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

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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. Only very few such motifs have been prepared, with their syntheses requiring 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 a plethora 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, pK_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 mono-fluorinated (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 pre-decorated 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 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 non-volatile *tert*-butyl (4-fluorophenoxy)dimethyl silane (**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 hydrodefluori-

nated cycloalkane **6a** as the major identified product (table S1). When employing 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 X. Zheng (**30**), these decomposition pathways were significantly diminished, though the hydrodefluorinated cycloalkane **6a** remained as the major product (52% yield, 1:2.1 ratio of hydrogenation vs hydrodefluorination, table S2, entry 3) under the described conditions. 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 mol% with conserved complete conversion 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 (13:1) was observed (table S4, entry 1).

Subsequently, the scope of the reaction was studied under the optimized conditions. The ready availability of fluorinated arenes, either from commercial suppliers or in a single step following literature methods, 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, dilution, substitution of molecular sieves with silica gel, and an increase of the catalyst loading to 0.5 or 1 mol% improved the yields. The observed *cis*-selectivity could be confirmed by NOE (Nuclear Overhauser Effect) 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**, **b**) and free (phenolic) alcohol (**7p**), pinacol boronic ester (**7c-e**), *tert*-butyloxycarbonyl (BOC)-protected amine (**7f**, **g**, **j**) 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 formerly 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-o**) 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**, **o**) 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**, **f** 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-d**) 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 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·HBF₄ NHC ligand precursor **10**. The electron-withdrawing fluorine could influence the catalytic activity of an NHC-metal complex. Furthermore, incorporation of the NMR-active fluorine offers an opportunity for spectroscopic mechanistic investigations, analogous to the established use of ³¹P 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 employed 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 occur via different mechanistic pathways (see SM). 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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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S3

Tables S1 to S4

References (32–45)

NMR Spectra

Crystallography Reports

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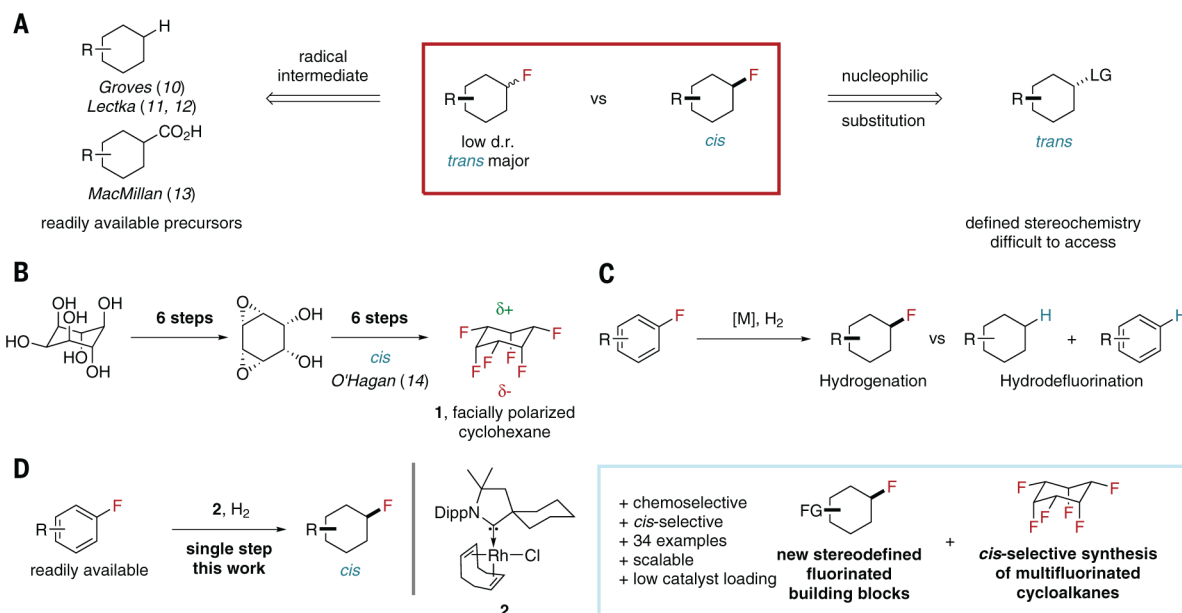


Fig. 1. *Cis*-selective synthesis of (multi)fluorinated cycloalkanes by arene hydrogenation. (A) Previously described methodologies for the preparation of fluorinated cycloalkanes. The *cis*-selective synthesis of fluorinated cycloalkanes requires diastereoselectively prefunctionalized substrates. (B) 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 development of a protocol for hydrogenation of fluorinated arenes to fluorinated cycloalkanes. (D) The method reported herein to access stereodefined (multi)fluorinated building blocks and highly polar multifluorinated cycloalkanes.

