REPORT

ORGANIC CHEMISTRY

# Hydrogenation of fluoroarenes: Direct access to all-*cis*-(multi)fluorinated cycloalkanes

**Mario P. Wiesenfeldt, Zackaria Nairoukh, Wei Li, Frank Glorius***

**All-*cis*-multifluorinated cycloalkanes exhibit intriguing electronic properties. In particular, they display extremely high dipole moments perpendicular to the aliphatic ring, making them highly desired motifs in material science. Very few such motifs have been prepared, as their syntheses require multistep sequences from diastereoselectively prefunctionalized precursors. Herein we report a synthetic strategy to access these valuable materials via the rhodium–cyclic (alkyl)(amino)carbene (CAAC)–catalyzed hydrogenation of readily available fluorinated arenes in hexane. This route enables the scalable single-step preparation of an abundance of multisubstituted and multifluorinated cycloalkanes, including all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane as well as cis-configured fluorinated aliphatic heterocycles.**

Fluorine is the most electronegative element in the periodic table. As a result, the carbon–fluorine bond has substantial electrostatic character, making it the most polarized carbon single bond in organic chemistry. The strong dipole moment introduced by the C–F bond, the high bond strength, and the relatively small steric demand are widely exploited in agrochemical and pharmaceutical science to fine-tune the polarity, p$K_a$ value, conformation, and metabolic stability of test compounds (*1*–*4*). Moreover, control of the relative orientation of several C–F bonds allows for the design of highly polar compounds that are applied in material science, for example, as dielectric materials in liquid crystals (*5*, *6*). In that regard, it has recently been demonstrated that achieving a cis alignment, in particular for 1,3-diaxial C–F bonds, is required for the synthesis of facially polarized fluorinated cycloalkanes (*7*–*9*), with all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane (**1**) being among the most polar organic molecules known (*9*). Syntheses of monofluorinated (substituted) cyclohexanes from unfunctionalized precursors (*10*–*12*) or with complete site selectivity from alkylcarboxylic acids (*13*) have been reported recently. The trans isomer is usually the major diastereomer and is often obtained in low selectivity, as the fluorination proceeds via an alkyl radical intermediate. Selectively multifluorinated cycloalkanes, however, remained out of reach. The desired cis selectivity can be obtained by nucleophilic substitution, for example, via ring-opening of epoxides, substitution of leaving groups, and deoxyfluorination, thus requiring the use of diastereoselectively predecorated substrates (Fig. 1, A and B). As a result, multisubstituted cyclohexanes require multistep sequences as exemplified by O'Hagan's prominent 12-step synthesis of all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane (Fig. 1B, **1**) (*9*).

Based on our experience with stereoselective (hetero)arene hydrogenation using ruthenium–*N*-heterocyclic carbene (NHC) complexes (*14*–*16*), we envisioned that such multistep processes could be obviated by the design of a protocol for the catalytic hydrogenation of the inexpensive and readily available fluoroarenes, as hydrogenation of arenes is usually highly cis-selective (*17*, *18*). However, all previously reported attempts to hydrogenate fluoroarenes were hampered by a competing hydrodefluorination pathway (Figs. 1C and 2) (*19*–*21*). Hence, a synthetically useful protocol for the hydrogenation of fluorinated arenes

