Enantioenriched quaternary α-pentafluoroethyl derivatives of alkyl 1-indanone-2-carboxylates

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ABSTRACT: An electrophilic enantioselective catalytic method for the α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates is described. Under the use of $La(OTf)_3$ in combination with (*S,R*)-indanyl-*pybox* ligand good results in terms of yield and enantioselectivities were achieved (up to 89% *ee*). The reaction proceeds under mild conditions leading to the formation of enantioenriched quaternary centers. This methodology uses an hypervalent iodine(III)-CF_2CF_3 reagent and mechanistic investigations are consistent with the involvement of a radical pathway.

INTRODUCTION

Over the last years, the incorporation of fluorine and fluorine containing groups into organic molecules in order to change its physical, biological and chemical properties has become a powerful tool in drug design due to its favourable effects on pharmacological profiles.[1] Among fluoroalkyl groups,[2] the pentafluoroethyl (CF_2CF_3), the bulkier analogue of CF_3 group, is nowadays one of the most attractive groups[3] in drug design. Due to its strong electron-withdrawing nature, a pentafluoroethylated drug would be less likely to be oxidized by P450 enzymes, leading to an increase of its metabolic stability.[4] Additionally, the lipophilicity of the pentafluoroethyl group is comparable to the one of the recognized lipophilic pentafluorosulfanyl ($-SF_5$) group. On the whole, the presence of a pentafluoroethyl group in drugs can improve their biological activity due to the combination of a unique steric factor with an increased electronegativity, lipophilicity and metabolic stability. In this context, Fulvestrant (estradiol containing a side chain in with CF_2CF_3 group at the end) was approved by the FDA in 2002 as a second-line theraphy for advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy (Figure 1).[5] Moreover, peptidyl pentafluoroethyl ketones have been reported to inhibit various enzymes, as for example, elastase and the hepatitis C virus N53 protease.[6] In addition, some pentafluoroethyl ketones are powerful inhibitors of Group VIA Calcium-Independent Phospholipase A2

proteases.[7] Recently, functionalisation of bicalutamide and enobosarm scaffold with pentafluorosulfanyl and pentafluoroethyl functionality lead to potent agents against prostate cancer (Figure 1).[8]

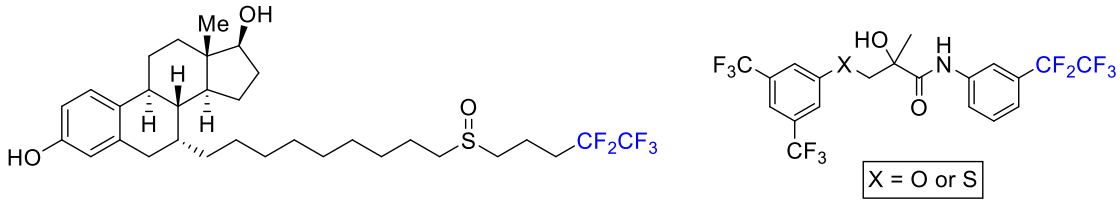


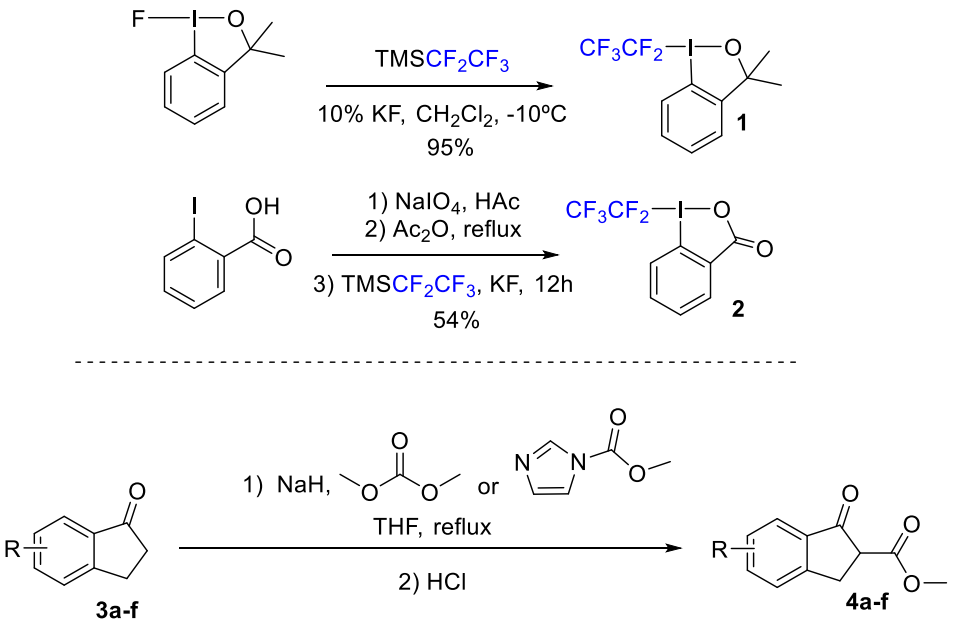
Figure 1. Pentafluoroethylated anticancer drugs

Despite the tremendous progress made in trifluoromethylation,[9] synthetic methods for the introduction of longer perfluoroalkyl chains remain underdeveloped. In contrast to trifluoromethyl, the pentafluoroethyl moiety is still poorly present in drugs in part because the methods for the incorporation of CF_2CF_3 are scarcely documented. For example, for the pentafluoroethylation of a nucleophilic carbon centre alfa to carbonyl, only a few electrophilic pentafluoroethylating reagents have been described,[10] such as (pentafluoroethyl)iodonium salts developed by Yaguposkii[11] and Umemoto,[12] and the hypervalent λ^3-iodane reagents **1**[13] and **2**[14] (Scheme 1). Shen's group[15] explored the direct pentafluoroethylation of β-keto esters using reagent **1** as electrophilic CF_2CF_3 source, DBU as base in CH_3CN affording moderate to good yields (36-82%). They showed that the bulkiness of the ester group lowered the yield. Togni´s group performed the α-perfluoroethylenation of a lactam-derived ketene silyl amide using **1**, obtaining an excellent yield under $TMSNTf_2$ catalyst (only one example).[13b]

Moreover, while important catalytic enantioselective trifluoromethylation methods of the alfa carbon in carbonyl compounds have been developped,[16] to date only one isolated asymmetric pentafluoroethylation of an oxindole has been reported (using $MgBr_2.Et_2O$/*pybox* and Togni's reagent **1**) in a remarkable Katayev's work dedicated to the asymmetric trifluoromethylation of substituted oxindoles.[17] As far as we know, there are no examples regarding the enantioselective α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates. In the past, our group have previously reported the asymmetric introduction of different electrophiles in β-dicarbonyl systems though lanthanide-*pybox* catalysis, from α-amination[18] to the most recent fluorination[19] and trifluoromethylation[20] reactions. Herein, we present our recent studies on the construction, for the first time, of enantioenriched pentafluoroethylated quaternary centres on alkyl 1-indanone-2-carboxylates using a combination of $La(OTf)_3$ with *pybox* type ligands.

RESULTS AND DISCUSSION

The first part of this work was dedicated to the synthesis of the reagents **1** and **2** (Scheme 1). The pentafluoroethylated benziodoxole **1** was fully synthesized as previously described[15] through a nucleophilic substitution of 1-fluoro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole and $TMSCF_2CF_3$ in the presence of anhydrous KF in a 95% yield. On the other hand, the 1-pentafluoroethyl-1,2-benziodoxol-3-(1H)-one reagent **2** was prepared in three steps from 2-iodobenzoic acid in 54% overall yield.[21]



Scheme 1. Preparation of reagents **1**, **2** and β-keto esters **4a-f**.

