Homochiral β-CF_3, -SCF_3 and -OCF_3 secondary alcohols: catalytic stereoconvergent synthesis, bioactivity and flexible crystals

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ABSTRACT: An optimized catalytic protocol for enantio- and diastereoselective reduction of racemic α-CF_3, α-SCF_3 and α-OCF_3 aryl ketones is described. The reaction involves a dynamic kinetic resolution (DKR) based on ruthenium catalyzed Noyori–Ikariya asymmetric transfer hydrogenation for simultaneous construction of two contiguous stereogenic centers. A range of previously inaccessible fluorinated secondary alcohols was prepared in excellent stereomeric purity (up to above 99.9% ee, up to above 99.9:0.1 dr) and in high isolated yield (up to 99%). The origin of DKR (exceptional stereoselectivity and racemization mechanism) is rationalized by density functional theory calculations. Pharmaceutically relevant further transformations of the products are demonstrated including incorporation into heat shock protein 90 inhibitor with in vitro anticancer activity. Moreover, needle-shaped crystals of representative stereopure products are mechanically responsive: either elastically or plastically flexible, opening the door to novel class of functional materials based on chiral molecular crystals.

Fluorine atom profoundly influences properties of bioactive molecules on multiple levels, which reflects in half of blockbuster drugs and one third of newly Food and Drug Administration-approved drugs being fluoro-pharmaceuticals.[1] Organofluorine chemistry is essentially man-made as only a dozen fluorinated natural products has been identified on Earth.[2] The consideration of new fluorinated chemotypes in drug development therefore inevitably follows the availability of the synthetic methods to access the relevant moieties. Outstanding progress was achieved in the preparation of a plethora of synthetic fluorine compounds.[3] A less developed area being highly challenging while very rewarding is the asymmetric synthesis of stereogenic fluorinated molecules.[4] In this context, we embarked on the asymmetric construction of chiral carbon atoms featuring a fluorinated motif with emphasis on the trifluoromethyl group C*–CF_3 and its heteroatomic homologues C*–SCF_3 and C*–OCF_3.

In particular, β-CF_3-substituted alcohols and amines are emerging motifs in medicinal chemistry (Figure 1). For example, **Compound I** as a mixture of stereomers exhibits antibacterial activity,[5] and racemic **Compound II** is an inhibitor of WD repeat-containing protein 5, which is over-expressed in some types of cancer.[6] Stereochemically defined trifluoromethylated omarigliptin exhibits better pharmacokinetic and pharmacodynamic profiles compared to the parent drug molecule, and is clinically evaluated as a super long-acting antidiabetic.[7]

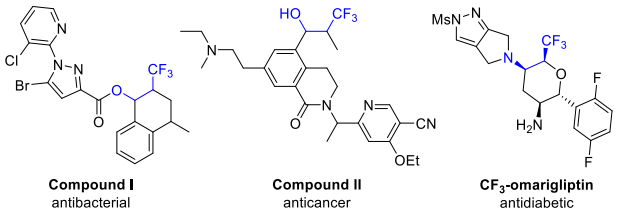
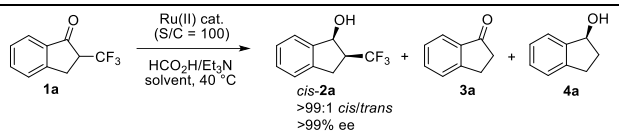


Figure 1. Bioactive compounds with β-CF_3 alcohol or amine motifs.

