Stereoselective $ZrCl_4$-Catalyzed Mannich-type Reaction of β-Keto Esters with Chiral Trifluoromethyl Aldimines

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ABSTRACT. A method for the synthesis of fluorinated β'-amino β-dicarbonyl compounds using a Zr-catalyzed Mannich-type reaction has been developed, starting from *N*-protected trifluoromethyl aldimines and cyclic or acyclic β-keto esters bearing different ester residues. The *in situ* generated metallic complex reacted with optically pure trifluoromethyl aldimine derived from (*R*)-α-methylbenzylamine giving a highly diastereoselective asymmetric Mannich-type addition with formation of a chiral quaternary center. The absolute configuration at the new chiral centers was assigned through 2D NOESY analysis coupled with computational studies.

INTRODUCTION

The carbon−carbon bond forming reactions are among the most important organic reactions and widely studied for synthetic purposes. Among these reactions, the Mannich reaction[1] is one of the most powerful methodologies. Imines can be used as preformed starting materials in addition

reactions with appropriate carbon nucleophiles, giving direct access to nitrogen functionalized compounds. In this field, α-trifluoromethyl amines were obtained by Mannich reactions of trifluoromethyl aldimines and suitable nucleophiles, such as malonates and ester enolates,[2] acetone,[3] and aldehydes.[4]

Many catalysts[5] have been explored in order to maximize the stereoselectivity of the reaction, but it is always important to develop new inexpensive and highly efficient catalytic methods for this reaction, possibly focusing on the synthetic procedures befitting the green and sustainable chemistry criteria.[6] Recently we reported the non-toxic, inexpensive, and stable $ZrCl_4$ as an ideal catalyst to promote addition reactions between trifluoromethyl aldimines and nitro alkanes, giving new fluorinated β-nitro amines.[7] The reported methodology can be considered a green procedure, not only because an eco-friendly catalyst was used, but also because the one-pot key step takes place under solvent-free conditions. In addition, working with optically pure fluorinated imines, the formation of a chiral metal complex key intermediate allowed us to control the stereoselective reaction outcome.[8]

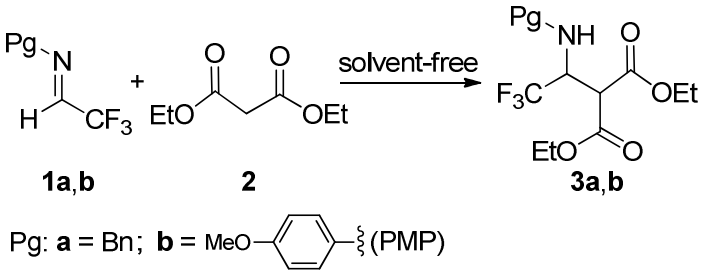
Continuing our studies, herein we report a direct $ZrCl_4$-catalyzed Mannich-type reaction of suitable trifluoromethyl aldimines with diethyl malonate and with β-keto esters. While malonate did not give relevant results, starting from chiral *N*-protected trifluoromethyl aldimines we were able to obtain a highly diastereoselective direct addition when the reactions were performed on β-keto esters, leading to nitrogen fluorinated dicarbonyl compounds. The usefulness of these selective catalytic Mannich-type reactions was enhanced by a diastereoselective decarboxylation reaction of the newly obtained β-keto esters.[9] In fact, it is well-known that the direct addition reaction of enolizable ketones to imines suffers from low yields and/or low selectivity.

Furthermore, the use of silyl enol ethers as ketone surrogates may result in higher yields, but diastereoselectivities remain low.[10]

RESULTS AND DISCUSSION

A first reaction was performed in equimolar ratio between trifluoromethyl aldimines **1a**,**b** and diethyl malonate **2**.

Table 1. Reaction Condition Optimization of Diethyl Malonate **2**



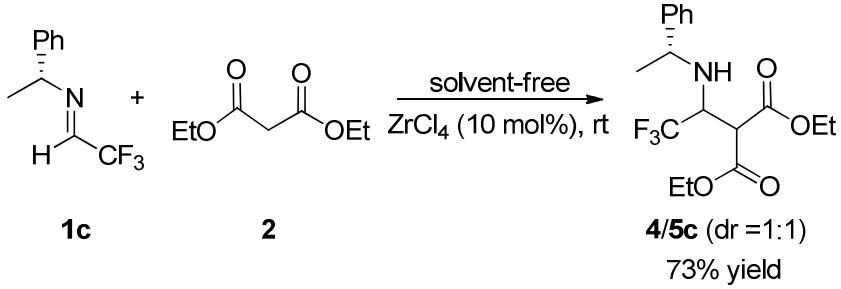
entry	Pg	catalyst	molar (%)	time (min)	temp (°C)	yield (%)[a]
1			25	5	25	50
2		$CuCl_2$	25	30	0	35
3			25	60	–20	40
4	Bn		50	30	25	–
5		$AlCl_3$	25	30	25	–
6			10	30	25	–
7		$ZrCl_4$	10	10	25	75
8			50	30	25	–
9		$CuCl_2$	25	30	25	–
10			10	30	25	–
11	PMP		50	30	25	–
12		$AlCl_3$	25	30	25	–
13			10	30	25	–
14		$ZrCl_4$	10	30	25	79

[a]After flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

As reported in Table 1, while no reaction was observed starting from either **1a** or **1b** (entries 4-6 and 11-13) in the presence of $AlCl_3$, the use of $ZrCl_4$ (entries 7 and 14) as catalyst gave compounds **3a**,**b** in higher yields and shorter times than when the reactions were performed with $CuCl_2$ (entries 1-3 and 8-10).

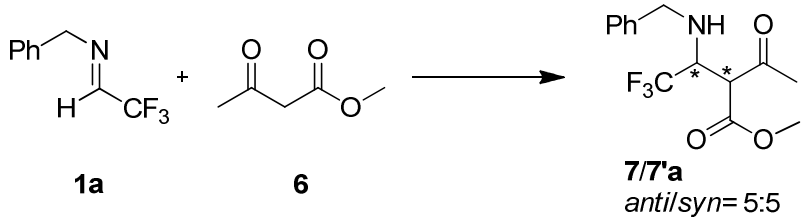
Thus, once optimized the reaction conditions, a direct diastereoselective $ZrCl_4$-catalyzed Mannich-type reaction was attempted starting from optically pure trifluoromethyl aldimine **1c**,[11] but no induction was observed (Scheme 1).