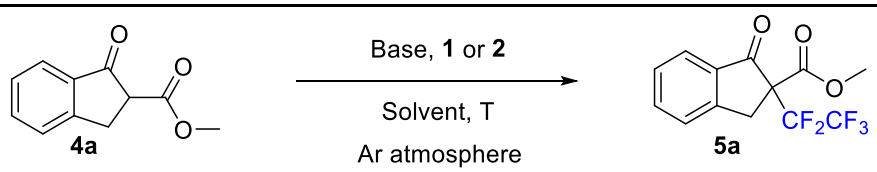
Secondly, we proceeded with the synthesis of β-keto esters **4**. These substrates were chosen as a model for the catalytic system. Most of the acylation reactions of differently substituted commercial indanones **3** were accomplished using sodium hydride as a base and dimethylcarbonate as electrophile in dried THF.[22] In some cases, methyl 1*H*-imidazole-1-carboxylate was selected as electrophile in order to avoid aromatic nucleophilic substitutions of the methoxide.[18d] The reactions (Scheme 1) underwent successfully, giving the desired products in excellent yields (86%-100%, see SI). The bulkier β-keto esters **4i-l** were prepared by treatment of methyl analogue with the corresponding alcohol using catalytic amounts of ZnO in refluxing toluene.[22]

We very soon realized that **1** and **2** were not stable when kept in a closed vial on bench. Especially for **1**, the white powder began to become slight yellow after a few days until

reaching an intense orange colour after some weeks. The ^{1}H NMR of this yellowish solid revealed the degradation of **1** to 2-(2-iodophenyl)propan-2-ol (see SI). Thus, it must be kept in a vacuum desiccator. Others have observed decomposition of solutions of analogues of reagent **1,** possessing a group CF_2CF_2R instead of CF_2CF_3, over three days in chloroform or acetonitrile solutions.[23]

Then, we studied the pentafluoroethylation reaction of **4a** as a model (Table 1). As said before, in 2016 Shen's group[15] reported the direct pentafluoroethylation of some β-keto esters using hypervalent iodine (III)-CF_2CF_3, **1**, and the organic base DBU (2 equiv.) obtaining 36-60% yields. We wanted to study the reaction using an inorganic base that could be separated by simple filtration. Potassium carbonate in THF yielded the product **5a** in a 23% yield. Other polar solvent as CH_2Cl_2 and CH_3CN enhanced the yield (51 and 59%, Table 1, entries 2 and 3). When using Cs_2CO_3 in CH_3CN the yield was raised until 69%. Disturbing is that neither higher nor lower temperatures improve the yield of **5a**. Changing the reagent **1** by **2** did not increase the reaction yield (Table 1, entry 5). Another way of activation of β-dicarbonyl compounds is the use of Lewis acids. Thus, following the idea of Katayev and Togni,[13b] magnesium bromide ethyl etherate (10%) was used obtaining **5a** in a 68% yield. With $La(OTf)_3$ (10%) the pentafluoroethylated compound was obtained in a lower 59% yield (entry 9). On the other hand, inspired by the racemic trifluoromethylations reactions developed by Cahard[9a] using the trifluoromethylcalconium salts, we added nBu$_4$NI but without higher great success. Finally, the organic base DIPEA was not a good selection for this reaction.

Table 1. Optimization of the α-pentafluoroethylation reaction of **4a**.



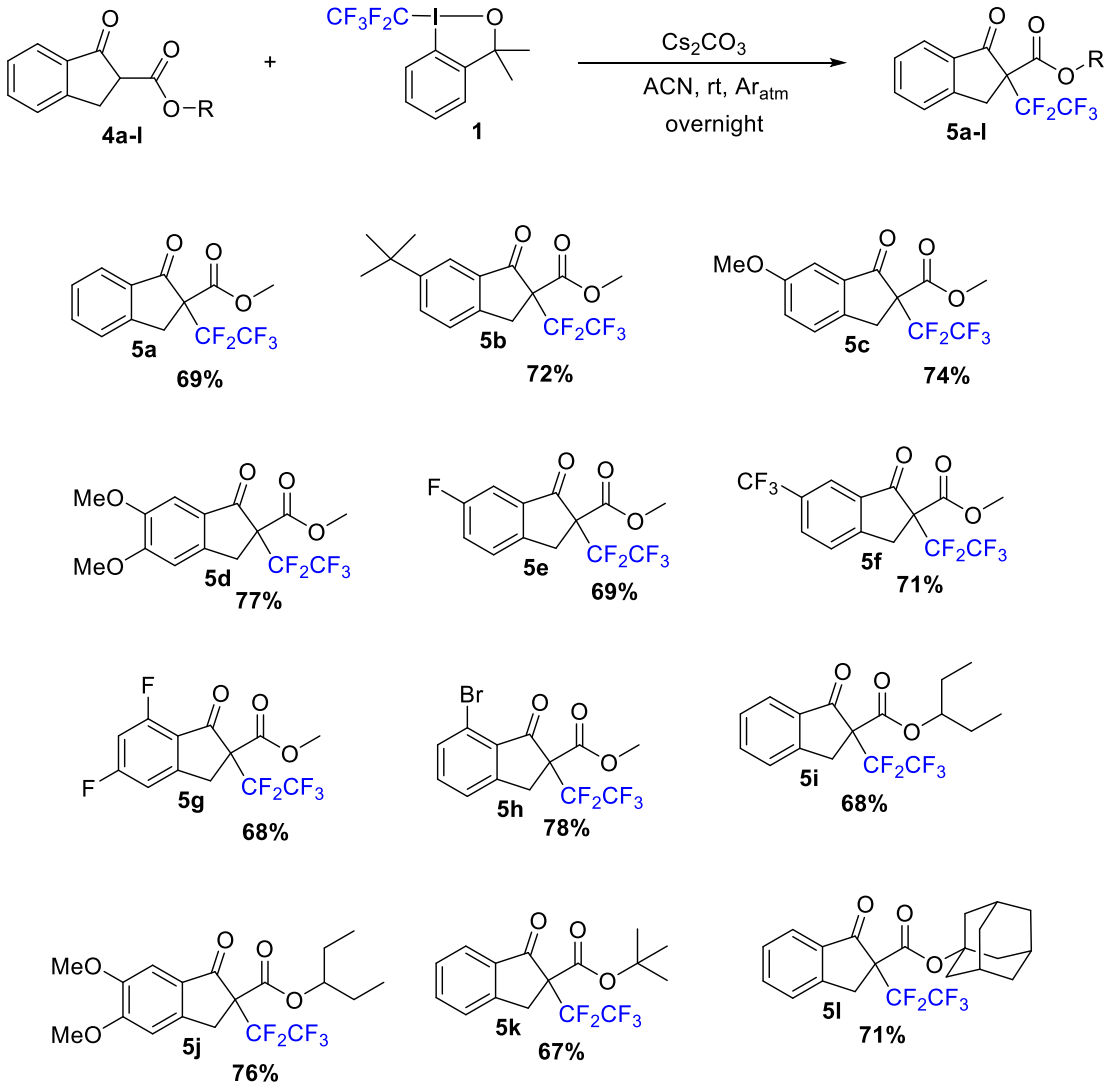
4a **5a**

Entry	Reagent	Solvent	Base	T (ºC)	Additives[a]	Yield (%)[b]
1	**1**	THF	K_2CO_3	rt	-	23
2	**1**	CH_2Cl_2	K_2CO_3	rt	-	51
3	**1**	CH_3CN	K_2CO_3	rt	-	59
4	**1**	CH_3CN	Cs_2CO_3	rt	-	69

5	**2**	CH_3CN	Cs_2CO_3	rt	-	60
6	**1**	CH_3CN	Cs_2CO_3	0	-	64
7	**1**	CH_3CN	Cs_2CO_3	50	-	57
8	**1**	CH_3CN	-	rt	$MgBr_2{\cdot}Et_2O$	68
9	**1**	CH_3CN	-	rt	$La(OTf)_3$	59
10	**1**	CH_3CN	K_2CO_3	rt	$^nBu_4NI$	62
11	**1**	CH_3CN	DIPEA	rt	-	11

Reaction conditions: **4a** (1 mmol), pentafluoroethylating reagent (1.5 mmol), base (1.5 mmol), and dry solvent. [a] Added in a 10% mol. [b] Isolated yield.

