Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201301115

Enantioselective Synthesis of α-Trifluoromethyl Arylmethylamines by Ruthenium-Catalyzed Transfer Hydrogenation Reaction

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Received: December 10, 2013; Published online: March 27, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201301115.

Abstract: A simple combination of dichloro(*para*-cymene)ruthenium(II) dimer, a chiral amino alcohol and isopropyl alcohol allowed for *in-situ* generation of the bifunctional catalyst responsible for the transfer hydrogenation reaction of trifluoromethyl ketimines in excellent yields with high enantioselectivities (up to 93% *ee*). Herein, we describe the optimization, scope, limitations, and applications of the method.

Keywords: amines; enantioselectivity; fluorine; ruthenium; transfer hydrogenation

Introduction

The trifluoromethyl group has been increasingly employed in the organic synthesis of pharmaceutical and agrochemical compounds, and outstanding results have recently emerged for the trifluoromethylation of arenes and heteroarenes.[1] Concurrently, innovation in methods for the construction of *sp*3 carbons featuring a CF_3 group is steadily progressing.[2] In this context, and emphasizing chiral species, α-trifluoromethyl amines hold great potential in diversifying the family of chiral amines. Indeed, chiral amines have a broad application, being prevalent motifs in natural products and in synthetic biologically active compounds. Chiral amines also find widespread application in asymmetric synthesis as chiral auxiliaries, organocatalysts, and as chiral bases.[3] In addition, the trifluoroethylamine motif $RCH(CF_3)NH$ has emerged as a remarkable surrogate of the natural peptide bond in the area of peptide mimics.[4] Peptide analogues featuring this fluorinated motif display both retarded proteolytic degradation and enhanced permeability through biological barriers. Furthermore, a number of drug candidates feature the trifluoroethylamine motif such as the cathepsin K inhibitor Odanacatib,[5] the anticancer agent CF_3-Ac-Docetaxel,[6] as well as others.[7] Several characteristic effects of fluorine can account for the importance of biologically active α-trifluoromethyl amino compounds. Indeed, the trifluoromethyl group reduces the basicity of an adjacent amine function while retaining its ability to act as an H-bond donor. The C–N–C bond angle of $(CF_3)CH–NH–CH$ is close to the 120° observed with an amide, and the C–CF_3 bond is isopolar with a carbonyl function.[8] In addition, the replacement of the planar amide bond by the $CH(CF_3)NH$ motif presents structural analogy with the tetrahedral proteolytic transition state associated with peptides.

The asymmetric construction of the stereogenic carbon centre in α-trifluoromethyl amines has been achieved through three key disconnections as depicted in Figure 1. In view of the simple preparation of ketimines from the corresponding trifluoromethyl ketones, it is not surprising that several approaches were based on the C=N bond reduction. Notably, this was achieved by enantioselective palladium-catalyzed hydrogenation of either α-trifluoromethyl imino esters,[9]

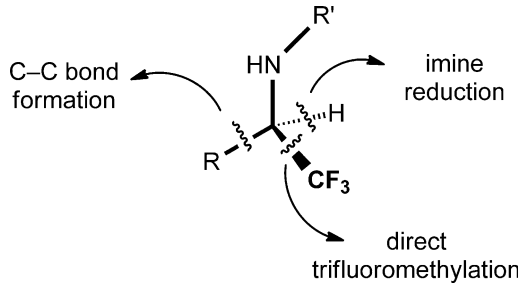
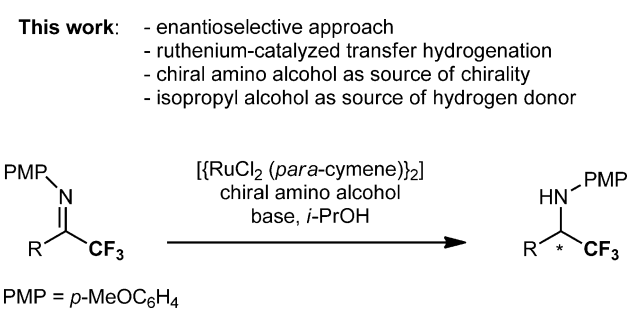


Figure 1. Key disconnections to access enantioenriched α-trifluoromethyl amines.

or from aryl and alkyl ketimines[10] under high pressure of hydrogen in up to 91 and 94% *ee*, respectively. To avoid handling high pressure H_2 gas, Akiyama's group reported a highly enantioselective Brönsted acid-organocatalyzed transfer hydrogenation of aromatic and heteroaromatic trifluoromethyl ketimines (up to 98% *ee*). This group used benzothiazoline as a source of hydride and chiral phosphoric acid as a source of chirality.[11] More recently, Benaglia's group proposed the enantioselective Lewis base-organocatalyzed hydrosilylation of not only aryl but also alkyl ketimines by means of trichlorosilane in up to 98% *ee*.[12] Diastereoselective reductive aminations were also reported exploiting either simple amino acids[13] or *N*-*tert*-butanesulfinamide[14] as chiral auxiliaries to get high *dr* values. In addition, *N*-benzyl trifluoromethyl ketimines were catalytically isomerized into α-trifluoromethyl amines with the aid of chiral bases.[15] As an alternative, the C–C bond disconnection has also been investigated through direct nucleophilic trifluoromethylation of aldimines with the Ruppert–Prakash reagent.[16] The other C–C bond could be constructed starting from trifluoroacetaldehyde imines, hydrazones, or *N*,*O*-acetals of trifluoroacetaldehyde;[17] for example, the reaction of the acetal with arylboroxines and a Pd(II)/chiral pyridine-oxazolidine complex afforded enantioenriched secondary α-trifluoromethyl amines.[18] Although some of these methods allowed high stereoselectivities, some drawbacks still limit scalability and transfer to other applications (of concern are the use of toxic reagents, and expensive sources of chirality). In addition, a method applicable to non-fluorinated substrates may prove ineffective on fluorinated analogues as observed in the hydrogenation of *N*-arylimines catalyzed by iridium bis(phosphine) complexes.[19]

Of the different approaches for the reduction of imines, the asymmetric transfer hydrogenation (ATH) has attracted considerable attention due to its operational simplicity in not requiring the handling of hazardous hydrogen gas, metallic hydrides, or silanes. Other advantages are that a low loading of metal catalyst can be used, and purification of products is facilitated thanks to the formation of volatile by-products, such as acetone or carbon dioxide. In this context, Akiyama's pioneering work on chiral phosphoric acid-catalyzed transfer hydrogenation paved a new route for chiral α-trifluoromethyl amines.[11] Recently, our group illustrated an efficient ruthenium-catalyzed hydride transfer in the isomerization of trifluoromethyl allylic alcohols.[20] As a new example of hydride transfer applied to fluorinated molecules, we herein disclose the first enantioselective ruthenium-catalyzed transfer hydrogenation of trifluoromethyl ketimines that has the advantage of both using isopropyl alcohol as a simple source of hydride and an inexpensive amino alcohol as a source of chirality (Scheme 1).

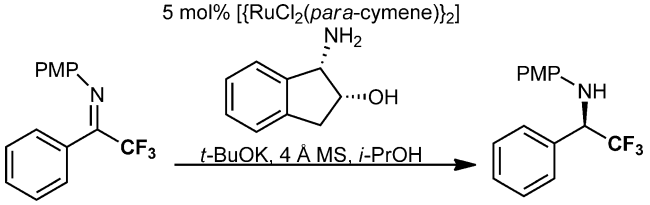


Scheme 1. Our approach towards optically enriched α-trifluoromethyl amines.

