Diastereoselective Synthesis of Perfluoroalkylmethyl-Substituted 1,2,3,4-Tetrahydroquinolines Derivatives through 1-Iodo-1,3-bis(acetoxy) Synthons

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Diastereoselective Synthesis of Perfluoroalkylmethyl-Substituted 1,2,3,4-Tetrahydroquinolines Derivatives through 1-Iodo-1,3-Bis(acetoxy) Synthons

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Dedication:
In memory of our colleague Prof. Patrick Calas (1943–2021), whose carreer has been devoted to both organic- and electro-chemistry of organofluorine compounds.

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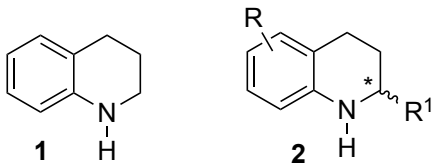
Abstract:
Novel 2-perfluoroalkylmethyl,4-arylamino substituted tetrahydroquinolines (THQ) were expeditiously synthesized from perfluoroalkyl iodides R_F–I and monosubstituted anilines. First, radical *bis*-addition of vinylacetate on R_F–I afforded *gem*-iodoacetoxy derivatives (newly characterized by NMR and MS) being actually masked/activated aldol synthons. Their reaction in 1:4 ratio with arylamines afforded title THQ under mild conditions in good yields (60–95%) and diastereoselectivities (65:35 – 95:5 *cis*/*trans* isomer ratio); *m*-substituted anilines regiospecifically lead to 7-substituted THQ. Mechanistic investigation suggested the THQ formation to proceed through Michael then imine addition of two aniline units on an R_F-substituted crotonaldehyde intermediate; then through the cyclization of the resulting *bis*(arylamino/imino) intermediate through electrophillic aromatic substitution. Various R_F (C_6, C_2, C_4) and arylamine substitutions (*p*-,*o*-,*m*- alkyl, alkoxyl, halogen…) were thus exemplified.

Introduction

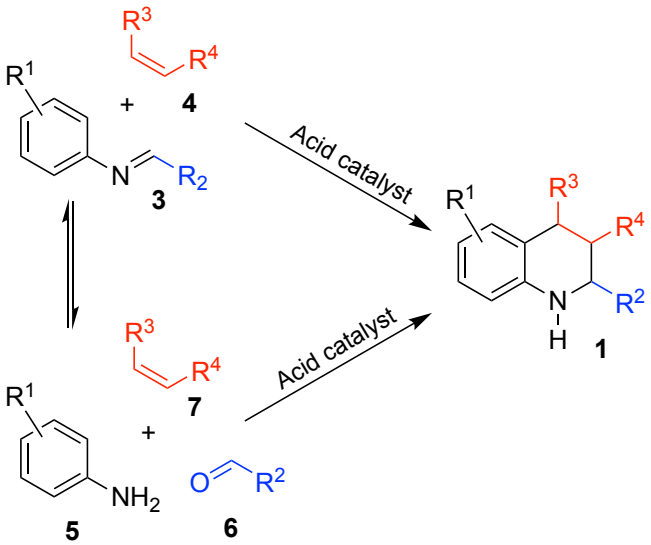
1,2,3,4-tetrahydroquinolines (THQ, **1**) belonging to a class of benzo-fused nitrogen heterocycles are privileged scaffolds[1–3] present in many bioactive alkaloids,[3f-g] coordination ligands,[3a-c] and functional materials.[3] Numerous natural and synthetic analogs of tetrahydroquinolines (**1**) or chiral tetrahydroquinolines (**2**) display a wide range of biological activities and were used as (chemo)therapeutic agents including antiviral,[4] antiparasitic,[5] antimicrobial,[6] antitumor,[7] anti-inflammatory[8] etc., besides acting as ligands of G-coupled protein receptors[9] and nuclear receptors such as androgen receptor modulators,[10] glucocorticoid receptor,[11] and retinoid receptor.[12]

Particularly, chiral 2-substituted 1,2,3,4-tetrahydroquinolines derivatives (**2**) are the most valuable.[1f,3c,d,13] and exhibit interesting biochemical activities.[3,14] For example, 2-methyl-tetrahydroquinoline (**2**, R = H, R^1 = CH_3, Scheme 1) is naturally occurring in human brain, and its derivatives (**2**, R = OH, R^1 = alkyl) have been discussed as affine ligands for CNS receptors[14] possessing sedative and antinociceptive activities[14c,d] (Scheme 1).



Scheme 1. Structure of 1,2,3,4-tetrahydroquinoline (THQ) and of its neuro-active derivatives.

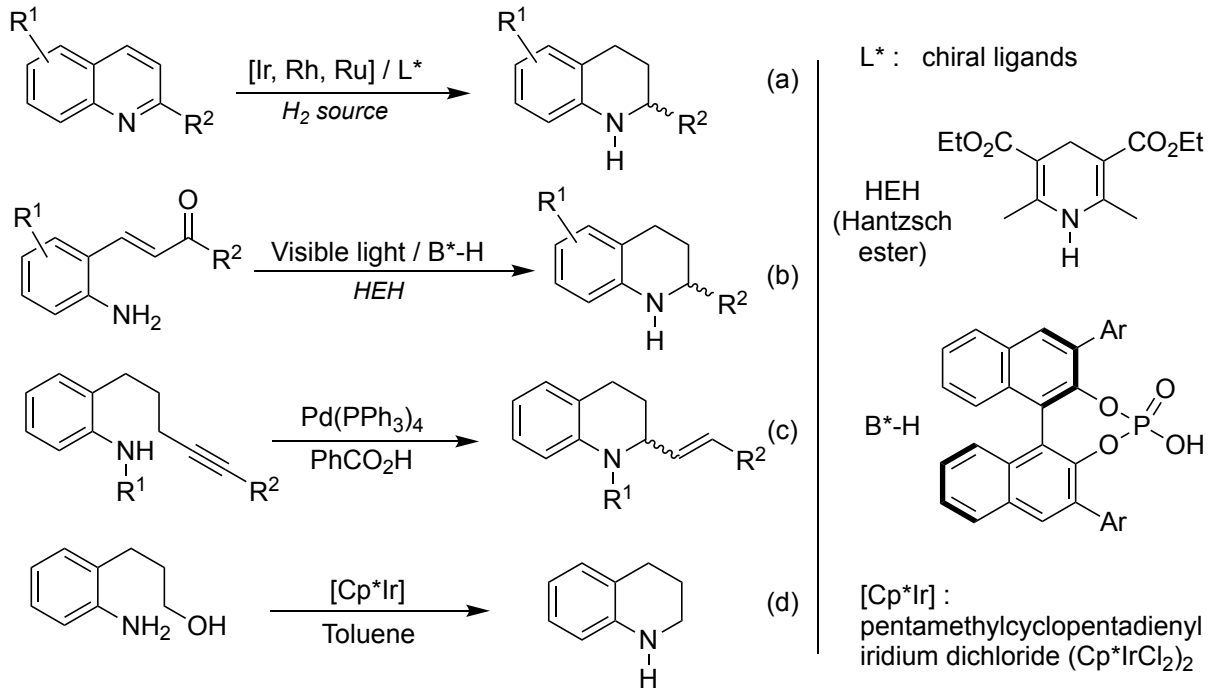
The development of new efficient and convenient synthetic approaches toward these heterocyclic molecules remains an active research area.[1–3] One of these approaches is the Povarov reaction,[15] an hetero-Diels-Alder variant in which a functionalized *N*-aryl aldimine (**3**), as azadiene, and an activated olefin (**4**), as dienophile, are coupled (Scheme 2). This reaction and its multicomponent version[16] (*in situ* condensation of anilines (**5**), aldehydes (**6**), and electron-rich alkenes (**7**) using acid catalysts under mild conditions) can provide tetrahydroquinoline derivatives (**1**) with several degrees of structural diversity (Scheme 2).



Scheme 2. Two- and three-component Povarov reactions.

Besides, other approaches for efficient synthetic methods for tetrahydroquinolines have gained considerable research interest,[17–18] and numerous catalytic methods have been established.[1–3,17–21] The

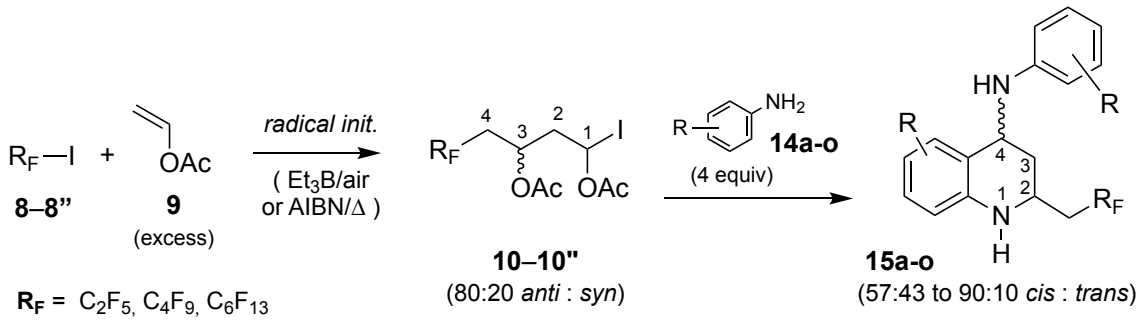
most used methods proceed through hydrogenation of quinolines (reaction **a** on Scheme 3),[19] photocyclization asymmetric transfer hydrogenation (reaction **b,** Scheme 3),[20] and organo- or metal-catalyzed cascade reactions (examples in reactions **c** and **d**, Scheme 3).[21] Generally, although affording good to excellent yields, these methods require the use of expensive ligands and toxic metals.



Scheme 3. Examples of catalytic syntheses of 1,2,3,4-THQ.[17–21]

However, in the wide spectrum of described synthetic routes,[1–3,15–21] versatile methods toward trifluoroethyl/perfluoroalkylmethyl derivatives from simple starting materials, are limited compared to trifluoromethylated/perfluoroalkylated compounds[22] — in spite of the increasing interest of trifluoromethyl and perfluoroalkyl-containing heterocycles,[23–25] for which considerable attention has been focused to developing new synthetic methodologies during the past years since these compounds are now widely recognized as important organic compounds showing interesting biological activities for their potential use in medicinal, agricultural and scientific fields.[23,24] Indeed, the introduction of a trifluoromethyl or a perfluoroalkyl group into molecules could potentially enhance a range of positive effects such as steric, electrostatic interaction, acidity, lipophilicity.[23]

In this paper, we report an original synthetic pathway toward perfluoroalkylmethyl substituted THQ in two steps, starting from perfluoroalkyl iodide and substituted aniline substrates. First, we prepared and characterized new 1-iodo-1,3-*bis*(acetoxy)4-perfluoroalkylbutane compounds **10–10"** (Scheme 4; noteworthy, since the *gem*-iodoacetoxy group is a masked aldehyde, **10–10"** are also masked aldols, as such deserving of further investigation however beyond the scope of the present report). Then we investigated the reactivity of this new tri-functional *gem*-iodoacetoxy derivative with substituted anilines, leading to the stereoselective synthesis of new substituted 4-arylamino-2-perfluoroalkylmethyl-1,2,3,4-tetrahydroquinolines **15a-o**.



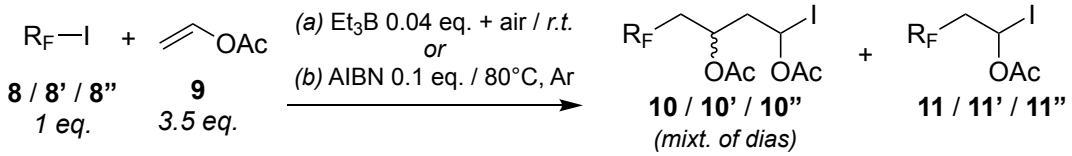
Scheme 4. Synthetic pathway from iodoperfluoroalkane toward THQ.

The numbering scheme for the investigated examples in compound series **10**, **14** and **15**, is the following: (i) in compounds **15** the letter **a**–**o** denotes the aryl substituent inherited from the aniline substrate **14**; (ii) the appended **'** or **"** in series **8**, **10** and **15** denotes the perfluoroalkyl chain being R_F = C_2F_5 or C_4F_9 respectively instead of (most exemplified) $R_F = C_6F_{13}$. For instance, **15a** is derived from **14a** and **10** ($R_F = C_6F_{13}$); **15n'** is derived from **14n** and **10'** ($R_F = C_2F_5$). In general and mechanistic discussions (unless stating precise examples) compound numbers **8**, **10**, **15** and **16** stand for the whole series regardless of the R_F length.

