Synthetic Methods

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Radical Cyclization/*ipso*-1,4-Aryl Migration Cascade: Asymmetric Synthesis of 3,3-Difluoro-2-propanoylbicyclo[3.3.0]octanes**

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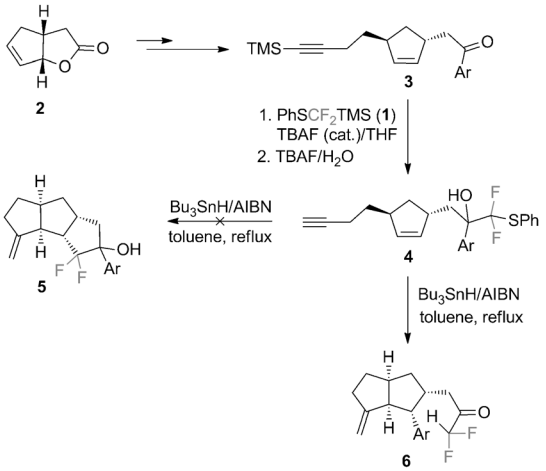
Abstract: *A novel method for the asymmetric synthesis of 3,3-difluoro-2-propanoylbicyclo-[3.3.0]octanes involves an unprecedented intramolecular radical cyclization/ipso-1,4-aryl migration cascade.*

In recent years radical chemistry has played a great role in the development of modern organic synthesis. The synthetic methodologies based on radical species have been extensively exploited, including intermolecular C–C bond formations, cyclizations, annulations, and cascade reactions, thus leading to construction of various types of compounds.[1] Among these synthetic transformations, radical 1,2-, 1,4-, and 1,5-aryl migrations by radical *ipso* substitution at the aromatic ring have been reported in the literature.[2] We and others have recently reported the syntheses of *gem*-difluoromethylenated carbocyclic and dihydroxy-1-azabicyclic compounds by employing a fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ and subsequent radical cyclization.[3] Organofluorine compounds have found wide applications in pharmaceuticals, agrochemicals, and materials science.[4] Therefore, numerous works aimed at developing general methods for the introduction of the *gem*-difluoromethylene group into organic compounds have rapidly increased.[5] In an effort to develop methodologies for asymmetric preparation of fluorine-containing molecules (**5**; for structure see Scheme 1), we report herein an unprecedented asymmetric synthesis of the 3-difluoro-2-propanonylbicyclo[3.3.0]octanes **6** by a radical cyclization/*ipso*-substitution at the aromatic ring of the cyclopentene derivatives **4**.

As shown in Scheme 1, the required precursors **4** were readily prepared by treatment of the chiral ketones **3**,[6] derived from the chiral bicyclic lactone (3a*R*,6a*S*)-**2**[7] (see the Supporting Information), with $PhSCF_2TMS$ (**1**) and tetrabutylammonium fluoride (TBAF) as a catalyst in tetrahydrofuran (THF; 0 °C→RT) for 24 hours. In all cases, the compounds **4** were obtained as an inseparable mixture of diastereomers. The results are summarized in Table 1.



Scheme 1. Preparation of the compounds **4** by fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**1**) to the chiral ketones **3** and their radical cyclization/*ipso*-1,4-aryl migration cascade to give the compounds **6**.

Table 1: Synthesis of **4** by fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**1**) to the chiral ketones **3**.[a]

Entry	Ar	Yield [%][b]	d.r.[c]
1	**3a** (Ph)	**4a**, 96	50:50
2	**3b** (4-MeC_6H_4)	**4b**, 81	51:49
3	**3c** (4-$MeOC_6H_4$)	**4c**, 82	47:53
4	**3d** (2-$MeOC_6H_4$)	**4d**, 85	48:52
5	**3e** (4-$Me_2NC_6H_4$)	**4e**, 82	49:51
6	**3f** (4-ClC_6H_4)	**4f**, 99	50:50
7	**3g** (2-Naphthyl)	**4g**, 86	50:50
8	**3h** (3-FC_6H_4)	**4h**, 85	51:49
9	**3i** (2,4-$(MeO)_2C_6H_3$)	**4i**, 92	49:51
10	**3j** (2-Me,4-FC_6H_3)	**4j**, 97	49:51

[a] For the preparation of **3**, see the Supporting Information. [b] Yield of the isolated product. [c] Determined by ^{19}F NMR spectroscopy.