Results and Discussion

The first series of experiments examined the asymmetric transfer hydrogenation of ketimine **1a** (Scheme 1, $R = C_6H_5$) in a 5:2 formic acid-triethylamine azeotropic mixture with {RuCl[(*S*,*S*)-TsDPEN](η^6-*para*-cymene)} (TsDPEN = *N*-*para*-tosyl-1,2-diphenylethylenediamine) under Noyori's conditions.[21] The reaction proceeded in moderate to good enantioselectivities (*ee* up to 81%); however, the yield of the expected chiral α-CF_3 amine **2a** did not exceed 58% because of the formation of 2,2,2-trifluoro-1-phenylethanol as a side product. To avoid the ketimine hydrolysis we modified the reaction parameters, in particular the ratio formic acid:triethylamine and the use of isopropyl alcohol as an alternative hydrogen source; however, again, the yield in **2a** was not enhanced. Thus, we turned our attention to a catalytic transfer hydrogenation system using *N*,*O*-type ligands to perform the reduction of the trifluoromethyl ketimine **1a**. For this purpose, we were inspired by the independent works of Noyori,[22] Wills,[23] Püntener,[24] and Guijarro and Yus[25] on related ATH of non-fluorinated ketones and ketimines. Specifically, this latter work described the diastereoselective transfer hydrogenation of optically pure *N*-(*tert*-butylsulfinyl)imines in the presence of an achiral amino alcohol ligand, or a chiral ligand with matched effect.[25a,b] With regard to this work, we decided to examine an enantioselective version by means of prochiral ketimines and chiral ruthenium complexes featuring an optically pure amino alcohol ligand. Because *N*,*O*-type ligands are incompatible with the formic acid-triethylamine reduction system,[26] we used isopropyl alcohol as hydrogen donor. We first selected a simple achiral ligand, 2-amino-2-methylpropan-1-ol, in combination with [{$RuCl_2$(*para*-cymene)}$_2$] at room temperature in isopropyl alcohol. Pleasingly, the expected α-trifluoromethyl amine was obtained in 88% yield without 2,2,2-trifluoro-1-phenylethanol side product. The next step was obviously to evaluate a chiral non-racemic amino alcohol ligand; to this end, we selected (1*S*,2*R*)-1-amino-2-in-

Table 1. Optimization of reaction conditions for the enantioselective transfer hydrogenation of ketimine **1a**.



[**1a**]$_i$ = 0.06 mol/L

2a

PMP = *p*-MeOC$_6$H$_4$

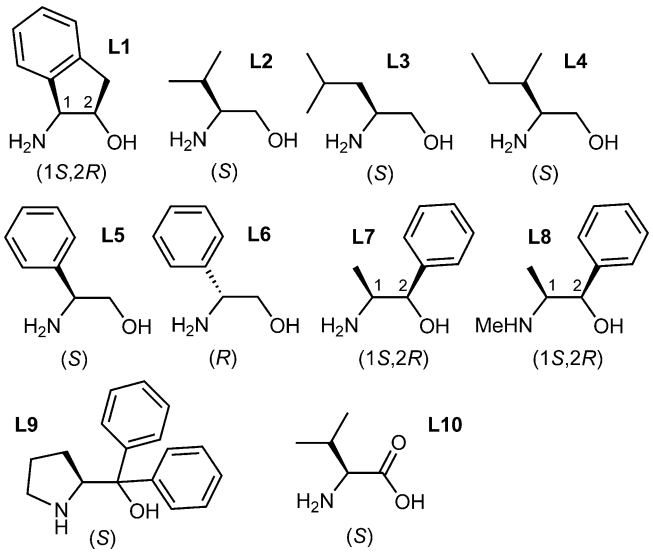
Run	Base	Ratio Ru dimer/L[a]/base	Temperature [°C]	Time [h]	Yield[b] [%]	*ee* [%]
1	KOH	1:2:5	25	14	>98	92
2	*t*-BuOK	1:2:5	25	14	>98	93
3	*i*-PrONa	1:2:5	25	14	>98	93
4	Cs_2CO_3	1:2:5	25	14	0	-
5	K_2CO_3	1:2:5	25	14	0	-
6	*t*-BuOK	1:2:5	0	21	59	94
7	*t*-BuOK	1:2:5	40	5	>98	93
8	*t*-BuOK	1:2:5	80	5	>98	92
9	*t*-BuOK	1:2:5[c]	25	14	79	93
10	*t*-BuOK	1:2:5[c]	40	14	>98	91
11	*t*-BuOK	1:4:5	25	22	87	93
12	*t*-BuOK	1:2:10	25	14	>98	93
13	*t*-BuOK	1:2:5[d]	25	14	>98	87
14	*t*-BuOK	1:2:5[e]	25–90	18	0[f]	-

[a] L = ligand.
[b] Yields were determined by ^{19}F NMR using trifluorotoluene as internal standard.
[c] 3 mol% of ruthenium dimer was used.
[d] [{$RuCl_2$(benzene)}$_2$] was used.
[e] [RuCp*$(ACN)_3]^+PF_6^-$ was used.
[f] Only 2,2,2-trifluoro-1-phenylethanol was obtained.

danol that gave an excellent 93% *ee* value. With these suitable conditions in hand, we next conducted the optimization of the reaction conditions by scrutinizing the nature of the base, the ratio of the reagents, the imine concentration, the temperature, and the source of ruthenium (Table 1).

A base was essential for the reaction and its nature appeared crucial for the reactivity with a strong requirement for alkoxides over carbonates; indeed, K_2CO_3 and Cs_2CO_3 did not allow the reaction whereas KOH, *i*-PrONa and *t*-BuOK gave full conversions of the starting ketimine **1a** (Table 1, runs 1–5). We chose to keep *t*-BuOK as the base to study the effect of the temperature on the course of the reaction. At 0 °C, the reaction was not complete, even after a prolonged reaction time, whereas an increase of the temperature allowed us to significantly reduce the reaction time without impacting the enantioselectivity; in the range 0–60 °C the *ee* value difference was only 2% (Table 1, runs 6–8). The optimal amount of catalyst was established at 5 mol% with a ratio Ru dimer/ligand/base of 1:2:5. A lower loading of catalyst had the effect of lowering the conversion for a fixed reaction time. The same tendency was also observed when the quantity of ligand was doubled. Moreover, twice the amount of base did not improve the reaction. It is important to note that these changes had a very small impact on the enantioselectivities (Table 1, runs 9–12). The concentration of ketimine **1a** in isopropyl alcohol was fixed at 0.06 M and variations were conducted in the range 0.01–0.2 M; but, here again, no perceptible effect was observed on the enantioselectivity. These experiments were conducted with the aid of a catalyst prepared *in-situ* by heating, at reflux, a mixture of [{$RuCl_2$(*para*-cymene)}$_2$], (1*S*,2*R*)-1-amino-2-indanol, and 4 Å molecular sieves in isopropyl alcohol. We found that changing the ruthenium source to [{$RuCl_2$(benzene)}$_2$], showing a less bulky arene moiety, lowered the *ee* value of **2a** to 87% (Table 1, run 13). Alkylated η^6-arene such as the η^6-*para*-cymene enhanced stabilization of the transition state due to the increased π-donation of the arene as well as contributing to a favourable secondary C(sp^3)–H/π interaction with the aryl moiety of the substrate.[27] The use of [RuCp*$(ACN)_3]^+PF_6^-$ (Cp* = η^5-pentamethylcyclopentadienyl, ACN = CH_3CN) showed no efficiency, yielding the 2,2,2-trifluoro-1-phenylethanol as the sole product (Table 1, run 14).

Table 2. Screening of chiral ligands in the transfer hydrogenation of **1a**.[a]



Run	Ligand	Yield [%][b]	*ee* [%] (Configuration)[c]
1	**L1**	>98	93 (*R*)
2	**L2**	53	42 (*S*)
3	**L3**	92	26 (*S*)
4	**L4**	96	48 (*S*)
5	**L5**	85	23 (*R*)
6	**L6**	69	20 (*S*)
7	**L7**	>98	67 (*R*)
8	**L8**	72	69 (*R*)
9	**L9**	0	-
10	**L10**	0	-

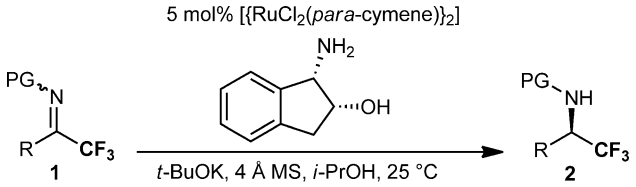
[a] Reactions were run under optimized conditions (see Table 1, run 2).
[b] Yields were determined by ^{19}F NMR using trifluorotoluene as internal standard.
[c] The absolute configuration was determined by comparison with data reported in the literature.[11,16f]

Ethanol was also examined as an alternative source of hydrogen donor but the reaction resulted only in a moderate yield.