Results and Discussion

I. Synthesis of 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds 10–10"

In continuity with our previous investigations on the synthesis and reactivity of *gem*-iodoacetoxy derivatives,[26–28] here we report that 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds **10–10''** can be formed upon radical reaction of perfluoroalkyl iodide (R_F–I) **8–8''** with an excess of vinyl acetate **9** in good to excellent yields (88–95%), accompanied by the formation of minor amounts of 1-acetoxy-2-perfluoroalkyl-1-iodoethane **11** in 5–12% yield (Scheme 5). Either Et_3B/air (at room temperature) or AIBN (upon heating to 80°C) is efficient as the radical initiator, allowing the reaction to proceed with similar reaction times and yields, however with better **10** vs. **11** selectivity upon Et_3B/air initiation.



Cpd	R_F
8	C_6F_{13}
8'	C_2F_5
8"	C_4F_9

R_F	C_6F_{13}		R_F	C_2F_5	R_F	C_4F_9	
cond	*(a)*	*(b)*	*cond*	*(a)*	*cond*	*(a)*	*(b)*
10	95%	88%	**10'**	88%	**10"**	95%	90%
11	5%	12%	**11'**	12%	**11"**	5%	10%

Scheme 5. Conditions, yields and chemoselectivities of the radical reaction of perfluoroalkyl iodides **8–8"** with 3.5 equivalents of vinyl acetate **9**.

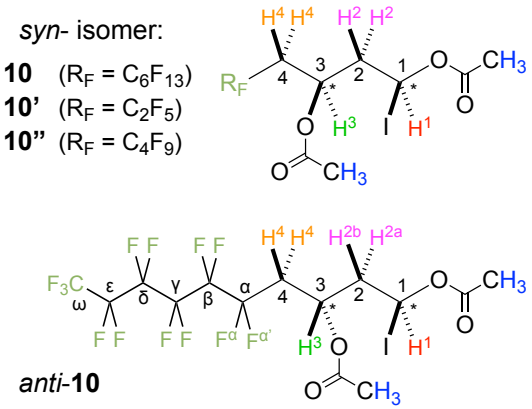
Thorough screening of reactants stoichiometries and reaction conditions (upon ^{19}F NMR monitoring), allowed to identify optimized conditions giving best overall yields: namely 1 equivalent of perfluoroalkyl iodides **8–8"**, 3.5 equivalents of vinyl acetate **9** and either 0.04 equivalent of triethylborane Et_3B (plus air) or 0.1 equivalent of AIBN under inert atmosphere (bubbling Ar), strirring

either at room temperature (Et_3B), or heating below 80°C (AIBN). Reactions were typically completed within 30–90 minutes. At the end of the reaction assessed by TLC and ^{19}F NMR monitoring, column chromatography over silica gel eluted with petroleum ether/ethyl acetate: 95/5 v/v, allows to separate the resulting products **10–10"** and **11–11"** and to isolate the desired 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds **10–10"** (mixtures of *syn*/*anti* isomers) as yellow brownish oils, therefore fully characterized. Compounds **10–10"** are rather stable at room temperature; nevertheless they are better stored at –20°C in a freezer — previously prepared *gem*-iodoacetoxy compounds **11–11"** did not show significant decomposition after several months at –20°C, as monitored by TLC and NMR spectroscopy (the brief description of **11–11"** in our previous works,[26] has been completed here with full NMR, MS and elemental analysis characterisation; see experimental section and Supporting Information).

It was found most convenient to proceed in bulk reactants without solvent,[26,28,29] since highly electrophilic perfluoroalkyl radicals readily abstract hydrogen atoms from usual organic solvents.[30] Finally, a better *bis*-/mono-adduct (**10–10"**/**11–11"**) chemoselectivity was achieved upon radical initiation by Et_3B/air rather than with AIBN, possibly because the former does not requires heating.

II. Structure determination of 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds 10–10"

The structures of the 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds **10–10"** were confirmed without ambiguity by ^1H and ^{19}F NMR spectroscopy and supported by mass spectrometry data. Compounds **10–10''** having two asymmetric centers, exist as two diastereomers, here named according to the relative positions of 1-iodo and 3-acetoxy substituents on Scheme 6 — therefore *syn*-**10–10''** is (1*R*,3*R*/1*S*,3*S*) while *anti*-**10–10''** is (1*R*,3*S*/1*S*,3*R*).



Scheme 6. Structure of *syn* (1*R*,3*R*/1*S*,3*S*, top) and *anti* (1*R*,3*S*/1*S*,3*R*, bottom) diastereomer configurations of compounds **10–10''** (*syn*/*anti* naming refers to 1-iodo vs. 3-acetoxy related positions). *Anti* configuration exemplified on C_6F_{13} derivative *anti*-**10** to explicit atom numbering of R_F chain and H^{2a}/H^{2b} relative configurations (clearly identified only for *anti*- stereomer). Atom label numbers and colors follow $^1H/^{19}F$ NMR assignments, *cf.* Figures 1–2, Tables 1–2 and Supporting Information.

II-1. NMR description of *syn*-/*anti*-1,3-diacetoxy-1-iodo-4-perfluorohexylbutane 10

Typical of such characterization, is the example of spectroscopic analysis of 1,3-diacetoxy-1-iodo-4-perfluorohexylbutane **10** that will be described in detail. The mass spectrum of **10** showed the molecular ion ($M{\cdot}H^+$) peak at m/z: 619, which was consistent with the expected compound structure. In the ^1H NMR spectra of *syn*- and *anti*-**10** mixtures, the two diastereomers can be distinguished clearly

since the methyl resonances of acetyl groups of appear as four distinct singlets between δ_H 2–2.2 ppm. Then one pair of diastereotopic protons H^4 resonate between δ_H 2.2–2.5 ppm and showed unresolved mutliplets and a second pair of diastereotopic protons H^2 showed unresolved signals δ_H 2.5–2.9 ppm. Furthermore, isomeric H^3 protons signals of *anti*- and *syn*- isomers are well separated in all the compounds. H^3 protons of *syn*- isomers is deshielded and appears at δ_H 5.6 ppm in comparison to that of *anti*-isomers that appears at δ_H 5.4 ppm. Finally, H^1 protons appeared as two overlapped signals at δ_H 6.7–6.8 ppm, however the signal of proton H^1 of the major *anti*-isomer appeared to be a doublet of doublets ($^3J_{H1\text{-}H2}$ = 10.7 and 2.8 Hz) (Figure 1 and Table 1).

In the ^{19}F NMR spectrum of *syn*- and *anti*-**10** mixtures, two overlapped pairs of symmetrically disposed doublets of doublets of doublets (*ddd*) seen between –115 ppm and –112 ppm readily recognized as two AB-systems. The two *ddd* at δ_F –114.4 and δ_F –112.6 ppm part of the first AB-system are attributed to α-CF_2 groups of *anti*-**10** and show a geminal ^{19}F,^{19}F coupling, causing a doublet splitting with $^2J_{F\alpha\text{-}F\alpha'}$ = 282 Hz, and is split further into a doublet of doublets by coupling with vicinal nonequivalent H^4 protons ($^3J_{F\alpha/\alpha'\text{-}H4}$ = 22.5 and 11.2 Hz). However, the two doublet of doublets at –113.9 and –112.8 ppm part of a second AB-system are attributed to α-CF_2 groups of *syn*-**10** and show a geminal ^{19}F-^{19}F coupling, causing a doublet splitting with $^2J_{F\alpha\text{-}F\alpha'}$ = 225.8 Hz, and is split further into a doublet of doublets ($^3J_{F\alpha/\alpha'\text{-}H4}$ = 20.5 and 11 Hz) (Table 1)**.** In the cases of **10–10"** fluorine atoms F_α and $F_{\alpha'}$ of α-CF_2 groups are magnetically non-equivalent, which could occur when the group is adjacent to a chiral center or when a restricted rotation around nearby C-C bonds occurs.[31]

The signals seen at –121.9, –123, –123.7 and –126.4 ppm are attributed to β-CF_2, γ-CF_2, δ-CF_2 and ε-CF_2 respectively, while the multiplet at –81.1 ppm is assigned to the ω-CF_3 end-group (Table 1).

Diastereomer ratios of **10–10''** were determined by ^1H and ^{19}F NMR on basis of integration of H^3 and functional α-CF_2 resonances of major and minor products in the crude isomer mixtures, showing 72:28 to 80:20 *anti*-/*syn*- ratios, the latter increasing with the perfluoroalkyl chain length from C_2F_5 to C_6F_{13}, thus showing that the *anti*-/*syn*- diastereoselectivity significantly depends on the steric hindrance of the R_F chain.

Table 1. ^1H (300 MHz) and ^{19}F (282.4 MHz) NMR ($CDCl_3$) structural analysis of 1,3-diacetoxy-1-iodo-4-perfluorohexylbutane **10**, mixture 20:80 of *syn*-/*anti*- diastereomers: resonance attributions, chemical shift, multiplicity and coupling assessments.

Attrib.	**δ_H** or **δ_F** / ppm		**Mult.** [a]	**Coupling constants** / Hz	
	syn-**10**	*anti*-**10**		*syn*-**10**	*anti*-**10**
H^1		6.7	*dd*		$^3J_{H1\text{-}H2}$: 10.7 & 2.8
H^1	6.8		*m*	n/d	
2 H^2	2.5–2.9		*m*	n/d	
H^3	5.7	5.4	*m*	n/d	
2 H^4	2.2–2.5		*m*	n/d	
CH_3	2.2	2.1	*s*	n/a	
CH'_3	2.05	2.0	*s*	n/a	
F^α	–113.9	–114.4	2*ddd* [b]	$^2J_{F\alpha\text{-}F\alpha'}$: 225.8	$^2J_{F\alpha\text{-}F\alpha'}$: 282
$F^{\alpha'}$	–112.8	–112.6	2*ddd* [b]	$^3J_{F\alpha/\alpha'\text{-}H4}$: 20.5 & 11	$^3J_{F\alpha/\alpha'\text{-}H4}$: 22.5 & 11.2
2 F^β	–121.9		*m*	n/d	
2 F^γ	–123.0		*m*	n/d	
2 F^δ	–123.7		*m*	n/d	
2 F^ε	–126.4		*m*	n/d	
3 F^ω	–81.1		*m*	n/d	

[a] Resonance description: *s* = singlet; *dd* = doublet of doublets; *m* = multiplet; [b] Part of AB-system.

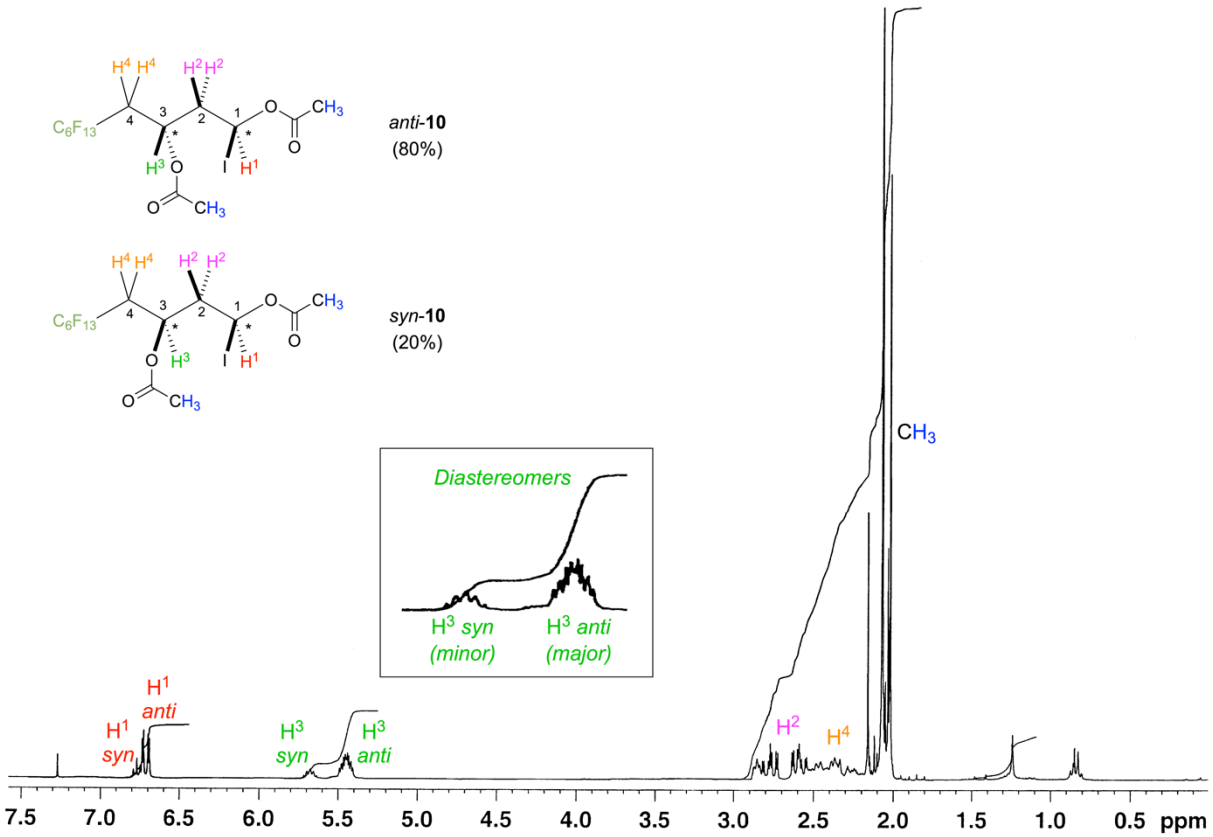


Figure 1. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 1,3-diacetoxy-1-iodo-4-perfluorohexylbutane **10**, mixture 20:80 of *syn*-/*anti*- diastereomers. Inset: zoom on the 5.3–5.8 ppm region (H^3 resonances).