Having the compounds **4** in hand, we initially focused our study on a radical cyclization of **4a**. Thus, **4a** (1:1 mixture of two diastereomers) was treated with Bu_3SnH (1.75 equiv) in the presence of a catalytic amount of AIBN in toluene (0.02 M) at reflux for 9 hours (Table 2, entry 1). Interestingly, instead of obtaining the expected tricyclic compound **5a**, the reaction provided a mixture of the radical cyclization product **7a** (23%) together with radical cyclization/*ipso*-1,4-aryl

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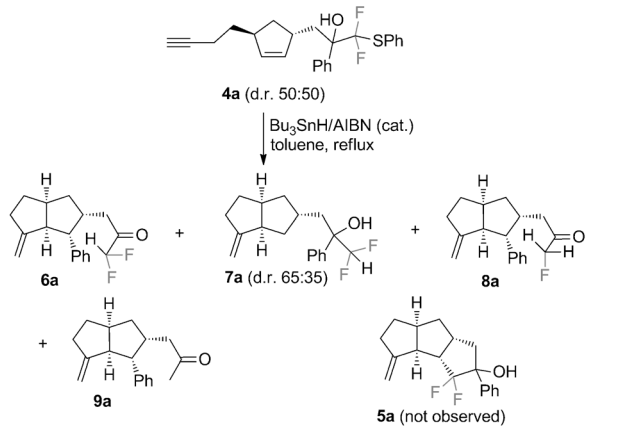
Table 2: Radical cyclization of **4a** under various reaction conditions.

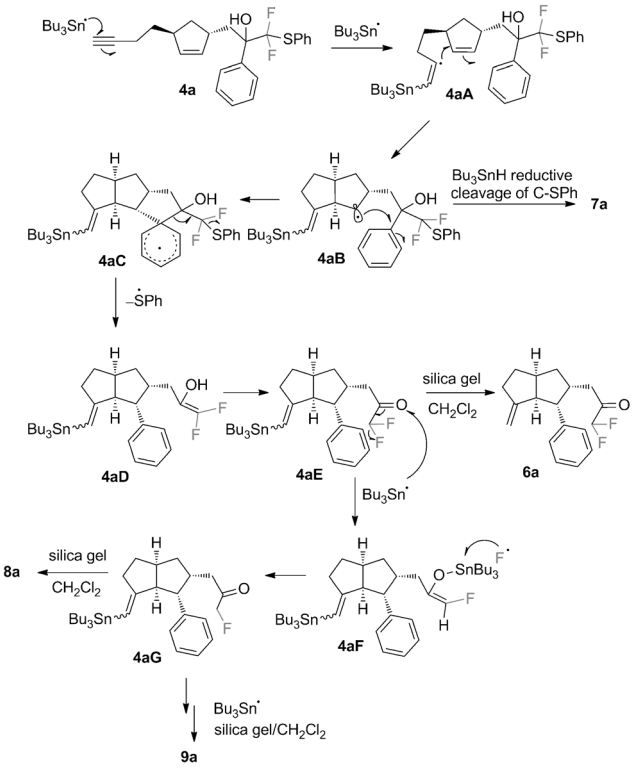


Entry	Bu_3SnH [eqiuv]	Concentration [M]	*t* [h]	Yield [%][a]			
				6a	**7a**	**8a**	**9a**
1	1.75	0.02	9	–	23	10	40
2	1.2	0.02	2	–	16	42	3
3	1.0	0.005	5	78	3	–	–

[a] Yield of isolated product.