The effect of the β-amino alcohol ligand was addressed by evaluating various structures having either one or two stereogenic centres. A series of ten ligands **L1–L10** was studied and the results are reported in Table 2. At first sight, ruthenium complex with **L1** ligand, (1*S*,2*R*)-1-amino-2-indanol, was the most efficient and stereodiscriminating catalyst; however, the results obtained with other ligands also deserved special attention. In the literature, it was reported that the outcome of asymmetric induction in asymmetric transfer hydrogenation of ketones is determined primarily by the configuration of the hydroxy-bearing carbon.[22,24,28] These studies also reported that the amine-substituted carbon affects the enantioselection but to a lesser extent and mainly through steric effects. In the major part, our results were in agreement with these previous observations. Surprisingly, however, we observed an inversion of the main enantiomer configuration caused by a simple change in the nature of the substituent, alkyl or aryl at the amine-substituted carbon, while keeping the same absolute configuration at this carbon (Table 2, runs 2–6). Indeed, with **L5**, (*S*)-2-amino-2-phenylethanol, the (*R*) enantiomer of **2a** was obtained, in an identical way to the use of **L1**, but the use of **L2**, **L3**, or **L4**, which have the 2-phenyl group replaced by a 2-alkyl chain, gave the opposite (*S*) enantiomer of **2a**. This is a quite unique observation for which we could not find a precedent in the literature. A case was reported in ATH of ketoisophorone with ligands having both a 2-alkyl chain: (*S*)-prolinol gave the (*R*) alcohol while (*S*)-*tert*-leucinol gave the (*S*) alcohol. Unfortunately, the required data were not detailed.[24] Otherwise, **L5** and **L6** provided opposite enantiomers of **2a**, as expected. Reversing the position of alkyl and aryl groups on the ligands, while retaining the same absolute configurations at the two centres such as in **L7** compared to **L1**, led to a lower enantioselectivity for the *R* enantiomer of **2a** (Table 2, runs 1 and 7). *N*-Alkylated derivative **L8**, having a secondary amino group, exhibited a lower reactivity and a slightly increased enantioselectivity by comparison with **L7**. (*S*)-Diphenylprolinol **L9** as ligand was unsuccessful in the reaction, possibly due to bulkiness.[29] We also considered a ruthenium aminocarboxylate complex with the amino acid **L10** that has found application in the transfer hydrogenation of ketones[30] but not of ketimines; however, no reaction occurred.

After having demonstrated that the ruthenium complex bearing **L1** as ligand was the most efficient in terms of reactivity and stereodiscrimination, we then went on to a series of ketimines in the enantioselective transfer hydrogenation reaction. This work included aryl and alkyl ketimines with various protecting groups (PG) for the nitrogen atom (Table 3). It is important to mention that all the aryl ketimines described hereafter were obtained as a single *E* isomer. It was essential that the ketimine geometry was clearly established because it has a strong impact on the stereochemical course of the reaction (see later in the text). For aryl ketimines **1a–m**, excellent yields and high *ee* values were obtained, irrespective of the electronic nature and position of the substituents on the benzene ring, except for the 2-MeO substituted ketimine **1l** (Table 3, runs 1–13). This substrate did not react, even at 90 °C, possibly because of the steric demand next to the imine function. The absolute configuration of the amine **2a** was determined by polarimetry and comparison with published data.[11,16f] The absolute configurations of the other aryl methylamines were assigned by analogy. The scope of the reaction was further explored with benzyl and *n*-hexyl

Table 3. Variation of substrates and protecting groups.



$[\mathbf{1}]_i$ = 0.06 mol/L

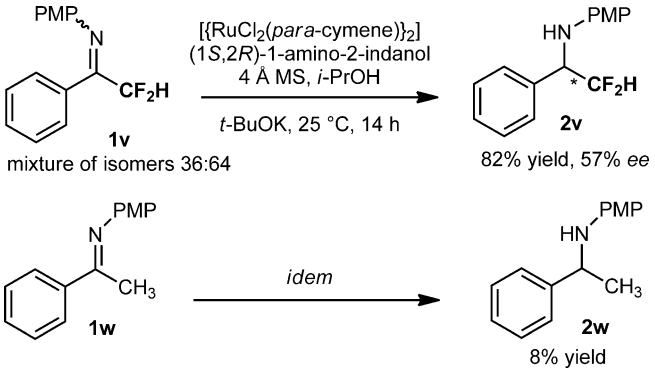
Run	R	PG	2	Yield [%][a]	*ee* [%]
1	C_6H_5	PMP	**2a**	98	93 (*R*)
2	4-BrC_6H_4	PMP	**2b**	94	90 (*R*)
3	4-$MeOC_6H_4$	PMP	**2c**	99	91 (*R*)
4	4-ClC_6H_4	PMP	**2d**	98	90 (*R*)
5	4-MeC_6H_4	PMP	**2e**	99	92 (*R*)
6	4-*t*-BuC_6H_4	PMP	**2f**	99	92 (*R*)
7	3-ClC_6H_4	PMP	**2g**	99	89 (*R*)
8	4-$CF_3C_6H_4$	PMP	**2h**	99	89 (*R*)
9	3-*i*-PrC_6H_4	PMP	**2i**	98	91 (*R*)
10	3,4-$Cl_2C_6H_3$	PMP	**2j**	81	84 (*R*)
11	3,4-$Me_2C_6H_3$	PMP	**2k**	94	90 (*R*)
12	2-$MeOC_6H_4$	PMP	**2l**	0	–
13	2-naphthyl	PMP	**2m**	99	91 (*R*)
14	Bn	PMP[b]	**2n**	–	–
15	hexyl	PMP[c]	**2o**	52	22 (nd[e])
16	C_6H_5	*t*-BuSO[c]	**2p**	–[d]	–
17	C_6H_5	Bn	**2q**	86	0
18	C_6H_5	1-naphthyl	**2r**	99	72 (+)
19	C_6H_5	2-naphthyl	**2s**	99	84 (−)
20	C_6H_5	2,4-$(MeO)_2C_6H_3$	**2t**	80	90 (−)
21	C_6H_5	H[c]	**2u**	99	32 (nd[e])

[a] Yields of isolated pure products.
[b] Mixture of imine–enamine tautomers (1:1).
[c] Mixture of diastereoisomers.
[d] Only 2,2,2-trifluoro-1-phenylethanol was obtained.
[e] nd = not determined.

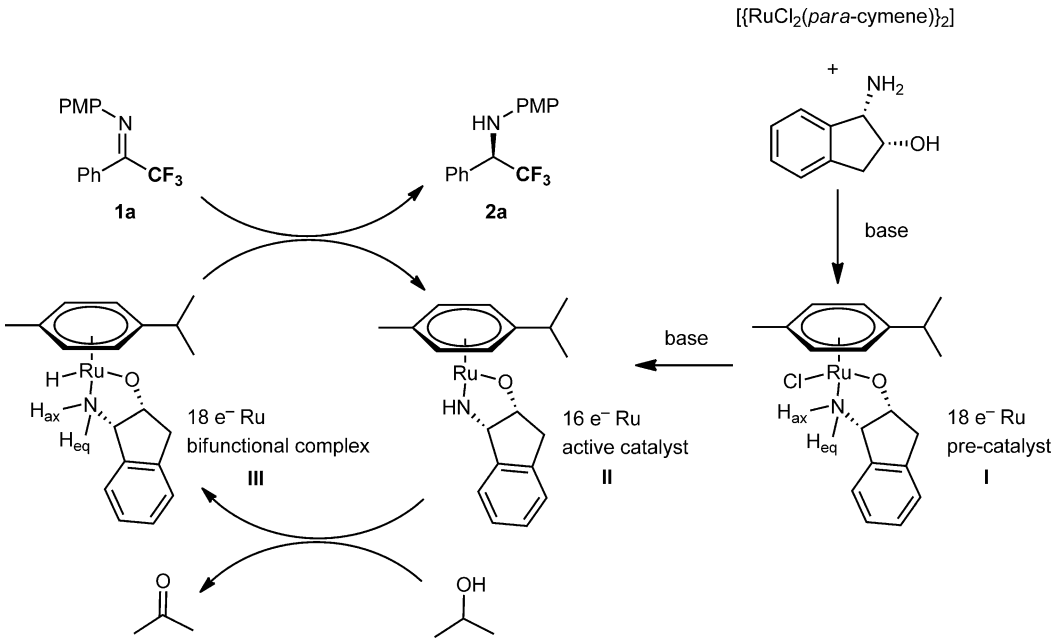
ketimines. Ketimine **1n** with a benzyl group showed imine–enamine tautomerization (1:1) and failed to react under our ATH conditions. In the case of *n*-hexyl ketimine **1o**, the desired amine was obtained in a moderate yield and a low *ee* value of 22% (Table 3, run 15). Apart from the PMP group, other protecting groups were also examined to evaluate their steric and electronic effects on reactivity and enantioselectivity. The ketimine **1p**, with *N*-(*tert*-butylsulfinyl) protecting and activating group, is significantly more electrophilic than its *N*-PMP analogue, albeit with a greater instability and tendency to hydrolysis. Hence, **1p** was fully converted into 2,2,2-trifluoro-1-phenylethanol under our ATH conditions (Table 3, run 16). This result indicated that the conditions reported by Guijarro, Yus and co-workers[25a] could not be transposed to trifluoromethyl aryl ketimines.[31]