II-2. Stereochemistry determination of the diastereomer *anti*-10

The major *anti*- diastereomer was further separated from the minor *syn*- isomer by flash-chromatography of the isomer mixture with petroleum ether/ethyl acetate (98:2 v/v), then fully characterized by MS and NMR spectrometry.

It is known[32–33] that the determination of relative configuration of diastereomers of such acyclic 1,3-difunctional derivatives based on ^{1}H NMR analyses is challenging due to the overlap of proton signals in their spectra.[32] Some alternative methods were described,[33] for example, in the case of 1,3-diols diastereomers, the assignment of the relative stereochemistry of the 1,3-*syn* and 1,3-*anti* diols was confirmed using derivatization with formation of rigid cyclic structures, such as acetonides. Thus, acetonide ^{13}C NMR chemical shifts could be correlated to their syn/anti configuration.[33] Very few works describe diastereomeric *syn*-/*anti*- discrimination of conformationally flexible molecules using NMR coupling constants.[34] Nevertheless, examples of stereochemical assignments of some acyclic fluorinated diastereomers using ^{1}H NMR coupling constants have been reported.[35] *Gem*-iodoacetoxy chiral compounds bearing bulky acetoxy substituents,[29] have been described as sterically hindered from rotation along their C-C bonds resulting in unequal population of their possible rotational conformations,[29] what led to clear splitting patterns and sharp ^{1}H NMR signals.[29a] In the case of compounds **10** having two chiral centers separated by a methylene group (-CH_2-), well resolved proton NMR signals are obtained.

The starting point for the stereochemical assignment of *anti*-**10** was the observation of a doublet of doublets for proton H^1 showing an *anti*-coupling constant with H^{2b} proton ($^{3}J_{(anti-)H1-H2b}$ = 10.7 Hz), followed by a *syn*-coupling constant with H^{2a} ($^{3}J_{(syn-)H1-H2a}$ = 2.8 Hz) (Figure 2 and Table 2)**.** It is generally

assumed that in rigid molecular conformations two vicinal protons with *syn* disposition exhibit smaller $^3J_{H\text{-}H}$ couplings constants than for the *anti*-relationship.[36]

H^{2a} and H^{2b} protons show two clear doublets of doublets of doublets (*ddd*) at δ_H 2.55 ppm and δ_H 2.7 ppm, formed first by a *geminal*-coupling between these methylene non-equivalent protons ($^2J_{H2a\text{-}H2b}$ = 14.6 Hz) followed by two vicinal couplings of each of H^{2a} and H^{2b} protons with H^1 and H^3 protons ($^3J_{H2a\text{-}H3}$ = 10.2 Hz, $^3J_{H2a\text{-}H1}$ = 2.8 Hz and $^3J_{H2b\text{-}H1}$ = 10.7 Hz, $^3J_{H2b\text{-}H3}$ = 3 Hz) (Figure 2 and Table 2).

However, H^3 proton forming a broad multiplet at δ_H 5.4ppm, its stereochemistry could be deduced form the two lasting coupling constants in the *ddd*-signals of H^{2a} and H^{2b} protons. The magnitudes of these couplings were consistent with proton H^3 showing an *anti*-coupling constant with H^{2a} proton ($^3J_{H3\text{-}H2a}$ = 10.2 Hz), followed by a *syn*-coupling constant with H^{2b} ($^3J_{H3\text{-}H2b}$ = 3 Hz) (Figure 2 and Table 2).

This was confirmed in the ^{1}H-^{1}H COSY chart where clear cross peaks are observed between resonances of both H^{2a} and H^{2b} with those of both H^1 and H^3; what is consistent with a configuration where H^3 occupies an *anti*-position relatively to H^1 (otherwise H^2 resonances would have been doublets of triplets), hence the naming *anti*-**10** of this diastereomer (Figure 2 and Table 2).

Table 2. ^{1}H (300 MHz) and ^{19}F (282.4 MHz) NMR ($CDCl_3$ solution) structural analysis of isolated diastereomer *anti*-**10**: resonance attributions, chemical shift, multiplicity and coupling assessments. Configuration assignments were based on coupling constants.

Attrib.	**δ_H** or **δ_F** / ppm	**Mult.** [a]	**Coupling constants** / Hz
H^1	6.7	*dd*	$^3J_{H1\text{-}H2b}$: 10.7; $^3J_{H1\text{-}H2a}$: 2.8
H^{2a}	2.55	*ddd*	$^2J_{H2a\text{-}H2b}$: 14.6; $^3J_{H2a\text{-}H3}$: 10.2; $^3JH_{2a\text{-}H1}$: 2.8
H^{2b}	2.7	*ddd*	$^2J_{H2b\text{-}H2a}$: 14.6; $^3J_{H2b\text{-}H1}$: 10.7; $^3JH_{2b\text{-}H3}$: 3.0
H^3	5.4	*m*	n/d
2 H^4	2.2–2.5	*m*	n/d
CH_3	2.1	*s*	n/a
CH'_3	2.0	*s*	n/a
F^{α}	–114.5	*ddd* [b]	(for both F^{α} and $F^{\alpha'}$: $^2J_{F\alpha\text{-}F\alpha'}$: 282;
$F^{\alpha'}$	–112.5	*ddd* [b]	$^3J_{(trans\text{-})F\alpha/\alpha'\text{-}H4}$: 22.5; $^3J_{(cis\text{-})F\alpha/\alpha'\text{-}H4}$: 11.2)
2 F^{β}	–122.0	*m*	n/d
2 F^{γ}	–123.1	*m*	n/d
2 F^{δ}	–123.8	*m*	n/d
2 F^{ε}	–126.5	*m*	n/d
3 F^{ω}	–81.2	*m*	n/d

[a] Resonance description: *s* = singlet; *dd* = doublet of doublets; *m* = multiplet; [b] Part of AB-system.

Moreover, the protons of the two acetyl groups resonate as two distinct singlets at δ_H 2.0 and 2.1 ppm. However, the two non-equivalent protons H^4 appear as complex multiplets between δ_H 2.2–2.5 ppm, due to vicinal couplings with both H^3 and non-equivalent fluorine atoms F_{α} and $F_{\alpha'}$ of the α-CF_2 group, as confirmed in ^{19}F NMR spectra where the latter give rise to an AB system, whereas F_{α} and $F_{\alpha'}$ atoms forming the A- and B-parts, appear each as a doublet of doublets of doublets (*ddd*) at δ_F –112.5 ppm and δ_F –114.5 ppm. Both signals show *geminal* F_{α}-$F_{\alpha'}$ coupling, causing a doublet splitting with $^2J_{F\alpha\text{-}F\alpha'}$ = 282 Hz, then F-H coupling with the two vicinal H^4 protons split further into doublets of doublets $^3J_{(anti\text{-})F\alpha/\alpha'\text{-}H4}$ = 22.5 and $^3J_{(syn\text{-})F\alpha/\alpha'\text{-}H4}$ = 11.2 Hz.

The signals of β-CF_2, γ-CF_2, δ-CF_2 and ε-CF_2 groups appear as unresolved multiplets at δ_F –122, –123.1, –123.8 and –126.5 ppm respectively, finally the -CF_3 end-group signal resonate at δ_F –81.2 ppm (Table 2).

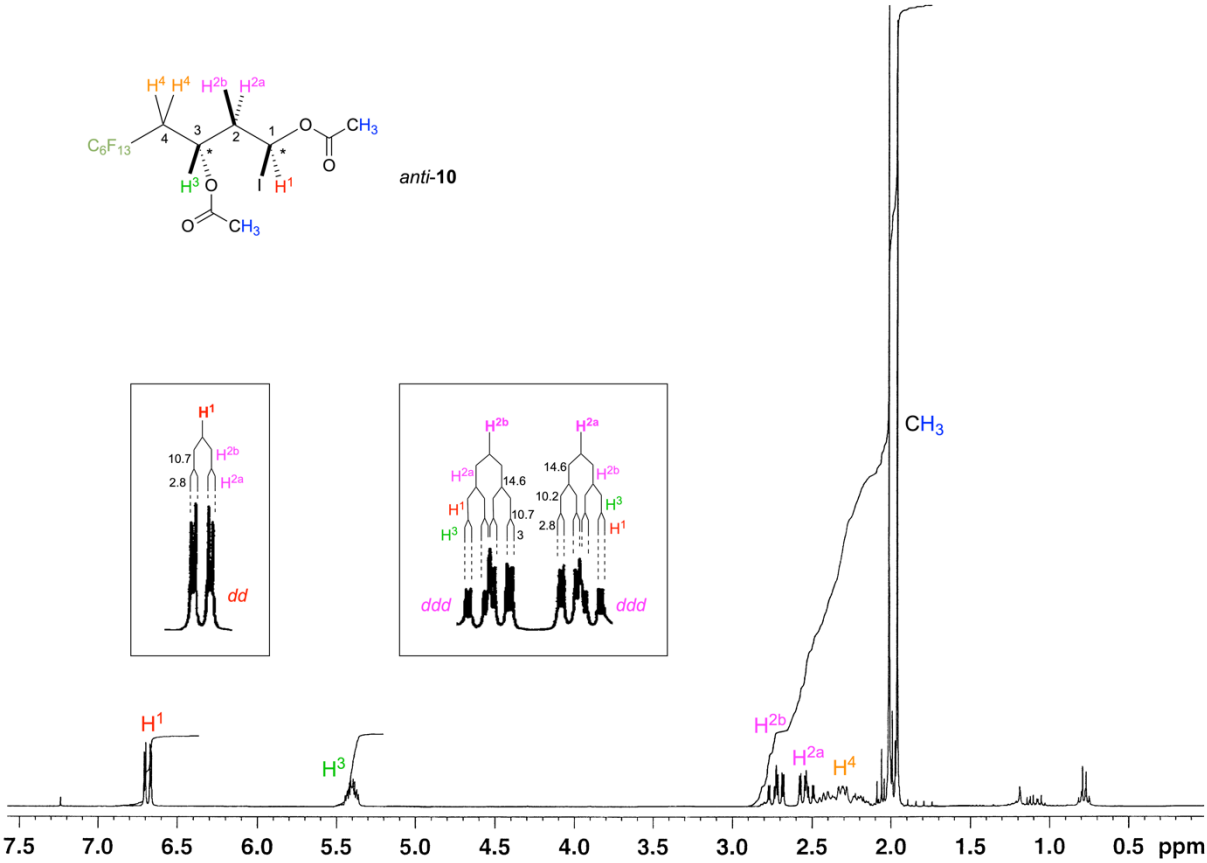
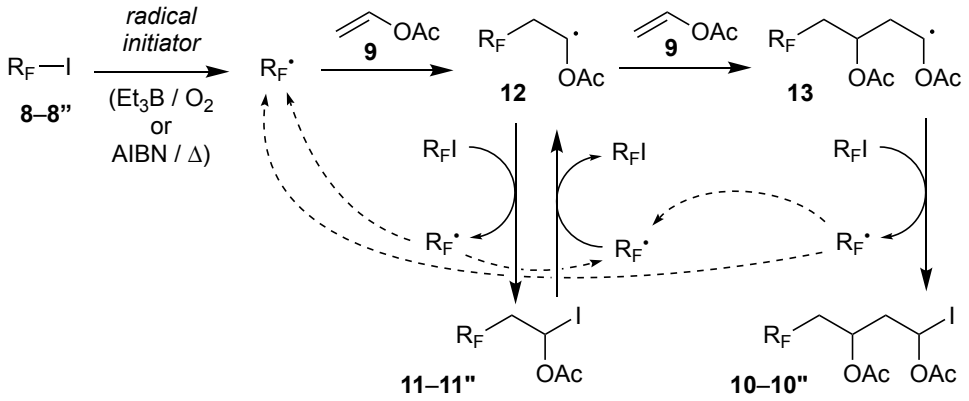


Figure 2. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of isolated diastereomer *anti*-**10**. Insets: zooms on 6.6–6.8 and 2.5–2.8 ppm regions (resp. H^1 and H^{2ab} resonances).