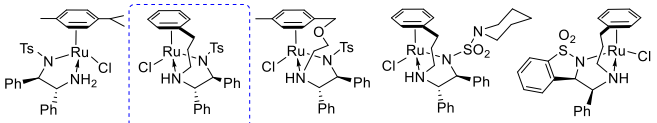
Given the potential of stereogenic β-CF_3-substituted alcohols and amines for medicinal chemistry applications, and eager to use them in our hit-to-lead endeavors, we were surprised to find no preceding literature reports on asymmetric synthesis of the model 2-CF_3-1-indanol **2a**, its amino analog nor their higher homologues. Non-asymmetric approaches towards such cyclic benzo-fused β-trifluoromethyl alcohols or amines received significant attention in the past five years, and are based on photoredox, electrochemical or transition metal-catalyzed oxy-trifluoromethylation[8] or amino-trifluoromethylation[9] of the corresponding olefins. There is only a handful of literature reports on stereoselective synthesis of β-trifluoromethyl secondary alcohol motif, based on diastereoselective hydrogenation of 2-CF_3 allylic alcohols[10] or $NaBH_4$ reduction of stereopure α-CF_3 ketone,[11] or diastereoselective aldol or Reformatsky reactions using a chiral auxiliary,[12] but to the best of our knowledge no catalytic enantioselective access to this class of molecules has ever been reported.

Dynamic kinetic resolution based on Noyori–Ikariya transfer hydrogenation (DKR-ATH) seemed like a fitting synthetic strategy for addressing the challenging simultaneous control of both chiral centers of the target compound class.[13] DKR-ATH is a robust method for stereoconvergent access to enantiomerically pure secondary alcohols with multiple contiguous chiral centers starting from the readily available racemic ketones,[14] including fluorinated examples.[15] Considering broad availability of the Noyori–Ikariya type ruthenium complexes (Table 1), and their relative stability towards air and moisture, this would offer not only conceptually new but also highly practical access to stereopure β-CF_3-substituted alcohols and their analogs.

Table 1. Catalyst and solvent screening for Ru(II)-catalyzed DKR-ATH of **1a**. [a]



	Ru(II) cat.	F/A	Cosolvent	Time	1a:2a:3a:4a
1	(*R,R*)-C1	3:2	PhCl	3 h	0:73:19:8
2	(*S,S*)-C2	3:2	PhCl	3 h	0:75:6:19
3	(*S,S*)-C3	3:2	PhCl	3 h	0:75:19:6
4	(*S,S*)-C4	3:2	PhCl	3 h	4:55:35:6
5	(3*R*,1′*S*)-C5	3:2	PhCl	3 h	0:75:0:25
6	(*S,S*)-C2	3:2	-	3 h 18 h	5:24:71:0 0:25:60:16
7	(*S,S*)-C2	5:2	-	3 h 18 h	21:74:5:0 5:75:20:0
8	(*S,S*)-C2	5:2	PhCl	3 h	0:99:0:1
9	(*S,S*)-C2	5:2	DMF	3 h	0:97:0:3
10	(*S,S*)-C2	5:2	dioxane	3 h	0:98:0:2
11	(*S,S*)-C2	5:2	1,2-DCE	3 h	0:98:0:2



*[a]DKR-ATH of **1a** (50 mg, 0.25 mmol) was carried out using Ru(II) cat. (1 mol%), HCO_2H/Et_3N (0.25 mL) and cosolvent (0.5 mL) at 40 °C. The product ratio was determined by NMR analysis of reaction mixture aliquots, and the ratio of **2a** stereomers (cis/trans >99:1; >99% ee in all cases) was determined after isolation by ^{19}F NMR and HPLC analysis using chiral stationary phase. F/A equals HCO_2H/Et_3N.*