Benzyl-protected ketimine **1q** gave the desired amine in the form of a racemic compound because of a base-mediated 1,3-hydrogen shift. Indeed, this isomerization reaction led to the regioisomeric imine, which, after transfer hydrogenation, gave an amine not possessing a stereogenic centre (Table 3, run 17).[32] In addition, three bulky *N*-aryl-protected ketimines **1r**, **1s**, and **1t** were employed in the ATH reaction; in outcomes, we got the corresponding imines in high yields but lower *ee* values were obtained compared the *N*-PMP ketimines (Table 3, runs 18–20). A step-economic synthetic plan would be to utilize N–H imines to avoid a deprotection step after ATH reaction.[33] By chance the 2,2,2-trifluoro-1-phenylethanimine **1u** was reported to be a stable, readily isolable N–H ketimine existing as a dynamic mixture of *Z* and *E* isomers.[34] However, the existence of two imine geometries could cause the multiplication of transition states and a poor enantiodiscrimination during the course of enantioselective additions to these imines. In our study, ketimine **1u** gave full conversion into the expected free amino product **2u** but with only 32% *ee* (Table 3, run 21). Although the investigation of N–H ketimines is a very important area to explore, no attempt was done to screen other amino alcohol ligands.

The difluoromethyl group has received less attention than the CF_3 group due to synthetic difficulties associated with this motif. Nevertheless, it is a motif of great interest in modern organofluorine chemistry.[35] Difluoromethyl ketimine **1v** was prepared following a literature procedure that gave a mixture of inseparable geometric isomers in a ratio 36:64.[10,36] This mixture was subjected to our ATH conditions. Amine **2v** was obtained in a good yield and a moderate *ee* value that we reasonably ascribed to the starting mixture of stereoisomers (Scheme 2, *top*). In order to provide a comparison of the behaviour of fluorinated *versus* non-fluorinated ketimines and to highlight the effect of fluorine, we conducted the ATH reaction on phenyl methyl ketimine **1w** (*E* isomer). We only obtained an 8% yield of the expected amine **2w** (Scheme 2, *bottom*), clearly indicating



Scheme 2. A comparative study with α-difluoromethylated amine **1v** and non-fluorinated ketimine **1w**.



Scheme 3. Catalytic cycle for the ATH reaction of ketimine **1a**.

that the presence of the electron-withdrawing CF_3 group in **1a** significantly enhanced the electrophilic character of the iminic carbon and thus the ketimine reactivity. This result confirmed, one more time, that the chemistry developed for fluorinated substrates cannot be simply transposed to non-fluorinated molecules and *vice versa*.[31]

The mechanism of ATH reaction as well as the origin of the stereoselectivity are well documented in the literature, although the C=N bond reduction was less investigated than the C=O bond reduction.[25d,28,37] The pre-catalyst **I** was generated by reaction of the ruthenium dimer with the amino alcohol and further reacted, in presence of the base, to provide the active catalyst **II** (Scheme 3). This 16 electron deficient ruthenium complex dehydrogenated the isopropyl alcohol to form the ruthenium hydride complex **III** with the release of acetone. The bifunctional complex **III** transferred a hydride to the ketimine, together with a proton, in a stepwise process to end up with the amine and regeneration of the active catalyst **II**.

Upon formation of the pre-catalyst, the complex became chiral-at-metal with the possibility of formation of diastereomers owing to the chirality of the amino alcohol ligand. An X-ray diffraction study along with NMR spectroscopic data showed that the pre-catalyst exists as a single diastereoisomer.[38] In order to rationalize the enantiofacial discrimination of the prochiral ketimines, we needed to know their precise structures that is, *E* or *Z* configuration. Although the geometry of the trifluoromethyl ketimines is a parameter of prime importance, it was not often properly taken into account in the literature for transition state models of the enantiodiscriminating step. Indeed, in reactions involving ketimine **1a**, mechanisms were proposed employing either the *E* or the *Z* configuration of the ketimine C=N bond.[10–12,39] We therefore conducted a comprehensive study to ascertain the geometry of aryl trifluoromethyl ketimines. Imine **1m** featuring a 2-naphthyl moiety was crystallized and studied by X-ray diffraction to show the *E* configuration.[40] Next, the $^{19}F,^{1}H$-HOESY NMR spectrum of ketimine **1a** was recorded; it showed an interaction with an aromatic C–H of the phenyl group but not with the aromatic C–H of the PMP group, confirming the *E* configuration. In addition, DFT calculations were realized. The geometries of the *E* and *Z* isomers were first optimized at the B3LYP/6-311++G(d,p) level of theory. As stacking interactions could stabilize the *E* isomer, we also performed calculations at the ωB97X-D/6-311++G(d,p) level of theory. The use of the latter functional indicated that the *E* isomer was 4.5 kcal mol^{-1} more stable than the *Z* isomer whereas the difference was only 2 kcal mol^{-1} with the widespread B3LYP functional. In the light of our own observations together with published information this led us to propose a transition state to deduce the origin of the enantioselectivity (Figure 2). Transfer of the hydride to the iminic carbon took place through the *Si*-face of the ketimine, followed by a proton transfer to the iminic nitrogen, to produce the *R* enantiomer of the amine.

As an illustration of the utility of these chiral trifluoromethyl amines, (*R*)-**2d** was readily converted into the corresponding free amine **3d** without loss of the stereochemical integrity at the stereogenic centre.

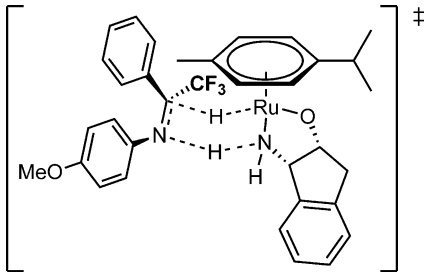
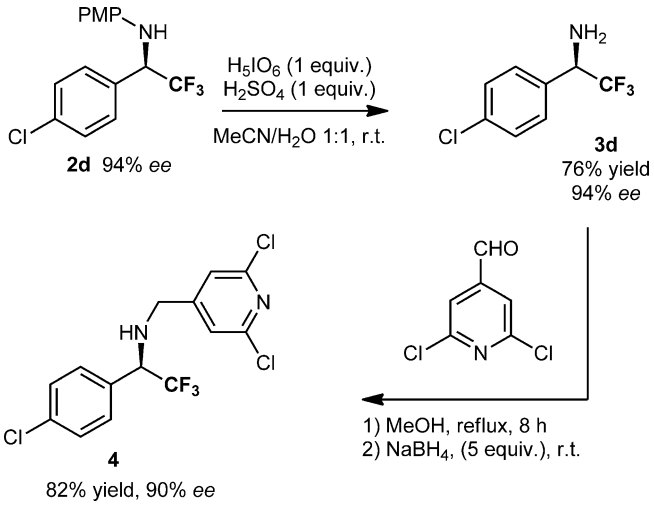


Figure 2. Transition state for hydrogen transfer *via* metal–ligand bifunctional catalysis.

Next, the imine formation with 2,6-dichloroisonicotinaldehyde followed by reduction by means of sodium borohydride provided compound **4** that is a trifluoro analogue of a potent plant disease control agent (Scheme 4).[41] Erosion of the *ee* value was noticed but will hopefully be avoided by testing other conditions for the reductive amination step. We believe that our asymmetric transfer hydrogenation reaction should be readily applicable to compounds such as Odanacatib or CF_3-Ac-Docetaxel (see earlier in the text).



Scheme 4. Synthesis of the trifluoro analogue of a plant disease control agent.

Conclusions

We have investigated an enantioselective ruthenium-catalyzed transfer hydrogenation of CF_3 ketimines that allows the synthesis of optically enriched α-trifluoromethyl amines in high yields and enantioselectivities. Aryl ketimines led to high *ee* values for the corresponding aryl trifluoromethyl amines; however, the most challenging aliphatic ketimines gave much lower enantioselectivities, presumably caused by diastereomeric mixtures of the starting ketimines. The method is remarkable for its simplicity using isopropyl alcohol and an inexpensive chiral amino alcohol. It contributes a suitable alternative to asymmetric hydrogenation using molecular hydrogen and chiral ruthenium-bisphosphine catalysts. Furthermore, the *E*-configuration of aryl trifluoromethyl ketimines was ascertained and the origin of the enantioselectivity was rationalized. Finally, we showed how the PMP protecting group could be easily cleaved and the free amine engaged in the synthesis of a trifluoro analogue of an active compound.