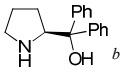
Scheme 1. $ZrCl_4$-Catalyzed Mannich-Type Reaction with Optically Pure **1c**



Therefore, we turned our attention towards the reactivity of β-keto esters. To optimize the reaction conditions for direct catalytic Mannich-type additions of β-keto esters to trifluoromethyl aldimines, imine **1a** and ethyl acetoacetate (**6**) in equimolar ratio were considered as opportune starting materials and reacted under different catalytic conditions (Table 2).

Table 2. Reaction Condition Optimization of β-Keto Ester **6**.



entry	catalyst	molar (%)	solvent	time	temp (°C)	yield (%)[a]
1	–	–	–	2 d	25	–
2	Et_3N	100	THF	4 h	25	–
3	KF	100	THF	4 h	25	–
4	cinchonidine	10	CH_2Cl_2	1 d	0	–
5		10	–	24 h	25	–
6		30	–	2 h	25	–
7	L-proline	10	DMSO	24 h	25	–
8		10	NMP	3 h	25	<5[c]
9		10	THF	2 d	25	<5[c]
10	 [b]	10	–	1 d	25	–
11		10	NMP	3 d	25	<5[c]
12		25	–	5 min	25	50
13	$CuCl_2$	25	–	30 min	0	35
14		25	–	1 h	–20	40
15		25	–	15 min	25	40
16	$AlCl_3$	25	–	25 min	0	36
17		25	–	45 min	–20	30
18		10	–	10 min	25	75
19		10	–	1 h	0	35
20	$ZrCl_4$	10	–	3 h	–20	30
21		10	–	6 h	–70	–
11		25	–	6 h	–70	–

[a]After flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2). [b](*S*)-α,α-diphenylprolinol. [c]Conversion determined by ^{19}F NMR.

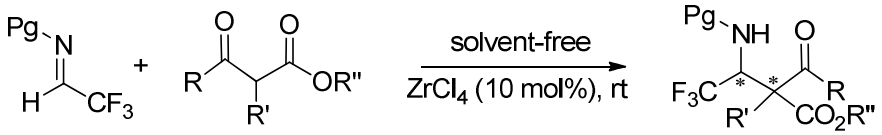
Considering that the reaction performed without catalyst did not give the expected product (entry 1), different catalysts were chosen to test the imine reactivity, from the most common organic or inorganic bases (entries 2 and 3) or cinchonidine, L-proline or its derivative (entries 4-11). As

reported in Table 2, only when using L-proline (entries 8 and 9) or (*S*)-α,α-diphenylprolinol (entry 11) in the presence of a suitable solvent it has been possible to observe the formation of the expected Mannich adducts, but only in trace amounts (<5%) by NMR.

Then, we considered $CuCl_2$ as catalyst (entries 12-14), widely used to promote different addition reactions,[11] $AlCl_3$ (entries 15-17), and $ZrCl_4$,[7,8,12] (entries 18-22) as easily disposable, eco-friendly, and efficient Lewis acid.[13] Finally, the reactions performed under solvent-free conditions gave the expected product, the best conditions being those reported in entry 18. In all cases, **7/7'a** were obtained in an equimolar ratio, even by changing the reaction temperature (entries 19-20).

Under the best conditions, the $ZrCl_4$-catalyzed Mannich-type reactions were performed starting from different β-keto esters and using *N*-protected trifluoromethyl aldimines **1a**,**b**, as opportune substrates. The results are reported in Table 3.

Table 3. Solvent-free $ZrCl_4$-Catalyzed Mannich-Type Reaction of Different β-Keto Esters



1a,**b**

8: R, R' = CH_3, R'' = C_2H_5
9: R-R' = -$(CH_2)_3$-, R'' = C_2H_5
10: R-R' = -$(CH_2)_4$-, R'' = C_2H_5

11/11'a,**b**
12/12'a,**b**
13a,**b**

entry	Pg	β-keto ester	product	time (min)	major/minor[a]	yield (%)[b]
1		**8**	**11a/11'a**	30	7:3[c]	65
2	Bn	**9**	**12a/12'a**	10	7:3[c]	75
3		**10**	**13a**	10	9:1	78
4		**8**	**11b/11'b**	30	7:3[c]	68
5	PMP	**9**	**12b/12'b**	10	7:3[c]	73
6		**10**	**13b**	10	9.9:0.1	85

[a]Determined by ^{19}F NMR spectra performed on the crude mixtures. [b]After flash chromatography on silica gel. [c]The ratio did not change by working at lower temperatures.

In all cases the reactions occurred with success in a short time, affording the Mannich adducts in good yields and very high stereoselectivity, especially when six-membered cyclic β-keto esters were used (entries 3 and 6). A catalytic pathway can be proposed (Figure 1).