A model racemic ketone 2-CF_3-1-indanone **1a** was prepared in one step by triflic acid mediated annulation of benzene with 2-CF_3-acrylic acid.[16] It was subjected to DKR-ATH using commonly used formic acid/triethylamine 3:2 mixture as a source of hydrogen and chlorobenzene as a co-solvent, and five representative Noyori–Ikariya type Ru(II) catalysts were tested (Table 1, runs 1–5). **C1** is the archetypical Noyori catalyst,[17] and the rest are the so-called tethered catalysts, which proved to be superior for the reduction of structurally complex ketones.[18] Chronologically, **C2** was developed by Wills et al.,[19] followed by oxy-tethered catalyst **C3** by Ikariya et al.,[20] sulfamoyl-DPEN-cored **C4**,[21] and benzosultam-cored **C5** by Mohar et al.[22] The reactions using 1 mol% of catalysts **C1**–**C5** all reached >95% conversion within 3 h (Table 1, entries 1–5). Delightfully, all the catalysts yielded the product **2a** with excellent stereoselectivity[23] (*cis*/*trans* > 99:1 and >99% ee) as determined by ^{19}F NMR and chiral HPLC, respectively. The absolute configuration of **2a** being (*S,S*) was determined by single-crystal X-ray diffraction (SCXRD) analysis of a product from run with (*S,S*)-**C2.** Disappointedly, significant amount of by-product, indanone **3a** and/or indanol **4a** (up to 41% total), was also detected in the reaction mixtures, indicating that an unexpected detrifluoromethylation took place during DKR-ATH. The catalysts performed differently regarding side product formation and **C2** was chosen for further studies because of its wide availability and favorable reaction kinetics (Table S1). Control experiments indicated that trifluoromethyl moiety is eliminated from the ketone **1a** rather than the product *cis*-**2a**, that it is not a ruthenium-catalyzed process, and involves formation of Et_3N/HF adduct (see SI). To mitigate fluoride elimination, the use of HCO_2H/Et_3N in 5:2 molar ratio with the most efficient (*S,S*)-**C2** was attempted. Performing the DKR-ATH in neat HCO_2H/Et_3N 3:2 or 5:2 (Table 1, entries 6 and 7) indeed revealed that by increasing the relative amount of formic acid, detrifluoromethylation level dramatically decreases while excellent stereoselectivities are still obtained. Further solvent screening revealed that the use of any cosolvent together with HCO_2H/Et_3N 5:2 was beneficial for the reaction yield as less than 3% of the side products were observed in chlorobenzene, DMF, 1,4-dioxane or 1,2-dichloroethane (Table 1, entries 8–11). The first one was deemed optimal with only 1 mol% of 1-indanol accompanying the target product **2a**.

Computational modeling was further performed to collaborate high level of stereoselectivities and realize the possible mechanism of **1a**-racemization being the core process of DKR. The reaction between **1a** and the active form of precatalyst (*S,S*)-**C2** was studied by M06-2X-D3/SMD(chlorobenzene)/def2-qzvp//def2-svp method. Four diastereomeric transition states are possible (Figure 2). For the R_{Ru},λ-catalyst structural arrangement,[24] observed in the solid-state of (*S,S*)-**C2**,[19] computations predict the ratio of the reaction rates leading to each stereoisomer as ~ 10^9 (*S,S*) : 1800 (*R,R*) : 400 (*S,R*) : 1 (*R, S*).[25] This transforms into the *cis*/*trans* ratio of 2.5 × 10^6 and the enantioselectivity of 99.9996% for the *cis* product.[26] The discrepancy between experimentally and theoretically predicted % ee is likely due to the additional mechanisms of the generation of chirality.[27a] However, the calculation reproduces and points to high-level of stereodiscrimination. Two spatial regions of the catalyst simultaneously control the final stereoselectivity: the region of the tethered η^6-arene ligand and the region of the SO_2 moiety.[27] Dynamic equilibrium and interplay of attraction and repulsion in each region through various noncovalent interactions lead to stabilization/destabilization of the corresponding stereoselectivity determining transition state. The presence of α-CF_3 functionality is crucial for exceptionally high stereoselectivity. As a comparison, DKR-ATH of 2-methyl-1-indanone using **C3** yielded the corresponding alcohol with a lower *cis*-selectivity (*cis*/*trans* = 98:2, 98% ee),[14d] whereas DKR-ATH of 2-acetamido-1-indanone (hydrogen bond donor α-substituent) using **C5** was even *trans*-selective (*cis*/*trans* = 9:91).[22c]

