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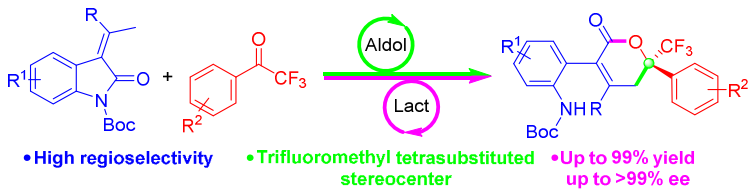
Enantioselective Synthesis of Trifluoromethyl α,β-Unsaturated-δ-lactones via Vinylogous Aldol-Lactonization Cascade

Simone Crotti,† Nicola Di Iorio,† Andrea Mazzanti, Paolo Righi, and Giorgio Bencivenni*

Department of Industrial Chemistry "Toso Montanari", University of Bologna, Viale del Risorgimento 4, 40136, Bo-Italy.



ABSTRACT

The novel vinylogous aldol-lactonization cascade of alkylidene oxindole with trifluoromethylketones is presented. The reaction, catalyzed by a bifunctional tertiary amine, provides an efficient application of the vinylogous reactivity of alkylidene oxindoles for the preparation of enantioenriched trifluoromethylated α,β-unsaturated-δ-lactones.

INTRODUCTION

Alkylidene oxindoles are suitable substrates for vinylogous processes.[1] They have been successfully employed as nucleophiles in many reactions with different electrophilic partners.[2] Among these, the recent works by Han on the reaction of oxindoles with 2,3-indolinediones, extended their vinylogous reactivity to cascade processes for the first time.[3] The excellent yields and the high stereoselectivity obtained, also with alkylidene oxindoles bearing prochiral site at the γ-position, showed the potentiality of these reactions as promising tools for synthetic protocols. Organofluorine compounds find many applications in agrochemical industry and in medicinal chemistry.[4] In particular, chiral compounds containing the trifluoromethyl group (CF_3) bonded to a stereogenic center, showed potent activity against various diseases (Figure 1).[5]

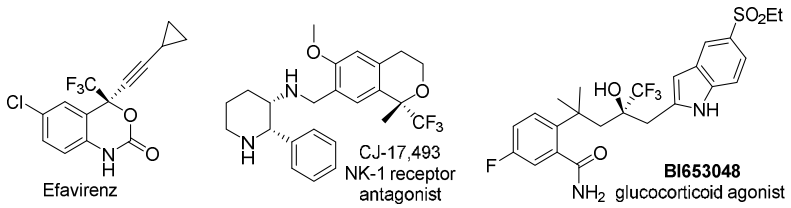
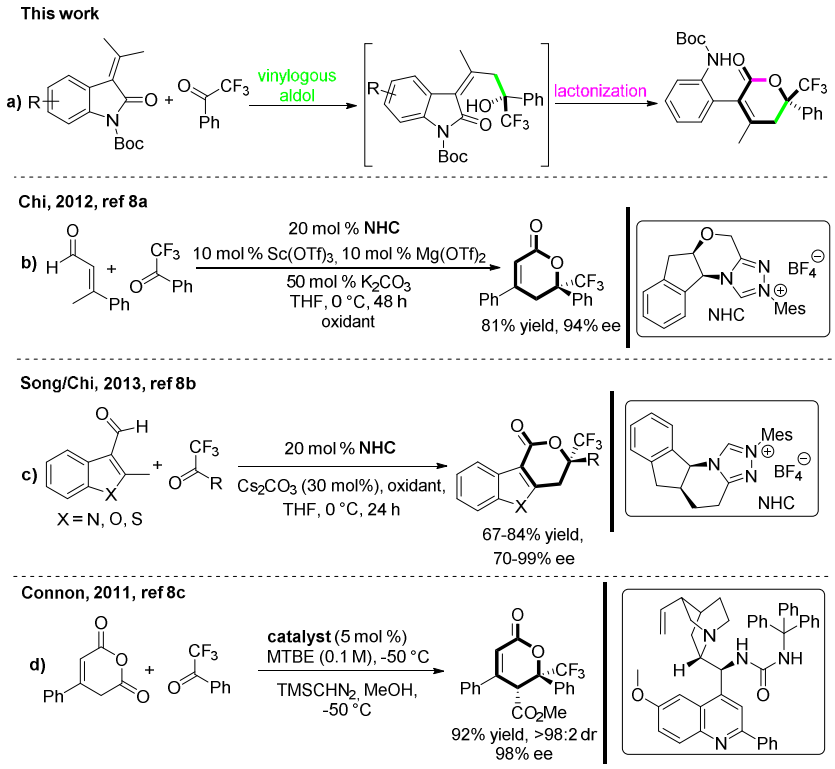


Figure 1. Examples of biologically active trifluoromethyl compounds

The search of novel and always more efficient methodologies for the synthesis of fluorinated compounds is an actual and challenging research field which has constantly seen the commitment of many research groups to the development of innovative reactions.[6] Recently, organocatalytic Henry and cross-aldol reactions of trifluoromethyl aryl ketones,[7] emerged as a valid alternative to the classical Ruppert-Prakash reaction.[6c-e] With the aim to pursue our studies on the vinylogous reactions of oxindoles, we wondered if it was possible to realize the unprecedented vinylogous

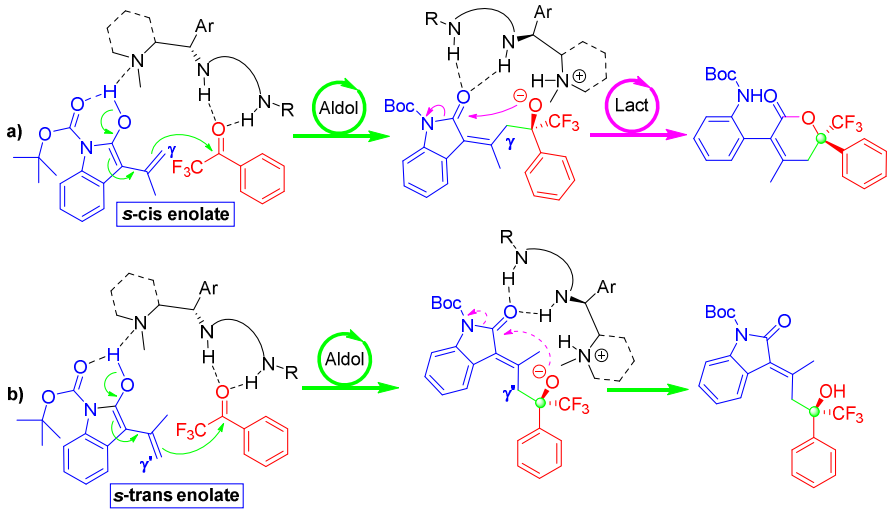
aldol-lactonization cascade using trifluoromethyl ketones (Scheme 1a).[1f, 4] This vinylogous aldol-lactonization represents an alternative strategy to the methods reported by Chi and Connon based on NHC/Lewis Acid and base catalyzed cycloadditions, for the synthesis of α,β-unsaturated-δ-lactones bearing a CF_3-group as part of a tetrasubstituted stereocenter (Scheme 1b-d).[8] The α,β-unsaturated-δ-lactone core is responsible for the activity of many natural and unnatural compounds against cancer, HIV and artery diseases. Considering that the catalytic synthesis of optically active 5,6-dihydropyran-2-ones is limited to few examples, new methods for their preparation are highly desirable.[9]

Scheme 1. Access to enantioenriched CF_3-containing α,β-unsaturated-δ-lactone



We believe that for the realization of the cascade reaction, the use of a bifunctional catalyst[10] is fundamental to activate the two reagents and direct the reaction through the desired double synthetic sequence (Scheme 2a). It is furthermore essential that the catalyst controls the regiochemistry of the addition, that should occur mainly at the γ-site rather than the γ'-site of the oxindole since the resulting (Z)-aldol adduct intermediate would cyclize easily onto the amidic carbonyl group than the (E)-aldol adduct (Scheme 2b).