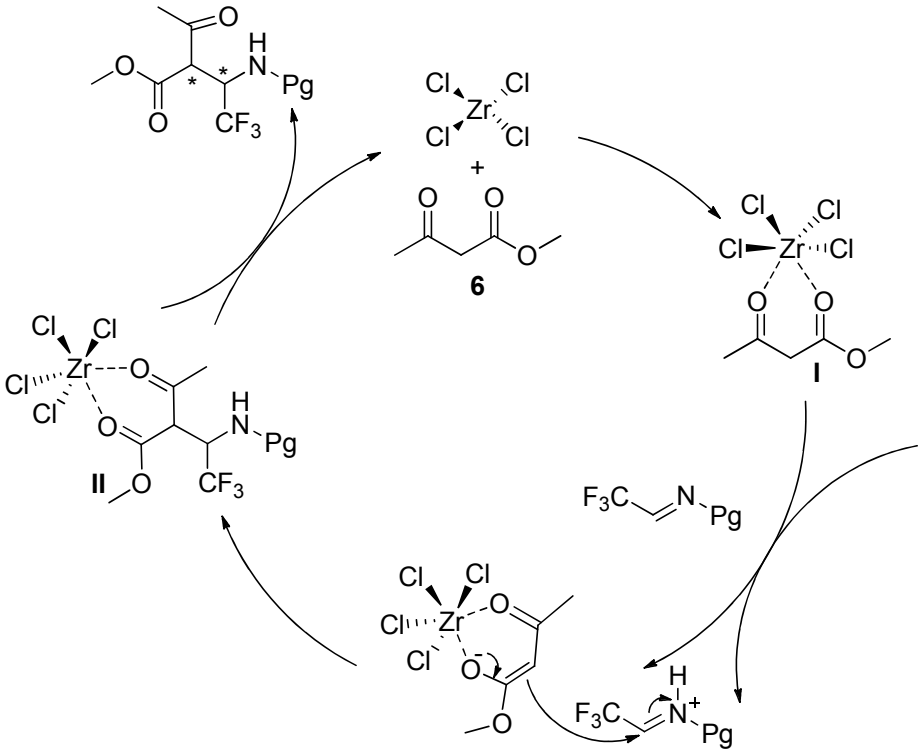
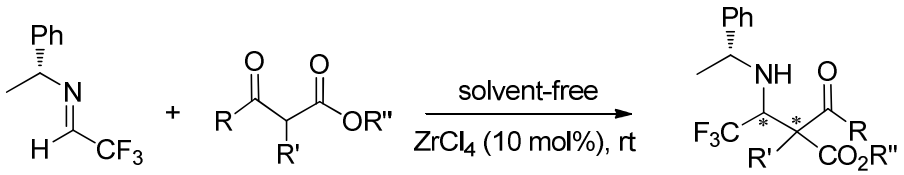


Figure 1. Proposed pathway for $ZrCl_4$-catalyzed Mannich-type addition of **6**

Zr(IV) coordinates both β-dicarbonyl oxygen atoms (**I**) so determining an increase of acidity of methylene protons, which can be then deprotonated by trifluoromethyl aldimine. Finally, an intermolecular nucleophilic attack to form **II** brings to the formation of the expected fluorinated β'-amino β-dicarbonyl compounds and restores the catalytic cycle.

Then, considering the hypothesized reaction outcome, we thought to perform the Mannich-type reaction starting from the optically pure trifluoromethyl aldimine **1c**, hoping that the presence of a chiral resident center on the electrophilic imine could lead to a diastereoselective addition reaction without the need of a chiral ligand addition (Table 4).

Table 4. $ZrCl_4$-Catalyzed Mannich-Type Reaction with Optically Pure **1c**



1c **6**: R = CH_3, R' = H, R'' = CH_3 — major-**16**,**17** minor-**16'**,**17'**
8: R, R' = CH_3, R'' = C_2H_5 — **18**
9: R-R' = -$(CH_2)_3$-, R'' = C_2H_5 — **19**
10: R-R' = -$(CH_2)_4$-, R'' = C_2H_5 — **20**
14: R = CH_3, R' = H, R'' = $C(CH_3)_3$ — major-**21**,**22** minor-**21'**,**22'**
15: R, R' = CH_3, R'' = $C(CH_3)_3$ — **23**

entry	β-keto ester	time (min)	product	dr[a]	major/minor[a]	yield (%)[b]
1	**6**	30	major-**16**,**17** minor-**16'**,**17'**	5:5	5:5	72
2	**8**	10	**18**	≥ 9.9	9.9:0.1	68
3	**9**	10	**19**	≥ 9.9	9.9:0.1	78
4	**10**	20	**20**	≥ 9.9	9.9:0.1	78
5	**14**	30	major-**21**,**22** minor-**21'**,**22'**	5:5	5:5	65
6	**15**[14]	30	**23**	≥ 9.9	9.9:0.1	64

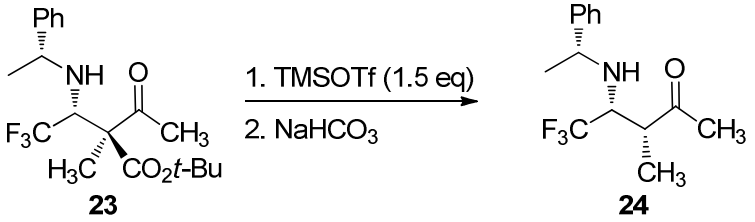
[a]Determined by ^{19}F NMR spectra performed on the crude mixtures. [b]After flash chromatography on silica gel.

As reported in Table 4, the stereoselective control failed in the absence of a steric hindrance on the methylene active group of β-keto compounds (entries 1 and 5). Moreover, under our reported reaction conditions, changing the ester residue did not influence the reaction stereochemistry, unlike in the literature.[15] In fact, in *tert*-butyl ester **14** (entry 5), dr and major/minor ratio did not change compared with methyl ester **6** (entry 1). Instead, very high dr values and major/minor ratios were obtained starting from methyl substituted or cyclic methylene active compounds **8-10** and **15** (entries 2-4, 6), in all cases forming only one of the four possible diastereomers, a quaternary chiral center being selectivity formed.

To determine the absolute configuration of the new chiral centers, as well as the *anti* or *syn* configuration of the major or minor obtained diastereomers, the diastereoselective

decarboxylation of compound **23** was performed (Scheme 2), following the procedure reported in the literature.[15]

Scheme 2. Decarboxylation Reaction of **23**



Considering that the equally high selectivity has been retained during the decarboxylation step[15] and following the already reported methodology,[5] 2D NOESY analysis on **24** coupled with computational studies (see Supporting Information) permitted to assign the (*R*,*R*,*R*) absolute configuration to the obtained *syn*-isomer **24**. As a consequence, the (*R*,*R*,*S*) absolute configuration can be assigned to the starting β'-amino β-keto ester *anti*-isomer **23**. Thanks to the ability of Zr to coordinate both oxygen atoms, thus forming an octahedral-like intermediate, in which the enolate is constrained in a planar geometric disposition, the nucleophilic attack takes place only on the sterically less hindered prochiral *Re* face of optically pure aldimine **1c** (Figure 2).

