirred solution of **5b** (1.04 g, 3.3 mmol) in CH₂Cl₂ (12 mL) at room temperature and the mixture was heated at reflux for 3 h. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. Filtration followed by evaporation gave a crude product, which was purified by preparative thin-layer chromatography (SiO₂, 10% EtOAc in hexanes) to give a white solid of **9a** as a *trans*-isomer (0.75 g, 67% yield, mp = 91–93 °C). ¹H NMR (500 MHz, CDCl₃): δ 7.83 (d, *J* = 7.6 Hz, 1H, ArH), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.54 (td, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.50 (d, *J* = 7.6 Hz, 1H, ArH), 7.35 (t, *J* = 7.6 Hz, 2H, ArH), 7.30–7.25 (m, 3H, ArH), 5.31 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, CH), 5.03 (dd, *J* = 17.1, 1.4 Hz, 1H, CHH), 4.97 (d, *J* = 10.0 Hz, 1H, CHH), 3.73 (dd, *J* = 12.1, 8.7 Hz, 1H, CHH), 3.56 (dd, *J* = 12.1, 9.5 Hz, 1H, CHH), 3.39–3.29 (m, 1H, CH), 3.11 (dd, *J* = 13.9, 5.3 Hz, 1H, CHH), 2.91 (dd, *J* = 14.1, 7.0 Hz, 1H, CHH), 2.75 (dd, *J* = 13.9, 9.4 Hz, 2H, CHH). ¹³C NMR (125 MHz, CDCl₃): δ 172.1 (C=O), 142.8 (d, *J* = 4.3 Hz, C), 137.9 (C), 133.8 (C), 132.4 (CH), 129.7 (CH), 129.4 (CH), 128.74 (2 × CH), 128.67 (2 × CH), 126.8 (CH), 124.9 (dd, *J* = 263.4, 255.4 Hz, CF₂), 124.2 (CH), 122.5 (CH), 120.2 (CH₂), 74.5 (t, *J* = 25.3 Hz, C), 48.3 (t, *J* = 22.6 Hz, CH), 45.1 (d, *J* = 7.4 Hz, CH₂), 37.0 (d, *J* = 2.4 Hz, CH₂), 32.9 (d, *J* = 7.8 Hz, CH₂). ¹⁹F NMR (470 MHz, CDCl₃): δ -118.14 (dd, *J* = 226.5, 23.0 Hz, 1F), -121.05 (dd, *J* = 226.5, 7.1 Hz, 1F). IR (KBr): ν_{max} 1703s, 1643w, 1612w, 1491w, 1467m, 1363s, 1220s, 1049s, 751m, 704s cm⁻¹. MS: *m/z* (%) relative intensity 340 (M⁺ + 1, 11), 339 (M⁺, 2), 298 (100), 249 (20), 91 (64), 65 (11). HRMS (ESI-TOF) Calcd for C₂₁H₁₉F₂NONa [M + Na]⁺, 362.1332; found, 362.1319.

Preparation of (2R*,9bR*)-9b-Allyl-2-benzyl-1,1-difluoro-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-*a*]isoindole (11). To a suspension of LiAlH₄ (4.3 mg, 1.13 mmol) in THF (3 mL) was added a solution of **9a** (0.153 g, 0.45 mmol) in THF (4 mL). The mixture was heated at reflux overnight and quenched at 0 °C by careful addition of water (0.5 mL) followed by 1 M NaOH (0.5 mL). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification of the crude