Experimental Section

General Information

^{1}H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F (282 MHz) NMR spectra were recorded on a Bruker AVANCE 300. Chemical shifts in NMR spectra are reported in parts per million from TMS or $CFCl_3$ resonance as the internal standard. IR spectra were recorded on a Perkin–Elmer IR-FT 1650 spectrometer. The wave numbers (ν) of recorded IR signals are quoted in cm^{-1}. The conversion and ratio of the corresponding products were determined by ^{19}F NMR analysis adopting α,α,α-trifluorotoluene as internal standard with D1 value = 5 s. The enantiomeric excesses were determined by HPLC analysis. HPLC analysis were performed on Agilent HPLC 1100 Series system, column Daicel Chiralcel OD-H, OJ-H or AD-H, mobile phase *n*-heptane/isopropyl alcohol, UV detector at 254 or 210 nm. High-resolution mass spectrometry was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. Isopropyl alcohol was dried over molecular sieves under an argon atmosphere. Trifluoromethyl ketimines **1a–u** were prepared through the corresponding trifluoromethyl ketones[42] according to literature procedures.[11,43] Some of the ketimines employed in this work are known: **1a**,[39b,44] **1b**,[39b,45] **1c**,[10] **1d**,[39b] **1e**,[39b] **1h**,[39b] **1l**,[39b] **1m**,[11,39a] **1n** (mixture of tautomers),[12,46] **1o**,[39b] **1p**,[14,47] **1q**,[32] **1s**,[44] **1u**,[34] **1v**,[10,39a,46] **1w**.[48]

Typical Procedure for the Synthesis of CF_3 Ketimines (1)

(*E*)-*N*-[1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1f): To a 50-mL round-bottom flask fitted with a Dean–Stark water trap and reflux condenser were added 1-(4-*tert*-butylphenyl)-2,2,2-trifluoroethanone (2.30 g, 10 mmol) and *p*-anisidine (1.48 g, 12 mmol), along with dry toluene (25 mL) and *p*-toluenesulfonic acid (51.66 mg, 0.3 mmol). The mixture was refluxed until the theoretical amount of water had collected into the trap. The reaction was also monitored by ^{19}F NMR. After completion, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography to give the ketimine as a yellow oil; yield: 99%. ^{1}H NMR ($CDCl_3$): δ = 7.31–7.34 (m, 2H),

7.15–7.18 (m, 2H), 6.70–6.78 (m, 4H), 3.76 (s, 3H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$): δ=157.7, 155.6 (q, $J_{C,F}$=33 Hz), 153.6, 140.1, 128.6, 127.5, 125.8, 123.4, 120.3 (q, $J_{C,F}$=277 Hz), 114.1, 55.5, 35.0, 31.2; ^{19}F NMR ($CDCl_3$): δ=−70.2; IR (neat): ν=2965, 1602, 1503, 1463, 1329, 1233, 1189, 1124, 1033, 971, 830 cm^{-1}; HR-MS: m/z=336.1569, calcd. for $C_{19}H_{21}NF_3O$ ([M+H]$^+$): 336.1575.

(*E*)-*N*-[1-(3-Chlorophenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1g): Yellow oil; yield: 65%. ^{1}H NMR ($CDCl_3$): δ=7.28–7.29 (m, 1H), 7.17–7.20 (m, 2H), 7.28–7.29 (m, 1H), 7.00 (d, J=8.0 Hz, 1H), 6.67 (m, 4H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=158.2, 153.6 (q, $J_{C,F}$=33.8 Hz), 139.2, 135.0, 132.5, 130.5, 130.3, 128.6, 127.0, 123.6, 120.0 (q, $J_{C,F}$=277 Hz), 114.3, 55.5; ^{19}F NMR ($CDCl_3$): δ=−70.4; IR (neat): ν=2958, 1602, 1503, 1293, 1231, 1193, 1125, 982, 835, 759 cm^{-1}; HR-MS: m/z=314.0552, calcd. for $C_{15}H_{12}NF_3O^{35}Cl$ ([M+H]$^+$): 314.0560.

(*E*)-*N*-[1-(3-Isopropylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1i): Yellow oil; yield: 99%. ^{1}H NMR ($CDCl_3$): δ=7.28–7.31 (m, 2H), 7.15 (d, J=7.0 Hz, 1H), 7.07 (s, 1H), 6.74–6.80 (m, 4H), 3.78 (s, 3H), 2.85 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=157.8, 156.0 (q, $J_{C,F}$=33 Hz), 149.4, 140.1, 130.5, 128.8, 128.5, 127.1, 126.0, 123.3, 120.2 (q, $J_{C,F}$=277.5 Hz), 114.1, 55.5, 34.0, 23.8; ^{19}F NMR ($CDCl_3$): δ=−70.2; IR (neat): ν=2963, 1602, 1503, 1465, 1325, 1237, 1186, 1125, 1118, 1033, 988, 835, 763, 700 cm^{-1}; HR-MS: m/z=322.1413, calcd. for $C_{18}H_{19}NF_3O$ ([M+H]$^+$): 322.1419.

(*E*)-*N*-[1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (1j): Yellow oil; yield: 99%. ^{1}H NMR ($CDCl_3$): δ=7.39–7.42 (m, 2H), 7.01–7.04 (m, 1H), 6.72–6.79 (m, 4H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=158.4, 152.5 (q, $J_{C,F}$=34.5 Hz), 139.0, 135.0, 133.6, 131.1, 130.6, 130.5, 128.2, 123.5, 119.8 (q, $J_{C,F}$=276.8 Hz), 114.4, 55.5; ^{19}F NMR ($CDCl_3$): δ=−70.3; IR (neat): ν=2967, 1601, 1503, 1470, 1326, 1247, 1195, 1126, 1033, 984, 839, 763, 732 cm^{-1}; HR-MS: m/z=348.0176, calcd. for $C_{15}H_{11}Cl_2F_3NO$ ([M+H]$^+$): 348.0170.

(*E*)-*N*-[1-(3,4-dimethylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1k): Yellow oil; yield: 89%. ^{1}H NMR ($CDCl_3$): δ=7.03–7.08 (m, 2H), 6.93 (d, J=7.8 Hz, 1H), 6.71–6.78 (m, 4H), 3.75 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=157.7, 155.8 (q, $J_{C,F}$=33.8 Hz), 140.1, 139.2, 137.3, 130.0, 129.5, 128.1, 126.3, 123.4, 120.3 (q, $J_{C,F}$=276.8 Hz), 114.1, 55.4, 19.9; ^{19}F NMR ($CDCl_3$): δ=−70.3; IR (neat): ν=2954, 1651, 1602, 1503, 1442, 1328, 1239, 1203, 1153, 1123, 1032, 980, 871, 766, 733 cm^{-1}; HR-MS; m/z=308.1264, calcd. for $C_{17}H_{17}NF_3O$ ([M+H]$^+$): 308.1262.

(*E*)-*N*-(1-Phenyl-2,2,2-trifluoroethylidene)naphthalen-1-amine (1r): Yellow oil; yield: 45%. ^{1}H NMR ($CDCl_3$): δ=8.01–8.04 (m, 1H), 7.81–7.84 (m, 1H), 7.52–7.58 (m, 3H), 7.28–7.32 (m, 1H), 7.15–7.24 (m, 5H), 6.46 (d, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=157.9 (q, $J_{C,F}$=34.5 Hz), 143.9, 133.9, 130.5, 130.1, 128.6, 128.3, 128.2, 127.0, 126.7, 126.4, 123.3, 120.0 (q, $J_{C,F}$=277.5 Hz), 114.1; ^{19}F NMR ($CDCl_3$): δ=−70.0; IR (neat): ν=3065, 1661, 1392, 1328, 1190, 1127, 968, 780, 772, 696 cm^{-1}; HR-MS: m/z=300.0988, calcd. for $C_{18}H_{13}NF_3O$ ([M+H]$^+$): 300.1000.

