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In pursuit of β-amino α-nitro β-trifluoromethyl ketones: nitro-Mannich *vs* Mannich-type reactions

Alessia Pelagalli, Lucio Pellacani and Stefania Fioravanti*

Abstract: The reactivity of α-nitro ketones with trifluoromethyl aldimines is studied for the first time. While under nitro-Mannich conditions only the facial stereoselectivity can be controlled, organocatalysed Mannich-type reactions allowed a complete control of absolute and relative stereoselectivity, leading to highly functionalised β-amino α-nitro β-trifluoromethyl compounds as diastereomerically pure compounds. A key role on the geometrical and/or facial stereoselectivity is played by the structure of reactants.

Introduction

α-Nitro ketones are a versatile class of α-functionalised ketones that shows an intriguing and peculiar reactivity, also considering the chameleonic nature of the nitro group.[1] Currently trifluoromethyl ketones are of considerable interest due to their importance as synthetic intermediates of other trifluoromethyl-containing compounds[2] and also to their biological activity.[3] Of even greater importance and interest is the synthesis of trifluoromethyl-containing nitrogen carbonyl compounds and the Mannich-type reaction between masked enolates and aldimines is a convenient way to yield them.[4] A variety of different asymmetric catalytic procedures of this reaction has been developed,[5] the most effective of which involves the use of chiral Lewis acids, but you must consider that their use can promote the imine hydrolysis and so decrease the reaction yield. On the other hand, starting directly from ketones, the use of opportune organocatalysts, such as proline or its derivatives, can suffer from the difficulty to generate in situ the expected enaminic intermediate.

Trifluoromethyl aldimines are widely used as versatile starting materials in Mannich reactions to obtain trifluoromethyl-containing nitrogen compounds and a great number of chiral applications were reported in the literature either starting from chiral aldimines or performing the additions in the presence of organocatalytic systems.[6]

Starting from our previous results on stereoselective additions of enolisable nitro alkanes,[7] aldehydes[8] and especially α-nitro esters[9] on trifluoromethyl aldimines, our next challenge was the study of nitro-Mannich and Mannich-type additions of suitable α-nitro ketones on *C*-CF_3 substituted aldimimes to obtain interesting multi-functionalised β-amino α-nitro β-trifluoromethyl ketones.[10]

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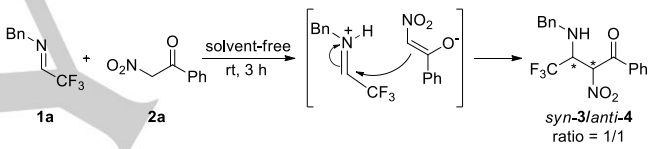
Results and Discussion

Nitro-Mannich addition

The nitro-Mannich addition[11] was tested on an equimolar mixture of aldimine **1a** and α-nitro ketone **2a**. The expected products were obtained in good yields, working at rt, under solvent-free conditions and without added catalyst. The same aldimine acts as both base and electrophile,[12] allowing a good example of green chemistry: the addition proceeds with total atom economy (Scheme 1) and with moderated environmental impact, no reaction work-up being needed.



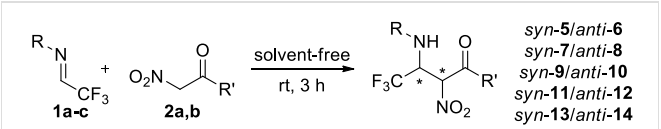
Scheme 1. Best conditions for nitro-Mannich addition.

Hoping to increase the *syn*/*anti* stereoselectivity, the reaction was attempted at low temperature (–20 °C) as well as in the presence of different solvents (THF, DMSO) and/or bases, but in all cases only the disappearance of aldimine was detected (NMR). Then, to compare the nitro-Mannich addition of α-nitro ketone **2a** with that of α-nitro acetate already reported by us,[8] $ZrCl_4$ (20 %mol) was added, but only undesired polymerisation reactions greatly increased bringing quickly to a complex mixture (see SI).