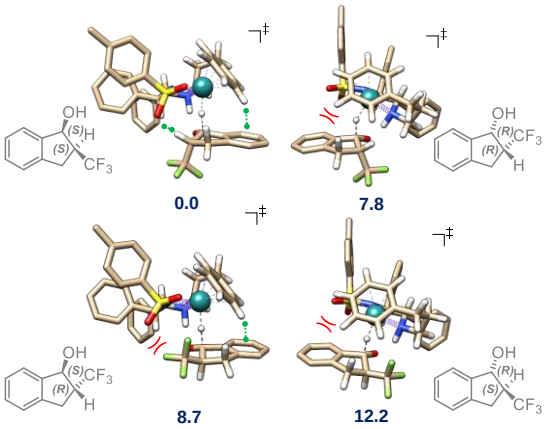
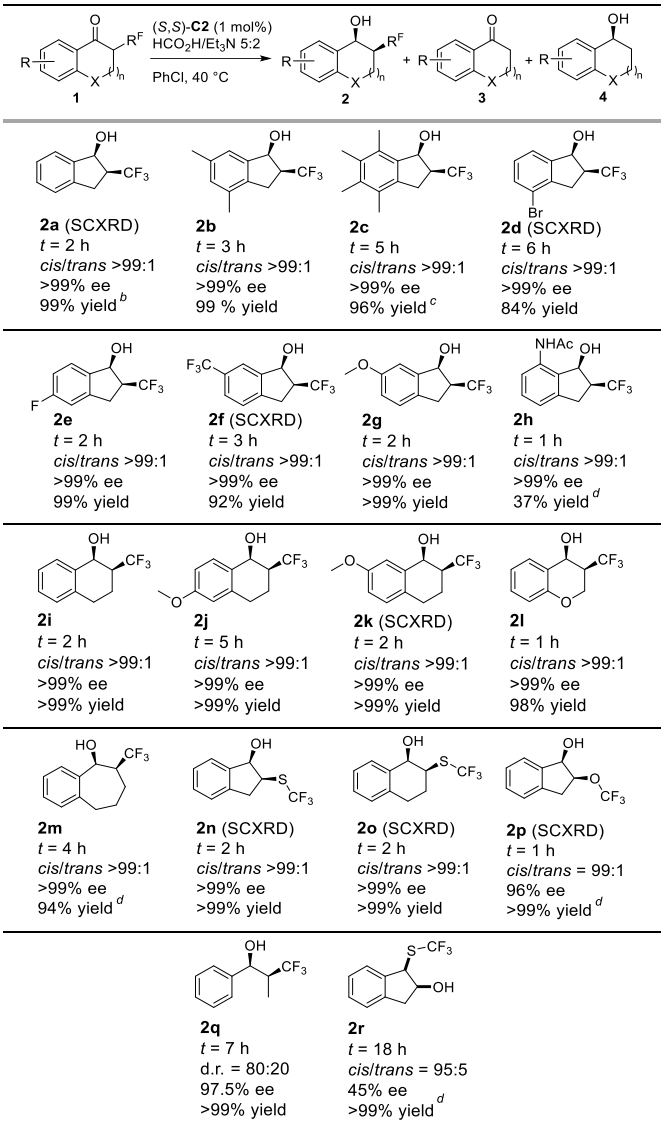


Figure 2. Optimized transition state geometries en route to the four stereomeric products **2a** taking place on R_{Ru},λ-structural arrangement of (*S,S*)-**C2** catalyst active form (see text). The relative free energies are given in kcal·mol^{-1}. Some attractive and repulsive interactions are highlighted by green and red symbols, respectively. Non-crytical H-atoms are omitted for clarity.

A 3:2 mixture of HCO_2H/Et_3N is a typical choice for DKR with Noyori–Ikariya catalysts,[28] whereas 5:2 mixture is usually used for ATH of simple ketones and imines.[29] Although generally not explained, Et_3N or Et_3N/HCO_2H mixture might serve as a catalyst for the DKR-enabling rapid in situ racemization of the α-substituted ketones, consistent with the 3:2 choice.[30] Indeed, computations point that direct non-catalyzed epimerization of **1a** is energetically prohibitive (Figure S1, top). On the contrary, **1a**-racemization catalyzed by Et_3N ("enolate-anion" pathway) and concerted Et_3N/HCO_2H process ("enol" pathway) is energetically plausible with the preference to the former (Figure S1, middle and bottom).