migration products **8a** and **9a**, in 10 and 40% yield, respectively (Table 2, entry 1). These results prompted us to carefully study this reaction in detail. Reduction of the amount of Bu_3SnH employed and a shorter reaction time resulted in the formation of **7a**, **8a**, and **9a** in 16, 42, and 3% yield, respectively (Table 2, entry 2). After some experimentation, it was found that the reaction carried out employing Bu_3SnH (1 equiv) at low concentration (0.005 M) in refluxing toluene for 5 hours provided the difluoroketone **6a** almost exclusively in 78% yield together with a small amount of **7a** (3%, Table 2, entry 3). It is worth noting that this radical cyclization/*ipso*-1,4-aryl migration cascade proceeded with excellent stereoselectivity, thus providing **6a**, **8a**, and **9a**, each as a single isomer as revealed by ^1H and ^{13}C NMR spectra. Their relative stereochemistries were also confirmed by the NOE experiments (see the Supporting Information).

Based on the obtained experimental results, the formation of phenyl-migrated products **6a**, **8a**, and **9a** resulted from a radical cyclization/*ipso*-1,4-phenyl migration cascade of **4a** (by 1,4-*ipso*-substitution at the phenyl ring). The mechanism supporting this process is proposed as illustrated in Scheme 2. First, a tributylstannyl radical chemoselectively adds to the terminal carbon atom of the alkyne moiety of **4a**,[8] thus resulting in the vinylic radical **4aA**, which undergoes *exo*-mode cyclization[9] to produce the bicyclic radical **4aB**. Stereospecific *ipso* substitution of the radical **4aB**, via the spirohexadienyl radical **4aC**, and subsequent fragmentation/elimination of the phenylsulfanyl group leads to **4aD** and subsequently to **4aE**. The *gem*-difluoromethylketobicyclic compound **6a** was obtained after passing the crude reaction mixture through silica gel, eluting with CH_2Cl_2.[10] Alternatively, **7a** resulted from **4aB** upon hydrogen atom abstraction from Bu_3SnH and subsequent reductive cleavage of the phenylsulfanyl group initiated by a tributylstannyl radical. At a high concentration of **4a** in toluene (0.02 M) and excess



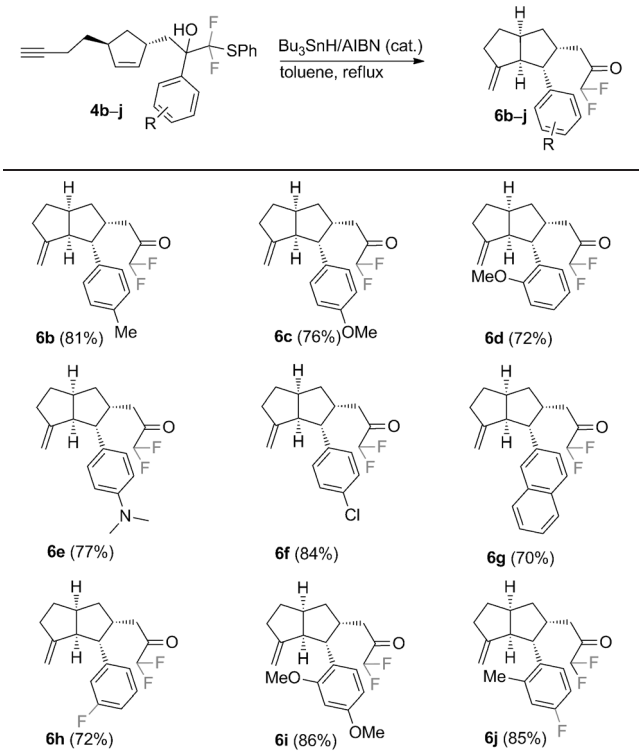
Scheme 2. A plausible mechanism for the formation of the compounds **6a**, **7a**, **8a**, and **9a**.