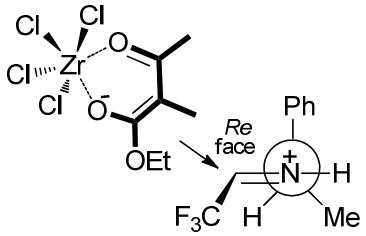
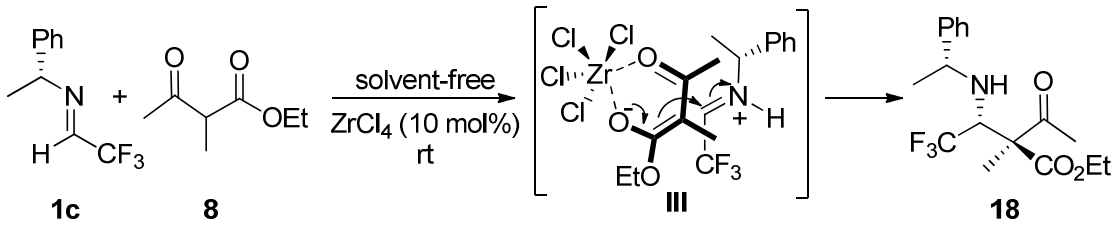


Figure 2. Model for the preferred face-selective addition reaction

Considering the stereochemical results reported in Table 3, a steric hindrance on the *E* double bond of zirconium complex **III** was required to obtain complete stereoselective control (Scheme 3).

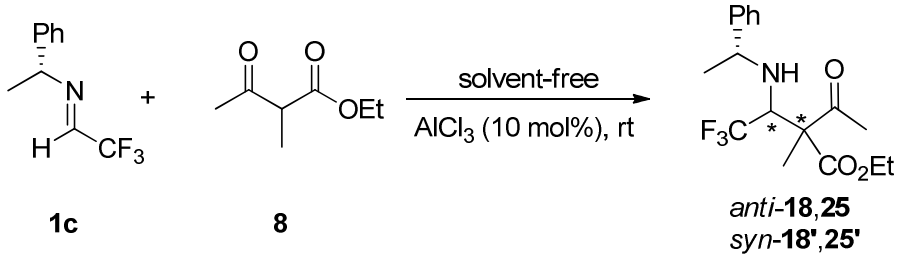
Scheme 3. Stereoselective Synthesis of β'-Amino β-Keto Ester **18**



In fact, starting from unsubstituted acyclic β-keto esters **6** or **15** low dr values and no *syn*/*anti* selectivity was observed.

To confirm the relevance of Zr on the highly stereoselective reaction outcome, a Mannich-type addition reaction was performed between trifluoromethyl aldimine **1c** and β-keto ester **8** by using $AlCl_3$ as catalyst (Scheme 4).

Scheme 4. $AlCl_3$-Catalyzed Mannich-Type Reaction



In this case, all the four possible diastereomers were obtained in equimolar ratios, the Al coordinating only the carbonyl oxygen (**IV**) and giving, as a consequence, the acyclic anionic intermediate **V** (Figure 3).

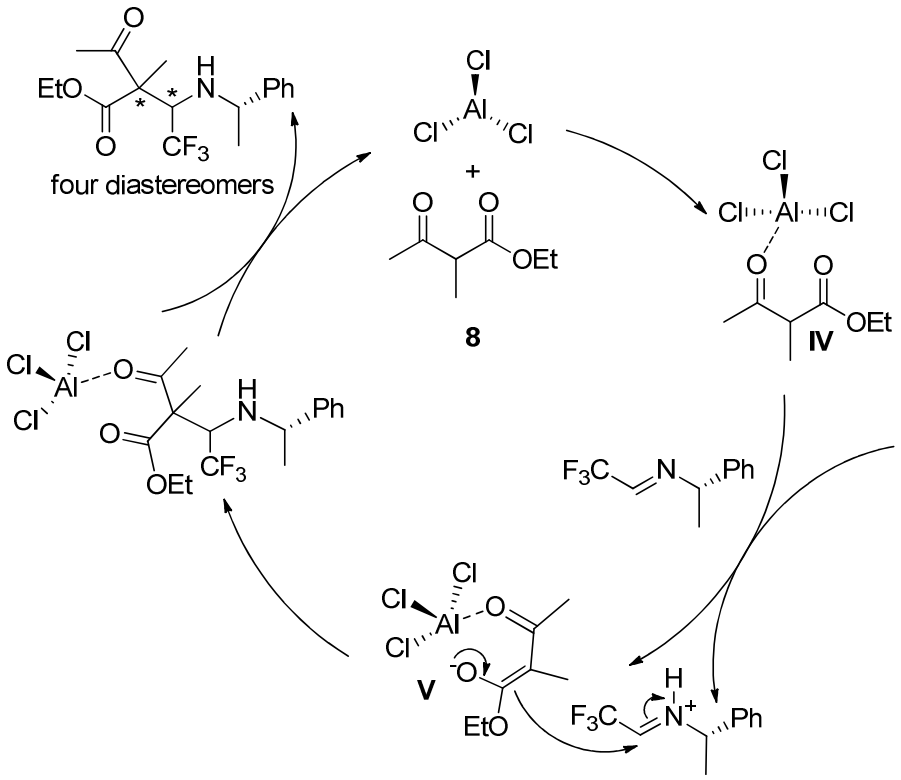


Figure 3. Proposed pathway for $AlCl_3$-catalyzed Mannich-type addition of **8**

Finally, the solvent effect on the reaction diastereoselectivity was investigated. Thus, the $ZrCl_4$-catalyzed Mannich-type reaction of **8** with chiral aldimine **1c** was performed by using some different organic solvents (DMSO, THF, $CHCl_3$, and $PhCH_3$).