With the optimized reaction conditions in hand, we explored the scope of the reaction for several indanones (Figure 2). The methodology worked with a broad range of five membered cyclic β-keto esters including primary (**5a-h**), secondary (**5i-j**) and tertiary alcohol (**5k,l**) derivatives. Moreover, β-keto esters with either electron donating (**5b-d** and **5j,** 72-77% yields) or electron-withdrawing groups (**5e-h**, 68-78% yields) at the benzene ring provided the pentafluoroethylated quaternary carbon centre compounds with good chemical yields.



Scheme 2. Scope of the racemic α-pentafluoroethylating reaction in alkyl 1-indanone-2-carboxylates

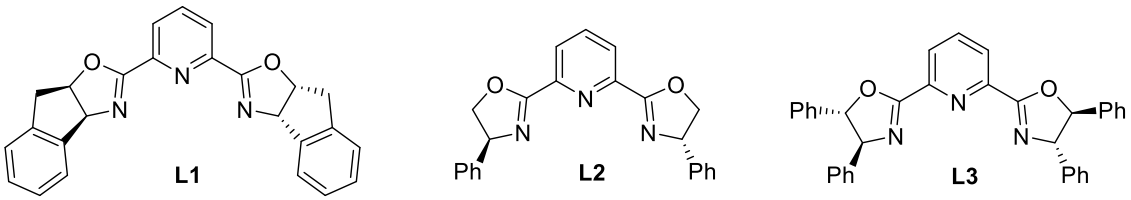
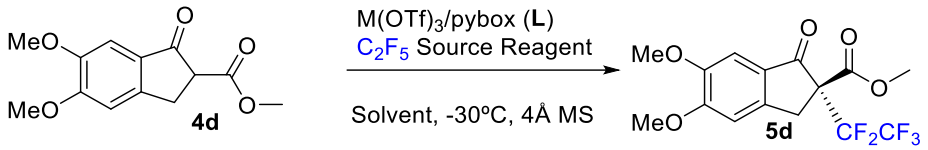


Figure 2. *Pybox* ligands used in the optimization of the electrophilic enantioselective pentafluoroethylation reaction.

Next, we studied the enantioselective version of this electrophilic reaction. In the first attempt, we selected **4d** and **1** under the combination of europium (III) triflate and (*S*,*R*)-indanyl-*pybox* (**L1**, Figure 2) as catalyst at -30ºC (Table 2, entry 1). The enantiopure *pybox* ligand will act as a chiral ligand and base. Compound **5d** was obtained in low yield and

enantioselectivity. Next, we changed the metal, moving to yterbium, achieving the fluorinated product in good yield (76%) and moderate enantioselectivity (45%). Then, we performed the reaction changing the metal source to lanthanum (III) triflate and we afforded **5d** in a 80% *ee* and good yield (entry 3). In order to improve these results, we moved to (*R*,*R*)-Ph-*pybox* (**L2**) and (*S,R*)-diPh-*pybox* (**L3)**, but the reaction was worst in both terms of yield and *ee* (entries 4 and 5). We checked CH_2Cl_2 as solvent at -78ºC, but acetonitrile at -30ºC gave better results (entry 3 vs 6). Performing the reaction at room temperature did not enhance the *ee* (entry 3 vs entry 7). Then, we used an automatic injector to make a slow addition of the pentafluorofluoroethylating agent **1** to the reaction mixture, affording the product with the same enantioselectivity but slightly lower yield (entry 3 vs entry 8). Finally, we decided to try $MgBr_2{\cdot}Et_2O$, a completely different Lewis acid that has been recently used by Katayev's group in combination with pybox-type ligands in the trifluoromethylation of oxindoles.[17] In our case we reached a 74% *ee* and a 76% yield.

Table 2. Optimization of the enantioselective pentafluoroethylation reaction.



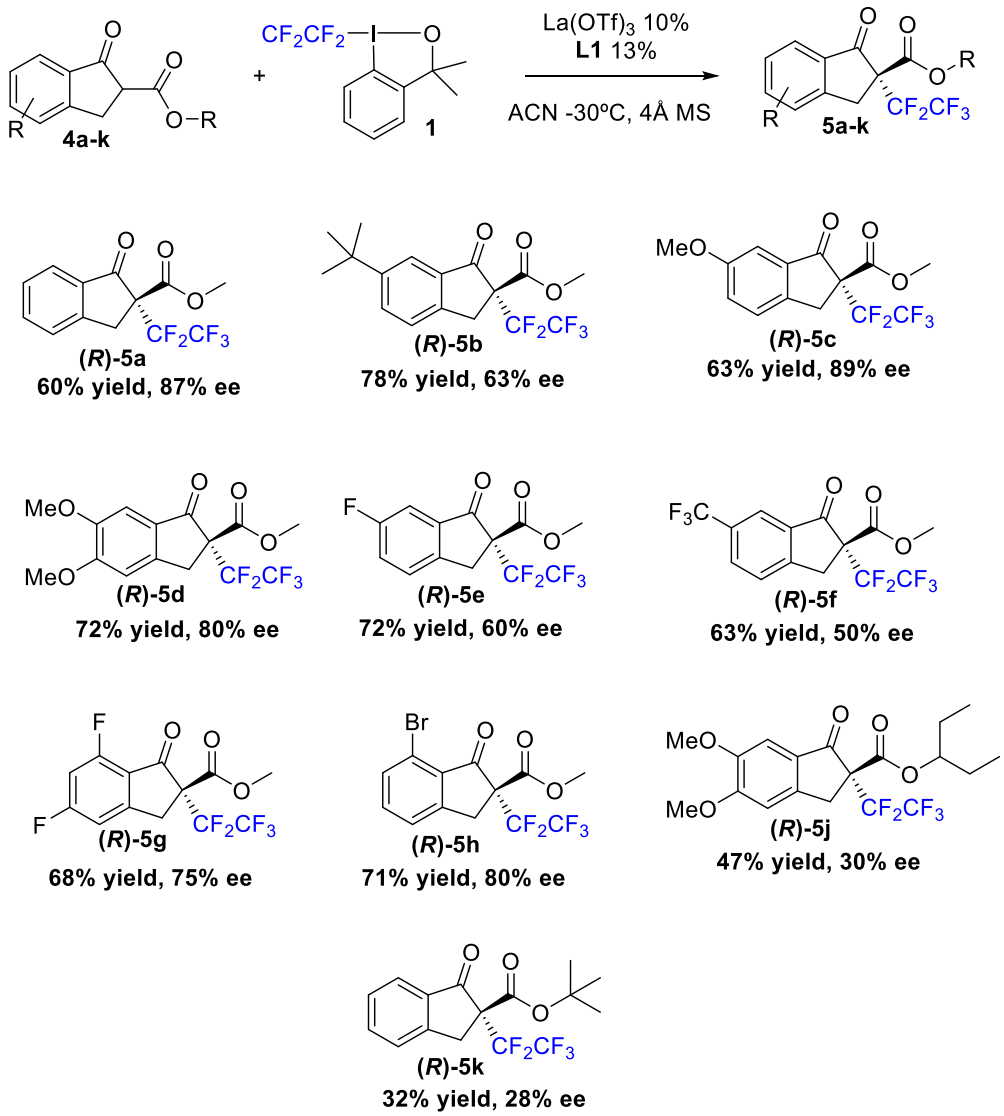
Entry	Metal	Pybox	Solvent	Reagent	Yield[a]	*ee*[b] *(major R)*
1	Eu^{+3}	**L1**	MeCN	**1**	11%	50%
2	Yb^{+3}	**L1**	MeCN	**1**	76%	45%
3	La^{+3}	**L1**	MeCN	**1**	72%	80%
4	La^{+3}	**L2**	MeCN	**1**	36%	10%
5	La^{+3}	**L3**	MeCN	**1**	56%	36%
6[c]	La^{+3}	**L1**	CH_2Cl_2	**1**	20%	25%
7[d]	La^{+3}	**L1**	MeCN	**1**	55%	63%
8[e]	La^{+3}	**L1**	MeCN	**1**	35%	75%
9	La^{3+}	**L1**	MeCN	**2**	60%	72%
10	Eu^{+3}	**L1**	MeCN	**2**	55%	70%