III. Mechanism of formation of 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane compounds 10–10”

Most likely, the formation of vinylacetate adducts proceeds through the well-known atom transfer radical chain reaction[29–30] (Scheme 7), starting with the formation of perfluoroalkyl radicals $R_F^{\bullet}$ from R_FI (after initiation by Et_3B/air or AIBN), followed by the addition of $R_F^{\bullet}$ on **9** to form a radical monoadduct **12**. The latter **12** can either further react on another **9** to form *bis*-adduct radical **13** (irreversible reaction), or reversibly abstract an iodine atom from another R_FI to generate a new $R_F^{\bullet}$ radical and the iodo monoadduct **11–11”** (present as minor products at the end of the reaction[28a]). Accordingly, the radical **13** will eventually react with an R_FI to generate a new $R_F^{\bullet}$ radical and the iodo-*bis*-adduct **10–10”**.

While oligomerization of **9** might extend beyond the *bis*-adduct (until exhaustion of monomer **9**), neither *tris*- nor further adducts were detected (the formation of which thus being likely limited to minute amounts). Both the good overall yield, *bis*-/mono-adduct ratio and the absence of oligomers, suggest the propagation step (addition of **9** on a radical) to be a bit slower than the initiation step, while anyway quite slower than the (reversible) iodine transfer process.[30]



Scheme 7. Mechanism of formation of mono- and *bis*-adducts **11–11"** and **10–10"** from $R_F I$ and vinylacetate through (iodine) atom-transfer radical chain reaction.

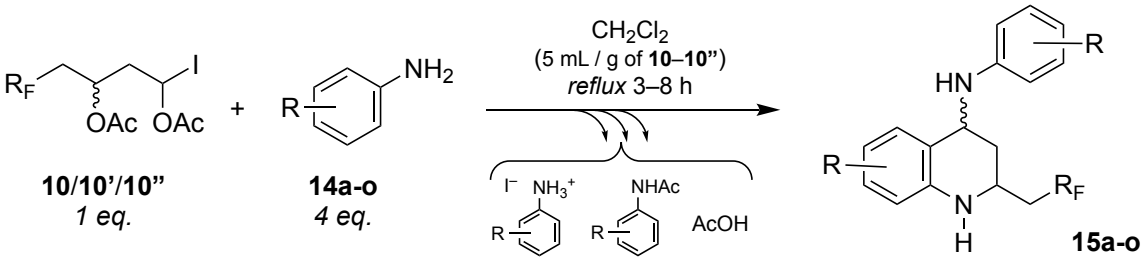
IV. Synthesis of 2-(perfluoroalkylmethyl)-1,2,3,4-tetrahydro-*N*-(R-phenyl)quinolin-4-amine 15a-o

In a next step (Scheme 8), the reaction of 1,3-diacetoxy-4-perfluoroalkyl-1-iodobutane **10–10"** with various anilines **14a-o**, lead to the formation of 2-(perfluoroalkylmethyl)-1,2,3,4-tetrahydro-*N*-(R-phenyl)quinolin-4-amine (THQ) **15a-o** in fair to excellent yields (60–95 %), while moderate to good stereoselectivity occurred in favor of *cis* diastereomers (Table 3) according to ^{1}H and ^{19}F NMR analysis of products.

In light of our previous works on the reactivity of *gem*-iodoacetoxy derivatives **11–11"** with arylamines **14**,[27–28] the reaction of 1,3-diacetoxy-4-perfluorohexyl-1-iodobutane **10** with aniline **14** was first carried out according to our previously reported reaction conditions,[28b] namely a 3/1 stoichiometric ratio of aniline **14a** vs. **10** in refluxing anhydrous dichloroethane (83°C), resulting in poor yield (28%) of THQ **15a** while the reactant **10** readily underwent degradation. Further screening of conditions showed that a 4:1 stoichiometric ratio of aniline **14a** vs. **10** in refluxing dichloromethane greatly increased the yields of THQ **15** up to ca. 95%.

A typical procedure for this reaction begins with dissolving *bis*(acetoxy)iodobutane **10** and 4 equivalents of aniline **14a** in anhydrous dichloromethane (5 mL/1g of **10**) then heating to reflux, the reactions thus being typically completed within 3–8 hours. A straightforward work-up through (i) filtering off the excess anilinium salts that had precipitated at the end of the reaction, then (ii) alkaline extraction, followed by (iii) flash-chromatography, allowed to isolate the THQ **15a** (clear yellowish oil) as a mixture of *cis*- (major) and *trans*- (minor) diastereomers, the NMR structure determination of which is detailed in the next section.

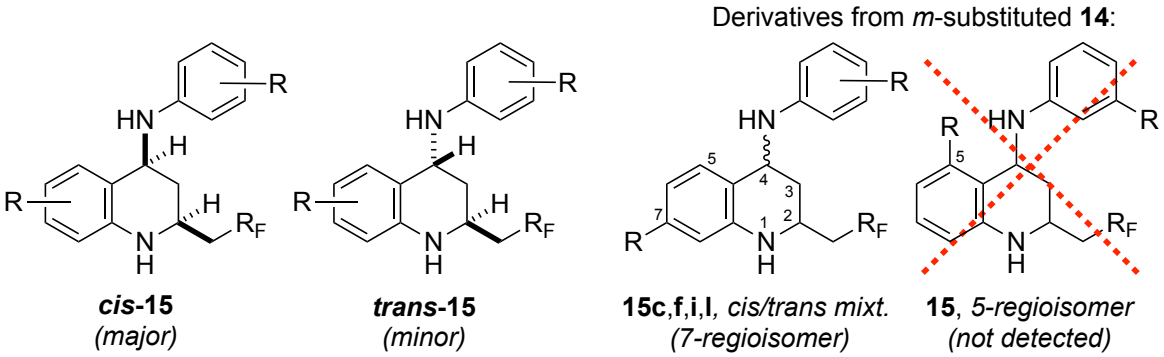
Such optimized reaction conditions were applied to study the scope of 2,4-disubstituted THQ **15a-o** synthesis, the results of which are listed in Table 3. In all cases the products **15** were isolated as mixtures of cis/trans diastereomer which were fully characterized by ^{1}H and ^{19}F NMR, MS and elemental analysis (cis/trans diastereomeric ratios were assessed after integration of characteristic resonances). In some examples (**15a, 15b, 15d, 15j** and **15n**) the major *cis*- diastereomer could further be isolated by column chromatography from the isomer mixture, what helped the structural determination of the series; unfortunately in spite of many attempts, no crystals suitable for X-ray analysis of **15a-o** could be obtained.



Cpd	R_F
10	C_6F_{13}
10’	C_2F_5
10”	C_4F_9

14	**R**	**14**	**R**
a	H	**i**	*m*-Cl
b	*o*-Me	**j**	*p*-Cl
c	*m*-Me	**k**	*o*-OMe
d	*p*-Me	**l**	*m*-OMe
e	*o*-Et	**m**	*p*-OMe
f	*m*-Et	**n**	*o*-OEt
g	*p*-Et	**o**	*p*-NO_2
h	*o*-Cl		

15	**R**	**R_F**	**15**	**R**	**R_F**	**15**	**R**	**R_F**
a	H	C_6F_{13}	**f**	*m*-Et	C_6F_{13}	**l**	*m*-OMe	C_6F_{13}
a’	H	C_2F_5	**g**	*p*-Et	C_6F_{13}	**m**	*p*-OMe	C_6F_{13}
a”	H	C_4F_9	**g’**	*p*-Et	C_2F_5	**m'**	*p*-OMe	C_2F_5
b	*o*-Me	C_6F_{13}	**h**	*o*-Cl	C_6F_{13}	**n**	*o*-OEt	C_6F_{13}
c	*m*-Me	C_6F_{13}	**i**	*m*-Cl	C_6F_{13}	**n'**	*o*-OEt	C_2F_5
d	*p*-Me	C_6F_{13}	**j**	*p*-Cl	C_6F_{13}	**o**	*p*-NO_2	C_6F_{13}
d’	*p*-Me	C_2F_5	**j'**	*p*-Cl	C_2F_5			
e	*o*-Et	C_6F_{13}	**k**	*o*-OMe	C_6F_{13}			



Scheme 8. Synthesis (optimized stoichiometries) of substituted THQ **15a-o** (formed as mixtures of cis/trans isomers) from **10**–**10”** and anilines **14a**-**o**. Bottom: structures of THQ *cis*/*trans* diastereomers and regioisomers in the *m*-aniline series (5- regioisomers were not detected).

Unsubstituted aniline **14a** gave the corresponding 1,2,3,4-THQ **15a-a”** in excellent yields (entries 1−3). Alkyl- and alkoxy-substituted arylamines **14b-g** and **14k-n** afforded the corresponding products **15b−15g’** and **15k−15n’** in good to excellent yields (entries 4−11, 16–21). Noteworthy, electron-withdrawing groups such as chloro and nitro on the arylamine ring (**14h-j** and **14o**) were well tolerated in the reaction, the corresponding substituted THQ **15h−15j’** and **15o** being formed in moderate yields while longer reaction times were required (entries 12−15, 22). Also noteworthy, *ortho*-substituted anilines **14b**,**e**,**h**,**k**,**n** unsurprisingly lead to lower yields (entries 4,8,12,16,20–21) likely because of higher steric hindrance against cyclization.

Unlike *ortho*- or *para*- subsitutions where only one THQ regiosiomer is possible, the reaction of *meta*-substituted anilines **14c**,**f**,**i**,**l** (entries 5, 9, 13, 17) could theoretically produce two regioisomers, namely 5- and 7-substituted THQ (Scheme 8). Actually the only detected regioisomer was the 7-substituted THQ **15c**,**f**,**i**,**l** – although rather entangled, aromatic range ^{1}H NMR resonances exhibit *two* characteristic singlets (e.g. at δ_H 6.35 and 6.4 ppm for **15c**), what cannot occur with the 5- regioisomer. Besides the inherently higher steric hindrance of a 5-substitution on **15** (vicinal to the 4- exocyclic arylamine) compared to a distant 7-substitution (similar hindrance may already occur in the preceeding transition state), stereoelectronic effects of the *meta*-substituent may also influence the 7- vs. 5- regioselectivity of THQ formation;[28b,e] additional studies would be necessary to fully elucidate this aspect.

Although incompletely stereoselective, the formation of THQ neatly favors the formation of the *cis* diastereomer, the latter being largely predominant in THQ **15** derived from non-substituted or *para*/*meta*-substituted anilines (**15a-a", 15c-d', 15f-g', 15i-j', 15l-m'**, **15o**, cis/trans *dr* ranging from 8:2 to 9:1). However the stereoselectivity was quite weaker in the case of *ortho*-substituted anilines derivatives **15b, 15e, 15h, 15k** and **15n-n'** (bearing either an alkyl, alkoxy or halogen group), correlatively to the lower overall THQ yield observed in this *ortho*- series compared to the others. Previous studies concluded from the Gibbs free energy profile of the Povarov THQ formation that the corresponding *cis*-THQ-isomer are being the kinetic control product.[15,37] Accordingly, in our case the reaction of **10–10"** with **14a-o** is kinetically highly stereoselective leading to the formation of THQ *cis*-**15a-o** as major stereoisomers.

Table 3. Reaction conditions and results for the synthesis of substituted THQ **15a-o** from iodo-*bis*(acetoxy) compound **10**–**10"** and substituted anilines **14a-o**.