Working in DMSO the reaction did not take place, probably because $ZrCl_4$ is coordinated to the solvent and no longer available to promote the catalytic cycle. In fact, the use of less polar THF or $CHCl_3$ gave, as expected, only the diastereomerically pure **18**, although in yields lower than those obtained in reactions performed under solvent-free conditions (32 and 43%, respectively). Finally, performing the reaction in almost non polar toluene, the Mannich addition takes place in satisfactory yields (68%), but surprisingly all the four possible diastereomers *anti*-**18**,**25** and *syn*-**18'**,**25'** are formed in equimolar ratios.

CONCLUSION

In conclusion, a new direct diastereoselective Mannich[2] reaction of β-keto esters with trifluoromethyl *N*-protected aldimines has been developed. The ester residue did not affect the reaction outcome: in fact no difference in reactivity was found by changing the ester moiety. On the contrary, very important seems the presence of an alkyl substituent on the methylene active group of β-keto esters and the use of Zr as coordinating metal to control the reaction stereoselectivity.

Furthermore, the use of common and inexpensive chiral (*R*)-α-methylbenzylamine,[16] easily removable by hydrogenolysis after Mannich-type addition, to synthesize the optically pure aldimine permits to obtain a complete stereoselective induction without the need for other added organocatalysts. Thus, working under solvent-free conditions and even at room temperature the only *anti*-isomer Mannich adducts, bearing a quaternary chiral center, were obtained as pure diastereomers.

EXPERIMENTAL SECTION

General. IR spectra were recorded on a FT/IR spectrophotometer in $CHCl_3$ as the solvent and reported in cm^{-1}. ^1H, ^{13}C, and ^{19}F NMR spectra NMR spectra were recorded by a 300 or a 400 MHz instrument and reported in δ units. $CDCl_3$ was used as the solvent and $CHCl_3$ (δ = 7.26 ppm for ^1H NMR), $CDCl_3$ (δ = 77.0 ppm for ^{13}C NMR) and C_6F_6 (δ = –164.9 for ^{19}F NMR) were used as internal standard. The NOESY experiments were performed by a 400 MHz instrument using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard and used to assist in structure elucidation.[17] ESI MS analyses were performed using a quadrupole-time of flight (Q-TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. Optical rotation was determined at 25 °C at a wavelength of 589 nm, using a quartz cell of 1 cm length. Imines **1a-c** were prepared by reaction of

trifluoroacetaldehyde ethyl hemiacetal and an opportune primary amine, following the reported procedure.[18] Diethyl malonate (**2**), *β*-keto esters **6**, **8**-**10**, and **14**, $ZrCl_4$, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) are commercially available and used as received. *β*-Keto ester **15** was prepared following the reported procedure.[14]

$ZrCl_4$-Catalyzed Mannich-Type Reactions. General Procedure.

To a mixture of trifluoromethyl aldimines **1a-c** (1 mmol) and diethyl malonate (**2**) or *β*-keto esters **6**, **8**-**10**, and **14** (1 mmol), $ZrCl_4$ (10 mol %) was added. The reactions were performed under solvent-free conditions and stirred at room temperature for 10-30 min. After H_2O addition, the crude mixtures were extracted with Et_2O. The collected organic layers were dried on anhydrous Na_2SO_4, the solvent evaporated in vacuo and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

Diethyl 2-[1-(benzylamino)-2,2,2-trifluoroethyl]malonate (3a). Yellow oil (299 mg, 80%). IR: 1748 cm^{-1}, 1760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22–1.33 (m, 6H), 2.40 (br, 1H), 3.71 (d, J = 6.0 Hz, 1H), 3.86–4.07 (m, 3H), 4.15–4.29 (m, 4H), 7.21–7.31 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –72.23 (d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 52.0, 52.3, 58.7 (q, J = 28.4 Hz), 61.8, 62.1, 125.8 (q, J = 286.3 Hz), 127.2, 128.1 (2C), 128.2 (2C), 139.2, 166.5, 166.6. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_4$ 348.1423, found 348.1424.

Diethyl 2-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]malonate (3b). Brown oil (287 mg, 79%). IR: 1750 cm^{-1}, 1758 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 3.74 (s, 3H), 3.82 (d, J = 3.5 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.61–4.76 (m, 2H), 6.69–6.79 (m, 4H). ^{19}F NMR ($CDCl_3$): δ –74.10 (d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 50.7, 55.6, 57.3 (q, J = 30.2 Hz), 62.1, 62.5, 114.7 (2C), 115.7 (2C),

125.1 (q, J = 284.7 Hz), 139.8, 153.3, 166.0, 167.0. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_5$ 364.1372, found 364.1375.

Diethyl 2-[2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]malonate (4,5c). Colorless (263 mg, 73%). IR: 1743 cm^{-1}, 1751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28–1.35 (m, 18H), 2.73 (br, 2H), 3.64 (d, J = 5.1 Hz, 1H), 3.71 (d, J = 5.1 Hz, 1H), 3.93–4.31 (m, 12H), 7.24–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): δ –73.39 (d, J = 7.4 Hz), –70.66 (d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9 (2C), 14.0, 23.6, 25.1, 51.3, 51.7, 55.4, 55.7, 56.4 (q, J = 28.0 Hz), 56.5 (q, J = 28.8 Hz), 61.7, 61.8, 62.0, 62.2, 125.5 (q, J = 284.3 Hz), 126.0 (q, J = 288.4 Hz), 126.8 (2C), 127.1 (2C), 127.2, 127.3, 128.3 (2C), 128.4 (2C), 143.7, 144.7, 166.4, 166.8 (2C), 166.9. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_4$ 362.1579, found 362.1582.

Methyl 2-acetyl-3-(benzylamino)-4,4,4-trifluorobutanoate (7,7'a). Yellow oil (227 mg, 75%). IR: 1740 cm^{-1}, 1715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.84 (br, 1H), 2.01 (br, 1H), 2.20 (s, 3H), 2.24 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.78 (d, J = 2.1 Hz, 1H), 3.79 (d, J = 3.7 Hz, 1H), 3.82–3.86 (m, 2H), 3.92–4.05 (m, 4H), 7.23–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): δ –72.03 (d, J = 7.2 Hz) –71.91 (d, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 29.1, 29.8, 52.3 (2C), 52.7, 52.9, 58.0 (q, J = 28.6 Hz), 58.6, 58.9 (q, J = 28.1 Hz), 59.4, 127.3, 127.4, 127.5 (q, J = 282.5 Hz, 2C), 128.3 (4C), 128.4 (4C), 138.8, 139.1, 167.2, 167.5, 198.8, 199.8. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO_3$ 304.1161, found 304.1165.