11	Mg^{+2}	**L1**	MeCN	**1**	76%	74%

[a] Yields of isolated pure compound **5d**. [b] Enantiomeric excesses determined by HPLC. [c] Reaction done at -78ºC. [d] Reaction done at room temperature. [e] The reagent **1** was added dropwise with an automatic injector.

Next, we wanted to explore the scope of the reaction (Scheme 3). So, a range of cyclic β-keto esters were tested using the optimized pre-catalyst combination, $La(OTf)_3$, **L1** and hypervalent iodine(III)-CF_2CF_3 **1** in acetonitrile at -30ºC, under argon atmosphere and in presence of 4Å molecular sieves. The reaction was performed with a series of compounds derived from primary esters (**4a-h**). In general, the presence of electron-withdrawing groups in an aromatic position injures the *ee's* (**5e**-**h,** 50-80% *ee*). In contrary, those primary β-keto esters with no substituents or with electron-donating groups (H, OMe) in the aromatic positions gave around or over 80% *ee*. The presence of sterically bulky ^tBu and CF_3 groups at sixth position (**5b** and **5f**) diminishes the *ee* independently of the electronic effects of the substituent. Once again, the effect of a bulkier ester is harmful for the enantiodifferentiation (**5a** vs **5k** and **5d** vs **5j**), as we have previously seen in our related previous work of trifluoromethylation.[20]

The assignment of the absolute configuration of compounds **5a-k** was based on the comparison of the signal of their Cotton Effect (all compounds **5** present a negative Cotton effect, see SI), as well as their negative specific rotation values. Both properties were consistent with the ones of the previosly prepared trifluoromethylated analogues.[9a,16c,20] We assigned the absolute configuration *R* to all compounds **5**.



Scheme 3. Scope of the enantioselective α-pentafluoroethylation of cyclic β-keto esters.

The activation of Togni type reagents have been previously studied by ^{19}F NMR in different research groups including us.[16g,17,20,24] In this work, we mixed **1** with $La(OTf)_3$ (1:1) in deuterated acetonitrile. After 5 minutes, **1** was converted to a new species with a chemical shift of the CF_3 from δ = -81.7 to δ = -79.5 ppm and a chemical shift of the CF_2 from δ = -99.7 to δ = -82.6 ppm. Thus, a very significant change was observed which indicates the coordination of **1** to lanthanide. Further ^{19}F NMR-based titration furnished a Job plot indicating a 1:1 complexation of **1** with $La(OTf)_3$ (Figure 3), in agreement with some examples in the literature.[13b,20] Thus, we propose the formation of the cationic iodonium species **6** shown in Figure 3.

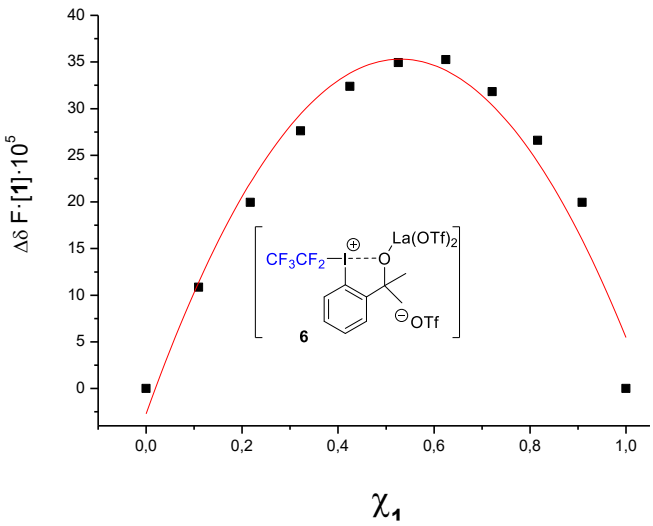
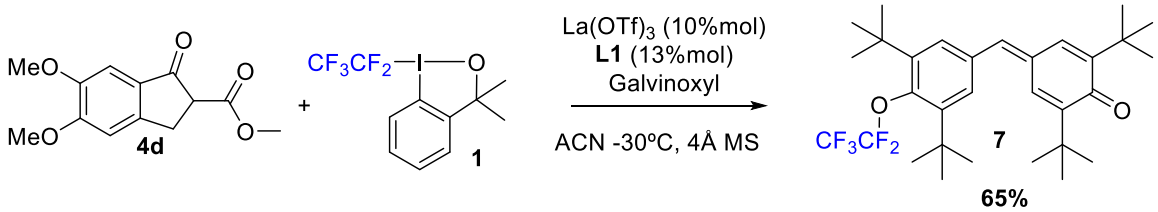
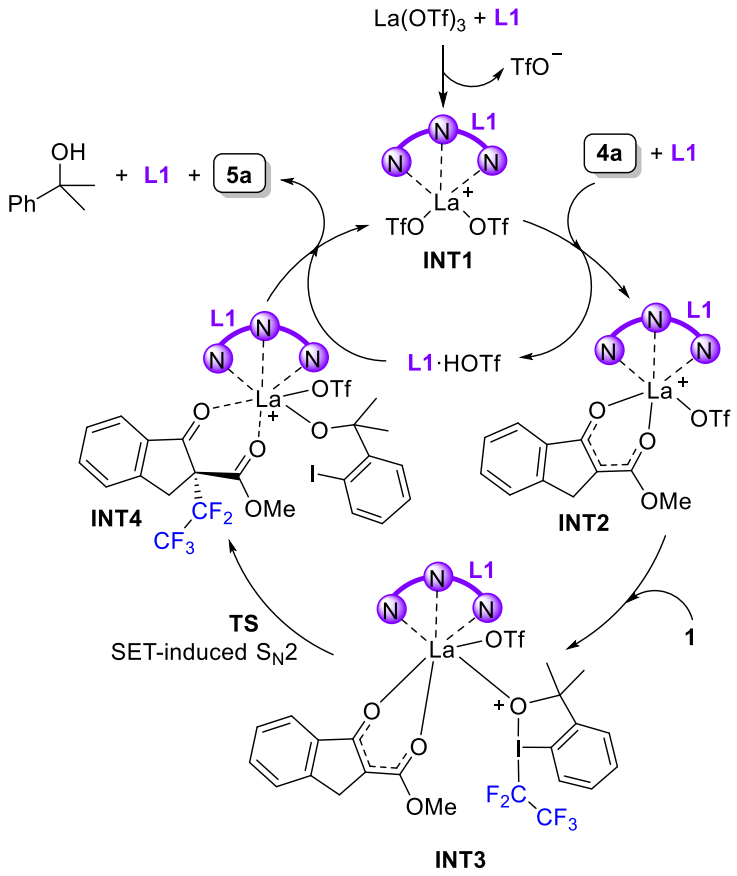


Figure 3. Job plot (**1**+La(OTf)$_3$) by ^{19}F NMR (CD_3CN, 25°C, 400 MHz) and the proposed cationic iodonium species **6** formation.