(*E*)-*N*-(1-Phenyl-2,2,2-trifluoroethylidene)-2,4-dimethoxyaniline (1t): Yellow solid; mp 87 °C; yield: 80%. ^{1}H NMR ($CDCl_3$): δ=7.22–7.37 (m, 5H), 6.55–6.58 (m, 1H), 6.34–6.36 (m, 1H), 6.27–6.31 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=158.8, 157.3, 150.7, 131.4, 130.1, 128.4, 128.1, 122.0, 120.1 (q, $J_{C,F}$=276.8 Hz), 104.2, 99.4, 55.5; ^{19}F NMR ($CDCl_3$): δ=−69.9; IR (neat): ν=2966, 1601, 1438, 1333, 1311, 1211, 1129, 1030, 971, 856 cm^{-1}; HR-MS: m/z=310.1057, calcd. for $C_{16}H_{15}NF_3O_2$ ([M+H]$^+$): 310.1055.

General Procedure for the Synthesis of CF_3 Imines (2) by ATH of CF_3 Ketimines (1)

A mixture of [{$RuCl_2$(*p*-cymene)}$_2$] (6.1 mg, 0.01 mmol), (1*S*,2*R*)-1-amino-2-indanol (3 mg, 0.02 mmol), 4 Å molecular sieves and anhydrous isopropyl alcohol (0.5 mL) was heated at 90 °C for 20 min. During this heating period, the initially orange reaction mixture turned dark red in colour. The reaction was then cooled to room temperature and a solution of trifluoromethyl ketimine (0.2 mmol) in isopropyl alcohol (2 mL) and a solution of *t*-BuOK (5.5 mg, 0.05 mmol) in 0.5 mL isopropyl alcohol were successively added. After 14 h, the reaction went to completion (monitoring by ^{19}F NMR). The reaction mixture was filtered through a small amount of silica gel and washed with ethyl acetate. The combined organic phase was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 30:1) to give the corresponding trifluoromethylamine **2**.

(*R*)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)-4-methoxyaniline (2a):[11] Colorless oil; yield: 99%; 93% *ee*; $[\alpha]_D^{20}$: −64.5 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=7.37–7.46 (m, 5H), 6.71–6.77 (m, 2H), 6.58–6.63 (m, 2H), 4.78–4.83 (m, 1H), 4.08 (d, J=7.1 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=153.9, 140.1, 134.9, 129.6, 129.5, 128.5, 125.7 (q, $J_{C,F}$=280.5 Hz), 116.3, 115.4, 62.3 (q, $J_{C,F}$=29.2 Hz), 56.2; ^{19}F NMR ($CDCl_3$): δ=−74.6 (d, J=7.3 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, λ=254 nm): τ_R=16.0 min (*S*), τ_R=16.8 min (*R*).

(*R*)-*N*-[1-(4-Bromophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2b):[11] White solid; yield: 94%; 90% *ee*; ^{1}H NMR ($CDCl_3$): δ=7.50–7.54 (m, 2H), 7.34 (d, J=8.4 Hz, 2H), 6.72–6.77 (m, 2H), 6.54–6.59 (m, 2H), 4.73–4.83 (m, 1H), 4.06 (d, J=7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=153.6, 139.1, 133.4, 132.2, 129.8, 124.9 (q, $J_{C,F}$=280.0 Hz), 123.4, 115.9, 115.0, 61.4 (q, $J_{C,F}$=29.5 Hz), 55.8; ^{19}F NMR ($CDCl_3$): δ=−74.7 (d, J=7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, λ=254 nm): τ_R=25.2 min (minor enantiomer), τ_R=29.2 min (major enantiomer).

(*R*)-*N*-[1-(4-Methoxyphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2c):[11] White solid; yield: 99%; 91% *ee*; ^{1}H NMR ($CDCl_3$): δ=7.38 (d, J=8.6 Hz, 2H), 6.91–6.94 (m, 2H), 6.74–6.79 (m, 2H), 6.59–6.65 (m, 2H), 4.76–4.81 (m, 1H), 4.08 (d, J=6.5 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=160.0, 153.2, 139.6, 129.1, 126.2, 125.2 (q, $J_{C,F}$=279.8 Hz), 115.7, 114.8, 114.3, 61.0 (q, $J_{C,F}$=29.2 Hz), 55.6, 55.2; ^{19}F NMR ($CDCl_3$): δ=−74.8 (d, J=7.4 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, λ=254 nm): τ_R=27.8 min (major enantiomer), τ_R=30.4 min (minor enantiomer).

(*R*)-*N*-[1-(4-Chlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2d):[11] White solid; yield; 98%; 90% *ee*; ^{1}H NMR ($CDCl_3$): δ = 7.35–7.42 (m, 4H), 6.73–6.77 (m, 2H), 6.55–6.61 (m, 2H), 4.76–4.86 (m, 1H), 4.09 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.5, 139.2, 135.2, 132.8, 129.4, 129.2, 125.0 (q, $J_{C,F}$ = 279.8 Hz), 115.9, 115.0, 61.0 (q, $J_{C,F}$ = 29.2 Hz), 55.6, 55.2; ^{19}F NMR ($CDCl_3$): −74.1 (d, J = 7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 23.6 min (minor enantiomer), τ_R = 27.5 min (major enantiomer).

(*R*)-*N*-(1-*para*-Tolyl-2,2,2-trifluoroethyl)-4-methoxyaniline (2e):[11] Colourless oil; yield: 99%; 92% *ee*; ^{1}H NMR ($CDCl_3$): δ = 7.38 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.73–6.78 (m, 2H), 6.60–6.65 (m, 2H), 4.75–4.84 (m, 1H), 4.08 (d, J = 7.3 Hz, 1H), 3.73 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.3, 139.7, 139.1, 131.4, 129.7, 127.9, 125.3 (q, $J_{C,F}$ = 279.8 Hz), 115.8, 114.9, 61.6 (q, $J_{C,F}$ = 29.2 Hz), 55.7, 21.3; ^{19}F NMR ($CDCl_3$): δ = −74.6 (d, J = 7.4 Hz); HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 52.5 min (minor enantiomer), τ_R = 58.7 min (major enantiomer).

(*R*)-*N*-[1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2f): Colourless oil; yield: 99%; 92% *ee*; $[\alpha]_D^{20}$: −85.6 (*c* 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.37–7.44 (m, 4H), 6.75–6.79 (m, 2H), 6.63–6.67 (m, 2H), 4.77–4.86 (m, 1H), 4.08 (d, J = 7.5 Hz, 1H), 3.74 (s, 3H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 153.3, 152.2, 139.8, 131.4, 127.6, 125.4 (q, $J_{C,F}$ = 280.5 Hz), 126.0, 115.7, 114.9, 61.4 (q, $J_{C,F}$ = 29.2 Hz), 55.7, 34.7, 31.4; ^{19}F NMR ($CDCl_3$): δ = −74.5 (d, J = 7.4 Hz); IR (neat): ν = 3394, 2968, 1513, 1233, 1182, 1177, 1118, 1028, 825, 684 cm^{-1}; HR-MS: m/z = 337.1653, calcd. for $C_{19}H_{22}NF_3O$ (M^+): 337.1653; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 13.4 min (minor enantiomer), τ_R = 15.2 min (major enantiomer).

(*R*)-*N*-[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (2g): Pale yellow oil; yield: 99%; 89% *ee*; $[\alpha]_D^{20}$: −52.7 (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.47 (s, 1H), 7.32–7.38 (m, 3H), 6.73–6.78 (m, 2H), 6.56–6.61 (m, 2H), 4.75–4.85 (m, 1H), 4.10 (d, J = 7.1 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.5, 139.1, 136.4, 135.0, 130.3, 129.5, 128.3, 126.3, 124.9 (q, $J_{C,F}$ = 280.5 Hz), 115.8, 115.8, 61.4 (q, $J_{C,F}$ = 30 Hz), 55.7; ^{19}F NMR ($CDCl_3$): δ = −74.5 (d, J = 7.2 Hz); IR (neat): ν = 3372, 2936, 1575, 1512, 1233, 1172, 1119, 1033, 818, 785, 697 cm^{-1}; HR-MS: m/z = 315.0635, calcd. for $C_{15}H_{13}NF_3O$ (M^+): 315.0638; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 26.0 min (minor enantiomer), τ_R = 29.5 min (major enantiomer).