Ethyl 2-acetyl-3-(benzylamino)-4,4,4-trifluoro-2-methylbutanoate (11,11'a). Red oil (215 mg, 65%). IR: 1743 cm^{-1}, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21–1.28 (m, 6H), 1.40 (s, 3H, minor *syn* isomer), 1.48 (s, 3H, major *anti* isomer), 1.83 (br, 2H), 2.18 (s, 6H), 3.79–3.85 (m, 2H), 4.07–4.30 (m, 7H), 4.38 (q, J = 7.3 Hz, 1H), 7.26–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): δ –65.60 (d, J = 7.6 Hz, minor *syn* isomer), –65.39 (d, J = 7.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$):

δ 13.4, 13.8, 13.9, 15.5, 25.8, 26.3, 52.7, 53.1, 61.9, 62.1, 62.2 (q, J = 26.6 Hz), 62.3, 62.6 (q, J = 26.7 Hz), 63.2, 126.0 (q, J = 288.6 Hz), 126.2 (q, J = 288.2 Hz), 127.3, 127.5, 128.0 (2C), 128.2 (2C), 128.3 (2C), 128.4 (2C), 138.8, 139.3, 169.4, 169.5, 200.7, 202.2. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_3$ 332.1474, found 332.1470.

Ethyl 2-acetyl-4,4,4-trifluoro-3-(4-methoxyphenylamino)-2-methylbutanoate (11,11'b). Red oil (236 mg, 68%). IR: 1750 cm^{-1}, 1729 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.16 (t, J = 7.1 Hz, 3H, major *anti* isomer), 1.25 (t, J = 7.0 Hz, 3H, minor *syn* isomer), 1.54 (s, 3H, *syn* isomer), 1.56 (s, 3H, major *anti* isomer), 2.19 (s, 6H), 3.73 (s, 6H), 4.02–4.27 (m, 6H), 4.76–4.87 (m, 1H, major *anti* isomer), 4.92–5.03 (m, 1H, minor *syn* isomer), 6.67–6.78 (m, 8H). ^{19}F NMR ($CDCl_3$): δ –67. (d, J = 7.4 Hz, minor *syn* isomer), –67.63 (d, J = 8.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): δ 13.7, 13.8, 15.1, 16.4, 26.2, 26.5, 55.5 (2C), 58.7 (q, J = 28.4 Hz), 59.8 (q, J = 28.2 Hz), 61.3 (2C), 62.0, 62.3, 114.7 (2C), 114.8 (2C), 115.2 (2C), 115.5 (2C), 125.3 (q, J = 286.9 Hz), 125.4 (q, J = 286.5 Hz), 139.3, 139.6, 153.2, 153.4, 169.5, 169.6, 201.8, 202.0. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_4$ 348.1423, found 348.1425.

Ethyl 1-[1-(benzylamino)-2,2,2-trifluoroethyl]-2-oxocyclopentanecarboxylate (12,12'a). Red oil (257 mg, 75%). IR: 1758cm^{-1}, 1725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21–1.31 (m, 6H), 1.59 (br, 2H), 1.98–2.05 (m, 6H), 2.17–2.76 (m, 6H), 3.78–4.09 (m, 4H), 4.12–4.41 (m, 6H), 7.24–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): δ –65.25 (d, J = 8.4 Hz, minor *syn* isomer), –65.50 (d, J = 8.4 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 19.5, 20.2, 27.0, 27.1, 37.2, 38.5, 52.7, 54.2, 62.0, 62.2 (q, J = 26.5 Hz, 2C), 62.2, 63.1, 64.5, 125.9 (q, J = 287.6 Hz, 2C), 127.3, 127.4, 128.0 (4C), 128.3 (4C), 139.0, 139.3, 166.7, 166.8, 210.1, 210.4. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_3$ 344.1474, found 344.1471.

Ethyl 2-oxo-1-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]cyclopentanecarboxylate (12,12'b). Brown oil (262 mg, 73%). IR: 1762 cm^{-1}, 1759 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.04 (t, J = 7.1 Hz, 3H, major *anti* isomer), 1.23 (t, J = 7.1 Hz, 3H, minor *syn* isomer), 1.93–2.47 (m, 10H), 2.54–2.83 (m, 2H), 3.54 (br, 1H), 3.74 (s, 6H), 3.85 (br, 1H), 3.90–4.04 (m, 2H), 4.10–4.25 (m, 2H), 4.82–4.96 (m, 2H), 6.69–6.78 (m, 8H). ^{19}F NMR ($CDCl_3$): δ –69.89 (d, J = 7.2 Hz, minor *syn* isomer), –68.37 (d, J = 7.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): δ 13.7, 13.9, 19.5, 20.0, 27.2, 28.2, 37.1, 38.3, 55.6 (2C), 59.7 (q, J = 28.1 Hz), 61.0 (q, J = 27.7 Hz), 62.0, 62.3, 62.5, 63.9, 114.7 (4C), 115.7 (2C), 116.4 (2C), 125.1 (q, J = 285.9 Hz), 125.6 (q, J = 286.6 Hz), 139.5, 139.9, 153.5, 153.8, 166.4, 167.2, 209.4, 210.7. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_4$ 360.1423, found 360.1427.

Ethyl 1-[1-(benzylamino)-2,2,2-trifluoroethyl]-2-oxocyclohexanecarboxylate (13a). White oil (278 mg, 78%). IR: 1743 cm^{-1}, 1729 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H), 1.64–1.94 (m, 6H), 2.36–2.52 (m, 3H), 3.73–4.10 (m, 2H), 4.13–4.28 (m, 3H), 7.22–7.33 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –63.79 (d, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 13.8, 21.9, 25.9, 30.9, 40.7, 52.8, 61.6 (q, J = 27.4 Hz), 61.9, 64.3, 126.0 (q, J = 288.7 Hz), 127.3, 128.1 (2C), 128.3 (2C), 139.1, 168.5, 203.8. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_3$ 358.1630, found 358.1635.