Entry	Reactants				reaction time /h	THQ product	% conv. [a]	cis/trans ratio [a]
	10/'/"	R_F	14	R				
1	**10**	C_6F_{13}	**14a**	H	4	**15a**	95	78/22 [c]
2	**10'**	C_2F_5	**14a**	H	4	**15a'**	95	74/26
3	**10''**	C_4F_9	**14a**	H	4	**15a''**	95	77/23
4	**10**	C_6F_{13}	**14b**	*o*-Me	4	**15b**	80	70/30 [c]
5	**10**	C_6F_{13}	**14c**	*m*-Me	3	**15c** [b]	85	75/25
6	**10**	C_6F_{13}	**14d**	*p*-Me	3	**15d**	88	90/10 [c]
7	**10'**	C_2F_5	**14d**	*p*-Me	3	**15d'**	88	88/12
8	**10**	C_6F_{13}	**14e**	*o*-Et	4	**15e**	75	65/35
9	**10**	C_6F_{13}	**14f**	*m*-Et	3	**15f** [b]	80	77/23
10	**10**	C_6F_{13}	**14g**	*p*-Et	3	**15g**	83	90/10
11	**10'**	C_2F_5	**14g**	*p*-Et	3	**15g'**	85	88/12
12	**10**	C_6F_{13}	**14h**	*o*-Cl	8	**15h**	60	57/43
13	**10**	C_6F_{13}	**14i**	*m*-Cl	6	**15i** [b]	66	89/11
14	**10**	C_6F_{13}	**14j**	*p*-Cl	6	**15j**	70	90/10 [c]
15	**10'**	C_2F_5	**14j**	*p*-Cl	6	**15j'**	70	88/12
16	**10**	C_6F_{13}	**14k**	*o*-OMe	4	**15k**	75	64/36
17	**10**	C_6F_{13}	**14l**	*m*-OMe	3	**15l** [b]	73	78/22
18	**10**	C_6F_{13}	**14m**	*p*-OMe	3	**15m**	78	89/11
19	**10'**	C_2F_5	**14m**	*p*-OMe	3	**15m'**	78	86/14
20	**10**	C_6F_{13}	**14n**	*o*-OEt	4	**15n**	65	60/40 [c]
21	**10'**	C_2F_5	**14n**	*o*-OEt	4	**15n'**	68	58/42
22	**10**	C_6F_{13}	**14o**	*p*-NO_2	8	**15o**	60	90/10

[a] Determined by ^{19}F NMR analysis; NMR yield based on consumed **10–10"** and formed **15a-o**. [b] cases of *m*-substituted anilines: only 7-substituted-THQ regioisomers **15c, 15f, 15i** and **15l** were formed. [c] The major *cis* isomer was further isolated from the *cis*/*trans* mixture.

V. Structure determination of 2-(perfluoroalkylmethyl)-1,2,3,4-tetrahydro-*N*-(R-phenyl)quinolin-4-amine 15a-o

In a first approach, the spectroscopic and elemental analysis data of compounds **15** are consistent with a 2,4-substituted 1,2,3,4-tetrahydroquinoline structure; especially, $^{1}H/^{13}C/^{19}F$ 1D and 2D NMR spectra showed the presence of two isomers in unequal amounts (ratios ranging from 6:4 to 9:1 according to ^{1}H and ^{19}F resonance integration). Most likely the latter correspond to both *cis*- and *trans*-configurations of both R_F and arylamine substituents on the THQ. Further elucidation of the relative configuration was done after isolation of the major isomer (what was possible for a few examples in the series **15a-o**).

Published experimental data about structural and conformational properties of tetrahydroheterocycles containing pnictogen (N, P, As) or chalcogen (O, S, Se) atoms, show that equilibrium conformation of these heterocycles is a half-chair in all cases.[38,39] These results were applied to the conformational analysis of 1,2,3,4-tetrahydroquinolines in which n–π conjugation between the lone pair of the heteroatom and the π-system of the aromatic nucleus, significantly influence the ring conformation.[38a,40,41]

While the nitrogen atom and carbon on position 4 must be coplanar with the condensed benzene moiety, carbons C^2 and C^3 can be either on opposite sides with respect to the plane (generating halfchair conformation **I**, Scheme 9) or on the same side (generating boat conformation **II**): in the latter case, though, severe eclipsing at the C^2–C^3 bond can be expected. Another possibility is represented by sofa conformation **III**, exhibiting just one carbon out of the plane and possibly less effective eclipsing than the boat. For this reason, sofa conformations received much attention as possible competitors of half-chairs.[42] However, it had been concluded from X-ray and NMR analyses that 1,2,3,4-tetrahydroquinoline compounds preferentially adopt a half-chair conformation **I** with the C^4 atom bearing pseudo-axial and pseudo-equatorial bonds (Scheme 9).[40–43]

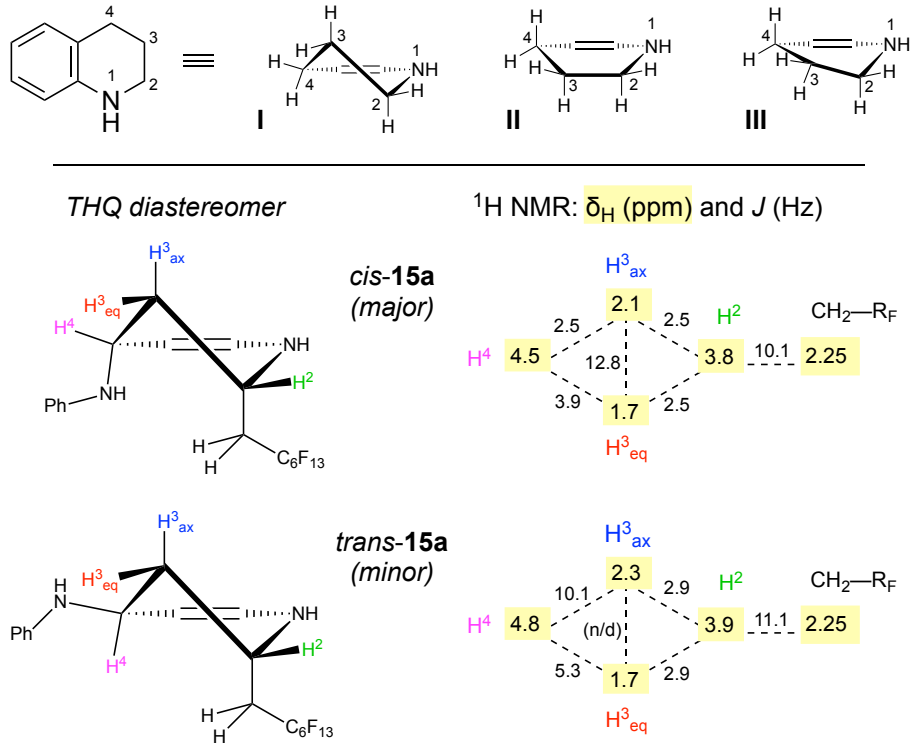
The assignment of *cis*-/*trans*-configurations was based on both the scalar coupling constant between protons H^2 (or H^4) with H^3_{ax} and H^3_{eq} and their multiplicity values, as well as the chemical shifts of aliphatic protons.[25,40,42a] In such cyclic systems, the Karplus-Conroy rule predicts high $^3J_{HH}$ values (10–15 Hz) for the *trans*-di-axial interaction of two vicinal protons and low $^3J_{HH}$ values (2–5 Hz) for the staggered 1,2-axial-equatorial or 1,2-di-equatorial interactions of protons.[44]

NMR spectra of pure *cis*- and *trans*-2-(perfluorohexylmethyl)-1,2,3,4-tetrahydro-*N*-(phenyl)quinolin-4-amine **15a** are typical of the series and will be discussed in detail. While the configuration of *cis*-**15a** was first determined by ^{1}H NMR analysis of the isolated stereomer,[40] for better overall clarity hereafter NMR data were taken form the spectrum of the *cis*+*trans* mixture. Thus, the small triplet couplings (J = 3.1 Hz) appearing at δ 4.5 ppm which should be considered as a doublet of doublets with two close splitting values ($^3J_{H4\text{-}H3ax} \approx {}^3J_{H4\text{-}H3eq}$), is characteristic of a pseudo-equatorial H^4 as reported earlier.[25,40,42] Furthermore, the triplet of doublets of doublets (J = 10.1 and 2.5 Hz) at δ_H 3.8 ppm corresponds to coupling of H^2 with vicinal CH_2 group then further almost identical coupling constants with H^3_{ax} and H^3_{eq} ($^3J_{H2\text{-}H3ax} \approx {}^3J_{H2\text{-}H3eq} \approx 2.5$ Hz) is characteristic of an equatorial H^2 proton[40,42] (Scheme 9).

The overall coupling constants for equatorial H^2 and pseudo-equatorial H^4 resonances, are consistent with a *cis* orientation of the corresponding substituents on carbon 2 and carbon 4 positions namely an axial R_F–CH_2- group and a pseudoaxial-arylamine group (Scheme 9).

Moreover, H^3_{ax} resonance at δ 2.1ppm is a doublet of doublet of doublets (J = 12.8 and 2.5 Hz) with a large coupling constant with the geminal H^3_{eq} ($^2J_{H3ax\text{-}H3eq}$ = 12.8 Hz) and two identical coupling constants with di-equatorial H^2 and H^4 ($^3J_{H3ax\text{-}H2} \approx {}^3J_{H3ax\text{-}H4} \approx 2.5$ Hz), whereas H^3_{eq} resonance at δ 1.7 ppm is as a

doublet of doublets of doublets ($^2J_{H3eq-H3ax}$ = 12.8 Hz, $^3J_{H3eq-H4}$ = 3.9 Hz and $^3J_{H3eq-H2}$ = 2.5 Hz). The methylene $C\underline{H}_2$-R_F shows a multiplet at δ 2.25 ppm, the amine protons gave a broad signal between δ 3.5 and 4.4 ppm and finally the aromatic protons resonate between δ 6.4 and 7.4 ppm. (Supporting Information p. S42)



Scheme 9. Top: possible conformations of the 1,2,3,4-tetrahydroquinoline skeletton: **I**, half-chair; **II**, boat; **III**, sofa. **Bottom**: assessed half-chair conformations of THQ diastereomers *cis*-**15a** and *trans*-**15a** (left, 2*S* isomers shown) from NMR structural analyis and (right) respective δ_H and coupling data; because of multiple resonance overlaps H^3_{ax}–H^3_{eq} *gem* coupling constant of isomer *trans*-**15a** could not be measured. In perspective views the backwards-pointing aromatic ring is simplified as a double bond.

Analysis of the ^{1}H resonances of *trans*-**15a** (on NMR spectra of the cis+trans mixture) showed that the hydrogen bound to carbon 4 is pseudo-axial. Thus, H^4 appeared as a doublet of doublets (δ 4.8 ppm, $^3J_{H4-H3ax}$ = 10.1 Hz and $^3J_{H4-H3eq}$ = 5.3 Hz), the large coupling constant of 10.1 Hz thus confirming the trans di-axial arrangement of H^4 and H^3 (Scheme 9).

The resonance of H^2 at δ 3.9 ppm give rise to a triplet of doublets of doublets due to its vicinal coupling to CH_2-R_F methylene protons ($^3J_{H2-CH2}$ = 11.1 Hz) and to small vicinal couplings with both H^3_{ax} and H^3_{eq} ($^3J_{H2-H3ax} \approx {}^3J_{H2-H3eq} \approx$ 2.9 Hz) what supports an equatorial position for H^2.

From these results, it appears that for the minor *trans*-diastereomer, the carbon-2 perfluoroalkylmethyl substituent is axial and the carbon-4 phenylamine group is pseudo-equatorial (Scheme 9).

However, multiplicities and couplings for H^3_{ax}, CH_2-R_F and H^3_{eq} resonances at δ 2.3; 2.25 and 1.7 ppm respectively, were difficult to determine by ^{1}H NMR because of signal overlap. Attempts to improve signal separation using high-temperature NMR or another solvent, were unsuccessful. However, a consideration of two-dimensional ^{1}H-^{1}H COSY data facilitated assignment of resonances to appropriate protons. Additionally, amine protons gave a broad signal at δ_H 3.5–4.4 ppm and finally the aromatic protons resonate between δ_H 6.4 and 7.4 ppm. (Supporting Information p. S44).

Accordingly, NMR signals of aliphatic protons were fully interpreted and assigned for both *cis*- and *trans*- isomers of all of **15a-o** derivatives. Striking differences occur between 2,4-*cis* and 2,4-*trans* diastereomers, not only in $^{3}J_{H\text{-}H}$ couplings (as expected) but also in the chemical shifts of H^2, $H^3{}_{ax}$ and H^4 resonances.