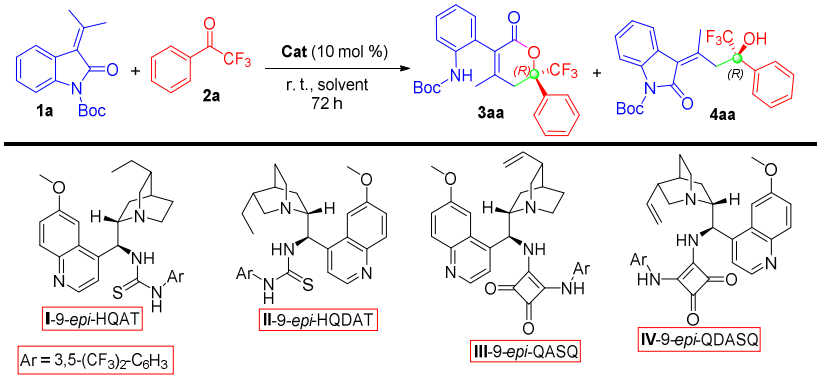
Scheme 2. Vinylogous aldol/lactonization process



RESULTS AND DISCUSSION

We started our investigation exploring the reactivity of diverse thiourea and squaramide derivatives of Cinchona alkaloids organocatalysts (Table 1). This class of catalysts has been successfully applied to vinylogous processes[2a-c, h] and demonstrated to be effective for the generation of an *s-cis* enolate after selective deprotonation at the γ-site.[2d]

Table 1. Screening of reaction conditions[a]



entry	cat	solvent	**3aa/4aa**[b]	yield (%) **3aa**[c]	ee (%) **3aa**[e]
1	I	DCM	9:1	70	>99
2	II	DCM	2:1	48	-99
3	III	DCM	4:1	56	97
4	IV	DCM	1:3	21	-91
5	I	$CHCl_3$	3:1	52	nd
6	I	Tol	6:1	82	nd
7	I	THF	1:2	20	nd
8	I	Et_2O	7:1	70	nd
9	I	MeOH	--	n.r.	--
10	I	MeCN	>19:1	96[d]	95

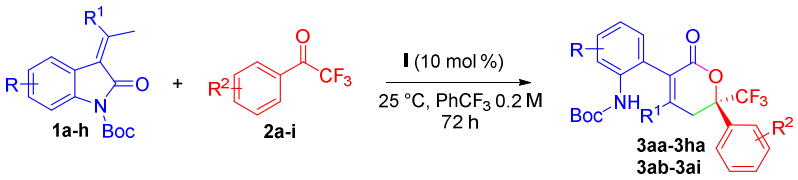
11	I	$PhCF_3$	>19:1	96[d]	99

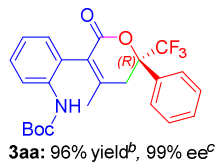
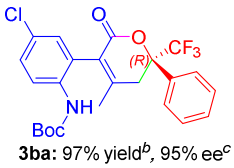
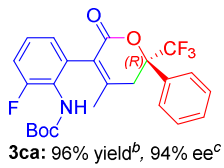
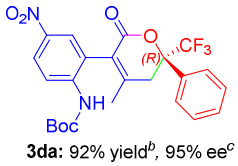
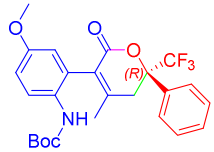
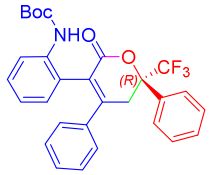
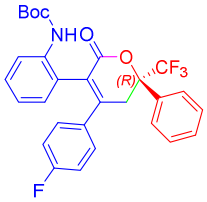
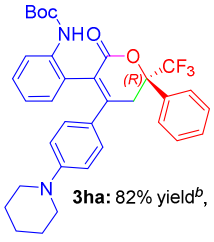
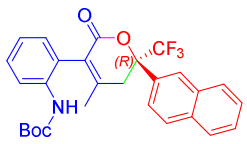
[a]The reactions were performed on a 0.1 mmol scale using a 1:1 ratio of **1a** and **2a** and 0.5 ml of solvent. [b]Determined via ^{1}H-NMR on the crude mixture. [c]Determined via ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard. [d]Isolated yield. [e]Determined by HPLC on chiral stationary phase.

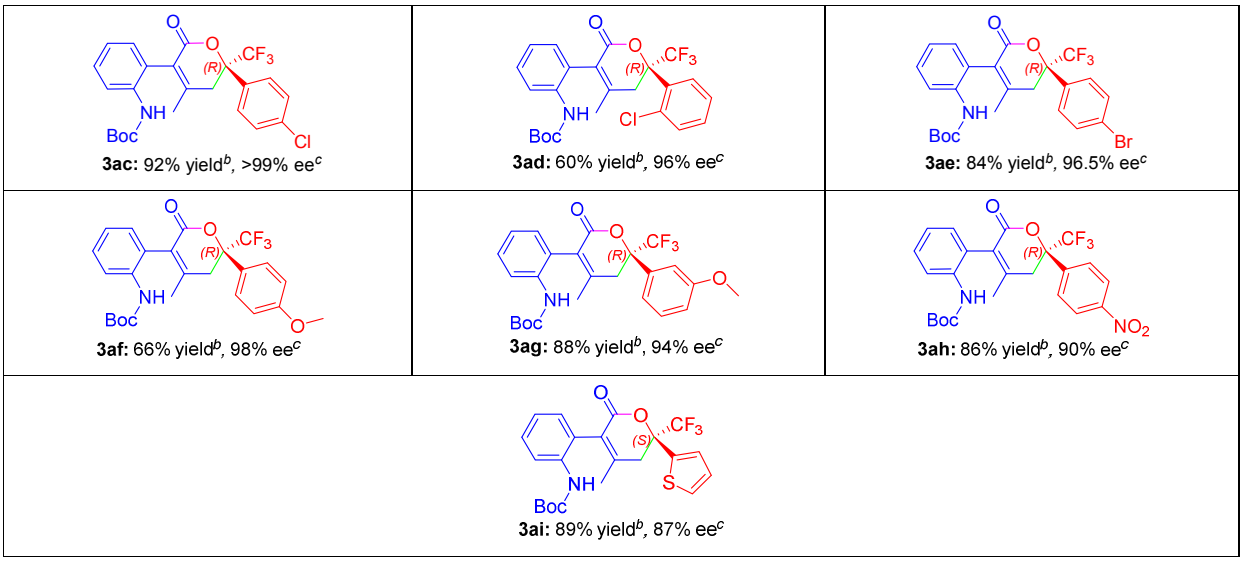
In general these catalysts were able to promote the formation of compound **3aa** in moderate to good yields and excellent enantioselectivity together with variable amounts of aldol adduct **4aa** (entries 1-4). The first attempt using the thiourea derivatives of 9-NH_2-9-(*epi*)dihydroquinine **I** gave **3aa** in a 70% yield and >99% ee. Catalyst **II**, the pseudoenantiomer of catalyst **I**, gave **3aa** in 48% yield and 99% ee, whilst squaramide derivatives 9-NH_2-9-(*epi*)quinine **III** and quinidine **IV** furnished worst results (entries 2-4). The solvents have a strong influence on the product selectivity since variable ratios between **3aa** and **4aa** were observed (entries 5-12). Only using MeCN and CF_3Ph a complete selectivity in favor of lactone **3aa** was realized. In particular in this last case, **3aa** was isolated in 96% yield and 99% ee after 72 hours of reaction at 25 °C.