Ethyl 2-oxo-1-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]cyclohexanecarboxylate (13b). White oil (317 mg, 85%). IR: 1745 cm^{-1}, 1728 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.11 (t, J = 7.1 Hz, 3H), 1.63–2.03 (m, 6H), 2.42–2.54 (m, 3H), 3.73 (s, 3H), 3.97 (q, J = 7.2 Hz, 1H), 4.08 (q, J = 7.1 Hz, 1H), 4.83–4.91 (m, 1H), 6.66–6.76 (m, 4H). ^{19}F NMR ($CDCl_3$): δ –67.03 (d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7, 22.0, 26.2, 31.4, 40.8, 55.7, 58.9 (q, J = 29.1 Hz), 62.2, 63.8,

114.8 (2C), 115.3 (2C), 125.1 (q, J = 286.2 Hz), 139.8, 153.3, 168.3, 203.9. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_4$ 374.1579, found 374.1571.

Methyl 2-acetyl-4,4,4-trifluoro-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-16,17/*syn*-16',17'). Yellow oil (228 mg, 72%). IR: 1739 cm^{-1}, 1725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29–1.34 (m, 12H), 1.67 (br, 1H), 2.05 (s, 3H), 2.12 (s, 3H), 2.21 (br, 1H), 2.29 (s, 3H), 2.32 (s, 3H), 2.50 (br, 1H), 3.65–3.81 (m, 20H), 3.98–4.09 (m, 5H), 7.23–7.36 (m, 20H). ^{19}F NMR ($CDCl_3$): δ –73.16 (d, J = 7.6 Hz), –72.63 (d, J = 6.9 Hz), –70.52 (d, J = 6.9 Hz), –70.07 (d, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 22.7, 23.1, 24.7, 24.8, 28.7, 29.3, 29.9, 30.9, 52.5, 52.7 (2C), 52.9, 55.3, 55.4, 55.6 (q, J = 26.3 Hz), 55.7 (2C), 55.7 (q, J = 27.8 Hz), 56.6 (q, J = 28.3 Hz), 56.7 (q, J = 27.7 Hz), 57.6, 58.2, 59.0, 59.1, 125.6 (q, J = 277.4 Hz), 126.0 (q, J = 288.1 Hz), 126.6 (2C), 126.7 (2C), 127.1 (q, J = 284.4 Hz), 127.2 (q, J = 280.4 Hz), 127.3 (2C), 127.4 (4C), 127.6 (2C), 128.3 (2C), 128.4 (4C), 128.5 (2C), 143.1, 143.2, 144.7, 144.8, 167.3, 167.5, 167.7, 167.8, 199.0, 199.1, 200.4 (2C). HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{15}H_{19}F_3NO_3$ 318.1317, found 318.1312.

Ethyl (2*S*,3*R*)-2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (18). Light yellow oil (234 mg, 68%). $[\alpha]_D$ = +86.0 (c = 1 g/100 mL, $CHCl_3$). IR: 1742 cm^{-1}, 1726 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28–1.31 (m, 6H), 1.46 (s, 3H), 1.97 (br, 1H), 2.22 (s, 3H), 4.04 (q, J = 6.2 Hz, 1H), 4.18 (q, J = 7.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 1H), 4.36 (q, J = 8.1 Hz, 1H), 7.22−7.32 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –64.99 (d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 13.9, 15.3, 21.6, 26.6, 55.5, 59.1 (q, J = 26.7 Hz), 62.1, 63.2, 126.0 (q, J = 288.4 Hz), 126.5 (2C), 127.4, 128.5 (2C), 145.5, 169.4, 202.2. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_3$ 346.1630, found 346.1633.

Ethyl (1*S*)-2-oxo-1-[(1*R*)-2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]cyclopentanecarboxylate (19). Light yellow oil (278 mg, 78%). $[\alpha]_D$ = +54.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1731 cm^{-1}, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23–1.28 (m, 6H), 1.60 (br, 1H), 1.85–1.96 (m, 3H), 2.12–2.23 (m, 1H), 2.19–2.28 (m, 1H), 2.59–2.63 (m, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 1H), 7.16−7.29 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –64.99 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 14.0, 19.6, 21.6, 27.2, 37.2, 55.3, 59.2 (q, *J* = 26.3 Hz), 62.3, 64.5, 126.5 (2C), 126.9 (q, *J* = 288.4 Hz), 127.5, 128.6 (2C), 146.4, 166.8, 210.0. HR-MS (ESI Q-TOF) (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_3$ 358.1630, found 358.1636.

Ethyl (1*S*)-2-oxo-1-[(1*R*)-2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]cyclohexanecarboxylate (20). Colorless oil (289 mg, 78%). $[\alpha]_D$ = +79.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1740 cm^{-1}, 1715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26–1.33 (m, 6H), 1.57–1.67 (m, 3H), 1.84–1.99 (m, 4H), 2.37–2.41 (m, 1H), 2.52–2.63 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 1H), 7.23−7.31 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –64.99 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 13.9, 21.5, 22.1, 25.7, 30.3, 40.9, 55.2, 58.2 (q, *J* = 26.6 Hz), 62.0, 64.3, 126.2 (q, *J* = 287.8 Hz), 126.5 (2C), 127.4, 128.5 (2C), 145.5, 168.4, 203.7. HR-MS (ESI Q-TOF) (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{25}F_3NO_3$ 372.1787, found 372.1785.

