Helical Compounds

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Efficient Helicene Synthesis: Friedel–Crafts-type Cyclization of 1,1-Difluoro-1-alkenes**

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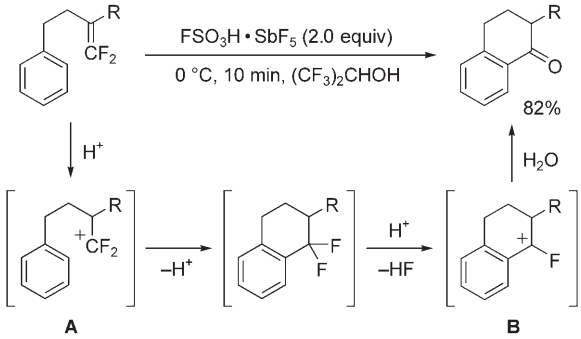
Helicenes are nonplanar *ortho*-fused aromatic compounds with helical chirality.[1] Their extraordinary optical and electronic properties have been of interest for a long time.[2] During the last decade, studies have been carried out toward their application in asymmetric synthesis,[3] molecular recognition,[4] and materials science, for example, as liquid crystals, sensors, and dyes.[5]

Helicenes have been synthesized by the classical oxidative photocyclization of stilbene derivatives.[6] Although useful, this reaction is not suitable for large-scale production because of the high-dilution conditions. Quite recently, new methods for helicene synthesis amenable to scale-up have been developed on the basis of the construction of a benzene ring by the Diels–Alder reaction,[7] radical cyclization,[8] metathesis,[9] or C–H arylation[10] as a key step.[11] In contrast to these reactions, the [2+2+2] cycloisomerization of triynes[12] can be used to construct three rings in a single step. The formation of multiple benzene rings in such a way has great potential for the construction of higher-order helicene skeletons.

A fluorine substituent has an α-carbocation-stabilizing effect due to the donation of its unshared electron pair to the vacant p orbital of the α carbon atom. At the same time, its high electronegativity makes it a potential leaving group as a fluoride ion (F^-). By exploiting these two unique properties, we recently developed an electrophilic cyclization of 1,1-difluoro-1-alkenes: a Friedel–Crafts-type alkylation (Scheme 1).[13] This Friedel–Crafts-type cyclization occurred via an α,α-difluorocarbocation **A** generated by the protonation of a starting difluoroalkene with magic acid ($FSO_3H{\cdot}SbF_5$). Magic acid then promoted the elimination of HF from the corresponding cyclized intermediate to give the α-fluorocarbocation **B**, which underwent hydrolysis of the C–F bond to afford a final cyclic-ketone product.



Scheme 1. Friedel–Crafts-type cyclization of 1,1-difluoro-1-alkenes.

These results prompted us to investigate the use of the Friedel–Crafts-type cyclization in a domino reaction by trapping the carbocation **B** with another aryl group. We expected to be able to construct fused tetracyclic structures in a one-pot operation by such a domino Friedel–Crafts-type cyclization of difluoroalkenes containing an aryl group in both branches of the difluorovinylidene unit to provide facile access to helicene precursors. A subsequent dehydrogenation step would give the target helicenes. The key feature of this method is the construction of two fused benzene rings from a difluoroalkene. Herein, we report a short, efficient route to helicenes that utilizes the characteristics of fluorine substituents.

The starting materials were designed as 1,1-difluoro-1-alkenes bearing two aryl groups, each of which was linked to the vinylic carbon atom by a two-methylene-unit tether. The symmetrical 1,1-difluoroalkenes **1b** and **1k** were synthesized readily by our previously reported method in a one-pot operation from commercially available 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (CF_3CH_2OTs) and trialkyl boranes prepared by the hydroboration of vinyl arenes (Scheme 2).[14] Other 1,1-difluoroalkenes, including nonsymmetrical 1,1-difluoroalkenes, were prepared by an S_N2' reaction[15] of aryl methyl anions with the trifluoromethyl-substituted vinyl compound **2**, which was obtained readily from ethyl trifluoroacetate by a Grignard reaction[16] followed by a Wittig reaction (Scheme 3).[17] Compound **2** can also be prepared by the alkylation with benzyl bromide of 2-(trifluoromethyl)allylsilane,[18] derived from CF_3CO_2Et.