With the optimized condition the scope of the reaction was performed (Table 2).

Table 2. Scope of the reaction[a]



 **3aa:** 96% yield[b], 99% ee[c]	 **3ba:** 97% yield[b], 95% ee[c]	 **3ca:** 96% yield[b], 94% ee[c]
 **3da:** 92% yield[b], 95% ee[c]	 **3ea:** 84% yield[b], 92% ee[c]	 **3fa:** 83% yield[b], >99% ee[c]
 **3ga:** 99% yield[b], >99% ee[c]	 **3ha:** 82% yield[b], 99% ee[c]	 **3ab:** 99% yield[b], 95% ee[c]



[a]The reactions were performed on a 0.2 mmol scale using a 1:1 ratio of **1** and **2** in 1.0 ml of $PhCF_3$. [b]Isolated yield. [c]Determined by HPLC on chiral stationary phase.

In general catalyst **I** gave high control on the stereochemistry with both electron-withdrawing and releasing substituents at the C(5) and C(7) of the oxindole core (**3ba**-**3ea**). Excellent yields and ee's were also obtained with oxindoles having different aromatic substituents at the double bond (**3fa-3ha**). However with great surprise the reaction failed to give the desired lactons or even traces of aldol adduct when 1-*t*-butoxycarbonyl-3-(pentan-3-ylidene)indolin- 2-one or 3-cyclohexylidene-1-*t*-butoxycarbonylindolin-2-one were employed. Various aromatic trifluoromethylketones **2b-i** were then prepared and used for the vinylogous aldol-cascade process in combination with oxindole **1a**. In almost all cases the corresponding cyclic esters were the sole products obtained after 72 hours in excellent yields and remarkable enantioselectivities (**3ab-3ai**). Moderate yields were however obtained with 2-chloro-trifluoroacetophenone **2d** and 4-methoxy trifluoroacetophenone **2f**. In these two cases the overall reaction rate is probably influenced negatively by steric and electron-donating effects. It is furthermore important to underline that in the case of compound **3ah** the reaction was performed using the hydrate form of 2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-one **2h**. It should be outlined that the reaction failed to give any products when alkyl trifluoromethylketones were employed. However, it is important to underline that these trifluoromethylated lactones were isolated as mixture of conformers due to the slow rotation of the C-C single bond between the aryl substituent and the α-carbon of the double bond. In the case of compound **3aa** the anti/syn ratio was 58:42 in $CDCl_3$ and the energy barrier to rotation was determined to be $\Delta G^{\ddagger}_{rot}$= 19.0 ± 0.5 kcal/mol in CD_3CN by means of 1D-EXSY experiments (Figure 2).

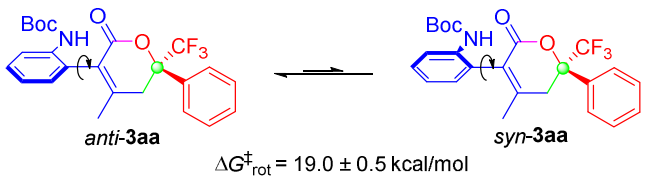
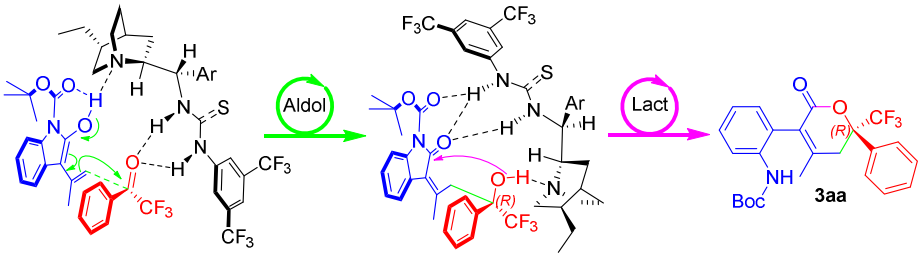


Figure 2. Conformational equilibrium observed

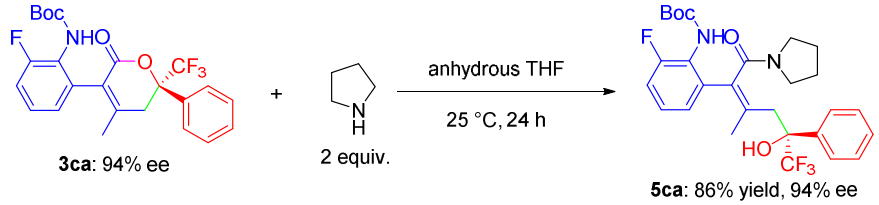
The absolute configuration of compound **3aa** was determined to be *R* by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra, as described in the Supporting Information. The *R* absolute configuration is the result of a vinylogous addition of the oxindole to the prochiral *Si* face of the trifluoromethyl ketone. In order to elucidate the reaction mechanism, we decide to analyze the reaction in DCM at regular interval of time. After 24 hours, **3aa** was obtained in a 30% and >99% ee and compound **4aa** was obtained in a 19% yield and 93% ee. After 48 hours, compound **3aa** was obtained as single enantiomer but in a 60% yield whilst **4aa** was recovered in a 11% yield and 88% ee. Finally after 72 hours of reaction **3aa** and **4aa** were obtained in a 70% and 7.8% yield and >99% and 90% ee respectively. These results would suggest that the present cascade proceeds by forming a stable aldol adduct which undergoes the ring-closing lactonization in a stepwise fashion (Scheme 3).

Scheme 3. Proposed mechanism for the cascade sequence



Finally by treating compound **3ca** with 2 equivalents of pyrrolidine in anhydrous THF the tetrasubstituted alkene **5ca** can be obtained in a 86% yield and with complete retention of the configuration of the stereocenter (Scheme 4).

Scheme 4. Derivatization of the enantioenriched trifluoromethylated lactone **3ca**



3ca: 94% ee

5ca: 86% yield, 94% ee

CONCLUSION

In conclusion we realized the enantioselective synthesis of novel trifluoromethyl-α,β-unsaturated-δ-lactones through the first vinylogous aldol-lactonization[11] cascade of 3-alkylidene oxindoles and unsaturated trifluoromethyl ketones. The reaction proceeded with high enantiocontrol and represents a valuable strategy to access fluorinated lactones, a moiety often present in important biological active compounds. Experiments are ongoing to elucidate the reaction mechanism.