Next, the enantioselective catalytic reaction was tested in the presence of Galvinoxyl free radical, which is a classical radical scavenger. After 36 hours, the only products detected in the reaction of **4d** and **1** were the starting material and the pentafluoroethylated Galvinoxyl **7** (Scheme 4). Thus, the presence of Galvinoxyl inhibits the pentafluoroethylation reaction. This new compound **7** was isolated in a 65% yield and it was completely characterized by spectroscopic techniques, including HR-ESI-MS. The radical reaction pathway indicated by this result is in line with the known propensity of hypervalent iodine (III)-CF_3 to generate CF_3 radicals.[13b, 17, 20, 25]



Scheme 4. Pentafluoroethylation conducted in the presence of Galvinoxyl with formation of **7.**



Scheme 5. Proposed catalytic cycle for the formation of **(*R*)-5a** from **4a** with $La(OTf)_3$, reagent **1** and the *pybox* ligand **L1**.

At the present stage we assume that the pentafluoroethylation step proceeds *via* a similar mechanistic scenario as we suggested in our recent work on the enantioselective α-trifluoromethylation of cyclic β-keto esters.[20] First, **INT1** is formed by coordination of the *pybox* ligand to the metal by displacement of a OTf. *Pybox* ligand is the responsible for the abstraction of the α-H in β-keto ester. Next, coordination of **enolate-4a** and reagent **1** to metal centre is produced to form **INT2** and the subsequent coordination of reagent **1** is based on a complex **6**, which formation has been demonstrated by this work by F NMR experiments (figure 3). Then, the coordination pattern of the β-keto ester **4a** in **INT3** reveals an efficient blockage of the prochiral *Si* face of the La(III) enolate. The hindrance of the *Si* face of this intermediate **INT3** results in an efficient S_N2-like saddle point TS, which consists of a *Re* attack of the C_α atom of the enolate moiety on the carbon atom of the CF_2CF_3 group in **1**, with concomitant departure of the iodine-aryl group. We propose a SET induced S_N2-type pathway, thus leading the formation of CF_3CF_2 radicals that can explain the control of selectivity. In fact, hypervalent iodine (III)-CF_3 reagent has been described as a precursor of electrophilic CF_3

radical species.[25] To date however, there exist only very few examples on their use in asymmetric trifluoromethylation.[13b, 17, 20] This report is thereby the first example on the construction of enantioenriched pentafluoroethylated carbon centres using hypervalent iodine-based reagents proceeding through a SET pathway.

Conclusions

In summary, an efficient method for the enantioselective α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates is described. Racemic conditions were optimized using Cs_2CO_3 as base in acetonitrile. The enantioenriched pentafluorinated β-oxo esters were prepared using an hypervalent iodine(III)-CF_2CF_3 reagent and a lanthanide-*pybox* pre-catalyst to achieve good chemical yields and *ee*'s (up to 89%). The enantioselectivity of the reaction stems from the efficient blockage of one of the prochiral faces of the La(III) enolate by one unit of the C2-symmetric ligand. We propose that the mechanism proceeds through a SET pathway involving CF_2CF_3 radicals.

EXPERIMENTAL SECTION

General information: The chemicals and solvents were purchased from Sigma-Aldrich or Fluorochem. Solvents were distilled and stored under argon in molecular sieves. IR spectra were determined either by transmission or by attenuated total reflectance mode (ATR). Enantiomeric excesses were determined, unless otherwise stated, by HPLC using a chiral column Daicel-AD-H. Optical rotations were measured with a Rudolph Autopol I polarimeter and they are reported as follows: $[\alpha]_D^{rt}$ (c in g per 100 mL, solvent). ^{1}H NMR spectra were recorded operating at 250, 360, and 400 MHz. ^{13}C NMR spectra were registered at 63, 91, and 101 MHz. ^{19}F NMR spectra were recorded decoupled to protons. Circular Dicroism were recorded in a spectropolarimeter J-715, JASCO, equipped with Peltier thermostat module. HRMS were recorded by a Bruker micrOTOF-QII mass spectrometer (fly time analyzer) through positive electrospray ionization. Compounds **4 (4a,**[20] **4b**,[20] **4c**,[20] **4d**,[15] **4e**,[20] **4f**[20], **4g**,[20] **4h**,[20] were prepared as previously reported in our group.[20] Compounds **4i**,[19] 4k,[19] and **4l**[19] were synthesized by a transesterification reaction from the corresponding methyl ester following a methodology adapted from a previously reported method of our group.[22]

Preparation of 3,3-dimethyl-1-(perfluoroethyl)-1,3-dihydro-1λ $_3$-benzo[d][1,2]iodoxole (**1**):[15] In flame dried Schlenk, 1.70 g (6.07 mmol, 1 equiv.) of 1-fluoro-3,3-dimethyl-1,3-dihydro-1λ$_3$-

benzo[*d*][1,2]iodoxole were dissolved in 12 mL of dry acetonitrile, the solution was cooled down until -20ºC. Then, 10 mg (0.1 equiv.) were added to the solution and 1.20 mL (6.07 mmol) of $TMSCF_2CF_3$ were added carefully to the solution. The reaction was stirred for 12 hours under inert atmosphere. When the reaction was over, the solution was evaporated under high vacuum affording a beige solid. This crude was purified by flash column chromatography (hexane 9: ethyl acetate 1) yielding **1** in a 95% yield (2.19 g, 5.7 mmol). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.51 (s, 6H), 7.42 (m, 2H), 7.56 ppm (m, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.7 (s, 3F), -99.7 ppm (s, 2F).

Preparation of 1-(perfluoroethyl)-1λ $_3$-benzo[d][1,2]iodoxol-3(1H)-one (**2**):[14] *Step 1*: In round-bottomed flask, $NaIO_4$ (4.04 mmol) and 2-iodo benzoic acid (4 mmol) were suspended in a mixture AcOH/water (2.5 mL : 5.0 mL) under air with vigorous stirring. The mixture was refluxed for 4h and then diluted with 60 mL of cold water. After vigorous stirring for 10 minutes, the suspension was filtered and washed with iced water and cold acetone, respectively. The white solid was dried in a vacuum desiccation at 50ºC, and it was identified as 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (94% yield). ^{1}H NMR (250 MHz, [D]DMSO, 25ºC, TMS): δ = 4.87 (bs, 1H), 7.89 (t, $^3J_{(H,H)}$ = 7.3 Hz, 1H), 8.03 (m, 1H), 8.14 (dd, $^3J_{(H,H)}$ = 7.3 Hz, $^4J_{(H,H)}$ = 1.4 Hz, 1H), 8.31 ppm (d, $^3J_{(H,H)}$ = 7.3 Hz, 1H). *Step 2*: In a round-bottomed flash, 4 mmol of 1-hydroxy-1,2-benziodoxol-3-(1H)-one were dissolved in 4 mL of acetic anhydride, then the suspension was heated under reflux for 30 minutes. The mixture was cooled in a freezer overnight. The crystalized solid isolated from the organic phase and dried in a vacuum oven to provide the 1-acetoxy-1,2-benziodoxol-3-(1H)-one in a 95% yield. ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.28 (s, 3H), 7.74 (t, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.99 (m, 2H), 8.29 ppm (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H). *Step 3*: In a well dried Schlenk flash, 1 mmol of 1-acetoxy-1,2-benziodoxol-3-(1H)-one were dissolved in a 5 mL of dry dichloromethane. Then, 2 mmol of the Ruppert-Prakash reagent ($TMSCF_3$) were added carefully. Next, 1%mol of KF were added in one portion. After 2 hours stirring, the solvent was removed under high vacuum. The crude purified by flash column chromatography, yielding the titled compound **2** in a 60% yield. ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 7.80 (m, 3H), 8.47 ppm (m, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ = -81.1 (s, 3F), -91.4 ppm (s, 2F).