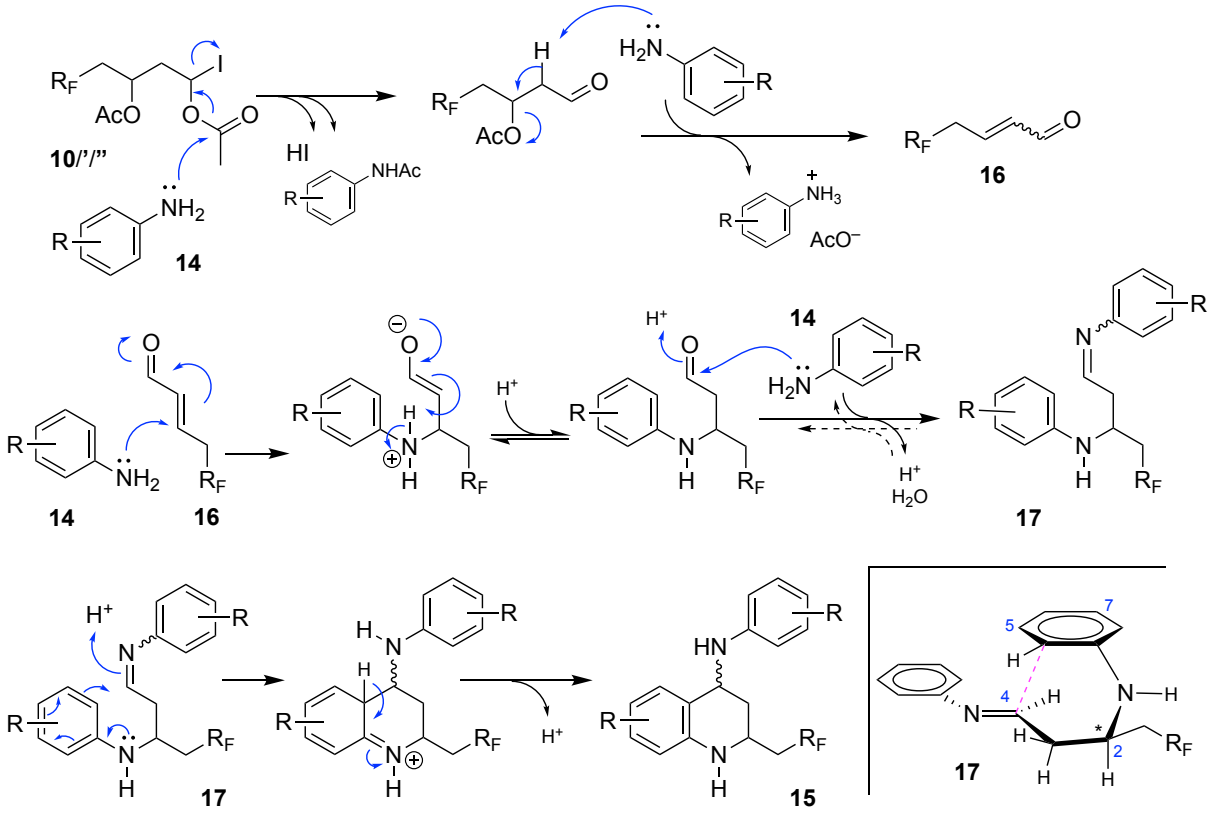
The assessed stereochemistry is highlighted in Scheme 9, where *cis*- and *trans*-configurations of THQ **15a** are shown in the half-chair conformations.[40,42]

VI. Mechanism of THQ 15a-o formation

In order to better understand the mechanism of THQ formation, the reaction was monitored by ^{19}F NMR analysis of aliquots of the medium (after dilution in $CDCl_3$), comparing with ^{19}F NMR spectra of the (reactant) perfluoroalkyl derivative **10** and of the already isolated THQ **15**. The consumption of **10** was accompanied by the formation of the intermediate **16** identified as 4-perfluoroalkylbut-2-enal (R_F-crotonaldehyde, Scheme 10). Subsequently, **16** gradually disappeared while the final THQ **15** was gradually formed. Besides, the side product arylacetamide was detected in the medium, while non-consumed arylamine **14** was recovered (as a salt) in precipitates at the end of the reaction.

Isolation of the intermediate **16** was easier upon a change of reaction conditions, namely a 2:1 stoichiometry of **14** vs. **10** (instead of 4:1), lower concentration (15 mL CH_2Cl_2 per 1g of **10** instead of 5 mL/g) and operating at room temperature instead of reflux for 1h, although **10** was not fully consumed while small amounts of THQ were already formed. After work-up and chromatography, **16** was isolated as an oil in moderate yield (20–48%) and characterized by ^{1}H, ^{13}C and ^{19}F NMR, MS and elemental analysis. The reaction of **16** with excess arylamine **14** was subsequently investigated in refluxing dichloromethane (in the presence of hydrogen iodide to mimic the conditions induced by in situ formation of **16**), where the expected THQ **15** was formed with similar cis/trans diastereoselectivity, however in significantly lower yields (40–60%) than upon starting from **10** and **14**.

On basis of above observations and of the knowledge of *gem*-iodoacetoxy-perfluoroalkyl derivative reactivity,[26–28] the postulated mechanism involved in THQ formation (Scheme 10) begins with a nucleophilic attack by the arylamine **14** on the 1-acetoxy group of **10**, which leads to the elimination of hydrogen iodide and acetanilide. The next step is a concerted *trans*-elimination of acetic acid assisted by another aniline molecule, which affords the substituted crotonaldehyde **16**. Subsequently, **16** may then undego a Michael attack by the nitrogen lone pair of **14**, what generates an amino-enol intermediate which can tautomerize into the corresponding β-amino-carbonyl derivative; the later then undergoes a nucleophilic addition by another arylamine **14** to afford the β-amino-imine intermediate **17**. Finally, the cyclization of **17** through an intramolecular electrophilic aromatic substitution, affords the final THQ **15** (both the 5/7 regioselectivity and cis/trans diastereoselectivity being determined by this cyclization step, Scheme 10). Although the postulated intermediate **17** (aromatic imine) is expected to be rather stable, it was not detected in the reaction medium under the conditions of THQ formation; what suggests the final cyclization step to be rather fast once **17** would be formed. The lower efficiency when proceeding in two steps through isolation of **16**, leaves room for alternate pathways or concerted/catalytic processes; the elucidation of which will require further investigation.



Scheme 10. Proposed mechanism for the formation of THQ **15** from **10** and **14** via a crotonaldehyde intermediate **16**. Bottom-right inset: a possible conformation of the postulated intermediate **17** before cyclization into (major) diastereomer *cis*-**15** (carbon numberings are those of the THQ, C^2 shown as 2*R*).

Conclusion

In this paper, two original series of perfluoroalkyl derivatives including tetrahydroquinolins, have been prepared and described. First, we developed a simple and efficient method for the preparation of so far undescribed trifunctional *gem*-iodoacetoxy derivatives **10–10"** (1-iodo,1,3-diacetoxy-4-perfluoroalkylbutane) through the *bis*-addition of vinyl acetate on a perfluoroalkyliodide R_FI (R_F= C_6F_{13}, C_4F_9, C_2F_5) through an iodine atom transfer radical chain reaction. Chemoselective *bis*-addition (although not total over single addition) was best achieved upon Et_3B/air radical initiation at room temperature (90:10 to 95:5 selectivity) rather than AIBN initiation at 80°C. Compounds **10–10"** were formed as mixtures of diastereomers in 80:20 *anti-*/*syn-* ratio (if necessary the major *anti-* isomer could be further isolated) and were characterized by $^1H/^{19}F$ NMR and mass spectrometry. Besides, since the *gem*-iodoacetoxy group is a masked aldehyde[28a] (*inter alia* having the same oxidation degree), compounds **10–10"** are masked/activated aldols; given the high popularity of this synthon,[45] **10–10"** or derivatives would deserve of future extensive reactivity investigation with a perspective of new aldol-based syntheses of perfluoroalkyl-containing compounds.

In the subsequent study described here, *gem*-iodoacetoxy compounds **10–10"** became the substrate for a new, efficient, diastereoselective one-pot synthesis of functionalized 1,2,3,4-tetrahydroquinolines **15** bearing 2-perfluoroalkylmethyl and 4-arylamino substituents. Thus the reaction of **10–10"** with substituted anilines in 1:4 stoichiometry under mild conditions (refluxing dichloromethane for a few hours), afforded the R_F/arylamine-substituted THQ **15** with fair to excellent yields (60–95%). The reaction was exemplified with various R_F (C_6F_{13}, C_4F_9, C_2F_5) and monosubstituted anilines (*o-*/*m-*/*p-* alkyl, alkoxyl, halogeno, nitro), the resulting THQ derivatives **15a-o** being fully

characterized by ^{1}H, ^{13}C and ^{19}F NMR and mass spectrometry. As for the *gem*-iodoacetoxy compounds **10–10"**, the structure of THQ **15a-o** was determined on basis of NMR chemical shifts and couplings.

THQ examples involving *meta*- substituted arylamines were regiospecific in favor of (less sterically hindered) 7-substituted regioisomers. In all examples the formation of THQ was diastereoselective, the *cis*- stereoisomer being formed in 65:35 to 95:5 ratio over the *trans*- isomer — in favorable cases, the major isomer *cis*-**15** could further be isolated from the cis/trans mixture. THQ **15** derived from non- or *meta*-/*para*-substituted anilines, were formed in very good yields and diastereoselectivities; however in the presence of *ortho*- or electron-withdrawing substituents, lower yields and stereoselectivities were achieved. Mechanistic investigation revealed the intermediacy of an R_F-crotonaldehyde **16**, the reaction of which with **14** also leads to THQ **15**, although much less efficiently. The key step is believed to be the regio- and stereoselective cyclization of a *bis*(arylamino/imino) intermediate **17** through electrophillic aromatic substitution. While further investigation would be necessary to better understand the mechanism and stereoselectivity of THQ formation, this first, multicomponent synthesis of 2-perfluoroalkylated THQ, may be useful to access new, highly functionalized heterocycles of importance in medicinal chemistry.

Experimental Section

Materials and methods. All reaction solvents were purchased from commercial suppliers and distilled before use. All synthetic reactions were performed in oven-dried glassware, their progress being monitored by thin layer chromatography (TLC) using silica gel plates, and/or by ^{19}F NMR spectroscopy of aliquots. Chromatographic column purifications were performed on silica gel (40–63 µm), typically using 30× weight of eluted sample. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in either CDCl3 solution on an Avance 300 (300 MHz) or an Avance 400 (400 MHz) spectrometer (Bruker, Billerica, MA, USA). Chemical shifts are reported in ppm, using the solvent chemical shift as a reference (or added $CFCl_3$ for ^{19}F). Abbreviations used in the description of NMR spectra: s: singlet, d: doublet, t: triplet, q: quadruplet, bs: broad signal. Coupling constants *(J)* are given in Hertz. Mass spectra (either low- or high-resolution) were recorded on a SX102 mass spectrometer (JEOL, Tokyo, Japan) in FAB^+ mode, using 3-nitrobenzyl alcohol matrix. Elemental analyses were carried out on a Flash 2000 elemental analyzer (Thermo Finnigan, Waltham, MA, USA). **Warning:** radical initiators such as Et_3B or AIBN may cause explosions when heated at gram scale in pure or concentrated state. Special care must be taken e.g. upon evaporation of crude reaction mixtures.

Synthesis of 1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane 10 (Et_3B initiation)

To a mixture of 10 mL or 20.63 g (4.62×10^{-2} mole) of tridecafluoro-1-iodohexane **8** (1 equiv.) and 14.9 mL (13.92 g, 0.161 mole) of vinyl acetate **9** (3.5 equiv.) in a three-necked flask equipped with a reflux condenser, was added 0.9 mL of 1.0 M triethylborane solution in hexane (0.925×10^{-3} mol Et_3B, 0.01 equiv.) under stirring. Dry air was injected in the reaction. After stirring for 15 minutes, additional 0.01 equiv. of 1.0 M Et_3B in hexane and dry air were introduced in the mixture (after some induction delay, important heat release occurred in the medium). The mixture was then stirred for 60 minutes with several dry air injections. After complete consumption of starting material **8** (monitoring by ^{19}F NMR analysis of aliquots), the mixture was allowed to cool to r.t., then was chromatographed on silica gel (eluent: petroleum ether/ethyl acetate, 95:5 v/v) to afford 27.15 g (yield: 95%) of 1,3-diacetoxy-4-(tridecafluorohexyl)-1-iodobutane **10** as a yellow brownish liquid, as a mixture of diastereomers in the ratio ***anti*-10** : ***syn*-10** = 80:20 (^{1}H and ^{19}F NMR); and 1.23 g (yield: 5%) of side-product 1-acetoxy-2-(tridecafluorohexyl)-1-iodoethane **11**.