1,1-Difluoroalkenes **1** were subjected to reaction conditions similar to those used for the synthesis of cyclic

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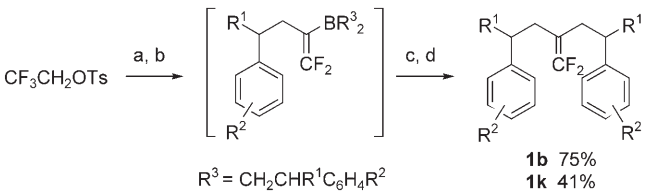
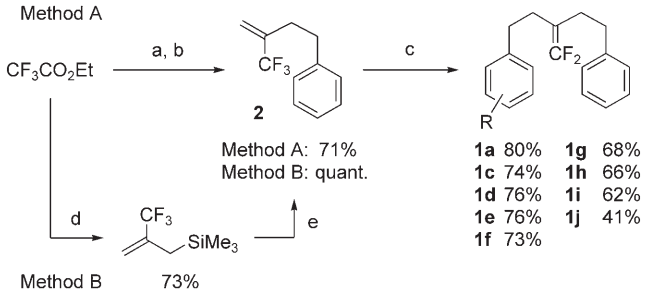
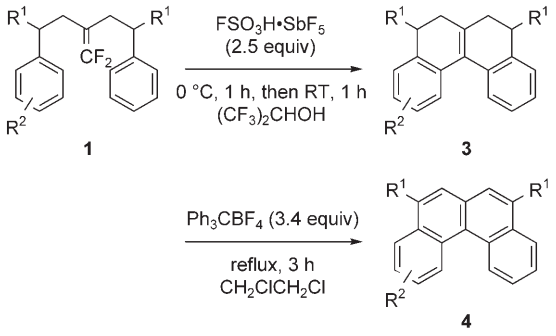


Scheme 2. Preparation of symmetrical 1,1-difluoro-1-alkenes **1**: a) *n*BuLi (2.1 equiv), THF, −78 °C, 0.5 h; b) BR^3_3 (1.1 equiv), −78 °C, 0.5 h; c) MeONa (3.1 equiv), room temperature, 3 h (for **1b**); room temperature, 2 h, then reflux, 1 h (for **1k**); d) Br_2 (3.0 equiv), −78 °C, 1 h, then room temperature, 1 h.



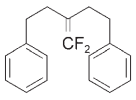
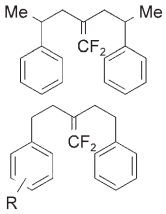
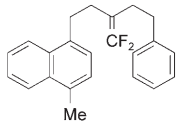
Scheme 3. Preparation of nonsymmetrical 1,1-difluoro-1-alkenes **1**: a) $Ph(CH_2)_2MgBr$ (0.9 equiv), Et_2O, −78 °C→RT, 1 h; b) $Ph_3P{=}CH_2$ (1 equiv), Et_2O, −78 °C→RT, 1.5 h; c) $RC_6H_4CH_2Li$ (1 equiv), $Me_2N(CH_2)_2NMe_2$ (1 equiv), THF, −78 °C, 1 h, then room temperature, 1 h; d) ref. [18]; e) $PhCH_2Br$ (1.1 equiv), CsF (1.1 equiv), $HCONMe_2$, 60 °C, 7 h.