Pentan-3-yl 5,6-dimethoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxy-late (**4j**): The methodology of preparation was adapted from a reported procedure:[22] In a round-bottomed flask 0.50 g of **4d** (1 eq.), ZnO (0.2 eq.) and the corresponding alcohol (10 equivalents) were dissolved in toluene. The reaction mixture was heated up to 140ºC, under a distillation setup, until total conversion was observed by TLC (8 hours). Then, the reaction

mixture was filtered through Celite® and the solvent was removed under reduced pressure. The product obtained was purified by column chromatography on silica-gel (hexane: ethyl acetate = 10:1) obtaining 0.51 g of **4j** (84% yield). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 0.84 (m, 6H), 1.53 (m, 4H), 3.23 (dd, $^{3}J_{(H,H)}$ = 7.2 Hz, $^{2}J_{(H,H)}$ = 18.0 Hz, 1H), 3.39 (dd, $^{3}J_{(H,H)}$ = 3.6, $^{2}J_{(H,H)}$ =18.0 Hz, 1H), 3.65 (dd, $^{3}J_{(H,H)}$ = 3.6 Hz, $^{3}J_{(H,H)}$ = 7.2 Hz, 1H), 3.84 (s, 3H), 3.92 (s, 3H), 4.85 (quint, $^{3}J_{(H,H)}$ = 7.2 Hz, 1H), 6.87 (s, 1H), 7.11 ppm (s, 1H). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 9.5, 9.6, 26.5, 26.5, 30.1, 53.8, 56.0, 56.3, 78.2, 104.7, 107.2, 127.9, 149.2, 149.6, 155.9, 169.3, 198.2 ppm. IR (ATR): 2967, 1731, 1591, 1313, 1194, 1021 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{22}O_5Na$ 349.0270; found 349.0264.

General procedure for the enantioselective electrophilic α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates: In a 10 ml dried Schlenk flask in presence of 4Å molecular sieves, $La(OTf)_3$ (0.10 eq.) and the ligand (*S,R*)-indanyl-*pybox* (0.13 eq.) were dissolved in dry acetonitrile (3 ml). The colourless reaction mixture was left stirring at room temperature under inert atmosphere overnight. Next, the corresponding β-keto ester (80 mg; 1 eq.) was added to the reaction mixture and it was left stirring at room temperature for 30 minutes. Then, the reaction mixture was cooled down until -35ºC and, once at this temperature, the pentafluoroethylating agent (1.3 eq.) was added to the mixture in one portion. The reaction mixture was left at this temperature under argon atmosphere until complete conversion of the reagent observed by TLC. Afterwards, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel.

Methyl (R)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5a**):[16] According to the general procedure, 77 mg (0.25 mmol) of **5a** were synthesized from 80 mg of starting material (60% yield) as colourless oil after purification on silica gel (hexane: ethyl acetate = 2:1). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.62 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 3.82 (s, 3H), 3.93 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 7.47 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.55 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.71 (td, $^{3}J_{(H,H)}$ = 7.5 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.85 ppm (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, 25ºC, TMS): δ = -79.6 (s, 3F), -115.0 (d, $^{2}J_{(F,F)}$ = 278.0 Hz, 1F), -116.8 ppm (d, $^{2}J_{(F,F)}$ = 278.0 Hz, 1F); $[\alpha]_D^{20}$ = -21.9 (c = 0.0032 in MeCN), 87% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 11.14 min and t_r(*S*) = 18.34 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-(tert-butyl)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5b**): According to the general procedure, 86 mg (0.24 mmol) of **5b** were synthesized from 75 mg of starting material (78% yield) as colourless oil after purification on silica gel (hexane:

dichloromethane = 2:1). ^{1}H NMR (360 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.36 (s, 9H), 3.57 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.83 (s, 3H), 3.87 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.47 (d, $^{3}J_{(H,H)}$ = 7.8 Hz, 1H), 7.57 (d, $^{3}J_{(H,H)}$ = 7.8 Hz, 1H), 7.82 ppm (bs, 1H); ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 278.1 Hz, 1F), -116.6 ppm (d, $^{2}J_{(F,F)}$ = 278.1 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 31.2, 33.0 (bs), 53.8, 62.7 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 77.2, 115.5 (m), 120.0 (m), 121.7, 125.7, 133.9, 134.4, 149.0, 152.2, 165.0 (d, $^{3}J_{(C,F)}$ = 6.8 Hz), 192.4 ppm. IR (ATR): 2961, 1785, 1730, 1435, 1191, 1072 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}F_5O_3Na$ 387.0990; found 387.0986. $[\alpha]_D^{20}$ = -12.6 (c = 0.0039 in MeCN), 63% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 6.37 min and t_r(*S*) = 6.93 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-methoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5c**): According to the general procedure, 110 mg of **5c** were synthesized from 100 mg of starting material (84% yield) as colourless oil after purification on silica gel (hexane: ethyl acetate = 2:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.53 (d, $^{2}J_{(H,H)}$ = 18.0 Hz, 1H), 3.81 (m, 7H), 7.23 (d, $^{4}J_{(H,H)}$ = 2.3 Hz, 1H), 7.27 (dd, $^{3}J_{(H,H)}$ = 8.4 Hz, $^{4}J_{(H,H)}$ = 2.3 Hz, 1H), 7.41 ppm (d, $^{3}J_{(H,H)}$ = 8.4 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 278.8 Hz, 1F), -116.5 ppm (d, $^{2}J_{(F,F)}$ = 278.8 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 32.8 (bs), 53.9, 55.7, 62.9 (dd, $^{2}J_{(C,F)}$ = 22.3 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 106.2, 112.8 (m), 127.7 (m), 126.1, 126.9, 135.2, 144.5, 160.1, 165.0 (d, $^{3}J_{(C,F)}$ = 6.7 Hz), 192.2 ppm. IR (ATR): 2924, 1725, 1495, 1434, 1194, 1026 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{11}F_5O_4Na$ 361.0470; found 361.0467; $[\alpha]_D^{20}$ = -10.0 (c = 0.0027 in MeCN), 85% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 8.59 min and t_r(*S*) = 10.58 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-5,6-dimethoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5d**):[15] According to the general procedure, 84 mg (0.23 mmol) of **5d** were synthesized from 80 mg of starting material (72% yield) as colourless solid after purification on silica gel (hexane: ethyl acetate = 2:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.51 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 3.82 (m, 4H), 3.94 (s, 3H), 4.02 (s, 3H), 6.93 (s, 1H), 7.21 ppm (s, 1H), ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 279.7 Hz, 1F), -117.5 ppm (d, $^{2}J_{(F,F)}$ = 279.7 Hz, 1F); $[\alpha]_D^{20}$ = -14.0 (c = 0.0032 in MeCN), 80% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 44.36 min and t_r(*S*) = 54.47 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99:1) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-fluoro-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5e**): According to the general procedure, 90 mg (0.28 mmol) of **5e** were synthesized from 80 mg of starting material (72% yield) as colourless oil after purification on silica gel (hexane: dichloromethane = 7:3). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.59 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.82 (s, 3H), 3.89 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.45 (m, 2H), 7.53 ppm (dd, $^{3}J_{(H,F)}$ = 8.3 Hz, $^{4}J_{(H,H)}$ = 2.1 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-78.6 (s, 3F), -112.9 (s, 1F), -114.8 (d, $^{2}J_{(F,F)}$ = 278.5 Hz, 1F), -116.6 ppm (d, $^{2}J_{(F,F)}$ = 278.5 Hz, 1F). ^{13}C[^{1}H] NMR (91 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 32.9 (d, $^{3}J_{(C,F)}$ = 3.2 Hz), 54.0, 63.1 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 111.2 (d, $^{2}J_{(C,F)}$ = 22.5 Hz), 112.2 (m), 117.6 (m), 124.2 (d, $^{2}J_{(C,F)}$ = 24.0 Hz), 127.7 (d, $^{3}J_{(C,F)}$ = 8.1 Hz), 135.7 (d, $^{3}J_{(C,F)}$ = 8.1 Hz), 146.9 (d, $^{4}J_{(C,F)}$ = 2.2 Hz), 161.5, 164.0, 164.5 (d, $^{3}J_{(C,F)}$ = 7.1 Hz), 191.2 ppm. IR (ATR): 2921, 1751, 1721, 1614, 1296, 1149 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_8F_6O_3Na$ 349.0270; found 349.0264. $[\alpha]_D^{20}$ = -19.7 (c = 0.0036 in MeCN), 60% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 7.34 min and t_r(*S*) = 8.01 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99:1) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-(trifluoromethyl)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5f**): According to the general procedure, 71 mg (0.16 mmol) of **5f** were synthesized from 80 mg of starting material (63% yield) as colourless oil after purification on silica gel (hexane: dichloromethane = 9:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.68 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.83 (s, 3H), 4.01 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.70 (d, $^{3}J_{(H,H)}$ = 8.1 Hz, 1H), 7.95 (dd, $^{3}J_{(H,H)}$ = 8.1 Hz, $^{4}J_{(H,H)}$ = 1.7 Hz, 1H), 8.11 ppm (d, $^{4}J_{(H,H)}$ = 1.7 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-63.2 (s, 3F), -79.6 (s, 3F), -114.7 (d, $^{2}J_{(F,F)}$ = 278.7 Hz, 1F), -116.7 ppm (d, $^{2}J_{(F,F)}$ = 278.7 Hz, 1F). ^{13}C[^{1}H] NMR (91 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 33.5 (m), 54.2, 62.6 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.8 Hz), 112.2 (m), 117.6 (m), 122.7 (q, $^{3}J_{(C,F)}$ = 3.9 Hz), 123.3 (q, $^{1}J_{(C,F)}$ = 273.1 Hz), 127.1, 131.5 (q, $^{2}J_{(C,F)}$ = 32.7 Hz), 132.7 (d, $^{3}J_{(C,F)}$ = 3.9 Hz), 134.3, 154.5, 164.2 (d, $^{3}J_{(C,F)}$ = 7.1 Hz), 191.0 ppm. IR (ATR): 2922, 1751, 1722, 1614, 1257, 1150. cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_8F_8O_3Na$ 399.0238; found 399.0229. $[\alpha]_D^{20}$ = -8.6 (c = 0.0022 in MeCN), 50% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 6.04 min and t_r(*S*) = 6.82 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-5,7-difluoro-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5g**): According to the general procedure, 73 mg (0.21 mmol) of **5g** were synthesized from 70 mg of starting material (68% yield) as a colourless oil after purification on silica gel (hexane: dichloromethane = 1:1). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.59 (d, $^{2}J_{(H,H)}$ = 18.1 Hz, 1H), 3.85 (s, 3H), 3.94 (dd, $^{2}J_{(H,H)}$ = 18.1 Hz, 1H), 6.85 (td, $^{3}J_{(H,F)}$ = 9.0 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.04 ppm (d, $^{3}J_{(H,F)}$ = 7.6 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ = -79.6 (s,

3F), -95.1 (d, $^{4}J_{(F,F)}$ = 14.8 Hz, 1F), -107.1 (d, $^{4}J_{(F,F)}$ = 14.8 Hz, 1F), -114.9 (d, $^{2}J_{(F,F)}$ = 279.5 Hz, 1F), -117.0 ppm (d, $^{2}J_{(F,F)}$ = 279.5 Hz, 1F). $^{13}C[^{1}H]$ NMR (91 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 33.3, 54.2, 62.9 (dd, $^{2}J_{(C,F)}$ = 22.0 Hz, $^{2}J_{(C,F)}$ = 18.5 Hz), 104.9 (dd, $^{3}J_{(C,F)}$ = 27.0 Hz, $^{3}J_{(C,F)}$ = 23.1 Hz), 109.5 (dd, $^{3}J_{(C,F)}$ = 23.1 Hz, $^{3}J_{(C,F)}$ = 4.3 Hz), 113.4 (m), 116.8 (m), 125.3 (m), 143.3, 155.1 (dd, $^{3}J_{(C,F)}$ = 12.3 Hz, $^{4}J_{(C,F)}$ = 3.1 Hz), 160.5 (dd, $^{1}J_{(C,F)}$ = 270.4 Hz, $^{3}J_{(C,F)}$ = 14.2 Hz), 164.2 (d, $^{3}J_{(C,F)}$ = 11.1 Hz), 168.8 (dd, $^{1}J_{(C,F)}$ = 270.4 Hz, $^{3}J_{(C,F)}$ = 14.2 Hz), 186.5 ppm. IR (ATR): 2968, 1751, 1721, 1622, 1495, 1258 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_7F_7O_3Na$ 367.0176; found 367.0176. $[\alpha]_D^{20}$ = -16.3 (c = 0.0032 in MeCN), 75% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 9.96 min and t_r(*S*) = 13.48 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-7-bromo-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5h**): According to the general procedure, 81 mg (0.21 mmol) of **5h** were synthesized from 80 mg of starting material (71% yield) as a colourless oil after purification on silica gel (hexane: dichloromethane = 6:4). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.56 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 3.83 (s, 3H), 3.89 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 7.50 (m, 2H), 7.84 ppm (dd, $^{3}J_{(H,F)}$ = 7.1 Hz, $^{4}J_{(H,H)}$ = 1.3 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25ºC, TMS): δ = -79.1 (s, 3F), -1145 (d, $^{2}J_{(F,F)}$ = 279.1 Hz, 1F), -116.4 ppm (d, $^{2}J_{(F,F)}$ = 279.1 Hz, 1F). $^{13}C[^{1}H]$ NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 32.4 (bs), 54.1, 63.9 (dd, $^{2}J_{(C,F)}$ = 22.0 Hz, $^{2}J_{(C,F)}$ = 18.5 Hz), 112.5 (m), 117.5 (m), 125.1, 131.5, 133.7, 136.5, 154.1, 164.5 (d, $^{3}J_{(C,F)}$ = 7.3 Hz), 189.2 ppm. IR (ATR): 2961, 1758, 1722, 1618, 1284 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_8BrF_5O_3Na$ 408.9469; found 408.9463. $[\alpha]_D^{20}$ = -14.3 (c = 0.0031 in MeCN), 80% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 13.58 min and t_r(*S*) = 19.80 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Pentan-3-yl 1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5i**): According to the general procedure, 99 mg (0.28 mmol) of **5i** were synthesized from 100 mg of starting material (68% yield) as a colourless oil after purification on silica gel (hexane: dichloromethane = 9:1). ^{1}H NMR (360 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 0.83 (m, 6H), 1.58 (m, 4H), 3.61 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.88 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 4.83 (quint, $^{3}J_{(H,H)}$ = 7.2 Hz, 1H), 7.46 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.54 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.69 (td, $^{3}J_{(H,H)}$ = 7.5 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.83 ppm (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-78.8 (s, 3F), -114.0 (d, $^{2}J_{(F,F)}$ = 279.4 Hz, 1F), -115.0 ppm (d, $^{2}J_{(F,F)}$ = 279.4 Hz, 1F). $^{13}C[^{1}H]$ NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 9.1, 26.0, 33.6 (d, $^{3}J_{(C,F)}$ = 2.6 Hz), 62.7 (dd, $^{2}J_{(C,F)}$ = 22.5 Hz, $^{2}J_{(C,F)}$ = 18.6 Hz), 80.5, 113.0 (m), 118.1 (m), 125.3, 126.1, 128.4, 134.2, 136.1, 151.4, 164.2 (d, $^{3}J_{(C,F)}$ = 11.1 Hz), 192.5 ppm. IR (ATR):