With optimal conditions in hand, we turned our attention to DKR-ATH of various α-trifluoromethyl substituted benzo-fused cyclic ketones **1b**–**1m** (Table 2). These were prepared as described for **1a**,[16] via radical desulfur-fragmentation and reconstruction of enol triflates,[31] and radical trifluoromethylation of the corresponding olefin[32] or enol acetate,[33] respectively (see SI). They were all converted to the corresponding stereopure alcohols **2** using the optimized reaction conditions (1 mol% of **C2** in HCO_2H/Et_3N 5:2 and chlorobenzene at 40 °C) with reaction times to reach full conversion between 1 and 6 h. Their (*S,S*)-absolute configuration was assigned based on SCXRD analysis of indan-cored **2a**, **2d**, and **2f**, and tetralin-cored **2k**. The values of *cis*/*trans* ratio and enantiomeric excess (ee) in Table 2 are given as ">99" not to oversell the results but the other three possible stereoisomers were in fact present below the limit of detection for most cases,[34] and the ee of the benzosuberol **2m** was determined to be 99.2%. The tetramethyl substituted indanone **1c** required a higher catalyst loading (5 mol%) to reach full conversion. The reaction yield was affected by detrifluoromethylaton which was generally more expressed during DKR-ATH of indan-cored ketones comparing to their six-membered analogs. 7-Acetamido analog **2h** was formed in only 37% NMR yield with fast decomposition coupled to fast reduction in HCO_2H/Et_3N 3:2, which still outperformed the 5:2 ratio with 25% NMR yield and full conversion only after 18 h. The decomposition products **3** and **4** were nevertheless readily removable by flash chromatography. The tetralin derivatives **1i**–**1k** were devoid of detrifluoromethylation and the corresponding stereopure products **2** were isolated directly after extraction.

Table 2. Scope of the DKR-ATH.[a]



*[a]Unless otherwise specified, the reactions were carried out using (S,S)-**C2** (1 mol%) in HCO_2H/Et_3N 5:2 and chlorobenzene at 40 °C. [b]NMR yield based on integration of **2** relative to **1**, **3** and **4**. Isolated yields after extraction and optional column chromatography were 1–15% lower. [c]5 mol% of (S,S)-C2 used. [d]HCO_2H/Et_3N 3:2 used.*

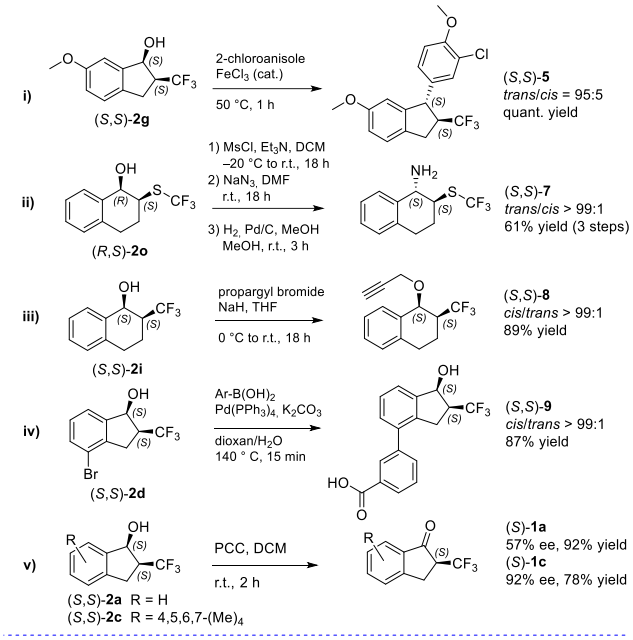
The method was then extended to the synthesis of stereopure 2-SCF_3 and 2-OCF_3 carbinols **2n**–**2p**, where no side reactions were observed in either HCO_2H/Et_3N ratio. Stereoselectivities for both trifluoromethylthioethers **2n** and **2o** were determined to be *cis*/*trans* = 99.9:0.1 and 99.8% ee by ^{19}F NMR and chiral GC, respectively, which gives an estimate of the detection limit. The starting 2-SCF_3 ketones **1n** and **1o** were prepared by means of Billard's reagent under acidic conditions from the corresponding bare ketones.[35] 2-Trifluoromethoxy-1-indanol **2p** was obtained with somewhat lower stereopurity (*cis*/*trans* = 99:1, 96% ee) with the same sense of enantioselectivity (SCXRD analysis); its ketone precursor **1p** was accessed via silver mediated