(*R*)-*N*-{1-[4-(Trifluoromethyl)phenyl]-2,2,2-trifluoroethyl}-4-methoxyaniline (2h):[11] Pale yellow oil; yield: 99%; 89% *ee*; ^{1}H NMR ($CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 6.73–6.78 (m, 2H), 6.55–6.60 (m, 2H), 4.85–4.95 (m, 1H), 4.14 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.7, 139.0, 138.4, 131.5 (q, $J_{C,F}$ = 32.2 Hz), 128.6, 126.0 (q, $J_{C,F}$ = 3.8 Hz), 124.9 (q, $J_{C,F}$ = 280.5 Hz), 124.0 (q, $J_{C,F}$ = 270.8 Hz), 115.9, 115.0, 61.6 (q, $J_{C,F}$ = 29.2 Hz), 55.7; ^{19}F NMR ($CDCl_3$): δ = −63.3, −74.4 (d, J = 7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 21.6 min (minor enantiomer), τ_R = 28.0 min (major enantiomer).

(*R*)-*N*-[1-(3-Isopropylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2i): Yellow oil; yield: 98%; 91% *ee*; $[\alpha]_D^{20}$: −55.7 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.21–7.32 (m, 4H), 6.72–6.76 (m, 2H), 6.60–6.63 (m, 2H), 4.73–4.83 (m, 1H), 4.05 (d, J = 7.3 Hz, 1H), 3.70 (s, 3H), 2.83–2.97 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.3, 149.7, 139.8, 134.4, 129.0, 127.2, 126.4, 125.3, 125.4 (q, $J_{C,F}$ = 280.5 Hz), 115.8, 114.9, 61.9 (q, $J_{C,F}$ = 29.2 Hz), 55.7, 34.2, 24.0; ^{19}F NMR ($CDCl_3$): δ = −74.4 (d, J = 7.3 Hz); IR (neat): ν = 3379, 2961, 1608, 1512, 1443, 1347, 1234, 1164, 1118, 1118, 1035, 818, 708 cm^{-1}; HR-MS: m/z = 324.1568, calcd. for $C_{18}H_{21}NF_3O$ ($[M+H]^+$): 324.1575; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 20.2 min (minor enantiomer), τ_R = 24.5 min (major enantiomer).

(*R*)-*N*-[1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2j): Yellow oil; yield: 81%; 84% *ee*; $[\alpha]_D^{20}$: −42.4 (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.57–7.58 (m, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.30–7.33 (m, 1H), 6.73–6.79 (m, 2H), 6.54–6.59 (m, 2H), 4.74–4.83 (m, 1H), 4.09 (d, J = 6.5 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.7, 138.8, 134.6, 133.6, 133.3, 131.0, 130.1, 127.4, 124.7 (q, $J_{C,F}$ = 280.5 Hz), 115.9, 115.0, 60.9 (q, $J_{C,F}$ = 30 Hz), 55.7; ^{19}F NMR ($CDCl_3$): δ = −74.6 (d, J = 7.1 Hz); IR (neat): ν = 3378, 2941, 1512, 1470, 1401, 1347, 1234, 1175, 1122, 1032, 917, 816, 769, 711 cm^{-1}; HR-MS: m/z = 350.0322, calcd. for $C_{15}H_{13}NF_3Cl_2O$ ($[M+H]^+$): 350.0326; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 27.8 min (minor enantiomer), τ_R = 34.1 min (major enantiomer).

(*R*)-*N*-[1-(3,4-Dimethylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2k): Colourless oil; yield: 94%; 90% *ee*; $[\alpha]_D^{20}$: −85.8 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.14–7.20 (m, 3H), 6.73–6.79 (m, 2H), 6.60–6.66 (m, 2H), 4.70–4.80 (m, 1H), 4.07 (d, J = 6.5 Hz, 1H), 3.73 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.3, 139.8, 137.8, 137.3, 131.8, 130.2, 129.2, 125.4, 125.4 (q, $J_{C,F}$ = 280.5 Hz), 115.7, 114.9, 61.6 (q, $J_{C,F}$ = 29.2 Hz), 55.8, 20.0, 19.6; ^{19}F NMR ($CDCl_3$): δ = −74.6 (d, J = 7.4 Hz); IR (neat): ν = 3372, 2923, 1511, 1455, 1348, 1233, 1179, 1158, 1115, 1035, 816, 757, 689 cm^{-1}; HR-MS: m/z = 310.1411, calcd. for $C_{17}H_{19}NF_3O$ ($[M+H]^+$): 310.1419; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 36.8 min (minor enantiomer), τ_R = 49.1 min (major enantiomer).

(*R*)-*N*-[1-(Naphthalen-2-yl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2m):[11] White solid; yield: 99%; 91% *ee*; ^{1}H NMR ($CDCl_3$): δ = 7.70–7.81 (m, 4H), 7.35–7.44 (m, 3H), 6.60–6.63 (m, 2H), 6.51–6.54 (m, 2H), 4.82–4.92 (m, 1H), 4.09 (d, J = 6.4 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 153.5, 139.6, 133.6, 133.3, 131.8, 129.0, 128.2, 127.8, 126.8, 126.7, 125.4 (q, $J_{C,F}$ = 280.3 Hz), 115.9, 115.0, 62.0 (q, $J_{C,F}$ = 29.4 Hz), 55.7; ^{19}F NMR ($CDCl_3$): δ = −74.2 (d, J = 7.3 Hz); HPLC (Chiralcel AD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min^{-1}, λ = 254 nm): τ_R = 26.4 min (major enantiomer), τ_R = 30.3 min (minor enantiomer).

***N*-(1,1,1-Trifluorooctan-2-yl)-4-methoxyaniline (2o)**: Yellow oil; yield: 52%; 22% *ee*; ^{1}H NMR ($CDCl_3$): δ = 6.76–6.81 (m, 2H), 6.60–6.65 (m, 2H), 3.75 (s, 3H), 3.65–3.72 (m,

1H), 3.26 (d, $J=9.0$ Hz, 1H), 1.81–1.92 (m, 1H), 1.11–1.59 (m, 8H), 0.87–0.92 (m, 4H); ^{13}C NMR ($CDCl_3$): $\delta=151.7$, 139.9, 125.4 (q, $J_{C,F}=282$ Hz), 113.8, 113.7, 55.8 (q, $J_{C,F}=28.5$ Hz), 54.6, 50.9, 30.7, 28.3, 26.6, 21.3, 12.8; ^{19}F NMR ($CDCl_3$): $\delta=-76.6$ (d, $J=6.9$ Hz); IR (neat): $\nu=3389$, 2957, 1619, 1511, 1465, 1234, 1167, 1130, 1037, 818, 691 cm^{-1}; HR-MS: $m/z=290.1724$, calcd. for $C_{15}H_{23}NF_3O$ ($[M+H]^+$): 290.1732; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=15.3$ min (minor enantiomer), $\tau_R=16.7$ min (major enantiomer).

***N*-Benzyl-1-phenyl-2,2,2-trifluoroethanamine (2q):**[49] Yellow oil; yield: 86%; 0% *ee*; ^{1}H NMR ($CDCl_3$): $\delta=7.40$–7.45 (m, 5H), 7.29–7.35 (m, 5H), 4.11–4.19 (m, 1H), 3.85 (d, $J=13.4$ Hz, 1H), 3.68 (d, $J=13.4$ Hz, 1H), 2.06 (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=139.1$, 134.3, 129.2, 128.9, 128.8, 128.7, 128.3, 127.5, 125.6 (q, $J_{C,F}=284.2$ Hz), 63.5 (q, $J_{C,F}=28.5$ Hz), 51.1; ^{19}F NMR ($CDCl_3$): $\delta=-74.4$ (d, $J=7.4$ Hz); HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=17.3$ min, $\tau_R=23.5$ min.

(+)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)naphthalen-1-amine (2r): Pale yellow oil; yield: 99%; 72% *ee*; $[\alpha]_D^{20}$: +171.7 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.90$–7.93 (m, 1H), 7.75–7.78 (m, 1H), 7.42–7.50 (m, 4H), 7.31–7.38 (m, 3H), 7.26–7.29 (m, 1H), 7.15–7.20 (m, 1H), 6.47 (d, $J=7.5$ Hz, 1H), 5.03–5.13 (m, 1H), 4.98 (d, $J=6.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=140.6$, 134.4, 133.9, 129.3, 129.1, 129.0, 128.0, 126.2, 125.6, 124.2, 125.3 (q, $J_{C,F}=280.5$ Hz), 119.9, 119.7, 107.3, 60.8 (q, $J_{C,F}=29.2$ Hz); ^{19}F NMR ($CDCl_3$): $\delta=-74.4$ (d, $J=7.0$ Hz); IR (neat): $\nu=3425$, 3064, 1583, 1527, 1407, 1245, 1168, 1119, 888, 766 cm^{-1}; HR-MS: $m/z=302.1159$, calcd. for $C_{18}H_{15}NF_3O$($[M+H]^+$): 302.1157; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=15.3$ min (major enantiomer), $\tau_R=19.3$ min (minor enantiomer).