2924 1721, 1607, 1464, 1274, 1185. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}F_5O_3Na$ 387.0990; found 387.0994.

Pentan-3-yl (R)-5,6-dimethoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5j**): According to the general procedure, 45 mg (0.11 mmol) of **5j** were synthesized from 70 mg of starting material (47% yield) as transparent oil after purification on silica gel (hexane: dichloromethane = 9:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 0.87 (m, 6H), 1.61 (m, 4H), 3.50 (d, $^2J_{(H,H)}$ = 17.3 Hz, 1H), 3.78 (d, $^2J_{(H,H)}$ = 17.3 Hz, 1H), 3.94 (s, 3H), 4.02 (s, 3H), 4.85 (quint, $^3J_{(H,H)}$ = 6.9 Hz, 1H), 6.93 (s, 1H), 7.21 ppm (s, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-78.6 (s, 3F), -114.2 (d, $^2J_{(F,F)}$ = 278.9 Hz, 1F), -115.4 ppm (d, $^2J_{(F,F)}$ = 278.9 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 9.3, 26.0, 33.2 (m), 56.2, 56.4, 62.9 (dd, $^2J_{(C,F)}$ = 22.0 Hz, $^2J_{(C,F)}$ = 18.5 Hz), 80.3, 105.3, 106.9, 112.0 (m), 117.5 (m), 127.0, 143.3, 147.3, 150.2, 164.6 (d, $^3J_{(C,F)}$ = 7.0 Hz), 190.9 ppm. IR (ATR): 2971, 1762, 1714, 1592, 1504, 1201 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{21}F_5O_5Na$ 447.1201; found 447.1198. $[\alpha]_D^{20}$ = -6.1 (c = 0.0040 in MeCN), 30% *ee* (absolute configuration *R*). HPLC: t_r(*S*) = 7.19 min and t_r(*R*) = 7.81 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Tert-butyl (R)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5k**):[16] According to the general procedure, 28 mg of **5k** were synthesized from 60 mg (0.25 mmol) of starting material (32% yield) as colourless oil after purification on silica gel (hexane: ethyl acetate = 9:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.45 (s, 9H), 3.56 (d, $^2J_{(H,H)}$ = 17.7 Hz, 1H), 3.85 (d, $^2J_{(H,H)}$ = 17.7 Hz, 1H), 7.45 (t, $^3J_{(H,H)}$ = 7.5 Hz, 1H), 7.53 (d, $^3J_{(H,H)}$ = 7.5 Hz, 1H), 7.68 (td, $^3J_{(H,H)}$ = 7.5 Hz, $^4J_{(H,H)}$ = 1.2 Hz, 1H), 7.83 ppm (d, $^3J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ =-78.6 (s, 3F), -113.6 (d, $^2J_{(F,F)}$ = 278.3 Hz, 1F), -115.6 ppm (d, $^2J_{(F,F)}$ = 278.3 Hz, 1F). $[\alpha]_D^{20}$ = -6.8 (c = 0.0033 in MeCN), 28% *ee* (absolute configuration *R*).

Adamantyl 1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**5l**): According to the general procedure, 107 mg (0.25 mmol) of **5l** were synthesized from 110 mg of starting material (71% yield) as a transparent liquid after purification on silica gel (hexane: ethyl acetate = 9:1). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.64 (bs, 6H), 2.08 (bs, 6H), 2.16 (bs, 3H), 3.55 (d, $^2J_{(H,H)}$ = 17.6 Hz, 1H), 3.84 (d, $^2J_{(H,H)}$ = 17.6 Hz, 1H), 7.48 (m, 2H), 7.68 (t, $^3J_{(H,H)}$ = 7.5 Hz, 1H), 7.83 ppm (t, $^3J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ = --78.5 (s, 3F), -113.6 (d, $^2J_{(F,F)}$ = 279.9 Hz, 1F), -115.60 ppm (d, $^2J_{(F,F)}$ = 279.9 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 30.9, 33.6 (bs), 35.9 40.8, 63.2 (dd, $^2J_{(C,F)}$ = 22.2 Hz, $^2J_{(C,F)}$ = 18.3 Hz), 84.7, 112.7 (m), 118.6 (m), 125.3, 126.1, 128.3, 134.2, 136.0, 151.6, 162.6 (d, $^3J_{(C,F)}$ = 10.9

Hz), 192.8 ppm. IR (ATR): 2914, 2853, 1752, 1725, 1607, 1457, 1204 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{21}F_5O_3Na$ 451.1303; found 451.1296.

2,6-Di-tert-butyl-4-(3,5-di-tert-butyl-4-(pentafluoroethoxy)benzylidene)cyclohexa-2,5-dien-1-one (**7**): ^1H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.30 (bs, 36H), 6.59 (bs, 3H), 6.84 ppm (bs, 2H). ^{19}F NMR (235 MHz, $CDCl_3$, 25ºC, TMS): δ = -77.8 (s, 3F), -117.1 ppm (s, 2F). $^{13}C[^1H]$ NMR (63 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 29.3, 29.6, 35.0, 35.6, 115.2 (m), 121.2 (m), 124.3, 133.5, 134.8, 135.5, 150.5, 186.3 ppm. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{31}H_{41}F_5O_2$ 563.2919; found 563.2911.

Associated content

The Supporting Information includes the ^1H NMR, ^{13}C NMR, ^{19}F NMR spectra and ESI and HPLC chromatograms.

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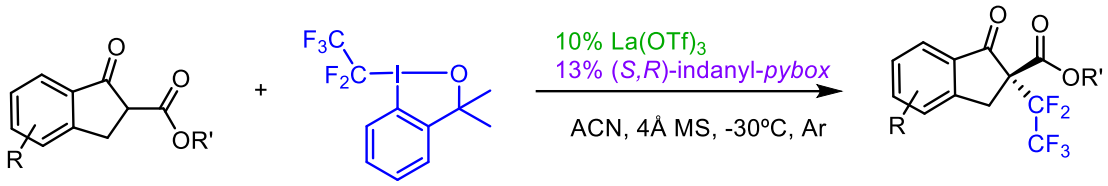
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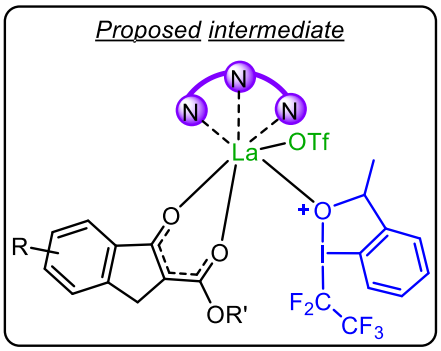
Proposed intermediate
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