EXPERIMENTAL

All the NMR spectra were recorded on Inova 300 MHz, Gemini 400 MHz or Mercury 600 MHz Varian spectrometers for ^{1}H, 75 MHz, 100 MHz and 150 MHz for ^{13}C and 282 MHz, 376 MHz, 564 MHz for ^{19}F respectively. The chemical shifts (δ) for ^{1}H, ^{19}F and ^{13}C are given in ppm relative to internal standard TMS (0.0 ppm) or residual signals of $CHCl_3$ (7.26 ppm). Coupling constants are

given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Concerning the ^{13}C spectra of the products, we were never able to see the signal (quartet) of the fluorinated carbon regardless of the delay and the acquisition time we employed (not even a 5 days-acquisition with a 60 seconds delay at 150 MHz showed any signal). It is likely that, due to the splitting of the signal and the very high relaxation time of this particular carbon, the corresponding signal is lost in the baseline. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High Resolution Mass spectra were obtained from the Mass Facility of the Department of Chemistry and Drug Technology of the University of Rome on a Orbitrap Exactive, source: ESI (+): capillary temp: 250°C, spray voltage: 4.0 (kV), capillary voltage: 65 V, tube lens: 125 V. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. HPLC traces for all compounds were compared to racemic sample prepared using DABCO as catalyst except for compound **3ea**-**3ai**, **5ca** where a quasi racemic samples was prepared by mixing the two product antipodes obtained performing the reactions with catalyst **I** and the pseudo-enantiomer **II** separately. Optical rotations are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL, $CHCl_3$) and the numerical values are relative to the products obtained from catalyst **I**. All reactions were carried out in air. Chiral catalyst **I**, **II**, **III**, **IV** and **V** were prepared following literature procedures.[12]

General procedure for the synthesis of N-Boc-alkylidene oxindoles

The appropriate isatin (15 mmol, 1 equiv) was placed in a 100 mL round flask and suspended in MeOH (37.5 mL, 0.4 M) before adding hydrazine (30.15 mmol, 2.6 ml of 55% solution in water, 2 equiv). The solution was left refluxing (2 to 3 hours) under magnetic stirring until the formation of a precipitate is observed, then cooled to room temperature. The precipitate was filtered on a gooch funnel, washed with water, cold MeOH and cold Et_2O to afford the pure hydrazone that was added to a freshly prepared solution of EtONa in EtOH (3.7 equiv of metallic Na dissolved in EtOH so that the hydrazone is 0.4 M). This new solution was heated to reflux until the reagent disappeared (TLC monitoring), then it was cooled and quenched with 10% HCl. The crude was now extracted with DCM, made anhydrous over $MgSO_4$ and purified by either flash column chromatography or crystallization to obtain the pure oxindole. The oxindole was then dissolved in a mixture of EtOH:Acetone 1:1 (0.5 M) before adding piperidine (4.0 equiv). After one night of reflux the temperature was allowed to go down and the crude was flushed through a plug of silica (50 mL of DCM:EtOAc 1:1 as eluent) to remove piperidine and the Knoevenagel adduct was purified by precipitation from Et_2O. The nitrogen protection was carried out dissolving the alkylidene oxindole in DCM (0.5 M) freshly filtered on basic alumina with Boc_2O (1.2 equiv) and a catalytic amount of DMAP (5% molar). The reaction was monitored via TLC and, when over, the crude was concentrated and the final product was purified by flash column chromatography. NMR spectra of oxindoles **1a**,[13] **1b**,[14] **1d**,[13] **1e**,[14] **1f**,[14] were consistent with those previously reported.

***tert*-Butyl 7-fluoro-2-oxo-3-(propan-2-ylidene)indoline-1-carboxylate (1c)**

The title compound was synthesized following the literature procedure on a 2 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 95:5 and then 90:10) with

an overall yield of 77% (91% for the Knoevenagel reaction and 85% for the protection) and a total of 450 mg of **1c** that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{16}H_{18}FNNaO_3]^+$ 314.1163, found 314.1159 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.15 – 6.97 (m, 2H), 2.62 (s, 3H), 2.40 (s, 3H), 1.61 (s, 8H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -121.52. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.4, 158.8, 149.8, 148.1, 147.3, 127.0 (d, *J* = 2.9 Hz), 124.3 (d, *J* = 7.1 Hz), 121.6 (d, *J* = 2.9 Hz), 119.1 (d, *J* = 3.7 Hz), 115.7 (d, *J* = 20.0 Hz), 84.5, 27.7, 25.8, 24.0.

***tert*-Butyl (E)-3-(1-(4-fluorophenyl)ethylidene)-2-oxoindoline-1-carboxylate (1g)**

The title compound was synthesized following the literature procedure on a 5 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 90:10) with an overall yield of 73% (85% for the Knoevenagel reaction and 86% for the protection) and a total of 1.29 g of 1g that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{21}H_{20}FNNaO_3]^+$ 376.1319, found 376.1322 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 8.3, 1.1, 0.6 Hz, 1H), 7.31 – 7.09 (m, 5H), 6.76 (ddd, *J* = 7.7, 1.1 Hz, 1H), 6.28 – 6.19 (m, 1H), 2.76 (s, 3H), 1.68 (s, 9H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -121.54. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.0, 164.0, 161.5, 155.1, 149.5, 138.8 (d, *J* = 3.8 Hz), 138.3, 128.5, 128.4 (d, *J* = 8.1 Hz), 123.3, 122.9 (d, *J* = 3.6 Hz), 122.5, 116.5 (d, *J* = 21.9 Hz), 114.5, 84.1, 28.2, 23.8.

***tert*-Butyl (E)-2-oxo-3-(1-(4-(piperidin-1-yl)phenyl)ethylidene)indoline-1-carboxylate (1h)**

The title compound was synthesized following the literature procedure on a 1 mmol scale. The product was purified by flash column chromatography (hexane:EtOAc = 85:15) with an overall yield of 56% (75% for the Knoevenagel reaction and 75% for the protection) and a total of 210 mg of **1h** that presented itself as an amorphous solid. HRMS-ESI-ORBITRAP (+): calculated for $[C_{26}H_{30}N_2NaO_3]^+$ 441.2149, found 441.2143 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.07 (m, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.77 (ddd, *J* = 7.7, 1.1 Hz, 1H), 6.69 – 6.58 (m, 1H), 3.32 – 3.24 (m, 4H), 2.76 (s, 3H), 1.67 (m, 15H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.3, 157.6, 152.2, 149.6, 137.8, 132.1, 128.3, 127.7, 123.6, 123.0, 122.3, 121.4, 115.6, 114.2, 83.7, 49.6, 28.1, 25.6, 24.2, 23.8.

General procedure for the synthesis of trifluoromethylketones

K_2CO_3 is added at room temperature to a DMSO (15 mL) solution of the appropriate aromatic aldehyde (5 mmol, 1.0 equiv.) and trifluoromethyl trimethylsilane (6.5 mmol, 1.3 equiv.). The reaction is completed, (check by TLC) the mixture is poured to ice/water mixture and extracted with ethyl acetate (3 x 30 ml). The collected organic phases are washed with water (2 x 50 ml) then threated with $MgSO_4$ and filtered. The crude alcohol is purified by column chromatography using 10-15% of acetone or ethyl acetate in hexane as eluent mixture and directly added to a suspension of IBX in ethyl acetate. The resulting suspension is refluxed overnight. The crude mixture is filtered and trifluoroketone was purified by column chromatography using 5-10% of Et_2O in hexane as the eluent mixture. All trifluoromethylketones prepared were consistent with those previously reported: **2c**,[15] **2f**,[15] **2g**,[16] **2h**.[17] Trifluoroketones **2a**, **2b, 2e, 2d** and **2i** were commercially available and used as is.

General procedure for the vinylogous aldol reaction

In an ordinary vial equipped with a teflon-coated magnetic stir bar, catalyst **I** (12 mg, 0.02 mmol, 0.1 equiv), oxindole (0.2 mmol, 1 equiv) and trifluoromethylketone (0.2 mmol, 1 equiv) were dissolved in 1 mL of $PhCF_3$. After 72 hours of stirring at 25 °C, the reaction was flushed through a short silica plug with a 1:1 mixture of DCM:EtOAc to remove the catalyst and the crude product was concentrated to perform a ^{1}H-NMR analysis to measure the yield (1,3,5-trimethoxybenzene was used as internal standard) and determine the ratio between aldol and cascade product. At this point the product was purified with flash column chromatography and the ee% was determined through HPLC on a chiral stationary phase. Yield after chromatography are all cases identical to those determined via NMR analysis.