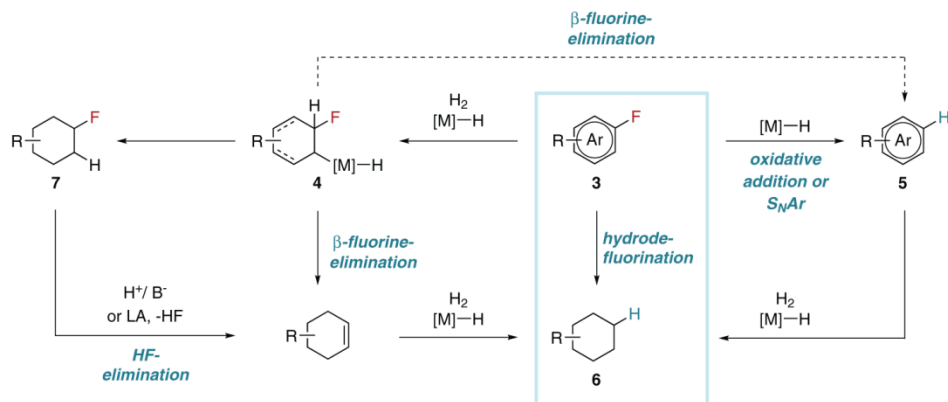
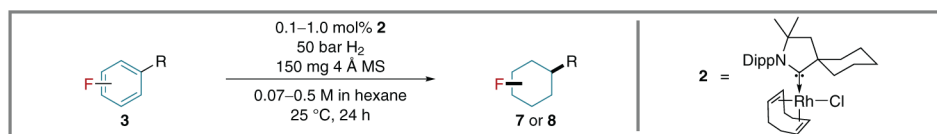
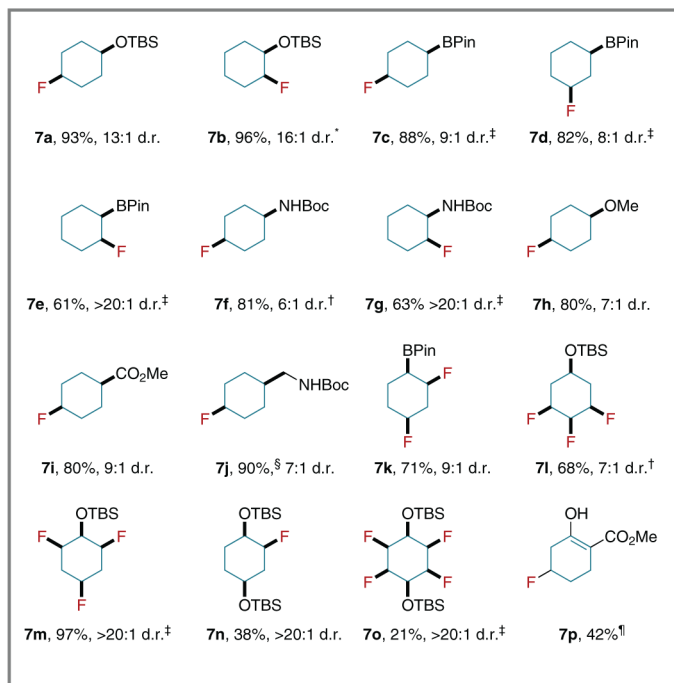
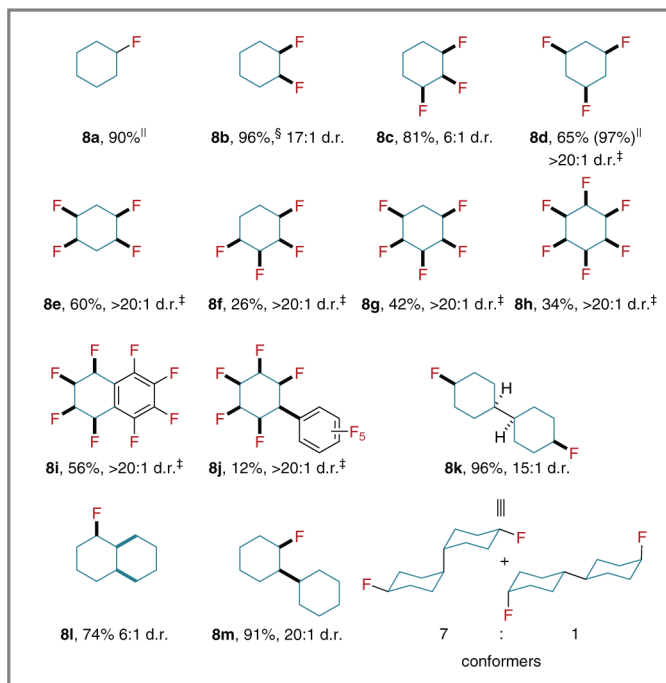