Bu_3SnH (1.20 or 1.75 equiv), the intermediate **4aE** can further react with the tributylstannyl radical, thus leading to defluorinated products **8a** and **9a**, after treatment with silica gel in CH_2Cl_2. As shown in the proposed mechanism, it is therefore crucial to perform the reaction at a low concentration of **4a**, and to use an equivalent of Bu_3SnH to prevent a successive α-reductive cleavage of the C–F bond from the firstly formed intermediate **4aE**. To the best of our knowledge, our finding reports the first asymmetric radical cyclization/*ipso*-1,4-aryl migration/elimination sequence, thus leading to an asymmetric synthesis of 3,3-difluoro-2-propanoylbicyclo[3.3.0]octanes.

Having the optimized reaction conditions (Table 2, entry 3), we then applied the optimal conditions to a variety of substrates to verify the generality of the method and the results are summarized in Table 3. The compounds **4b–j**, each as a 1:1 mixture of two diastereomers, containing either electron-deficient or electron-rich-substituted aryl groups smoothly underwent the reaction, thus affording the corresponding products **6b–j**, each as a single isomer, in good yields. It is worth noting that electronically different aryl groups on the substrates **4b–j** had negligible impact on the rate of the reactions as monitored by thin-layer chromatography and ^1H NMR spectroscopy, thus leading to the products **6b–j** in comparable yields. Finally, the stereochemistry of **6a–j** was established by the NOE and NOESY experiments (see the Supporting Information).

Intrigued by this finding, we further investigated the necessity of the difluoro(phenylsulfanyl)methyl motif ("$PhSCF_2$") in facilitating the *ipso* substitution at the aro-

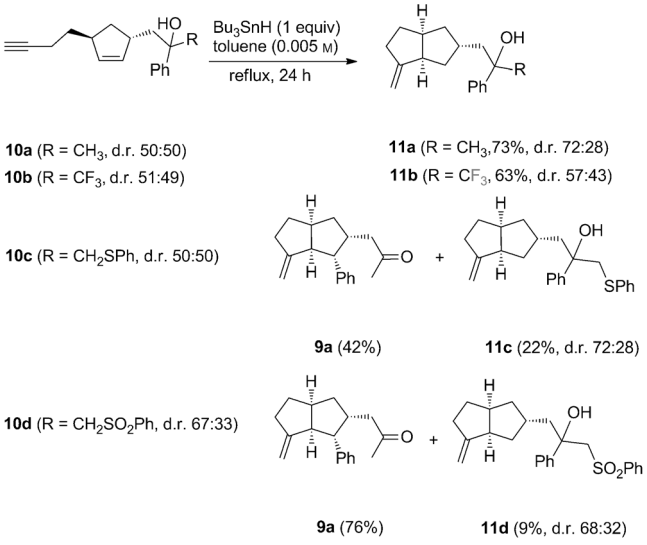
Table 3: Preparation of chiral compounds **6b–j** from **4b–j**.[a]



[a] Values in parentheses are yields of the isolated products.

matic ring with subsequent fragmentation and elimination of the phenylsulfanyl group. Therefore, radical cyclization of the compounds **10a–d** (each as approximately 1:1 mixture of two diastereomers) was examined to gain insight into the importance of the R group in the radical cyclization/*ipso*-1,4-aryl migration cascade (Scheme 3).

Under the standard reaction conditions (Table 2, entry 3), but at a prolonged reaction time (24 h), radical cyclization of **10a** ($R = CH_3$, d.r. 50:50) afforded the bicyclic alcohol **11a** in 73% yield without the detection of any *ipso*-1,4-aryl migration products (Scheme 3). Similarly, **10b**,[12] containing an electron-withdrawing trifluoromethyl group, gave only **11b** (63%) and recovery of **10b** (17%, Scheme 3). It should be noted here that the tributylstannyl-radical-mediated intramolecular radical cyclization of **10a** and **10b** proceeded with high stereoselectivity, thus affording the corresponding all-*cis*-bicyclic alcohols **11a** and **11b**, respectively. At this point, we assumed that the phenylsulfanyl moiety ("PhS") was important for driving the *ipso*-1,4-substitution at the phenyl ring to give **4aC**, which underwent rearomatization/aryl migration through an elimination of the phenylsulfanyl group. As a consequence, **10a** and **10b**, which do not contain the phenylsulfanyl moiety, are unable to undergo *ipso*-1,4-phenyl migration and subsequent elimination. On the basis of these experiments, and to further probe the importance of the *gem*-difluoro moiety, we next carried out the reactions of the phenylsulfanylmethyl carbinol **10c**[13] and phenylsulfonylmethyl carbinol **10d** (Scheme 3).[14]



Scheme 3. Intramolecular radical cyclization of compounds **10a–d**.