***tert*-Butyl (*R*)-(2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3aa)**

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.72/1.00 mixture of conformers in 96% yield (85.8 mg) and 99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.5 min, τ_{II} = 11.9 min. $[\alpha]_D^{25}$ -37.5 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{24}F_3NNaO_4]^+$ 470.1550, found 470.1544 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1.10 H), 7.64 – 7.40 (m, 5.14 H), 7.34 – 7.22 (m, 1.00 H), 7.17 – 7.03 (m, 0.84 H), 6.89 (td, *J* = 7.5, 1.2 Hz, 0.58 H), 6.53 (s, 0.56 H), 6.18 (dd, *J* = 7.6, 1.6 Hz, 0.57 H), 5.20 (s, 0.43 H), 3.44 (m, 1.00 H), 3.19 (m, 1.00H), 1.80 (s, 1.27 H), 1.74 (s, 1.73 H), 1.50 (s, 5.05 H), 1.43 (s, 3.70 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.32, -79.54. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.7, 160.9, 153.2, 152.8, 151.8, 151.7, 136.6, 135.9, 134.0, 133.9, 131.0, 130.1, 129.9, 129.8, 129.4, 129.3, 129.2, 128.9, 126.5, 126.3, 126.1, 125.9, 125.0, 124.1, 123.7, 123.4, 123.3, 122.2, 81.9 (q, *J* = 30.9 Hz), 81.4 (q, *J* = 30.9 Hz), 80.5, 80.4, 34.0, 33.6, 28.4, 28.3, 22.1, 22.0.

***tert*-Butyl (*R*)-(4-chloro-2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ba)**

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.76/1.00 mixture of conformers in 97% yield (93.5 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 5.8 min, τ_{II} = 7.9 min. $[\alpha]_D^{25}$-24.3 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1154 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1.09 H), 7.66 – 7.41 (m, 5.22 H), 7.30 – 7.20 (m, 1.20 H), 7.11 (d, *J* = 2.5 Hz, 0.40 H), 6.46 (s, 0.56 H), 6.17 (d, *J* = 2.5 Hz, 0.54 H), 5.16 (s, 0.42 H), 3.44 (m, 1.00 H), 3.20 (m, 1.00 H), 1.82 (s, 1.28 H), 1.77 (s, 1.70 H), 1.49 (s, 5.00 H), 1.42 (s, 4.00 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.31, -79.55. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 160.5, 153.0, 152.8, 152.7, 152.6, 135.5, 134.7, 133.8, 133.6, 130.7, 130.2, 130.0, 129.6, 129.4, 129.3, 129.2, 129.1, 128.5, 128.4, 126.2, 126.0, 125.3, 124.7, 124.1, 124.0, 122.2, 122.1, 82.0 (q, *J* = 30.8 Hz), 81.5 (q, *J* = 30.6 Hz), 80.9, 80.8, 34.0, 33.7, 28.3, 28.2, 22.1, 22.0.

tert-Butyl (_R_)-(2-fluoro-6-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)phenyl)carbamate (3ca)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.60/1.00 mixture of conformers in 96% yield (80.0 mg) and 94% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_{I} = 5.9 min, τ_{II} = 7.1 min. $[\alpha]_D^{25}$-198.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_4NNaO_4]^+$ 488.1455, found 488.1449 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.35 (m, 5.21 H), 7.22 (td, *J* = 8.0, 5.2 Hz, 0.43 H), 7.15 – 6.99 (m, 1.68 H), 6.99 – 6.91 (m, 0.40 H), 6.20 – 5.97 (m, 1.26 H), 4.85 (s, 0.40 H), 3.48 – 3.30 (m, 1 H), 3.17 (m, 1.00 H), 1.83 (s, 1.08 H), 1.77 (s, 1.97 H), 1.45 (s, 5.79 H), 1.37 (s, 3.58 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.41, -79.56. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 161.0, 159.4, 159.1, 157.7, 157.5, 153.5, 153.0, 151.5 (double), 134.2, 133.9, 133.4, 132.0, 130.0, 129.8, 129.2, 128.9, 127.5 (d, *J* = 27.7 Hz), 127.4 (d, *J* = 27.7 Hz), 126.3, 126.1, 125.3 (d, *J* = 3.7 Hz), 124.8 (d, *J* = 3.7 Hz), 124.6 (bs), 124.5 (bs), 124.2, 123.2 (q, *J* = 284.0 Hz), 123.1 (q, *J* = 284.0 Hz), 116.5, 116.4 (d, *J* = 11.0 Hz), 116.3 (d, *J* = 11.0 Hz), 81.9 (q, *J* = 31.0 Hz), 81.5 (q, *J* = 30.0 Hz), 80.4 (double), 34.1, 33.5, 28.1, 28.0, 22.1, 22.0.

tert-Butyl (_R_)-(2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)-4-nitrophenyl)carbamate (3da)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 9:1) and the title compound was obtained as a yellowish oil in a 0.79:1.00 mixture of conformers in 92% yield (90.7 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_{I} = 7.6 min, τ_{II} = 11.9 min. $[\alpha]_D^{25}$ -98.5 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_3N_2NaO_6]^+$ 515.1400, found 515.1393 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (m, 2.36 H), 8.19 – 8.12 (m, 2H), 8.01 (d, *J* = 2.6 Hz, 1.00H), 7.66 – 7.45 (m, 12.33 H), 7.11 (d, *J* = 2.6 Hz, 1.22 H), 6.80 (bs, 1.24 H), 5.53 (bs, 0.97 H), 3.54 (dd, *J* = 7.0, 1.2 Hz, 0.98 H), 3.48 (dd, *J* = 7.1, 1.2 Hz, 1.40 H), 3.30-3.24 (m, 2.37 H), 1.86 (s, 3.29 H), 1.81 (s, 4.04 H), 1.52 (s, 11.90 H), 1.45 (s, 9.45 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.12, -79.62. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 154.4, 154.3, 152.0, 151.7, 143.1, 142.4, 142.3, 142.3, 133.6, 133.6, 130.4, 130.3, 129.5, 129.2, 127.0, 126.2, 126.1, 125.9, 125.2, 124.9, 124.4, 123.3, 123.1, 122.2, 119.8, 119.7, 82.2, 82.1 (q, *J* = 30.8 Hz), 81.6 (q, *J*=30.8 Hz) , 34.0, 31.6, 28.3, 28.2, 25.4, 22.7, 22.2, 14.1.

tert-Butyl (_R_)-(4-methoxy-2-(4-methyl-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2_H_-pyran-3-yl)phenyl)carbamate (3ea)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.70:1.00 mixture of conformers in 84% yield (80.3 mg) and 92% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 0.8 mL/min, 50 °C, λ = 254 nm: τ_{I} = 9.9 min, τ_{II} = 11.8 min. $[\alpha]_D^{25}$-113.7 (*c* 1.0,

$CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1647 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.38 (m, 10.48 H), 6.85-6.82 (dd, *J* = 8.9, 3.0 Hz, 1.78 H), 6.67 (d, *J* = 3.0 Hz, 0.71 H), 6.33 (bs, 0.98 H), 5.73 (d, *J* = 2.9 Hz, 1.00 H), 5.02 (bs, 0.60 H), 3.76 (s, 2.04 H), 3.61 (s, 3.13 H), 3.47 – 3.36 (m, 1.79 H), 3.17 (m, 1.87 H), 1.81 (d, *J* = 0.9 Hz, 2.12 H), 1.76 (d, *J* = 0.9 Hz, 3.17 H), 1.47 (s, 8.98 H), 1.41 (s, 6.11 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.38, -79.51. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.6, 160.9, 156.1, 155.8, 153.9, 153.4, 151.8, 151.7, 134.1, 133.9, 130.1, 129.8, 129.6, 129.3, 129.0, 128.9, 126.5, 126.4, 126.1, 125.1, 116.1, 115.6, 114.7, 114.0, 82.5, 82.0 (q, *J*=30.8 Hz), 81.5 (q, *J*=30.5 Hz), 80.2, 80.2, 55.5, 55.3, 34.0, 33.6, 31.6, 28.4, 28.3, 22.7, 22.1, 22.1, 14.1.

tert-Butyl (*R*)-(2-(2-oxo-4,6-diphenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3fa)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.42/1.00 mixture of conformers in 83% yield (84.8 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 4.4 min, τ_{II} = 7.9 min. $[\alpha]_D^{25}$-187.9 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{29}H_{26}F_3NNaO_4]^+$ 532.1706, found 532.1700 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.38 (m, 8.56 H), 7.25 – 7.09 (m, 5.76 H), 7.04 (dd, *J* = 7.8, 1.7 Hz, 0.63 H), 7.00 – 6.85 (m, 3.57 H), 6.78 – 6.58 (m, 1.63 H), 6.02 (dd, *J* = 7.7, 1.6 Hz, 0.77 H), 5.27 (s, 0.54 H), 3.80 (d, *J* = 8.5 Hz, 0.42 H), 3.74 (d, *J* = 8.6 Hz, 0.98 H), 3.65 (d, *J* = 6.3 Hz, 1.00H), 3.59 (d, *J* = 6.3 Hz, 0.42 H), 1.49 (s, 7.50 H), 1.39 (s, 5.66 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.01, -79.22. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.8, 161.8, 153.2, 152.5, 151.3, 151.0, 137.1, 136.9, 136.7, 135.9, 133.7 (double), 131.9, 130.5, 130.2, 129.9, 129.7 (double), 129.4, 129.1, 129.0, 128.5, 127.6, 127.5, 126.9, 126.5, 126.3, 125.4, 125.1 (double), 124.1 (bs), 123.8, 123.4, 123.1 (bs), 122.3, 121.3, 82.3 (q, *J* = 30.9 Hz), 81.9 (q, *J* = 30.5 Hz), 80.4, 80.2, 34.3, 34.0, 28.4, 28.3.

tert-Butyl (*R*)-(2-(4-(4-fluorophenyl)-2-oxo-6-phenyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ga)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.70:1.00 mixture of conformers in 99% yield (105 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 6.8 min, τ_{II} = 9.8 min. $[\alpha]_D^{25}$ -218.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{29}H_{25}F_4NNaO_4]^+$ 550.1612, found 550.1603 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.44 (m, 10.52 H), 7.18 (qd, *J* = 8.5, 1.7 Hz, 1.84 H), 7.07 – 6.80 (m, 8.42 H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1.88 H), 5.99 (dd, *J* = 7.7, 1.6 Hz, 0.94 H), 5.27 (bs, 0.63 H), 3.81 – 3.68 (m, 1.74 H), 3.61 (d, *J* = 7.4 Hz, 1-16 H), 3.55 (d, *J* = 7.3 Hz, 0.54 H), 1.49 (s, 9.04 H), 1.39 (s, 6.54 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.03, -79.22. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.8, 162.7, 161.7, 161.4, 153.3, 152.5, 150.0, 149.7, 137.1, 135.9, 133.7, 133.7, 132.9, 132.9, 132.7, 132.7, 131.8, 130.5, 130.2, 130.0, 129.9, 129.8, 129.8, 129.7, 129.5, 129.3, 129.1, 127.1, 126.4,

126.3, 125.6, 124.1, 123.7, 115.9, 115.6, 82.2 (q, *J* = 34.5 Hz), 81.8 (q, *J* = 30.6 Hz), 80.5, 80.4, 34.2, 34.0, 28.4, 28.3, 25.4.

tert-Butyl (*R*)-(2-(2-oxo-6-phenyl-4-(4-(piperidin-1-yl)phenyl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ha)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 82:18) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 82% yield (97 mg) and 99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 11.0 min, τ_{II} = 12.0 min. $[\alpha]_D^{25}$ -281.0 (*c* 0.2, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{34}H_{35}F_3N_2NaO_4]^+$ 615.2432, found 615.2430 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.54 (m, 3.10 H), 7.53 – 7.39 (m, 3.07 H), 7.18 (dddd, *J* = 9.9, 8.6, 7.4, 1.6 Hz, 1.01 H), 7.10 (dd, *J* = 7.8, 1.6 Hz, 0.39 H), 7.02 – 6.85 (m, 2.48 H), 6.80 (s, 0.59 H), 6.71 (dd, *J* = 7.5, 1.2 Hz, 0.82 H), 6.62 (s, 1.80 H), 6.00 (dd, *J* = 7.7, 1.6 Hz, 0.62 H), 5.31 (s, 0.44 H), 3.75 – 3.56 (m, 2.00 H), 3.17 (d, *J* = 5.5 Hz, 3.94 H), 1.76 – 1.51 (m, 6.65 H), 1.47 (s, 5.31 H), 1.37 (s, 3.68 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.05, -79.32. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.4, 162.3, 153.3, 152.6, 152.2, 150.5, 150.1, 137.3, 136.0, 133.9, 131.9, 130.6, 129.9, 129.7 (double), 129.6, 129.3, 128.9, 128.8, 128.7, 126.5, 126.3, 124.7, 123.9, 123.4, 121.9, 113.9, 81.9 (q, *J* = 30.3 Hz), 81.5 (q, *J* = 30.3 Hz), 80.2, 80.0, 48.6, 33.3, 32.8, 28.4, 28.3, 25.3, 24.2.

tert-butyl (R)-(2-(4-methyl-6-(naphthalen-2-yl)-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2H-pyran-3-yl)phenyl)carbamate (3ab)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 99% yield (98.6 mg) and 95% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 5.5 min, τ_{II} = 6.1 min. $[\alpha]_D^{25}$ -42.0 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{28}H_{26}F_3NNaO_4]^+$ 520.1706, found 520.1692 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.0 Hz, 0.62 H), 8.06 – 8.05 (m, 1.05 H), 7.97 – 7.95 (m, 1.04 H), 7.94 – 7.93 (m, 0.62 H), 7.90 – 7.86 (m, 4.09 H), 7.77 (d, *J* = 8.3 Hz, 0.63H), 7.66 (dd, *J* = 8.7, 2.0 Hz, 0.1.3 H), 7.61 – 7.55 (m, 4.15 H), 7.28 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 0.63 H), 7.25 – 7.23 (m, 0.83 H), 7.16 – 7.15 (m, 0.59 H), 7.14 – 7.11 (m, 0.69 H), 6.80 (td, *J* = 7.5, 1.2 Hz, 1.0 H), 6.52 (bs, 1.02 H), 6.14 (dd, *J* = 7.6, 1.6 Hz, 1.08 H), 5.33 (bs, 0.69 H), 3.55 – 3.50 (m, 1.60 H), 3,38-3,35 (m, 0.62 H), 3.32 – 3.29 (m, 1.04 H), 1.84 (s, 1.61 H), 1.76 (s, 2.81 H), 1.50 (s, 8.18 H), 1.18 (s, 4.51 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -78.99, -79.09. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 160.7, 160.0, 152.3, 151.7, 150.7, 150.7, 135.6, 135.0, 132.5, 132.5, 131.8, 131.7, 130.3, 130.2, 129.9, 129.0, 128.3, 128.3, 128.3, 127.9, 127.7, 127.6, 126.7, 126.6, 126.5, 126.5, 126.1, 126.1, 125.6, 125.5, 125.4, 123.9, 122.7, 122.5, 121.9, 121.4, 81.2, 81.0 (q, *J* = 30.6 Hz) 80.6 (q, *J* = 30.4 Hz), 80.4, 79.5, 79.2, 33.2, 32.8, 30.6, 27.3, 27.0, 21.6, 21.1, 21.0.

tert-Butyl (*R*)-(2-(6-(4-chlorophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ac).