Fig. 2. Mechanistic pathways for the undesired hydrodefluorination side reaction. The hydrodefluorination reaction can take place via oxidative addition or nucleophilic aromatic substitution at the aryl halide **3**, via β -Fluorine elimination from alkyl-metal complex **4** or via Lewis acid (LA) or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

A



Fluorinated building blocks

All-*cis*-(multi)fluorinated cyclohexanes

B

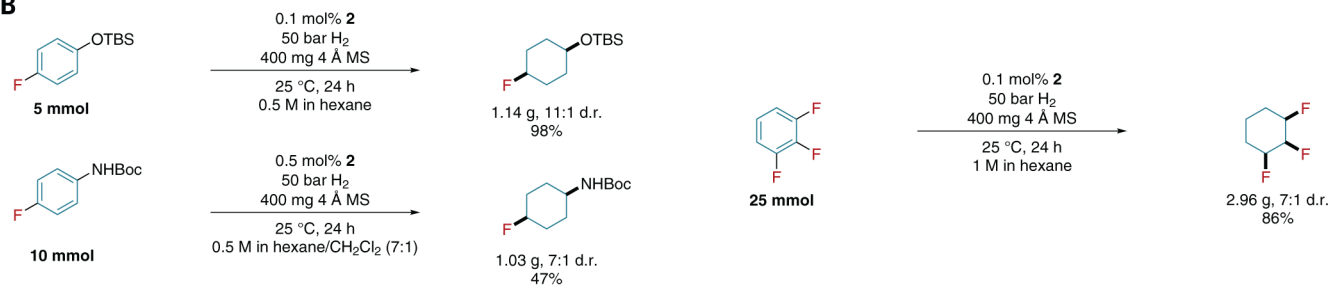


Fig. 3. Scope of the hydrogenation of fluorinated arenes. (A) Synthesis of fluorinated building blocks and all-*cis*-(multi)fluorinated cyclohexanes. Dipp, 2,6-diisopropylphenyl; BPin, pinacolboron; Me, methyl. All data are reported as isolated yields unless otherwise stated. For details concerning concentration and catalyst loading see SM. Diastereomeric ratio (d.r.) values of the major isomer relative to all other isomers were determined by ¹⁹F NMR or GC analysis prior to purification. *The major isomer could be isolated by standard column chromatography using pentane/diethylether = 99:1. †The major isomer could be isolated via recrystallization in pentane/diethyl ether. ‡The d.r. values of crude and isolated product were identical. §The yield was determined by ¹⁹F NMR spectroscopy with hexafluorobenzene as internal standard. ||The yield was determined via GC-FID with mesitylene as internal standard. ¶A 10:1 mixture of enol and alcohol was obtained. (B) Scale-up to gram scale. MS, molecular sieves.