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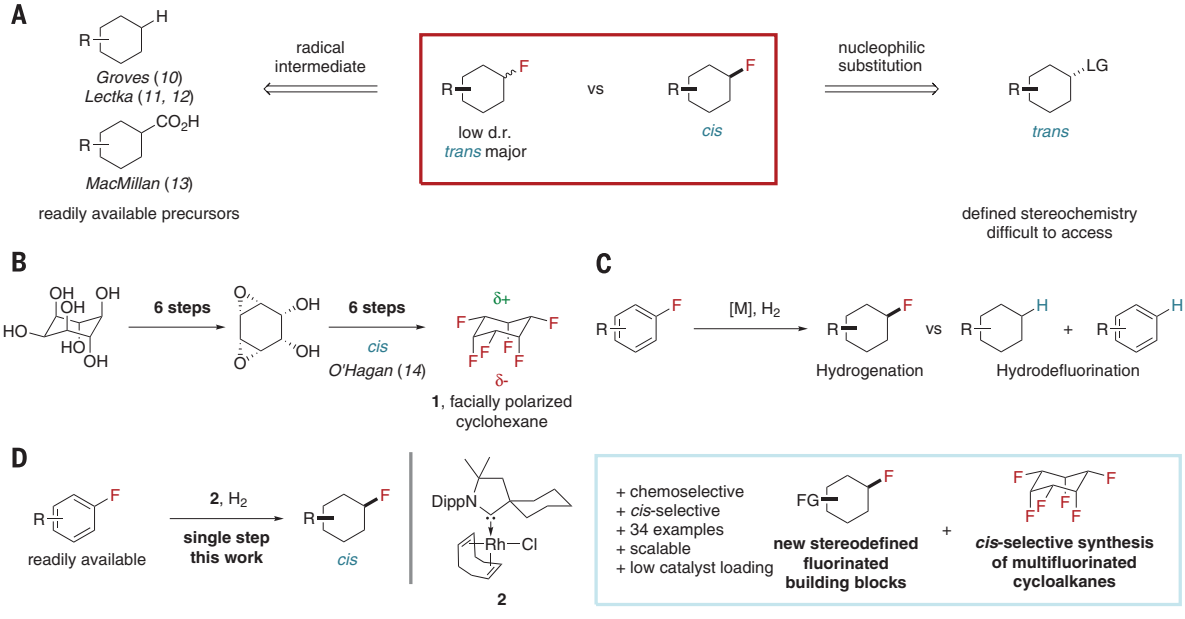


**Fig. 1. Cis-selective synthesis of (multi)fluorinated cycloalkanes by arene hydrogenation.** (**A**) Previously described methodologies for the preparation of fluorinated cycloalkanes. The cis-selective synthesis of fluorinated cycloalkanes requires diastereoselectively prefunctionalized substrates. d.r., diastereomeric ratio; R, generic substituent; LG, leaving group. (**B**) Synthetic route to the facially polarized all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane (**1**). (**C**) The competing hydrodefluorination side reactions that have previously precluded the development of a protocol for the hydrogenation of fluorinated arenes to fluorinated cycloalkanes. [M], metal catalyst. (**D**) The method reported herein to access stereodefined (multi)fluorinated building blocks and highly polar multifluorinated cycloalkanes. Dipp, 2,6-diisopropylphenyl; FG, functional group.

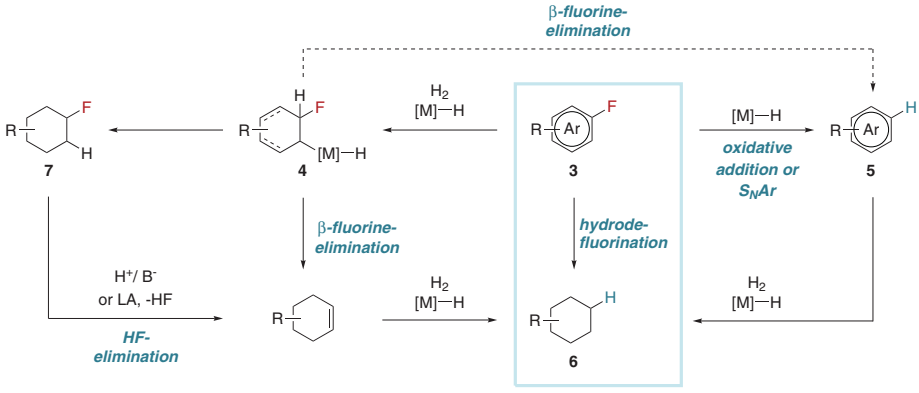


**Fig. 2. Mechanistic pathways for the undesired hydrodefluorination side reaction.** The hydrodefluorination reaction can take place via oxidative addition or nucleophilic aromatic substitution at the aryl halide **3**, via β-fluorine elimination from alkyl-metal complex **4** or via Lewis acid (LA) or Brønsted acid- or base-catalyzed HF elimination from the alkyl halide product **7**.