Finally, we tested the possible influence of the $-CF_3$ group on the aldimine reactivity. Suitable unfluorinated *C*-alkyl substituted aldimines[7a] were tested under the solvent-free nitro-Mannich conditions but uncontrollable exothermic reactions were observed in all cases leading to very complex crude mixtures also working at lower temperatures (see SI). It is possible to suppose that the presence on the imine carbon of an electron donating group (EDG) instead of a strong electron withdrawing group (EWG) such as the $-CF_3$ moiety could be responsible for the side reactions observed, determining both an increase of the availability of the imine nitrogen lone pair and a decreasing of the electrophilicity of the imine carbon.

Having found the best addition conditions of **2a** on **1a**, self-catalysed solvent-free nitro-Mannich reactions were performed on *N*-substituted trifluoromethyl aldimines **1a**-**c** and phenyl or alkyl α-nitromethyl ketones **2a**,**b** to study the substituent effects on the *syn*/*anti* selectivity (Table 1).

Table 1. Self-catalysed nitro-Mannich additions of **2a**,**b** on aldimines **1a**-**c**: *syn*/*anti* selective control.



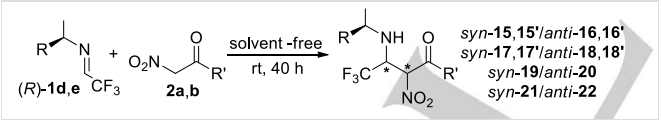
Entry	1	R	2	R'	Product	*syn*/*anti*[a]	Yield[b] (%)
1	**a**	Bn	**b**	iBu	**5/6**	1:2.5	75[c]
2			**a**	Ph	**7/8**	1:1	73
3	**b**	PMP	**b**	iBu	**9/10**	1:2.5	84[c]
4			**a**	Ph	**11/12**	1:1	80
5	**c**	iBu	**b**	iBu	**13/14**	1:2.5	85[c]

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. The data did not improve working at lower temperatures. [b] After flash chromatography on silica gel. [c] Obtained as 1:1 diastereomeric mixtures due to isomerisation during the purification step.

In all cases, phenyl nitro ketone **2a** did not lead to a *syn*/*anti* control (entries 2 and 4), due to the planarity of nucleophilic species, probably. In fact, the use of isobutyl nitro ketone **2b** (entries 1, 4, and 5) allowed a partial stereoselective control, the *anti* isomers being always the major products. No effect on the relative configuration was found by changing the imine *N*-substituents.

Thus, we considered the stereofacial outcome of the addition and, for the purpose, optically pure trifluoromethyl aldimines (*R*)-**1d**,**e** were synthesised.

Table 2. Self-catalysed nitro-Mannich addition of **2a**,**b** on chiral aldimines **1d**,**e**: stereofacial selective control.



Entry	1	R	2	R'	Product	*syn*/*anti*[a]	dr[a]	Yield[b] (%)
1			**a**	Ph	**15,15'** **16,16'**	1:1	50:50	63
2	**d**	Ph	**b**	iBu	**17,17'** **18,18'**	1: 2.5	50:50	65[c]
3			**a**	Ph	**19/20**	1:1	>95:5	64[c]
4	**e**	iPr	**b**	iBu	**21/22**	1: 2.5	>95:5	67[c]

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. The data did not improve working at lower temperatures. [b] After flash chromatography on silica gel. [c] Obtained as 1:1 diastereomeric mixtures due to isomerisation during the purification step.

Considering the data reported in Table 2, the geometric isomerism control was confirmed to be due to the nitro ketone structure (entries 2 and 4), while imine nitrogen substituent seems to control the stereofacial induction.