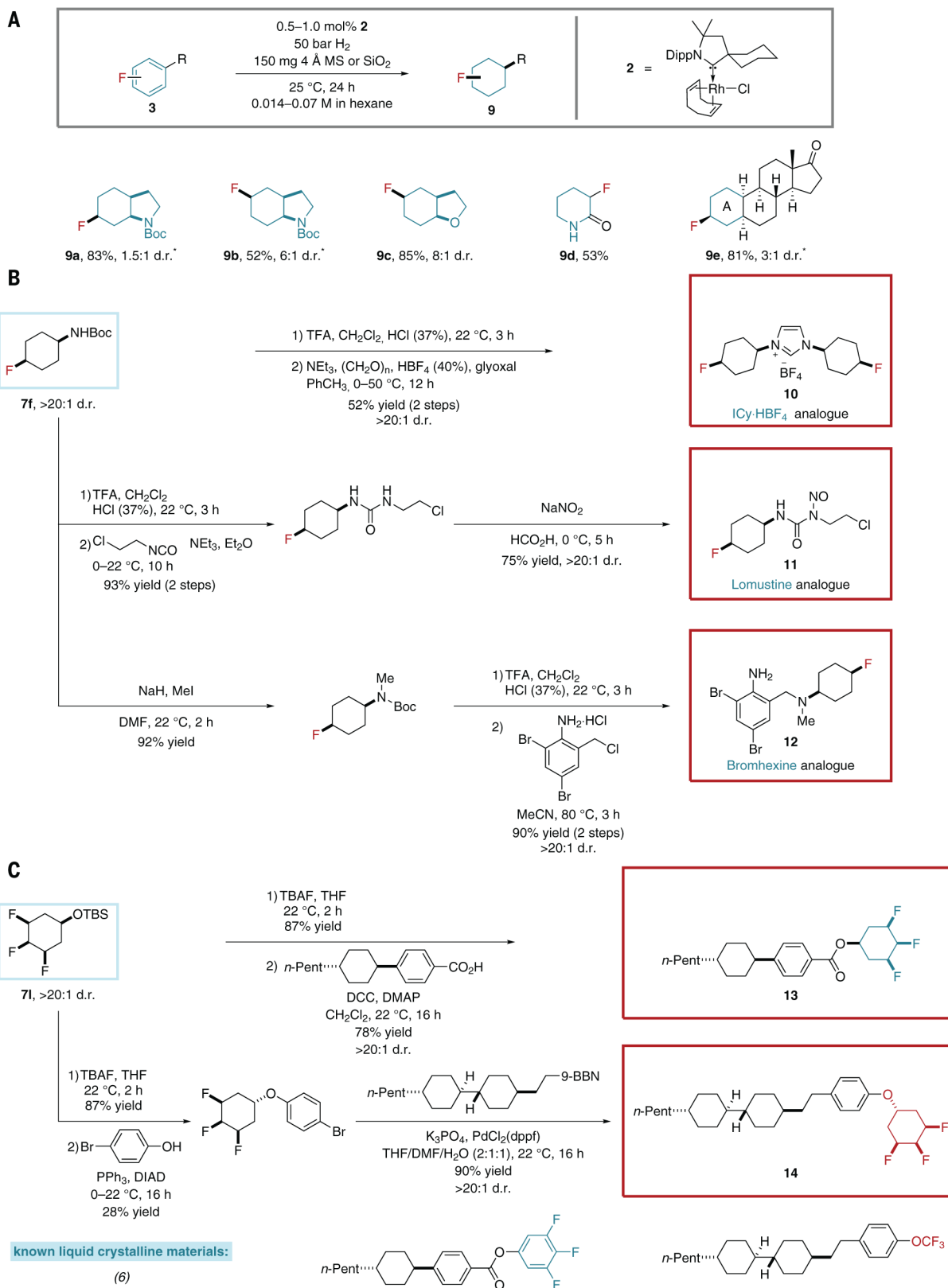


Fig. 4. Applications of the developed method for the hydrogenation of fluorinated arenes. (A) Synthesis of biologically relevant compounds. All data are reported as isolated yields unless otherwise stated. For details concerning concentration and catalyst loading see SM. d.r. values of the major isomer relative to all other isomers were determined by ^{19}F NMR or GC analysis prior to 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·HBF₄ derivative **10** and fluorinated analogs **11**, **12** of the commercial pharmaceuticals lomustine and bromhexine. ICy·HBF₄, 1,3-dicyclohexyl-imidazolium tetrafluoroborate. TFA, trifluoroacetic acid (C) Use of 3,4,5-trifluorinated TBS-protected cyclohexanol as building block for the synthesis of structural analogs **13**, **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.

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