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 19:1) and the title compound was obtained as a yellowish oil in a 0.75:1.00 mixture of conformers in 92% yield (88.7 mg) and >99% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak IC column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 7.9 min, τ_{II} = 9.5 min. $[\alpha]_D^{25}$ -87.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1156 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 1.97 H), 7.56 (d, *J* = 8.6 Hz, 1.63 H), 7.51 – 7.43 (m, 5.62 H), 7.34 – 7.28 (m, 1.96 H), 7.14 – 7.06 (m, 1.69 H), 6.97 – 6.93 (m, 1.33 H), 6.48 (bs, 1.13 H), 6.29 (dd, *J* = 7.6, 1.4 Hz, 1.24 H), 5.32 (bs, 0.79 H), 3.50 – 3.39 (m, 1.98 H), 3.21 – 3.07 (m, 2.11 H), 1.83 (s, 2.27 H), 1.76 (s, 3.00 H), 1.50 (s, 9.01 H), 1.45 (s, 6.25 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.38, -79.58. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.3, 160.7, 153.3, 152.8, 151.7, 151.6, 136.6, 136.3, 136.2, 136.0, 132.7, 132.6, 131.0, 130.0, 129.6, 129.5, 129.4, 129.3, 127.8, 127.6, 126.5, 125.1, 124.8, 124.0, 123.9, 123.6, 122.2, 122.1, 81.5 (q, *J* = 30.8 Hz), 81.1 (q, *J* = 30.8 Hz), 80.7, 80.6, 33.9, 33.6, 28.3, 22.2, 22.2.

tert-Butyl (*R*)-(2-(6-(2-chlorophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ad)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.72:1.00 mixture of conformers in 60% yield (57.8 mg) and 96% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.8 min, τ_{II} = 12.7 min. $[\alpha]_D^{25}$-45.9 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}ClF_3NNaO_4]^+$ 504.1160, found 504.1153 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.74 (m, 3.34 H), 7.55 – 7.47 (m, 1.65 H), 7.44 – 7.27 (m, 5.07 H), 7.18 – 7.07 (m, 1.57 H), 6.92 (td, *J* = 7.5, 1.2 Hz, 1.00 H), 6.50 (bs, 0.87 H), 6.25 (dd, *J* = 7.6, 1.5 Hz, 0.97 H), 5.36 (bs, 0.60 H), 4.18 (d, *J* = 11.4 Hz, 0.79 H), 4.11 (d, *J* = 11.8 Hz, 0.96 H), 3.49 (dd, *J* = 10.2, 1.1 Hz, 0.93 H), 3.43 (dd, *J* = 10.6, 1.1 Hz, 0.79 H), 1.87 (s, 2.21 H), 1.84 (s, 3.08 H), 1.50 (s, 8.87 H), 1.47 (s, 7.10 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -77.34, -77.36. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.6, 160.9, 153.2, 153.0, 152.9, 136.7, 135.9, 133.2, 132.8, 132.2, 132.1, 131.4, 131.2, 131.2, 130.9, 130.8, 130.4, 130.0, 129.4, 129.3, 127.7, 127.5, 125.9, 124.5, 124.4, 123.8, 123.7, 123.7, 122.5, 122.5, 83.4, 82.7 (q, *J* =31.5 Hz), 82.3 (q, *J* = 31.1 Hz), 80.6, 80.5, 33.1, 32.8, 28.4, 28.3, 21.5.

tert-Butyl (*R*)-(2-(6-(4-bromophenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ae)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 84% yield (88.2 mg) and 96.5% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_I = 8.6 min, τ_{II} = 5.9 min. $[\alpha]_D^{25}$ -54.6 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}BrF_3NNaO_4]^+$ 548.0655, found 548.0649 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 11.0, 8.3 Hz, 0.94 H), 7.67 – 7.54 (m, 2.07 H),

7.45 (m, 2.16 H), 7.36 – 7.26 (m, 1.07 H), 7.14 – 7.06 (m, 0.79 H), 6.94 (td, *J* = 7.5, 1.2 Hz, 0.61 H), 6.46 (s, 0.56 H), 6.29 (dd, *J* = 7.6, 1.6 Hz, 0.59 H), 5.33 (s, 0.36 H), 3.50 – 3.40 (m, 1.00 H), 3.13 (m, 1.00 H), 1.82 (s, 1.16 H), 1.75 (s, 1.78 H), 1.48 (s, 5.51 H), 1.45 (s, 3.85 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.36, -79.54. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.3, 160.6, 153.2, 152.8, 151.6, 151.5, 136.6, 135.9, 133.2, 133.1, 132.5, 132.2, 131.0, 129.9, 129.5, 129.4, 128.0, 127.8, 126.4, 125.1, 124.8, 124.6, 124.4, 123.9, 123.6, 123.4, 122.8, 122.3, 81.55 (double, q, *J* = 31.0 Hz), 80.7, 80.5, 33.8, 33.5, 28.3 (double), 22.2 (double).

tert-butyl (*R*)-(2-(6-(4-methoxyphenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3af)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.61:1.00 mixture of conformers in 66% yield (63.0 mg) and 98% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 75:25, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: $\tau_{\mathbf{I}}$ = 7.2 min, $\tau_{\mathbf{II}}$ = 4.9 min. $[\alpha]_D^{25}$ -123.2 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1649 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 0.96 H), 7.48 (m, 2.16 H), 7.35 – 7.23 (m, 1.80 H), 7.17 – 7.04 (m, 0.86 H), 7.03 – 6.86 (m, 2.77 H), 6.53 (s, 0.50 H), 6.27 (dd, *J* = 7.6, 1.6 Hz, 0.55H), 5.30 (s, 0.32 H), 3.85 (s, 1.58), 3.83 (s, 1.21 H), 3.41 (m, 1.00 H), 3.15 (m, 1.00 H), 1.81 (s, 1.28 H), 1.75 (s, 1.87 H), 1.50 (s, 5.78 H), 1.43 (s, 4.11 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -79.70, -79.90. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.8, 161.0, 160.5, 153.3, 152.9, 151.8, 136.6, 135.9, 131.1, 130.0, 129.4, 129.2, 127.8, 127.5, 126.4, 125.5, 125.0, 124.9, 123.7, 123.4, 123.3, 121.9, 114.7, 114.2, 81.8 (q, *J* = 30.6 Hz), 81.3 (q, *J* = 30.5 Hz), 80.7 (double), 55.4, 55.2, 33.9, 33.5, 38.3, 28.2, 22.2, 22.1.

tert-Butyl (*R*)-(2-(6-(3-methoxyphenyl)-4-methyl-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ag).