ketones.[13] The treatment of **1a** with magic acid (2.5 equiv) in 1,1,1,3,3,3-hexafluoropropan-2-ol induced the expected domino Friedel–Crafts-type cyclization to afford readily the fused tetracyclic compound **3a** in 87% yield (Scheme 4 and Table 1, entry 1). Similarly, difluoroalkenes **1b**–**1e** and **1h** underwent the domino cyclization to afford the corresponding fused ring systems containing methyl groups or a tolyl or methylnaphthyl group in good to excellent yields (Table 1, entries 2–5 and 8).[19] The domino cyclization proceeded even in the case of **1f** and **1g** with a methoxyphenyl group, despite the fact that protonation of the methoxy oxygen atom decreased the nucleophilicity of the aromatic ring (Table 1, entries 6 and 7). Subsequent dehydrogenation of the cyclized products **3** was carried out successfully by using trityl tetrafluoroborate or palladium on carbon to give [4]helicenes **4** in high yields (Table 1).



Scheme 4. Reaction conditions for the domino Friedel–Crafts-type cyclization of **1** and dehydrogenation.

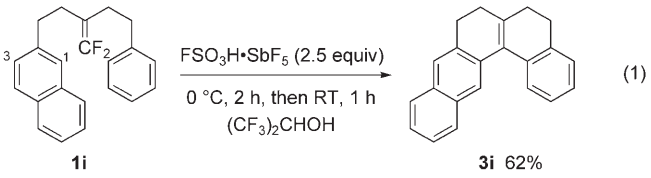
Table 1: Domino Friedel–Crafts-type cyclization of **1** and dehydrogenation.[a]

Entry	Precursor		Yield [%]	
			3	**4**
1		**1a**	87	80
2		**1b**	85	82[b]
3	R = *o*-Me	**1c**	84	81
4	R = *m*-Me	**1d**	89	80
5	R = *p*-Me	**1e**	80	96[b]
6	R = *o*-OMe	**1f**	27	80
7	R = *m*-OMe	**1g**	59	82
8		**1h**	92	82

[a] For the reaction conditions, see Scheme 4. [b] The dehydrogenation was conducted with Pd on carbon.

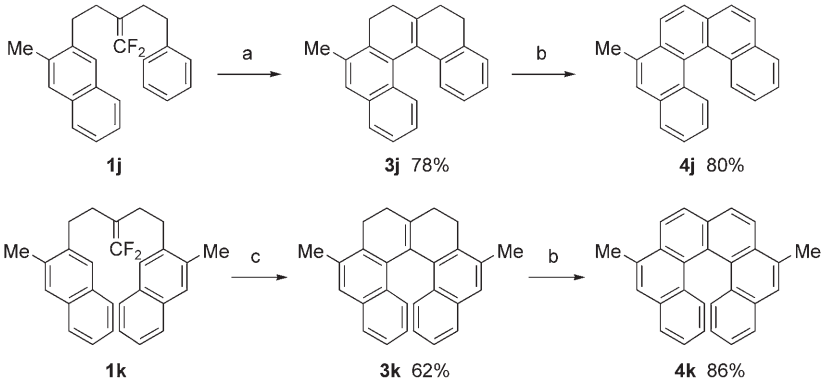
To elucidate the effect of fluorine substituents on the domino Friedel–Crafts-type cyclization, we exposed the dichloroalkene counterpart of **1a** and a carboxylic acid derivative, 2-(2-phenylethyl)-4-phenylbutanoic acid, to magic acid under similar conditions. Whereas the reaction of **1a** gave **3a** in 87% yield, the dichloroalkene was converted into **3a** in only 3% yield, even upon heating at reflux. 2-(2-Phenylethyl)-4-phenylbutanoic acid underwent a single cyclization to give the ketone 2-(2-phenylethyl)-3,4-dihydro-2*H*-naphthalen-1-one in 84% yield without the formation of **3a**. These results demonstrate the advantage of fluorine substituents in the construction of polycyclic systems.