Under similar reaction conditions as those used for **10a** and **10b**, radical cyclization of **10c** yielded **9a** in 42% yield as a single stereoisomer along with **11c** in 22% yield as a 72:28 diastereomeric mixture. Not to our surprise, the sulfonylmethyl ketone **10d** readily underwent the reaction to provide **9a** in good yield (76%) along with **11d** (9%) as a minor product. This outcome further emphasizes a greater leaving group ability of the phenylsulfonyl group versus the phenylsulfanyl group, and thus aids the elimination step. The mechanism for the formation of **9a** from both **10c** and **10d** is straightforward and is similar to that of the formation of **6a** from **4a** in that the tributylstannyl radical mediated an intramolecular radical cyclization/*ipso*-1,4-aryl migration cascade and subsequent elimination (Scheme 2). Comparatively, the rate of the reaction for the conversion of **10c** and **10d** into **9a** is much lower than that of **4a** into **6a**, as monitored by thin-layer chromatography and ^{1}H NMR analysis. This difference may be attributed to the electronegative *gem*-difluoro moiety, thus enhancing the rate of the radical cyclization/*ipso*-1,4-aryl migration cascade of **4a** to give **6a**.

In summary, we have developed a novel method for the asymmetric synthesis of the 3,3-difluoro-2-propanoylbicyclo-[3.3.0]octanes **6a–j** on the basis of the unprecedented intramolecular radical cyclization/*ipso*-1,4-aryl migration cascade of **4a–j**, which were readily obtained by fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**1**) to the chiral ketocyclopentenes **3**. The chiral compounds of type **6** may be useful in further synthetic applications. Furthermore, this approach was also successfully applied to the phenylsulfanylmethyl carbinol **10c** and phenylsulfonylmethyl carbinol **10d** to provide the chiral bicyclic ketone **9a**. Further applications of our reaction to the synthesis of fluorinated analogues of naturally occurring bioactive compounds are currently under investigation.

Experimental Section

Synthesis of the compounds **4** from the corresponding chiral ketones **3**: A mixture of $PhSCF_2TMS$ (**1**) (464 mg, 2 mmol), and **3** (1 mmol) in

anhydrous THF (2 mL) was treated with a solution of 10 mol% TBAF (1M in anhydrous THF, 0.1 mL, 0.1 mmol) at 0°C to RT for 24 h. The reaction mixture was quenched with an excess amount of saturated aqueous TBAF and the resulting mixture was stirred at RT for 2 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed successively with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave a crude reaction mixture, which was purified by gradient column chromatography (SiO_2, 5–10% EtOAc in hexanes) to yield the corresponding adducts **4** as mixtures of diastereomers.

Synthesis of the difluoroketones **6** from compounds **4**: An argon gas was bubbled through a solution of the compound **4** (0.3 mmol) in anhydrous toluene (60 mL) for 30 min, and a mixture of Bu_3SnH (0.08 mL, 0.3 mmol) and AIBN (5 mg, 0.03 mmol) in anhydrous toluene (60 mL) was then added dropwise at reflux over a 1 h period. After the completion of the reaction, the tin by-products were removed by column chromatography [SiO_2, hexanes (200 mL) and then CH_2Cl_2 (300 mL)] to give a crude reaction mixture, which was then purified by preparative thin-layer chromatography (SiO_2, 2% EtOAc in hexanes, ×3) to afford the compounds **6**.

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