oxidative trifluoromethylation of 2-hydroxy-1-indanone.[36] Pushing it further, the linear analog **1q** was successfully reduced within 7 h using the same standard conditions delivering the product **2q** as a 3:1 mixture of *anti* and *syn* diastereomer with 97.4% and 90.4% ee, respectively. The reduction of 1-SCF_3-2-indanone **1r** to the corresponding alcohol **2r** was unfortunately not highly enantioselective (45% ee) although a 95:5 *cis*/*trans* ratio was achieved.

From medicinal chemistry point of view, the stereopure products **2** represent hitherto synthetically inaccessible building blocks featuring intrinsic non-planarity, potential for specific interactions with the protein binding sites, and several growth vectors.[37] Selected stereopure products **2** were thus prepared on 1 mmol scale, and relevant further synthetic transformations were demonstrated (Scheme 1). **2g** was transformed to *trans*-configured **5** via iron-catalyzed diastereoselective Friedel-Crafts benzylation of 2-chloroanisole.[38] This hydroxy-substituted 1-arylindan motif is characteristic of resveratrol dimer natural products.[39] **2o** was converted to azide **6** (*trans*/*cis* = 92:8) via nucleophilic substitution (S_N2) of the corresponding mesylate ester. It was further reduced to the amine **7** which was isolated as a single stereomer after chromatography. **2i** was *O*-alkylated to get stereopure clickable building block **8**. **2d** was converted to biaryl **9** via Suzuki coupling reaction, illustrating that unprotected 2-CF_3-carbinols are compatible with palladium catalysis. And finally, stereopure **2a** and **2c** were reoxidized using pyridinium chlorochromate to get enantioenriched **1a** and **1c** with 57% and 92% ee, respectively. To showcase direct applicability of the developed synthetic methods in a medicinal chemistry setting, alkyne **8** was incorporated in **10** that represents a novel structural class of heat shock protein 90 (Hsp90) inhibitors. Compound **10** was designed using molecular dynamics-derived pharmacophore model (Figure S2).[40] It was shown to inhibit Hsp90 in luciferase refolding assay and display antiproliferative activity in SkBr3 breast cancer cell line (IC_{50} = 51 ± 2 μM).

Moreover, we were pleased to find out that some of the novel enantiopure compounds prepared by our method crystallize as needle-shaped crystals which are elastically (**2a**, **2d**, **2p, 4d**) or plastically flexible (**2o**) (Figure 3, and SI). Mechanically responsive molecular crystals are being recognized as an unexplored platform for applications ranging from adaptive systems and actuators to biocompatible devices and all-organic soft robots.[41] The crystal structures of **2a**, **2d**, **2o**, **2p** and **4d** exhibit some of the same features that were identified in other crystals with elastic[42] or plastic deformation behavior.[43] In particular, a short crystal axis (~5 Å), anisotropic packing, corrugated crystal packing, and a prominent intermolecular interaction being highly directional (i.e., hydrogen-bonded chains parallel to the short *a*-crystallographic axis in structures with $P2_12_12_1$ symmetry and parallel to the short *b*-crystallographic axis in compounds crystallizing in $P2_1$ space group) with much weaker interactions in perpendicular directions. The slippage of molecular layers lined with trifluoromethyl groups has been established to be the mechanism of the observed plastic deformation.[43c] In our case, chiral OH and indan scaffold clearly also contribute to mechanic responsiveness as detrifluoromethylated bromoindanol **4d** was also to some degree elastically flexible.[44] For plastically flexible **2o**, two polymorphs (RT $P2_1$, and 100 K $P2_12_12_1$) were identified.