The domino-cyclization–dehydrogenation sequence was extended to the synthesis of [5] and [6]helicenes from difluoroalkene precursors **1** containing naphthalene rings. As we had observed previously that naphthyl-substituted difluoroalkenes underwent the Friedel–Crafts-type cyclization regioselectively at the 1-position of the ring because of electronic effects,[13] we anticipated that the domino cyclization–dehydrogenation of the naphthalene derivative **1i** would lead to the corresponding [5]helicene. However, **1i** underwent cyclization exclusively at the 3-position of the naphthalene ring to give 5,6,7,8-tetrahydronaphtho[1,2-*a*]anthracene (**3i**) in 62% yield [Eq. (1)]. Thus, the regiochemistry of the reaction is controlled by steric effects rather than by electronic effects in the construction of sterically hindered polycyclic systems.



(1)

We therefore introduced a methyl group to protect the 3-position of the naphthalene ring. Upon the treatment of **1j** with magic acid (2.5 equiv), the desired pentacyclic compound **3j** was obtained in 78% yield. The dehydrogenation of **3j** provided the [5]helicene **4j** in 80% yield (Scheme 5).[20] We found that the methyl group on the naphthalene ring controlled the regiochemistry of the ring closure and also improved the solubility of the difluoroalkene in $(CF_3)_2CHOH$. We also attempted the synthesis of a [6]helicene from the difluoroalkene **1k** with two naphthalene rings. The domino Friedel–Crafts-type cyclization and dehydrogenation proceeded smoothly in 62 and 86% yield, respectively, to afford the [6]helicene **4k** (Scheme 5). These results show clearly that our domino-cyclization–dehydrogenation approach greatly simplifies the construction of sterically hindered helicene ring systems.



Scheme 5. Synthesis of [5] and [6]helicenes **4j** and **4k**: a) $FSO_3H{\cdot}SbF_5$ (2.5 equiv), $(CF_3)_2CHOH$, 0°C, 1 h, then room temperature, 1 h; b) Ph_3CBF_4 (3.4 equiv), CH_2ClCH_2Cl, reflux, 3 h; c) $FSO_3H{\cdot}SbF_5$ (2.5 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ (10:1), 0°C, 1 h, then room temperature, 1.5 h.

In summary, the construction of two adjacent benzene rings through a domino Friedel–Crafts-type cyclization of 1,1-difluoro-1-alkenes containing two aryl groups forms the basis of an efficient method for the synthesis of helicenes. Furthermore, the method that we have developed for the preparation of both symmetrical and nonsymmetrical precursor difluoroalkenes enables the introduction of substituents into helicenes. This sequence of reactions provides a synthetic route to helicenes in three or four steps from commercially available CF_3CH_2OTs or CF_3CO_2Et.

Experimental Section

Cyclization of **1a**: Compound **1a** (150 mg, 0.55 mmol) was added as a solution in $(CF_3)_2CHOH$ (2 mL) to a solution of $FSO_3H{\cdot}SbF_5$ (437 mg, 1.38 mmol) in $(CF_3)_2CHOH$ (4 mL) at 0°C under argon. The resulting mixture was stirred for 1 h at 0°C then warmed to room temperature and stirred for 1 h at room temperature. Phosphate buffer (pH 7) was then added to quench the reaction, and the mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane) to give **3a** (111 mg, 87%) as a colorless solid.

Dehydrogenation of **3a**: Triphenylmethylium tetrafluoroborate (370 mg, 1.12 mmol) and **3a** (76 mg, 0.33 mmol) were dissolved in 1,2-dichloroethane (4 mL), and the resulting mixture was heated at reflux for 3 h under argon. The solvent was removed under reduced pressure, and the residue was purified by thin-layer chromatography on silica gel (hexane/AcOEt, 10:1) to give **4a** (60 mg, 80%) as a colorless solid.

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[19] The methyl groups in the synthesized [4]helicenes **4e** and **4h** would enable the generation of the corresponding aryl methyl anions to repeat the process for the synthesis of higher helicenes.
[20] The structure of **4j** was confirmed by X-ray crystallography.