product by column chromatography (SiO₂, 5% EtOAc in hexanes) gave a pale yellow oil of **11** (0.123 g, 84% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.30–7.25 (m, 5H, ArH), 7.21–7.15 (m, 4H, ArH), 5.50 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H, CH), 4.95 (dd, *J* = 17.2, 1.8 Hz, 1H, CHH), 4.91 (d, *J* = 10.2 Hz, 1H, CHH), 4.23 (d, *J* = 15.1 Hz, 1H, CHH), 3.76 (d, *J* = 15.1 Hz, 1H, CHH), 3.29 (t, *J* = 7.4 Hz, 1H, CHH), 3.02 (dd, *J* = 13.9, 5.1 Hz, 1H, CHH), 2.90–2.86 (m, 1H, CH), 2.63–2.58 (m, 2H, CHH, CHH), 2.46 (dd, *J* = 13.9, 7.4 Hz, 1H, CHH), 2.42 (ddd, *J* = 11.2, 9.1, 1.7 Hz, 1H, CHH). ¹³C NMR (125 MHz, CDCl₃): δ 140.7 (C), 139.1 (C), 138.8 (d, *J* = 7.5 Hz, C), 132.8 (d, *J* = 1.4 Hz, CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.0 (CH), 126.9 (t, *J* = 261.0 Hz, CF₂), 126.3 (CH), 123.9 (CH), 122.5 (CH), 118.4 (CH₂), 81.5 (t, *J* = 22.8 Hz, C), 60.2 (CH₂), 57.3 (d, *J* = 9.1 Hz, CH₂), 46.6 (t, *J* = 21.6 Hz, CH), 43.1 (t, *J* = 3.0 Hz, CH₂), 31.0 (d, *J* = 6.0 Hz, CH₂). ¹⁹F NMR (470 MHz, CDCl₃): δ -109.23 (dd, *J* = 224.2, 23.0 Hz, 1F), -115.08 (dd, *J* = 223.7, 6.1 Hz, 1F). IR (neat): ν_{max} 1641m, 1456s, 1218s, 724s cm⁻¹. MS: *m/z* (%) relative intensity 278 (9), 236 (100), 216 (7), 194 (18), 176 (7), 130 (6). HRMS (ESI-TOF) Calcd for C₂₁H₂₂F₂N [M + H]⁺, 326.1722; found, 326.1767.

Preparation of (2R*,5S*,9bR*)-9b-Allyl-2-benzyl-5-butyl-1,1-difluoro-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-*a*]isoindole (13). To a solution of CeCl₃ (0.65 g, 1.75 mmol) in THF (5 mL) was added *n*-BuLi (1.2 mL, 1.74 mmol, 1.46 M solution in hexane) at -78 °C. After stirring at -78 °C for 1 h, a solution of **9a** (0.12 g, 0.35 mmol) in THF (5 mL) was added. The mixture was stirred at -78 °C for 10 h and then gradually warmed to -20 °C, and quenched by the addition of 4 M HCl-dioxane in MeOH (4 M HCl-dioxane/MeOH, 1:29, 5 mL) followed by excess NaBH₃CN. The resulting reaction mixture was stirred at 0 °C for 1 h and 10% aqueous NaOH solution (5 mL) was then added. The mixture was diluted with CH₂Cl₂ and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (SiO₂, 5% EtOAc in hexanes) to afford a colorless oil of **13** (0.094 g, 80% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.31–7.18 (m, 8H, ArH), 7.13–7.11 (m, 1H, ArH), 5.59 (ddt, *J* = 17.3, 10.4, 7.1 Hz, 1H, CH), 4.96–4.92 (m, 2H, CH₂), 3.83 (dd, *J* = 9.1, 3.4 Hz, 1H, CH), 3.40 (t, *J* = 7.9 Hz, 1H, CHH), 3.04 (dd, *J* = 13.7, 4.9 Hz, 1H, CHH), 2.97–2.90 (m, 1H, CH), 2.63 (dd, *J* = 13.7, 9.7 Hz, 1H, CHH), 2.57–2.53 (m, 2H, CHH, CHH), 2.47 (dd, *J* = 13.9, 7.3 Hz, 1H, CHH), 1.72–1.68 (m, 1H, CHH), 1.52–1.26 (m, 5H, CHH, 2 × CH₂), 0.89 (t, *J* = 7.3 Hz, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 144.9 (C), 139.2 (C), 138.2 (d, *J* = 6.8 Hz, C), 133.9 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.0 (dd, *J* = 263.5, 251.9 Hz, CF₂), 127.0 (CH), 126.3 (CH), 123.0 (CH), 122.3 (CH), 118.0 (CH₂), 80.5 (t, *J* = 22.0 Hz, C), 73.5 (CH), 58.4 (d, *J* = 9.6 Hz, CH₂), 46.3 (t, *J* = 22.0 Hz, CH), 43.0 (d, *J* = 3.8 Hz, CH₂), 38.1 (CH₂), 31.7 (d, *J* = 5.5 Hz, CH₂), 29.1 (CH₂), 22.7 (CH₂), 14.1 (CH₃). ¹⁹F NMR (470 MHz, CDCl₃): δ -113.12 (dd, *J* = 222.3, 24.4 Hz, 1F), -120.03 (d, *J* = 222.3 Hz, 1F). IR (neat): ν_{max} 1642w, 1496m, 1455m, 1220s, 760m, 700s cm⁻¹. MS: *m/z* (%) relative intensity 382 (M⁺ + 1, 14), 340 (100), 324 (9), 284 (7), 117 (12), 91 (16). HRMS (ESI-TOF) Calcd for C₂₅H₃₀F₂N [M + H]⁺, 382.2348; found, 382.2322.