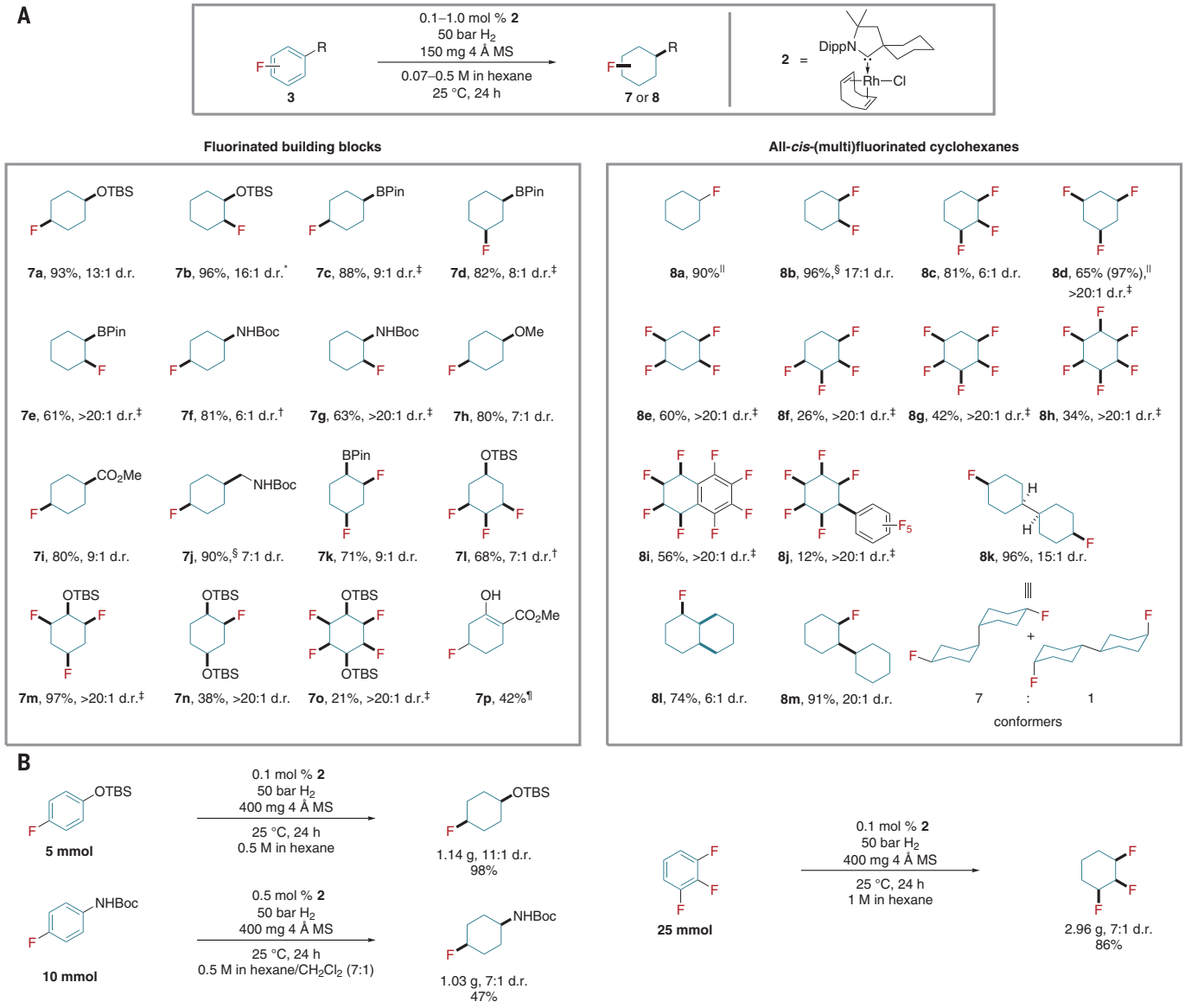


**Fig. 3. Scope of the hydrogenation of fluorinated arenes.** (**A**) Synthesis of fluorinated building blocks and all-*cis*-(multi)fluorinated cyclohexanes. BPin, pinacolboron; Me, methyl; MS, molecular sieves. All data are reported as isolated yields unless otherwise stated. For details concerning concentration and catalyst loading, see the supplementary materials. The d.r. values of the major isomer relative to all other isomers were determined by $^{19}F$ NMR or gas chromatography (GC) analysis before purification. *The major isomer could be isolated by standard column chromatography by using pentane/diethyl ether = 99:1. †The major isomer could be isolated by recrystallization in pentane and diethyl ether. ‡The d.r. values of crude and isolated product were identical. §The yield was determined by $^{19}F$ NMR spectroscopy with hexafluorobenzene as internal standard. ||The yield was determined by GC–free induction decay (FID) with mesitylene as internal standard. ¶A 10:1 mixture of enol and alcohol was obtained. (**B**) Scale-up to gram scale.