***Anti*-/*syn*-1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane (*anti*-10 and *syn*-10), mixture 80:20 of diastereomers**

Physical appearance: brownish liquid; R_f = 0.75 (ethyl acetate/petroleum ether 2:8);
^{1}H NMR (300.13 MHz, $CDCl_3$), major *anti*-diastereomer: δ = 2 (s, 3H; -OCOC$\underline{H}_3$), 2.1 (s, 3H; -OCOC$\underline{H}_3$), 2.2–2.5 (m, 2H; H^4), 2.5–2.9 (m, 2H; H^2), 5.4 (m, 1H; H^3), 6.7 (dd, $^3J_{H1\text{-}H2}$ = 10.7 and 2.8 Hz, 1H; H^1); minor *syn*-diastereomer: δ = 2.05 (s, 3H; -OCOC$\underline{H}_3$), 2.2 (s, 3H; -OCOC$\underline{H}_3$), 2.2–2.5 (m, 2H; H^4), 2.5–2.9 (m, 2H; H^2), 5.7 (m, 1H; H^3), 6.8 (m, 1H; H^1);
^{13}C NMR (75.46 MHz, $CDCl_3$), mixture of *anti*-/*syn*-diastereomers: δ = 20.2 (-OCO$\underline{C}H_3$), 20.4 (-OCO$\underline{C}H_3$), 22.4 (-OCO$\underline{C}H_3$), 26.7 (-OCO$\underline{C}H_3$), 34.4 (t, $^2J_{C\text{-}F}$ = 19.6 Hz; C_6F_{13}-$\underline{C}^4$), 34.7 (t, $^2J_{C\text{-}F}$ = 21.1 Hz; C_6F_{13}-$\underline{C}^4$), 45.6 (C^2), 46 (C^1), 47.9 (C^2), 48.9 (C^1), 63.7 (C^3), 65.5 (C^3), 104.4–123.2 (m; $\underline{C}_6F_{13}$), 167.5 ($\underline{C}$=O), 168.2 ($\underline{C}$=O), 168.8 ($\underline{C}$=O), 169.4 ($\underline{C}$=O);
^{19}F NMR (235.3 MHz, $CDCl_3$), major *anti*-diastereomer : δ = –126.3 (m; $2F_\varepsilon$), –123.7 (m; $2F_\delta$), –123 (m; $2F_\gamma$), –121.9 (m; $2F_\beta$), –114.4 (ddd, part A of AB system, $^2J_{F\alpha\text{-}F\alpha'}$ = 282 Hz, $^3J_{F\alpha\text{-}H4}$ = 22.5 and 11.2 Hz; $1F_\alpha$), –112.6 (ddd, part B of AB system, $^2J_{F\alpha'\text{-}F\alpha}$ = 282 Hz, $^3J_{F\alpha'\text{-}H4}$ = 22.5 and 11.2 Hz; $1F_{\alpha'}$), –81.1 (m; $3F_\omega$); minor *syn*-diastereomer: δ = –126.3 (m; $2F_\varepsilon$), –123.7 (m; $2F_\delta$), –123 (m; $2F_\gamma$), –121.9 (m; $2F_\beta$), –113.9 (ddd, part A of AB system, $^2J_{F\alpha\text{-}F\alpha'}$ = 225.8 Hz, $^3J_{F\alpha\text{-}H4}$ = 20.5 and 11 Hz; $1F_\alpha$), –112.8 (ddd, part B of AB system, $^2J_{F\alpha'\text{-}F\alpha}$ = 225.8 Hz, $^3J_{F\alpha'\text{-}H4}$ = 20.5 and 11 Hz; $1F_{\alpha'}$), –81.1 (m; $3F_\omega$);
MS (FAB$^+$): *m/z* (%): 619 (70) [*M+H*]$^+$;
HRMS (HR-FAB$^+$): *m/z* calcd for $C_{14}H_{13}F_{13}IO_4^+$: 618.9645 [*M+H*]$^+$; found 618.9655;
Elemental analysis calcd (%) for $C_{14}H_{12}F_{13}IO_4$: C 27.20, H 1.96, O 10.35; found: C 27.25, H 1.95, O 10.31.

***Anti*-1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane (*anti*-10)**

The 80:20 ***anti*-10**/***syn*-10** diastereomer mixture obtained above, was separated by column chromatography on silica gel eluted with ethyl acetate-petroleum ether (2:98), affording the pure ***anti*-10** diastereomer.
Physical appearance: brownish liquid; R_f = 0.75 (ethyl acetate/petroleum ether 2:8);
^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2 (s, 3H; -OCOC$\underline{\mathbf{H}}_3$), 2.1 (s, 3H; -OCOC$\underline{\mathbf{H}}_3$), 2.2–2.5 (m, 2H; H^4), 2.55 (ddd, part A of AB system, $^2J_{H2a\text{-}H2b}$ = 14.6 Hz, $^3J_{H2a\text{-}H3}$ = 10.2 and $^3J_{H2a\text{-}H1}$ = 2.8 Hz, 1H; H^{2a}), 2.7 (ddd, part B of AB system, $^2J_{H2b\text{-}H2a}$ = 14.6 Hz, $^3J_{H2b\text{-}H1}$ = 10.7 and $^3J_{H2b\text{-}H3}$ = 3 Hz, 1H; H^{2b}), 5.4 (m, 1H; H^3), 6.7 (dd, $^3J_{H1\text{-}H2}$ = 10.79 and 2.8 Hz, 1H; H^1);
^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.5 (-OCO$\underline{C}H_3$), 26.6 (-OCO$\underline{C}H_3$), 34.6 (t, $^2J_{C\text{-}F}$ = 19.9 Hz; C_6F_{13}- $\underline{C}^4$), 46.1 (C^1), 47.78 (C^2), 65.6 (C^3), 105–125 (m; $\underline{C}_6F_{13}$), 168.3 ($\underline{C}$=O), 169.2 ($\underline{C}$=O);
^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –126.54 (m; $2F_\varepsilon$), –123.8 (m; $2F_\delta$), –123.18 (m; $2F_\gamma$), –122 (m; $2F_\beta$), –114.5 (ddd, part A of AB system, $^2J_{F\alpha\text{-}F\alpha'}$ = 282 Hz, $^3J_{F\alpha\text{-}H4}$ = 22.5 and 11.2 Hz; $1F_\alpha$), –112.5 (ddd, part B of AB system, $^2J_{F\alpha'\text{-}F\alpha}$ = 282 Hz, $^3J_{F\alpha'\text{-}H4}$ = 22.5 and 11.2 Hz; $1F_{\alpha'}$), –81.28 (m; $3F_\omega$);
MS (FAB$^+$): *m/z* (%): 619 (75) [*M+H*]$^+$;
HRMS (HR-FAB$^+$): *m/z* calcd for $C_{14}H_{13}F_{13}IO_4^+$: 618.9645 [*M+H*]$^+$; found 618.9652;
Elemental analysis calcd (%) for $C_{14}H_{12}F_{13}IO_4$: C 27.20, H 1.96, O 10.35; found: C 27.22, H 1.98, O 10.37.

1-acetoxy-2-(tridecafluorohexyl)-1-iodoethane (11)

Physical appearance: yellowish liquid; R_f = 0.9 (ethyl acetate/petroleum ether 2:8);
^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2 (s, 3H; -OCOC$\underline{H}_3$), 2.9–3.1 (m, 1H; C_6F_{13}-C$\underline{H}^{2a}H^{2b}$), 3.2–3.4 (m, 1H; C_6F_{13}-C$H^{2a}\underline{H}^{2b}$), 7 (dd, $^3J_{H1\text{-}H2}$ = 10.3 and 2.2 Hz, 1H; H^1);
^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.4 (-OCO$\underline{C}H_3$), 39.6 (C^1), 43.6 (t, $^2J_{C\text{-}F}$ = 21.1 Hz; C_6F_{13}- $\underline{C}^2$), 103–123 (m; $\underline{C}_6F_{13}$), 167.5 ($\underline{C}$=O);
^{19}F NMR (235.3 MHz, $CDCl_3$): δ = –126.8 (m; $2F_\varepsilon$), –123.9 (m; $2F_\delta$), –123.3 (m; $2F_\gamma$), –122.2 (m; $2F_\beta$), –114.9 (ddd, part A of AB system, $^2J_{F\alpha\text{-}F\alpha'}$ = 282 Hz, $^3J_{F\alpha\text{-}H2}$ = 22.5 and 11.2 Hz; $1F_\alpha$), –112.6 (ddd, part B of AB system, $^2J_{F\alpha'\text{-}F\alpha}$ = 273 Hz, $^3J_{F\alpha'\text{-}H2}$ = 22.5 and 11.2 Hz; $1F_{\alpha'}$), –81.6 (m; $3F_\omega$);
MS (FAB$^+$): *m/z* (%): 533 (70) [*M+H*]$^+$;
HRMS (HR-FAB$^+$): *m/z* calcd for $C_{10}H_7F_{13}IO_2^+$: 532.9278 [*M+H*]$^+$; found 532.9286;
Elemental analysis calcd (%) for $C_{10}H_6F_{13}IO_2$: C 22.57, H 1.14, O 6.01; found: C 22.59, H 1.14, O 6.00.

Synthesis of 1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane 10 (AIBN initiation)

In a round bottom flask fitted with a reflux condenser and a magnetic stirrer, were mixed 11 mL (22.69 g, 5.08×10^{-2} mole) of tridecafluoro-1-iodohexane **8** (1 equiv.), 15.31 g (0.178 mole) of vinyl acetate **9** (3.5 equiv.) and then 0.83 g (5.08×10^{-3} mole, 0.1 equiv.) of azo-*bis*-isobutyronitrile (AIBN). The mixture was carefully deaerated by bubbling argon under stirring at rt, then heated to 80°C for 90 minutes, while a vigorous reflux was observed. When the reaction was completed (complete consumption of **8** monitored by ^{19}F NMR of aliquots) the mixture was allowed to cool to r.t., then was separated by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 95/5 v/v) to afford 27.66 g (yield: 88%) of the desired 1,3-diacetoxy-4-(tridecafluorohexyl)-1-iodobutane **10** (mixture of diastereomers in the ratio ***anti*-10** : ***syn*-10 =** 80:20) as a yellow brownish liquid; and 3.24 g (yield:12%) of the side-product 1-acetoxy-2-(tridecafluorohexyl)-1-iodoethane **11**.

Nota. For either Et_3B/AIBN initiation method, unreacted vinyl acetate that might remain mixed with **10** or **11** chromatographic fractions, was easily distilled off on a rotary evaporator.

Synthesis of substituted *cis*-/*trans*-2-(perfluoroalkylmethyl)-4-(arylamino)-1,2,3,4-tetrahydroquinolines 15a-o.

In a round-bottomed flask fitted with a magnetic stirrer and a reflux condenser, 1.5 g (2.42×10^{-3} mole) of 1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane **10** (1 equiv.) and 0.9 g of aniline **14a** (9.7×10^{-3} mole, 4 equiv.) were dissolved in 7.5 mL of anhydrous dichloromethane (5 mL per 1 g of **10**) then stirred upon heating to reflux for 4 h until complete consumption of **10** (monitored by ^{19}F NMR analysis of aliquots). The mixture was then allowed to cool to room temperature, then arylammonium salt precipitates were filtered off through a glass filter then washed twice with dichloromethane. The combined filtrates were extracted three times with water, twice with 3% aqueous $NaHCO_3$, then repeatedly washed with water until the pH of the aqueous layer reached neutrality (pH tape test). The organic layer was dried over sodium sulphate then the solvent was evaporated in vacuo to give the crude product which was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 90:10, v/v) to afford pure tetrahydroquinoline **15a** (1.21 g, yield: 90%) as a yellowish oil, mixture of *cis*-/*trans*-diastereomers in the ratio ***cis*-15a** : ***trans*-15a** 78:22 (^{1}H and ^{19}F NMR). The major (cis) diastereomer was subsequently isolated from the cis/trans mixture by further chromatography (same eluent). Both the cis/trans mixture and isolated cis-diastereomer, were characterized by ^{1}H and ^{19}F NMR, MS and elemental analysis.