(−)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)naphthalen-2-amine (2s): White solid; mp 83 °C; yield: 99%; 84% ee; $[\alpha]_D^{20}$: −14.8 (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.53$–7.58 (m, 2H), 7.38–7.46 (m, 3H), 7.22–7.32 (m, 4H), 7.10–7.15 (m, 1H), 6.83 (dd, $J=8.8$ Hz, 2.4 Hz, 1H), 6.70–6.71 (m, 1H), 4.91–5.00 (m, 1H), 4.39 (d, $J=7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=143.2$, 134.8, 134.0, 129.4, 129.3, 129.1, 128.3, 128.0, 127.7, 126.7, 126.4, 125.2 (q, $J_{C,F}=280.5$ Hz), 123.1, 118.0, 106.9, 60.6 (q, $J_{C,F}=29.2$ Hz); ^{19}F NMR ($CDCl_3$): $\delta=-74.3$ (d, $J=7.2$ Hz); IR (neat): $\nu=3397$, 2923, 1722, 1632, 1497, 1248, 1169, 1121, 844, 800, 747 cm^{-1}; HR-MS: $m/z=302.1171$, calcd. for $C_{18}H_{15}NF_3$ ($[M+H]^+$): 302.1157; HPLC (Chiralcel AD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=18.0$ min (minor enantiomer), $\tau_R=28.9$ min (major enantiomer).

(−)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)-2,4-dimethoxyaniline (2t): White solid; mp 86 °C; yield: 80%; 90% *ee*; $[\alpha]_D^{20}$: −31.4 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=7.37$–7.48 (m, 5H), 6.43–6.47 (m, 2H), 6.30–6.32 (m, 1H), 4.80–4.89 (m, 1H), 4.73 (d, $J=6.2$ Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta=153.2$, 148.5, 134.6, 129.7, 129.1, 128.9, 128.1, 125.4 (q, $J_{C,F}=279.8$ Hz), 112.1, 103.8, 99.4, 61.4 (q, $J_{C,F}=29.2$ Hz), 55.8; ^{19}F NMR ($CDCl_3$): $\delta=-74.6$ (d, $J=7.2$ Hz); IR (neat): $\nu=3408$, 2957, 1598, 1512, 1457, 1268, 1206, 1119, 1025, 840, 762 cm^{-1}; HR-MS: $m/z=312.1217$, calcd. for $C_{16}H_{17}NF_3O_2$ ($[M+H]^+$): 312.1211; HPLC (Chiralcel AD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=12.0$ min (minor enantiomer), $\tau_R=15.2$ min (major enantiomer).

(*R*)-1-Phenyl-2,2,2-trifluoroethanamine (2u):[15c,16f] Yellow oil; yield: 99%; 32% *ee*; ^{1}H NMR ($CDCl_3$): $\delta=7.38$–7.44 (m, 5H), 4.36–4.43 (m, 1H), 1.78 (br s, 2H); ^{13}C NMR ($CDCl_3$): $\delta=135.6$, 131.4, 129.1, 128.8, 125.8 (q, $J_{C,F}=279.8$ Hz), 58.1 (q, $J_{C,F}=30$ Hz); ^{19}F NMR ($CDCl_3$,: $\delta=-77.2$ (d, 7.5 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=210$ nm): $\tau_R=22.4$ min (minor enantiomer), $\tau_R=26.7$ min (major enantiomer).

***N*-(1-Phenyl-2,2-difluoroethyl)-4-methoxyaniline (2v):**[50] Pale yellow oil; yield: 82%; 57% *ee*; ^{1}H NMR ($CDCl_3$): $\delta=7.34$–7.44 (m, 5H), 6.70–6.76 (m, 2H), 6.55–6.60 (m, 2H), 5.99 (td, $J=55.9$ Hz, 3.2 Hz, 1H), 4.63 (td, $J=13.2$ Hz, 2.9 Hz, 1H), 4.16 (br s, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta=153.0$, 140.1, 135.7, 129.0, 128.7, 127.9, 116.0 (t, $J_{C,F}=245.2$ Hz), 115.6, 114.9, 61.3 (t, $J_{C,F}=21$ Hz), 55.8; ^{19}F NMR ($CDCl_3$): $\delta=-126.4$ (d, $J=7.5$ Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=254$ nm): $\tau_R=26.6$ min (minor enantiomer), $\tau_R=31.2$ min (major enantiomer).

(*R*)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanamine (3d)[11]

(*R*)-*N*-[1-(4-Chlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline **2d** (52.6 mg, 0.17 mmol) was dissolved in 4 mL of MeCN/H_2O (1:1). Periodic acid (38 mg, 0.17 mmol) and concentrated H_2SO_4 (16.7 mg, 0.17 mmol) were subsequently added into the solution. After 24 h, the reaction went to completion (monitoring by ^{19}F NMR analysis). The aqueous solution was made alkaline by adding 10% aqueous NaOH to pH 8 and then extracted with ethyl acetate. The combined organic solution was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to afford the chiral primary amine **3d** as a pale yellow oil; yield: 76%; 94% *ee*; ^{1}H NMR ($CDCl_3$): $\delta=7.34$–7.40 (m, 4H), 4.37–4.40 (m, 1H), 1.76 (br s, 2H); ^{13}C NMR ($CDCl_3$): $\delta=135.1$, 134.0, 129.3, 129.0, 125.5 (q, $J_{C,F}=279.8$ Hz), 57.5 (q, $J_{C,F}=29.1$ Hz); ^{19}F NMR ($CDCl_3$): $\delta=-77.3$ (d, $J=7.3$ Hz); IR (neat): $\nu=3402$, 1598, 1494, 1257, 1116, 1091, 1015, 889, 830 cm^{-1}; HR-MS: $m/z=210.0294$, calcd. for $C_8H_8NF_3Cl$ ($[M+H]^+$): 210.0297; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1}, $\lambda=210$ nm): $\tau_R=22.5$ min (minor enantiomer), $\tau_R=24.2$ min (major enantiomer).

(*R*)-1-(4-Chlorophenyl)-*N*-[(2,6-dichloropyridin-4-yl)methyl]-2,2,2-trifluoroethanamine (4)

(*R*)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanamine **3d** (18.9 mg, 0.09 mmol) and 2,6-dichloroisonicotinaldehyde (17.6 mg, 0.1 mmol) were dissolved in MeOH (3 mL) and refluxed for 7 h until the reaction went to completion (monitoring by ^{19}F NMR analysis). The reaction mixture was allowed to cool down to room temperature and was then treated with $NaBH_4$ portionwise (34 mg, 0.9 mmol, 10 equiv.). Then, the mixture was quenched with NH_4Cl so-

lution and extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to give the desired product **4** as white solid; mp93 °C; yields: 82%; 90% *ee*; ^{1}H NMR ($CDCl_3$): $\delta = 7.32$–7.41 (m, 4H), 7.22 (s, 2H), 4.11 (q, $J = 7.1$ Hz, 1H), 3.75 (q, $J = 12.9$ Hz, 1H), 2.14 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 154.4$, 150.9, 135.6, 131.9, 129.9, 129.4, 124.9 (q, $J_{C,F} = 279.8$ Hz), 121.9, 63.4 (q, $J_{C,F} = 29.2$ Hz), 49.1; ^{19}F NMR ($CDCl_3$): $\delta = -74.5$ (d, $J = 7.1$ Hz); IR (neat): $\upsilon = 3352$, 1544, 1492, 1365, 1258, 1164, 1121, 1015, 813, 610 cm^{-1}; HR-MS: $m/z = 312.1217$, calcd. for $C_{16}H_{17}NF_3O_2$ ($[M+H]^+$): 312.1211; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 99:1, flow rate = 0.4 mL min^{-1}, $\lambda = 210$ nm): $\tau_R = 37.2$ min (major enantiomer), $\tau_R = 41.3$ min (minor enantiomer).

Acknowledgements

X.D. thanks the China Scholarship Council for a PhD fellowship. This work was supported by Normandie Université, CNRS, CRUNCH and LABEX SYNORG (ANR-11-LABX-0029). The authors thank Professor Georges Dupas for DFT calculations on ketimine geometries.

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