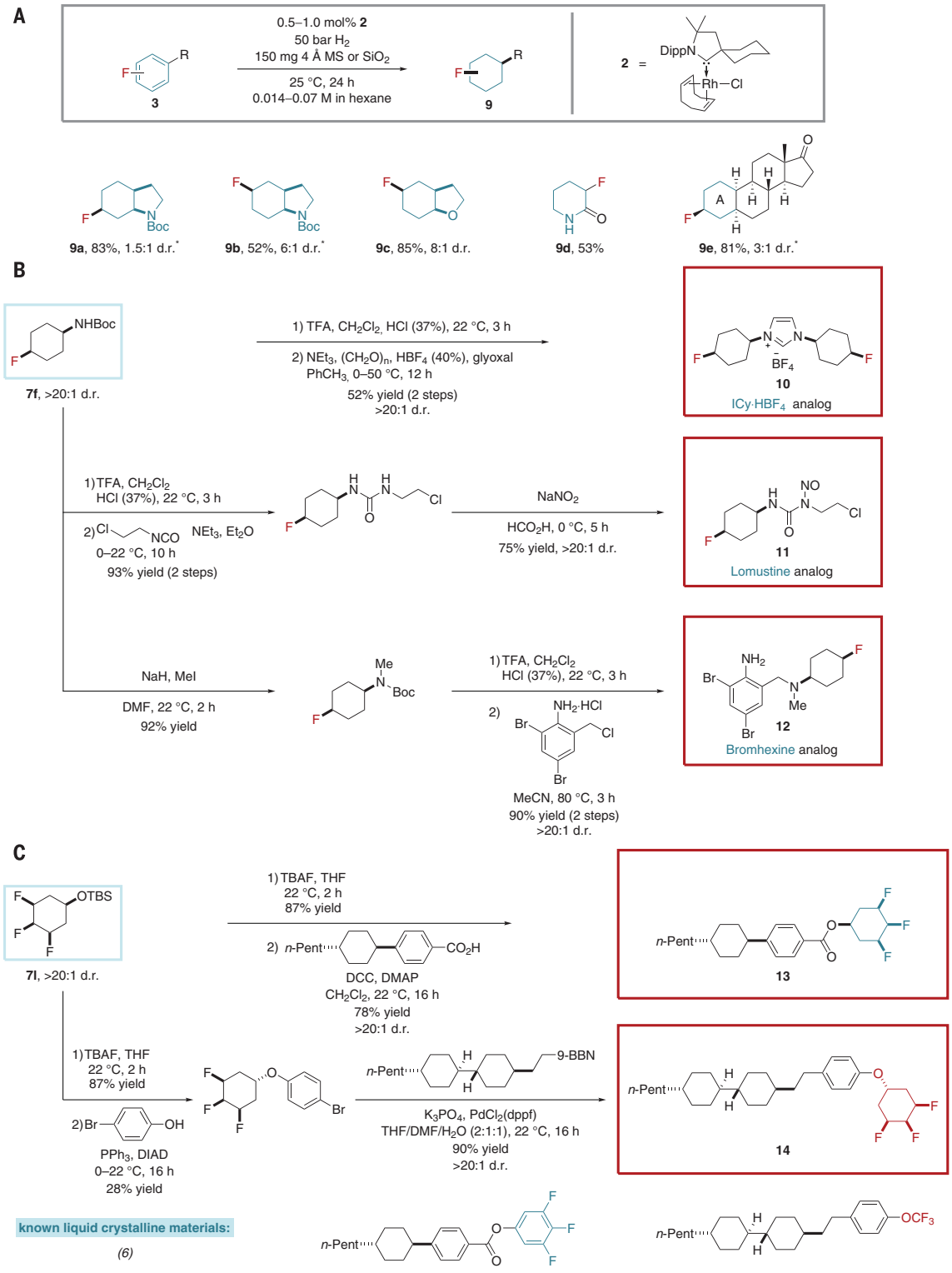


**Fig. 4. Applications of the developed method for the hydrogenation of fluorinated arenes.** (**A**) Synthesis of biologically relevant compounds. All data are reported as isolated yields unless otherwise stated. For details concerning concentration and catalyst loading, see the supplementary materials. The d.r. values of the major isomer relative to all other isomers were determined by $^{19}F$ NMR or GC analysis before purification. *The d.r. values of crude and isolated product were identical. (**B**) Use of fluorinated Boc-protected amine **7f** as cis-fluorinated building block for the synthesis of ICy·$HBF_4$ derivative **10** and fluorinated analogs **11** and **12** of the commercial pharmaceuticals lomustine and bromhexine. ICy·$HBF_4$, 1,3-dicyclohexyl-imidazolium tetrafluoroborate; TFA, trifluoracetic acid. (**C**) Use of 3,4,5-trifluorinated TBS–protected cyclohexanol as building block for the synthesis of structural analogs **13** and **14** of known liquid crystalline materials. TBAF, tetra-*n*-butylammonium fluoride; THF, tetrahydrofuran; *n*-Pent, *n*-pentyl; DMAP, 4-dimethylaminopyridine; DIAD, diisopropyl azodicarboxylate; 9-BBN, 9-borabicyclo(3.3.1) nonane; dppf, 1,1′-bis(diphenylphosphino) ferrocene; DMF, dimethylformamide.

remained elusive. Several mechanistic pathways are known to lead to a net hydrodefluorination (Fig. 2) (*22*), and synthetic protocols for the selective substitution of fluorine with hydrogen, following seminal work by Milstein, have been designed (*23*).

Herein we describe a protocol for the highly selective hydrogenation of a broad scope of (multi)fluorinated arenes and heteroarenes, offering convenient access to cis-diastereoselectively (multi)fluorinated building blocks, highly polar all-*cis*-(multi)fluorocycloalkanes, and fluorinated aliphatic heterocycles. Studies toward the chemo- (and enantio-)selective hydrogenation of simple fluorine-substituted alkenes have resulted in a limited number of successful examples employing ruthenium (*24*), rhodium (*25*), and iridium complexes (*26*). However, in contrast to the hydrogenation of alkenes, the hydrogenation of stabilized arenes is dominated by heterogeneous catalysis (*27*). Hence, the hydrogenation of the relatively nonvolatile *tert*-butyl(4-fluorophenoxy)dimethylsilane