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.66:1.00 mixture of conformers in 88% yield (84 mg) and 94% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 75:25, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: $\tau_{\mathbf{I}}$ = 9.3 min, $\tau_{\mathbf{II}}$ = 4.6 min. $[\alpha]_D^{25}$ -211.4 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{25}H_{26}F_3NNaO_5]^+$ 500.1655, found 500.1650 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 0.96 H), 7.48 (m, 2.16 H), 7.35 – 7.23 (m, 1.80 H), 7.17 – 7.04 (m, 0.86 H), 7.03 – 6.86 (m, 2.77 H), 6.53 (s, 0.50 H), 6.27 (dd, *J* = 7.6, 1.6 Hz, 0.55H), 5.30 (s, 0.32 H), 3.85 (s, 1.58), 3.83 (s, 1.21 H), 3.41 (m, 1.00 H), 3.15 (m, 1.00 H), 1.81 (s, 1.28 H), 1.75 (s, 1.87 H), 1.50 (s, 5.78 H), 1.43 (s, 4.11 H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -79.20, -79.40. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.7, 160.9, 160.1, 159.9, 153.2, 152.8, 151.9, 151.8, 136.6, 136.0, 135.6, 135.4, 131.0, 130.3, 130.0, 129.9, 129.4, 129.2, 126.4, 125.9, 124.9, 124.1, 124.0, 123.7, 123.4, 123.2, 122.2, 122.1, 121.9, 118.5, 118.0, 115.7, 115.0, 112.7, 112.2, 81.8 (q, *J* = 30.8 Hz), 81.3 (q, *J* = 30.8 Hz), 80.5, 80.4, 55.4, 55.3, 34.0, 33.7, 28.3 (double), 22.1, 22.0.

tert-Butyl (*R*)-(2-(4-methyl-6-(4-nitrophenyl)-2-oxo-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ah)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 80:20) and the title compound was obtained as a yellowish oil in a 0.63:1.00 mixture of conformers in 86% yield (84.8 mg) and 90% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_{I} = 6.6 min, τ_{II} = 10.4 min. $[\alpha]_D^{25}$ -97.2 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{24}H_{23}F_3N_2NaO_6]^+$ 515.1400, found 515.1391 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.39 – 8.33 (m, 3.42 H), 7.85 (d, *J* = 8.6 Hz, 1.83 H), 7.79 (d, *J* = 8.7 Hz, 2.02 H), 7.39 – 7.29 (m, 2.56 H), 7.16 – 7.07 (m, 1.41H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1.02 H), 6.42 (bs, 0.96 H), 6.29 (dd, *J* = 7.5, 1.5 Hz, 1.00 H), 5.36 (bs, 0.77 H), 3.52 (m, 1.65 H), 3.22 (m, 1.64 H), 1.86 (s, 1.74 H), 1.81 (s, 2.77 H), 1.50 (s, 8.50 H), 1.40 (s, 5.25 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -78.80, -78.82. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 154.4, 154.3, 152.0, 151.7, 143.1, 142.4, 142.3, 142.3, 133.6, 133.6, 130.4, 130.3, 129.5, 129.2, 127.0, 126.2, 126.1, 125.9, 125.2, 124.9, 124.4, 123.3, 123.1, 122.2, 119.8, 119.7, 82.2, 82.1 (q, *J* = 30.8 Hz), 81.6 (q, *J* = 30.8 Hz) , 34.0, 31.6, 28.3, 28.2, 25.4, 22.7, 22.2, 14.1.

tert-Butyl (*S*)-(2-(4-methyl-2-oxo-6-(thiophen-2-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-yl)phenyl)carbamate (3ai)

The reaction was carried out following the general procedure. The crude mixture was purified by flash column chromatography (hexane:EtOAc = 85:15) and the title compound was obtained as a yellowish oil in a 0.99:1.00 mixture of conformers in 89% yield (87.7 mg) and 87% enantiomeric excess. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 50 °C, λ = 254 nm: τ_{I} = 8.3 min, τ_{II} = 14.6 min. $[\alpha]_D^{25}$ -43.3 (*c* 1.0, $CHCl_3$). HRMS-ESI-ORBITRAP (+): calculated for $[C_{22}H_{22}F_3NNaO_4S]^+$ 476.1114, found 476.1108 $[M+Na]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1.43 H), 7.44 (td, *J* = 5.0, 1.2 Hz, 2.16 H), 7.36 – 7.27 (m, 4.51 H), 7.13 – 7.07 (m, 4.32 H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1.22 H), 6.49 (bs, 1.18 H) 6.34 (dd, *J* = 7.6, 1.4 Hz, 1.18 H), 5.31 (bs, 0.87 H), 3.45 (m, 2.28 H), 3.09 (m, 2.32 H), 1.86 (s, 3.00 H), 1.81 (s, 3.03 H), 1.50 (s, 8.93 H), 1.48 (s, 9.56 H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -80.17, -80.49. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.1, 160.2, 153.3, 152.8, 151.8, 151.6, 137.0, 136.9, 136.7, 136.0, 131.0, 130.0, 129.4, 129.3, 128.5, 128.4, 128.1, 127.7, 127.6, 127.4, 126.3, 124.9, 123.8, 123.5, 123.5, 123.4, 122.9, 121.6, 121.6, 80.8 (q, *J* = 31.8 Hz), 80.5, 80.3 (q, *J* = 31.9 Hz), 77.2, 77.0, 76.8, 35.3, 35.0, 31.6, 28.4, 28.3, 22.6, 22.1, 22.0.

tert-Butyl (*R*,*Z*)-(2-fluoro-6-(6,6,6-trifluoro-5-hydroxy-3-methyl-1-oxo-5-phenyl-1-(pyrrolidin-1-yl)hex-2-en-2-yl)phenyl)carbamate (5ca)

Product **3ca** (40.5 mg, 0.09 mmol, 1 equiv) was dissolved in 225 µL of anhydrous THF before addition of pirrolidine (15 µL, 0.18 mmol, 2 equiv) and the solution was allowed to stir at room temperature for 24 hours. After this time a control TLC (hexane:EtOAc 70:30) showed the reaction was complete so the crude mixture was purified directly by flash column chromatography (hexane:EtOAc = 70:30) and the title compound was obtained with an isolated yield of 86% (41.5 mg of white amorphous solid). HRMS-ESI-ORBITRAP (+): calculated for $[C_{28}H_{32}F_4N_2NaO_4]^+$ 559.2190, found 559.2193 $[M+Na]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.42 – 7.28 (m, 3H), 7.18 – 7.00 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.55 (s, 1H), 3.65 – 3.37 (m, 2H), 3.37 –

3.13 (m, 2H), 3.02 – 2.74 (m, 2H), 2.03 – 1.63 (m, 4H), 1.52 (s, 9H), 1.04 (s, 3H). ^{19}F-NMR (286 MHz, $CDCl_3$) δ -79.93, -116.6. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.1, 156.2, 153.0, 138.9, 138.4, 134.5, 133.1, 128.2, 128.1, 126.5, 126.3, 126.2, 126.1, 124.8, 124.7, 116.1, 115.8, 80.6, 74.7 (q, *J* = 28.0 Hz), 47.6, 46.67, 41.3, 28.2, 26.2, 23.9, 20.1.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. NMR spectra, HPLC chromatograms, computational details and thermodynamic data.

AUTHOR INFORMATION

Corresponding Author

*Email: giorgio.bencivenni2@unibo.it

†These authors contributed equally to this work.

ORCID

Simone Crotti: 0000-0003-3659-0551

Nicola Di Iorio: 0000-0002-4431-4007

Andrea Mazzanti: 0000-0003-1819-8863

Paolo Righi: 0000-0003-1419-2560

Giorgio Bencivenni: 0000-0002-0855-1232

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