Preparation of (2R*,5S*,9bR*)-9b-Allyl-2-benzyl-1,1-difluoro-5-isopropyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-*a*]isoindole (14). *i*-Propylmagnesium chloride (0.3 mL, 0.6 mmol, 2 M solution in THF) was slowly added to a solution of **9a** (0.04 g, 0.12 mmol) in THF (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 °C and 4 M HCl-dioxane in MeOH (4 M HCl-dioxane/MeOH, 1:29, 5 mL) was added, followed by the addition of excess NaBH₃CN. After removal of the ice-bath, the reaction mixture was stirred for an additional 1 h and 10% aqueous NaOH solution (5 mL) was then added. The mixture was diluted with CH₂Cl₂ and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were

washed with brine and dried over anhydrous Na_2SO_4 . Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (SiO_2 , hexanes then 5% EtOAc in hexanes) to afford a pale yellow solid of **14** (0.029 g, 65% yield, mp = 87–89 °C). ^1H NMR (500 MHz, CDCl_3): δ 7.31–7.14 (m, 9H, ArH), 5.88–5.80 (m, 1H, CH), 5.06 (d, $J = 17.2$ Hz, 1H, CHH), 5.02 (d, $J = 10.1$ Hz, 1H, CHH), 3.79 (d, $J = 4.7$ Hz, 1H, CH), 3.41 (dd, $J = 9.3, 7.7$ Hz, 1H, CHH), 3.03 (dd, $J = 13.8, 4.7$ Hz, 1H, CHH), 3.03–2.93 (m, 1H, CH), 2.65–2.59 (m, 2H, CHH, CHH), 2.55 (t, $J = 9.9$ Hz, 1H, CHH), 2.49–2.45 (m, 1H, CHH), 1.97–1.90 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.04 (d, $J = 6.8$ Hz, 3H, CH_3), 0.76 (d, $J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CDCl_3): δ 143.3 (C), 139.4 (d, $J = 6.8$ Hz, C), 139.3 (C), 134.3 (CH), 128.7 (2 \times CH), 128.5 (2 \times CH), 127.8 (CH), 127.0 (dd, $J = 264.0, 251.8$ Hz, CF_2), 126.9 (CH), 126.3 (CH), 122.8 (CH), 122.7 (CH), 118.0 (CH_2), 80.0 (t, $J = 22.0$ Hz, C), 79.8 (CH), 59.2 (d, $J = 9.8$ Hz, CH_2), 46.5 (t, $J = 21.1$ Hz, CH), 43.0 (d, $J = 4.3$ Hz, CH_2), 34.0 (CH), 31.9 (d, $J = 5.9$ Hz, CH_2), 20.6 (CH_3), 18.0 (CH_3). ^{19}F

NMR (470 MHz, CDCl_3): δ -112.35 (dd, $J = 222.8, 24.9$ Hz, 1F), -120.23 (d, $J = 222.3$ Hz, 1F). IR (KBr): ν_{max} 3074br, 1458m, 1210s, 1017s, 761s, 699s cm^{-1} . MS: m/z (%) relative intensity 368 ($\text{M}^+ + 1, 7$), 326 (100), 284 (26), 117 (14), 91 (14). HRMS (ESI-TOF) Calcd for $\text{C}_{24}\text{H}_{28}\text{F}_2\text{N}$ [$\text{M} + \text{H}$] $^+$, 368.2192; found, 368.2243.

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Supporting Information Available: Experimental details and characterization data for all compounds and CIF data for single-crystal X-ray analyses of *trans*-**5a** and *trans*-**6a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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