***Cis*-/*trans*-2-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroheptyl)-4-phenylamino-1,2,3,4-tetrahydroquinoline (*cis*-15a and *trans*-15a)**

Physical appearance: yellowish liquid; R_f = 0.6 (ethyl acetate/petroleum ether 2:8);

^{1}H NMR (400.13 MHz, $CDCl_3$), major *cis*-diastereomer: δ = 1.7 (ddd, $^2J_{H3eq\text{-}H3ax}$ = 12.8 Hz, $^3J_{H3eq\text{-}H4}$ = 3.9 Hz and $^3J_{H3eq\text{-}H2}$ = 2.5 Hz, 1H; $\underline{H}^3_{eq}$), 2.1 (ddd, $^2J_{H3ax\text{-}H3eq}$ = 12.8 Hz, $^3J_{H3ax\text{-}H2}$ = $^3J_{H3ax\text{-}H4}$ = 2.5 Hz, 1H; $\underline{H}^3_{ax}$), 2.25 (m, 2H; $C\underline{H}_2\text{-}C_6F_{13}$), 3.8 (tdd, $^3J_{H2\text{-}C\underline{H}2}$ = 10.1 Hz, $^3J_{H2\text{-}H3ax}$ = $^3J_{H2\text{-}H3eq}$ = 2.5 Hz, 1H; $\underline{H}^2$), 3.5–4.4 (bs, 2H; 2 N$\underline{H}$), 4.5 (dd, $^3J_{H4\text{-}H3eq}$ = 3.9 Hz and $^3J_{H4\text{-}H3ax}$ = 2.5 Hz, 1H; $\underline{H}^4$), 6.4–6.8 (m, 5H; H_{Ar}), 6.9–7.4 (m, 4H; H_{Ar}); minor *trans*-diastereomer: δ = 1.7 (m, 1H; $\underline{H}^3_{eq}$), 2.25 (m; $C\underline{H}_2\text{-}C_6F_{13}$), 2.3 (m, 1H; $\underline{H}^3_{ax}$), 3.9 (tdd, $^3J_{H2\text{-}C\underline{H}2}$ = 11.1 Hz, $^3J_{H2\text{-}H3ax}$ = $^3J_{H2\text{-}H3eq}$ = 2.9 Hz, 1H; $\underline{H}^2$), 3.5–4.4 (bs, 2H; 2 N$\underline{H}$), 4.8 (dd, $^3J_{H4\text{-}H3ax}$ = 10.1 Hz and $^3J_{H4\text{-}H3eq}$ = 5.3 Hz, 1H; $\underline{H}^4$), 6.4–6.8 (m, 5H; H_{Ar}), 6.9–7.4 (m, 4H; H_{Ar});

^{13}C NMR (100.61 MHz, $CDCl_3$), mixture of *cis*-/*trans*-diastereomer: δ = 33.2 (C^3, cis), 35.1 (C^3, trans), 35.8 (t, $^2J_{C\text{-}F}$ = 20.1 Hz ; -$\underline{C}H_2\text{-}C_6F_{13}$, cis), 36.2 (t, $^2J_{C\text{-}F}$ = 16 Hz; -$\underline{C}H_2\text{-}C_6F_{13}$, trans), 40.2 ($C^2$, cis), 44 ($C^2$, trans), 47.5 ($C^4$, cis), 48.5 ($C^4$, trans), 107–121 (m; $\underline{C}_6F_{13}$), 111.8, 112.1, 112.4, 113.7, 114.1, 116.71, 116.77, 117.4, 117.5, 117.6, 117.8, 119.9, 121.8, 126.4, 127.5, 127.9, 128.2, 128.4, 128.5, 129.6, 142.6, 142.8, 145, 145.3;

^{19}F NMR (282.4 MHz, $CDCl_3$), major *cis*-diastereomer: *δ* = –126 (m; $2F_{\varepsilon}$), –123.5 (m; $2F_{\delta}$), –122.8 (m; $2F_{\gamma}$), –121.7 (m; $2F_{\beta}$), –113.2 (ddd, part A of AB system, $^2J_{F\alpha\text{-}F\alpha'}$ = 276 Hz, $^3J_{F\alpha\text{-}C\underline{H}2}$ = 27.5 and 14.01 Hz; $1F_{\alpha}$), –111.1 (ddd, part B of AB system, $^2J_{F\alpha'\text{-}F\alpha}$ = 276 Hz, $^3J_{F\alpha'\text{-}C\underline{H}2}$ = 27 and 14.1 Hz; $1F_{\alpha'}$), –80.7 (m; $3F_{\omega}$); minor *trans*-diastereomer: *δ* = –126 (m; $2F_{\varepsilon}$), –123.5 (m; $2F_{\delta}$), –122.8 (m; $2F_{\gamma}$), –121.7 (m; $2F_{\beta}$), –113.3

(ddd, part A of AB system, $^{2}J_{F\alpha\text{-}F\alpha'}$ = 280 Hz, $^{3}J_{F\alpha\text{-}C\underline{H}2}$ = 21 and 10 Hz; 1F$_{\alpha}$), –111.8 (ddd, part B of AB system, $^{2}J_{F\alpha'\text{-}F\alpha}$ = 280 Hz, $^{3}J_{F\alpha'\text{-}C\underline{H}2}$ = 21 and 10 Hz; 1F$_{\alpha'}$), –80.7 (m; 3F$_{\omega}$);
MS (FAB^{+}): *m/z* (%): 557 (100) [*M+H*]$^{+}$;
HRMS (HR-FAB^{+}): *m/z* calcd for $C_{22}H_{18}F_{13}N_2^{+}$: 557.1257 [*M+H*]$^{+}$; found 557.1266;
Elemental analysis calcd (%) for $C_{22}H_{17}F_{13}N_2$: C 47.49, H 3.08, N 5.04; found: C 47.51, H 3.10, N 5.06.

Cis-2-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroheptyl)-4-phenylamino-1,2,3,4-tetrahydroquinoline (_cis_-15a)

Cis-isomer separation of **15a** was performed using column chromatography on silica gel eluted with petroleum ether/ethyl acetate 90/10, v/v to give pure *cis*-tetrahydroquinoline ***cis*-15a**.
Physical appearance: yellowish liquid; R_f = 0.6 (ethyl acetate/petroleum ether 2:8);
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.8 (ddd, $^{2}J_{H3eq\text{-}H3ax}$ = 12.9 Hz, $^{3}J_{H3eq\text{-}H4}$ = 3.9 Hz and $^{3}J_{H3eq\text{-}H2}$ = 2.5 Hz, 1H ; $\underline{H}^{3}_{eq}$), 2.2 (ddd, $^{2}J_{H3ax\text{-}H3eq}$ = 12.9 Hz, $^{3}J_{H3ax\text{-}H2}$ = $^{3}J_{H3ax\text{-}H4}$ = 2.5 Hz, 1H; $\underline{H}^{3}_{ax}$), 2.4 (m, 2H; C$\underline{H}_2$-C_6F_{13}), 3.9 (tdd, $^{3}J_{H2\text{-}C\underline{H}2}$ = 10.1 Hz, $^{3}J_{H2\text{-}H3ax}$ = $^{3}J_{H2\text{-}H3eq}$ = 2.5 Hz, 1H; $\underline{H}^{2}$), 4–4.1 (bs, 1H; N$\underline{H}$), 4.3–4.4 (bs, 1H; N$\underline{H}$), 4.6 (dd, $^{3}J_{H4\text{-}H3eq}$ = 3.1 Hz and $^{3}J_{H4\text{-}H3ax}$ = 2.5 Hz, 1H; $\underline{H}^{4}$), 6.5–6.8 (m, 5H; H_{Ar}), 7–7.5 (m, 4H; H_{Ar});
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 33.2 (C^{3}), 35.8 (t, $^{2}J_{C\text{-}F}$ = 20.5 Hz; -$\underline{C}H_2$-C_6F_{13}), 40.2 (C^{2}), 47.5 (C^{4}), 111.7, 114.1, 116.77, 117.4, 119.9, 127.5, 127.9, 128.2, 128.5, 129.5, 142.8, 145.1;
^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –126.1 (m; 2F$_{\varepsilon}$), –123.5 (m; 2F$_{\delta}$), –122.8 (m; 2F$_{\gamma}$), –121.7 (m; 2F$_{\beta}$), –113.2 (ddd, part A of AB system, $^{2}J_{F\alpha\text{-}F\alpha'}$ = 276 Hz, $^{3}J_{F\alpha\text{-}C\underline{H}2}$ = 27 and 13.9 Hz; 1F$_{\alpha}$), –111.1 (ddd, part B of AB system, $^{2}J_{F\alpha'\text{-}F\alpha}$ = 276 Hz, $^{3}J_{F\alpha'\text{-}C\underline{H}2}$ = 26.7 and 14.1 Hz; 1F$_{\alpha'}$), –80.7 (m; 3F$_{\omega}$);
MS (FAB^{+}): *m/z* (%): 557 (100) [*M+H*]$^{+}$;
HRMS (HR-FAB^{+}): *m/z* calcd for $C_{22}H_{18}F_{13}N_2^{+}$: 557.1257 [*M+H*]$^{+}$; found 557.1265;
Elemental analysis calcd (%) for $C_{22}H_{17}F_{13}N_2$: C 47.49, H 3.08, N 5.04; found: C 47.50, H 3.11, N 5.06.

Isolation of intermediate (*E*)-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodec-2-enal 16

A solution of 1.88 g (3.04 × 10^{-3} mole, 1 equiv.) of 1,3-diacetoxy-1-iodo-4-(tridecafluorohexyl)-butane **10** in 28.5 mL dichloromethane (15 mL DCM per 1g of **10**) was prepared in a round-bottom flask. To this were added 0.56 g (6.08 × 10^{-3} mole, 2 equiv.) of aniline **14a** then the solution was stirred at room temperature for 4 hours until the formation of intermediate **16** was observed by ^{19}F NMR monitoring of aliquots. Arylamonium salt precipitates were then filtered off and washed with dichloromethane, then the combined filtrates were extracted twice with water, twice with 0.1M HCl, then twice with water. The organic layer was dried over sodium sulphate and the solvent was evaporated to give the crude product which was purified by column chromatography on silica gel (eluent: with petroleum ether/ethyl acetate 95/5, v/v) to afford 0.56 g (yield: 48%) of pure compound **16** as a liquid; identified by ^{1}H NMR as the (E) isomer.
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.1 (td, $^{3}J_{H4\text{-}F}$ = 17.5 Hz, $^{3}J_{H4\text{-}H3}$ = 7.1 Hz, 2H; 2 $\underline{H}^{4}$), 6.25 (dd, $^{3}J_{H2\text{-}H3}$ = 15.7 Hz and $^{3}J_{H2\text{-}CHO}$ = 7.58 Hz, 1H; $\underline{H}^{2}$), 6.7 (dt, $^{3}J_{H3\text{-}H2}$ = 15.7 Hz, $^{3}J_{H3\text{-}H4}$ = 7.1 Hz, 1H; $\underline{H}^{3}$), 9.55 (d, $^{3}J_{CHO\text{-}H2}$ = 7.57 Hz, 1H; C$\underline{H}$=O);
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 35.5 (t, $^{2}J_{C\text{-}F}$ = 20.2 Hz; -$\underline{C}H_2$-C_6F_{13}), 105–125 (m; $\underline{C}_6F_{13}$), 135.2 (C^{2}), 154.1 (C^{3}), 194.7 (C$\underline{H}$O);
^{19}F NMR (376.49 MHz, $CDCl_3$): δ = –126.1 (m; 2F$_{\varepsilon}$), –122.8 (m; 4F$_{\delta/\gamma}$), –121.9 (m; 2F$_{\beta}$), –112.1 (m; 2F$_{\alpha}$), –80.8 (m; 3F$_{\omega}$);
MS (FAB^{+}): *m/z* (%): 389 (100) [*M+H*]$^{+}$;
HRMS (HR-FAB^{+}): *m/z* calcd for $C_{10}H_6F_{13}O^{+}$: 389.0206 [*M+H*]$^{+}$; found 389.0210;
Elemental analysis calcd (%) for $C_{10}H_5F_{13}O$: C 30.95, H 1.30, O 4.12; found: C 30.98, H 1.33, O 4.14.

Reactivity study: formation of THQ 15a from isolated intermediate 16 and aniline 14a

On a 10–100-mg scale, 5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodec-2-enal **16** (1 equiv.) was reacted with 2 equivalents of aniline **14a** in dichloromethane (5 mL/ 1g of **16**). The mixture was stirred under reflux at 40°C for 8 hours, with monitoring by ^{19}F NMR spectroscopy of aliquots (diluted in $CDCl_3$). At the end of the reaction, chromatography on silica gel column (eluent: petroleum ether/ ethyl acetate: 90/10; v/v) left a yellow liquid exhibiting identical physical characterization as the previously isolated

THQ **15a**. The same reaction was repeated on several examples, starting from either substrate **16**, **16'** or **16"** and various arylamines **14a-o** with identical results; yields in **15a-o**: 40 to 60%.

Supplementary Material available: Experimental details and characterizations of additional examples; ^{1}H, ^{13}C and ^{19}F NMR spectra of compound series **10**, **11**, **15**, **16**.

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Author Contributions: S. K. and P. L. designed the research and carried out the experiments and physical analyses; S. K., P. L. and L. B. analyzed the results and wrote the paper.

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Keywords: Diastereoselectivity • Fluorine • Michael Addition • Nitrogen Heterocycles • Synthetic Methods

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Entry for the Table of Contents:

A fast, efficient, diastereoselective 2-step synthetic route to substituted tetrahydroquinolines bearing a perfluoroalkylmethyl group, was achieved via a perfluoroalkylated, iodo-*bis*-acetoxy (masked aldol) intermediate resulting from selective radical *bis*-addition of vinylacetate on R_F–I.