(**3a**) was attempted with a variety of standard heterogeneous catalysts known to be capable of arene hydrogenation (*28*). However, these reactions yielded multiple products, with the hydrodefluorinated cycloalkane **6a** as the major identified product (table S1). When using a combination of rhodium with a strongly electron-donating cyclic (alkyl)(amino)carbene (CAAC) ligand (*29*), which was first reported for an arene hydrogenation reaction by the Zeng group (*30*), these decomposition pathways were substantially diminished, though the hydrodefluorinated cycloalkane **6a** remained as the major product under the described conditions (52% yield, 1:2 ratio of hydrogenation versus hydrodefluorination; table S2, entry 3). Exchange of the trifluoroethanol solvent with the less polar hexane resulted in a highly selective reaction (25:1) in which the desired product **7a** was formed in 95% yield (table S2, entry 10). The catalyst loading could be lowered to 0.1 mole % (mol %) with complete conversion conserved and improved selectivity (53:1) (table S3, entry 6). The hydrogenation reaction proceeded smoothly at pressures as low as 10 bar, although a decrease in selectivity (19:1) was observed (table S4, entry 1).

Subsequently, the scope of the reaction was studied under the optimized conditions (Figs. 3 and 4A). The ready availability of fluorinated arenes, either from commercial suppliers or in a single step following methods described in literature, allowed us to perform the reaction on a synthetically useful 1-mmol scale. Gram-scale reactions were carried out for three representative examples (Fig. 3B). The high selectivity made product isolation straightforward. Likewise, isolation of the major diastereomer by standard column chromatography or recrystallization was often possible, especially for multisubstituted products. In the case of less reactive, highly sterically hindered, or electron-poor substrates, the dilution, substitution of molecular sieves with silica gel, and increase of the catalyst loading to 0.5 or 1 mol % improved the yields. The observed cis selectivity could be confirmed by nuclear Overhauser effect (NOE) experiments (fig. S1). Furthermore, a molecular structure for all-*cis*-1,2,4,5-tetrafluorocyclohexane (**8e**) was determined by single-crystal x-ray diffraction (fig. S2) and matched that of the previous report (*7*). Many useful functional groups were well tolerated—including *tert*-butyl(dimethyl)silyl (TBS)–protected-(**7a** and **7b**) and free (phenolic) alcohol (**7p**), pinacol boronic ester (**7c** to **7e**), *tert*-butyloxycarbonyl (Boc)–protected amine (**7f**, **7g**, and **7j**), and ester (**7i**)—thus demonstrating that the fluorinated cycloalkanes could be further functionalized. Despite the simplicity and preparative versatility of these products, *tert*-butyl (*cis*-4-fluorocyclohexyl) carbamate (**7f**) is the only member of the previously mentioned *cis*-fluorocyclohexyl-building blocks that is known in the literature. Multifluorinated arenes bearing additional functional groups such as a pinacol boronic ester (**7k**) or a TBS-protected alcohol (**7l** to **7o**) also underwent the hydrogenation reaction. We envision that these readily accessible all-*cis*-(multi)fluorinated building blocks will be useful for the fine-tuning of pharmaceuticals and agrochemicals. In a similar fashion, TBS-protected diol products (**7n** and **7o**) could be useful for the incorporation of fluorine into polymers.

A series of all-*cis*-(multi)fluorinated cyclohexane derivatives was also synthesized with this methodology. Three members of this family, namely all-*cis*-tetrafluorocyclohexanes (**8e** and **8f**) and all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane (**8h**), have previously been synthesized via nucleophilic substitution in 2, 8, and 12 steps, respectively (*7*–*9*). Our methodology gives access to these highly polar compounds, as well as to several previously unknown analogs, with complete diastereoselectivity in a single synthetic step. Convenient access to these all-*cis*-multifluorinated cycloalkanes in larger quantities will allow further investigation into their unique properties in the future. The highly diastereoselectively enriched all-*cis*-4,4′-difluoro-1,1′-bi(cyclohexane) (**8k**) was also isolated in high yields; however, it was found to contain a mixture of two stable conformers.

To further explore the limits of the reaction, the scope was extended to aliphatic heterocycles (**9a** to **9d**), including piperidine analog **9d**. In addition, a fluorinated estrone derivative could be hydrogenated smoothly with complete preservation of the easily reducible keto group (Fig. 4) (*31*).