***tert*-Butyl 2-acetyl-4,4,4-trifluoro-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-21,22/*syn*-21',22').** Colorless oil (233 mg, 65%). IR: 1737 cm^{-1}, 1712 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48–1.58 (m, 52H), 2.04 (s, 3H), 2.07 (s, 3H), 2.29–2.30 (m,6H), 3.50– 3.73 (m, 6H), 3.99–4.08 (m, 6H), 7.26−7.36 (m, 20H). ^{19}F NMR ($CDCl_3$): δ –70.08 (d, *J* = 8.6 Hz), –70.50 (d, *J* = 7.7 Hz), –72.21 (d, *J* = 8.5 Hz), –72.83 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 22.6, 23.3, 24.9, 25.5, 27.6 (2C),

27.8 (12C), 28.3 (2C), 54.6, 55.3, 55.4, 55.6, 56.1 (q, J = 28.0 Hz), 56.3 (q, J = 27.5 Hz), 56.4 (q, J = 30.0 Hz), 56.5 (q, J = 28.0 Hz), 59.2, 59.7, 59.9, 60.5, 82.8, 82.9, 83.0, 83.1, 125.7 (q, J = 278.8 Hz), 125.8 (q, J = 279.8 Hz), 125.9 (q, J = 285.5 Hz), 126.1 (q, J = 288.5 Hz), 126.7 (2C), 126.9 (2C), 127.0 (2C), 127.3 (2C), 127.4, 127.5, 127.6 (2C), 128.4 (4C), 128.5 (2C), 128.7 (2C), 143.0, 143.4, 143.8, 144.8, 165.9, 166.1, 166.7, 166.8, 199.7, 199.8, 200.5, 200.8. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{18}H_{25}F_3NO_3$ 360.1787, found 360.1789.

***tert*-Butyl (2*S*,3*R*)-2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (23).** Yellow oil (238 mg, 64%). $[\alpha]_D$ = +123.0 (c = 1 g/100 mL, $CHCl_3$). IR: 1752 cm^{-1}, 1719 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (d, J = 6.4 Hz, 3H) 1.34 (s, 3H), 1.40 (s, 9H), 1.95 (br, 1H), 2.15 (s, 3H), 3.98 (q, J = 6.4 Hz, 1H), 4.15−4.24 (m, 1H), 7.14−7.26 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –64.3 (d, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 15.8, 21.4, 26.5, 27.7 (3C), 55.3, 59.5 (q, J = 26.5 Hz), 63.6, 82.7, 126.1 (q, J = 288.9 Hz), 126.4 (2C), 127.2, 128.4 (2C), 146.5, 168.4, 202.6. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{19}H_{27}F_3NO_3$ 374.1943 found 374.1941.

(3*R*,4*R*)-5,5,5-trifluoro-3-methyl-4-{[(*R*)-1-phenylethyl]amino}pentan-2-one (24). Yellow oil (75 mg, 43%). $[\alpha]_D$ = +72.0 (c = 1 g/100 mL, $CHCl_3$). IR: 1715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.19 (d, J = 7.1 Hz, 3H), 1.26 (d J = 6.4 Hz, 3H), 1.51 (br, 1H), 2.15 (s, 3H), 2.76–2.83 (m, 1H), 3.60–3.67 (m, 1H), 3.91 (q, J = 6.4 Hz, 1H), 7.20−7.29 (m, 5H). ^{19}F NMR ($CDCl_3$): δ –72.35 (d, J = 8.9 Hz). ^{13}C NMR ($CDCl_3$): δ 11.1, 23.3, 28.6, 46.4, 55.6, 56.4 (q, J = 27.0 Hz), 126.8 (2C), 127.4, 127.7 (q, J = 245.8 Hz), 128.5 (2C), 144.7, 208.8. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{14}H_{19}F_3NO$ 274.1419, found 274.1421.

$AlCl_3$-Catalyzed Mannich-type reactions of β-keto ester 8 with aldimine 1c.

To a mixture of trifluoromethyl aldimines **1c** (1 mmol) and *β*-keto esters **8** (1 mmol), $AlCl_3$ (10 mol %) was added. The reaction was performed under solvent-free conditions and stirred at room

temperature for 30 min. After H_2O addition, the crude mixtures were extracted with Et_2O. The collected organic layers were dried on anhydrous Na_2SO_4, the solvent evaporated in vacuo and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

Ethyl 2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-18,25/*syn*-18',25'). Yellow oil (169 mg, 49%). IR: 1751 cm-1, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12−1.41 (m, 36H), 1.46−1.58 (br, 4H), 1.81 (s, 3H), 2.04 (s, 3H), 2.22 (s, 3H), 2.32 (s, 3H), 3.89–4.39 (m, 16H), 7.22−7.35 (m, 20H). ^{19}F NMR ($CDCl_3$): δ –63.29 (d, J = 7.0 Hz), –63.54 (d, J = 6.7 Hz), –64.99 (d, J = 8.3 Hz), –65.22 (d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.7, 13.8, 13.9, 14.2, 15.2, 16.5 (2C), 21.3 (2C), 21.6 (2C), 24.3, 24.8, 26.1, 26.4, 53.1, 55.3, 55.5, 55.8, 59.0 (q, J = 27.3 Hz), 59.1 (q, J = 26.6 Hz), 60.0 (q, J = 26.6 Hz), 60.8 (q, J = 26.3 Hz), 61.9, 62.0, 62.2 (2C), 62.6 (3C), 63.2, 125.8 (q, J = 280.8 Hz), 125.9 (q, J = 267.5 Hz), 125.9 (q, J = 288.1 Hz), 126.4 (2C), 127.0 (2C), 127.4 (4C), 127.7 (2C), 128.0 (2C), 128.3 (2C), 128.4 (2C), 128.6 (4C), 127.7 (q, J = 245.8 Hz), 142.8, 143.4, 145.2, 145.5, 169.4 (2C), 169.8, 169.9, 201.2, 201.3, 202.4, 202.6. HR-MS (ESI Q-TOF) (m/z) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_3$ 346.1630 found 346.1623.

ASSOCIATED CONTENT

Supporting Information

Complete characterization data (^1H, ^{13}C and ^{19}F NMR data) for all new compounds, computational details, 2D NMR spectra, and optimized geometries to determine the absolute configuration of the new chiral centers. The Supporting Information is available free of charge via the Internet at

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