Scheme 1. Further synthetic transformations of stereopure DKR-ATH products **2**.



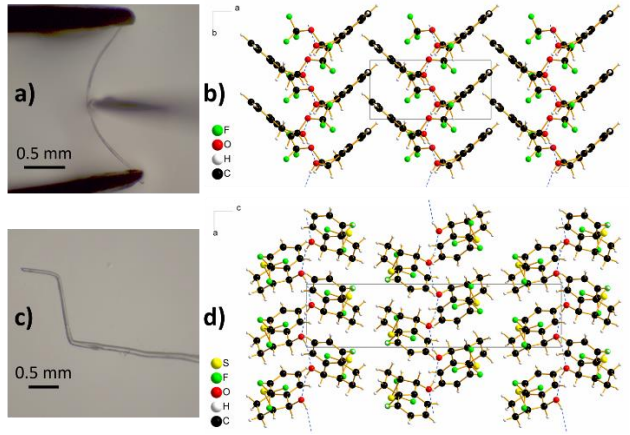


Figure 3. *a)* Three-point bending experiment with elastically flexible needle-shaped crystal of **2p**. *b)* Crystal packing of **2p**, view along *c* axis. *c)* Bent plastically flexible crystal of **2o**. *d)* Crystal packing of **2o**, view along *b* axis.

In conclusion, we have successfully developed a highly efficient dynamic kinetic resolution strategy for the Noyori-Ikariya asymmetric transfer hydrogenation of racemic α-CF_3, α-SCF_3 and α-OCF_3 aryl ketones with excellent stereoselectivities (up to above 99.9% ee, up to above 99.9:0.1 dr). The origin of DKR (in situ epimerization of the ketone substrate, and stereoselectivity) were investigated by DFT calculations. Applicability in the field of medicinal chemistry was demonstrated by several further transformations of the stereopure products including incorporation into in vitro anti-cancer compound. A new class of homochiral small organic molecules, which crystalize as mechanically responsive single-component crystals, was identified. The presented synthetic methodology opens the door to new chiral fluorinated bioactive compounds, and to material science applications based on adaptive chiral molecular crystals.

ASSOCIATED CONTENT

Supporting Information.
The supporting information is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures, chiral HPLC and GC chromatograms, NMR spectra of the prepared compounds, cell-based assays, computational and SCXRD details, photos of mechanically responsive behavior (PDF).
Movie 2d (AVI)
Movie 4d (AVI)
Accession codes.
CCDC 2151748–2151755 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Author Contributions

A. E. C., D. C., P. A. D., T. T. and M. L. conceived and planned the experiments. D. C. carried out the synthesis of fluorinated ketones, A. E. C. and M. S. carried out asymmetric reductions and product characterization, P. A. D. carried out computational mechanistic studies, T. T. and J. D. designed Hsp90 inhibitor, J. D. carried out transformations in Scheme 1, Ž. Z. performed cell-based assays, M. L. performed and interpreted SCXRD analysis and discovered flexibility of the crystals. A. E. C. took the lead in writing the manuscript with input from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(26) ee (%)= 100 × [exp(−Δ$G_{298K°}$/*RT*) − 1]/[exp(−Δ$G_{298K°}$/*RT*) + 1], where Δ$G_{298K°}$ is the free-energy difference in kcal·mol^{-1} between the transition states leading to *S*- and *R*-products, *RT* = 0.59 kcal·mol^{-1}

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