Diastereoselectively fluorinated analogs to the prominent 1,3-dicylohexyl-imidazol-2-ylidene (ICy) ligand (precursor, **10**) and the commercial anticancer drug lomustine (**11**), as well as the mucolytic agent bromhexine (**12**), were synthesized from *tert*-butyl (*cis*-4-fluorocyclohexyl)carbamate (**7f**), which could be accessed as a single diastereomer following recrystallization. A deprotection of **7f** with trifluoroacetic acid and formation of the ammonium chloride, followed by imidazolium synthesis, gave fluorinated ICy·$HBF_4$ NHC-ligand precursor **10**. The electron-withdrawing fluorine could influence the catalytic activity of an NHC-metal complex. Furthermore, incorporation of the nuclear magnetic resonance (NMR)–active fluorine offers an opportunity for spectroscopic mechanistic investigations, analogous to the established use of $^{31}$P NMR analysis. The ammonium chloride could also be transferred to the lomustine analog **11** by condensation of the in situ–formed primary amine with an isocyanate and subsequent nitrosylation. After methylation, and analogous deprotection, the methylated crude ammonium chloride could be condensed with in situ–formed benzyl chloride, derived from commercial 2-amino-3,5-dibromobenzaldehyde, to yield the desired bromhexine analog **12**. In pharmaceuticals, the introduction of fluorine is recognized to often improve the bioavailability. Moreover, structural analogs to known liquid crystalline materials, in which our building blocks replace the previously used polar head groups, were prepared from all-*cis*-*tert*-butyldimethyl[(3,4,5-trifluorocyclohexyl)oxy]silane (**7l**). After recrystallization and deprotection, the diastereomerically pure alcohol could be converted via *N*,*N*′-dicyclohexylcarbodiimide (DCC)–mediated coupling to ester **13**, or via Mitsunobu etherification and subsequent Suzuki coupling with an in situ–formed alkylborane to ether **14**.

We undertook preliminary mechanistic experiments to understand the observed increase in selectivity for the hydrogenated product compared to the hydrodefluorinated side products when moving from polar solvents, such as methanol (1:9) or trifluoroethanol (1:2), to less polar solvents, such as dichloromethane (5:1) and eventually hexane (25:1) (table S2). Our results suggest that the observed defluorination in methanol and dichloromethane occurs through different mechanistic pathways (see the supplementary materials). The influence of different solvents on the catalyst, and consequently the mechanism of defluorination, are the subject of ongoing mechanistic studies.

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17. The trans isomer can be formed if a π-face exchange, e.g., via a catalyst-substrate dissociation and recoordination step, precedes the further hydrogenation of a highly reactive dearomatized intermediate (*18*).
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31. Several isomers were detected in the $^{19}$F NMR spectrum. The two major ones are believed to exhibit cis substitution at the A ring and result from the hydrogenation of the different faces of the molecule. The presented structure was confirmed by single-crystal x-ray analysis (fig. S3) and by multiplicity analysis of the signal in the $^{1}$H NMR spectrum.

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**SUPPLEMENTARY MATERIALS**

www.sciencemag.org/content/357/6354/908/suppl/DC1
Materials and Methods
Figs. S1 to S3
Tables S1 to S4
References (*32*–*45*)
NMR Spectra
Crystallography Reports

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# Hydrogenation of fluoroarenes: Direct access to all-*cis*-(multi)fluorinated cycloalkanes

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**Keeping all fluorines on the same side**

Carbon-fluorine bonds are highly polarized, and this effect is magnified when several of them reside on the same face of a saturated ring. However, most existing fluorination methods have difficulty consistently producing this all-cis mutual configuration. Wiesenfeldt *et al.* used a rhodium catalyst in nonpolar solvent to add hydrogens selectively to just one face of a wide variety of flat fluoroarene rings, pushing all fluorines toward the other face. The reaction also pushed fluorine toward the same face as nitrogen and oxygen in heterocycles such as indole and benzofuran.

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