In fact, starting from the strongly hindered aldimine **1e** both nitro ketones **2a**,**b** selectively added on the *Si* prochiral imine face (Figure 1).[13]

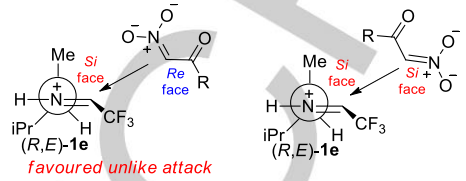


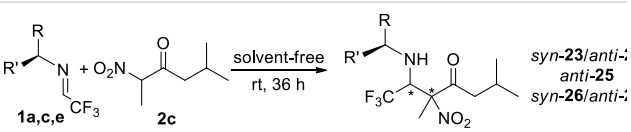
Figure 1. Attack on the prochiral *Si* imine face of (*R*,*E*)-**1e**.

Unfortunately, all attempts to obtain β-amino α-nitro ketones as optically pure compounds failed, due to the fast and uncontrollable epimerisation of both new chiral centres (see SI).[14]

To avoid the isomerisation reaction and with the aim of obtaining the construction of a quaternary chiral centre,[15] α-nitroethyl ketones **2c**[16]**d**,[17,18] were synthesised following the reported procedures and then reacted at room temperature under solvent-free nitro-Mannich conditions with trifluoromethyl aldimines **1a**,**c**,**e**.

As reported in Table 3, a complete *anti* selectivity was observed in the addition of ketone **2c** on aldimine **1c**, thanks to steric hindrance present in the β-position both in the nucleophilic and in the electrophilic species (Table 3, entry 2). On the contrary, a further steric hindrance in the α-position on the electrophilic partner permits to obtain a complete stereofacial control, although the relative configuration was completely lost in the reaction of the same **2c** on chiral aldimine **1e** (Table 3, entry 3).

Table 3. Self-catalysed nitro-Mannich addition of α-nitroethyl ketone **2c** on aldimines **1a,c,e**.



Entry	1	R	R'	Product	*syn*/*anti*[a]	dr[a]	Yield[b] (%
1	**a**	H	Ph	*syn*-**23** *anti*-**24**	1:1	–	25
2	**c**	H	iPr	*anti*-**25**	1:49	–	25
3	**e**	iPr	Me	*syn*-**26** *anti*-**27**	1:1	98:2	20

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. [b] After flash chromatography on silica gel. The low yield can be due to the steric hindrance that slow the addition and favour starting material degradation.

Unexpectedly, the same additions performed with ketone **2d** lead to obtain only the deacylated *syn*/*anti*-β-amino nitro compounds[7c] **28a-c** (Figure 2), even working at lower temperatures.

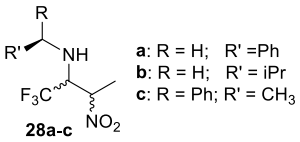


Figure 2. *syn*/*anti*-β-Amino nitro compounds from addition of **2d** on **1a,c,e**.

A hypothesis can be advanced to explain the formation of these compounds.[18] As reported in the literature,[1b,c] linear α-nitro ketones react at room temperature, without catalyst and/or solvent with primary amines, giving the corresponding amides in good yields through cleavage of carbon–carbon bond between the carbonyl group and the carbon–nitro moiety. Then, the observed β-amino nitro compounds could derive from a very fast deacylation reaction of unstable nitro-Mannich adducts, even if it cannot completely exclude that the same **2d** may undergo nucleophilic substitution reaction by the primary amines formed in situ as a consequence of the imine hydrolysis favoured by the very long reaction times (3-10 d). However, the nitro-Mannich reaction progress was followed by ^{1}H NMR spectra and the signals of *syn*/*anti*-β-amino nitro compounds seem to increase at the same time of the corresponding amides. Furthermore, we want to underline that, as already reported by us,[7c] nitro alkanes added to trifluoromethyl aldimines only through a Lewis acid catalysed reaction, thereby reinforcing our hypothesis.

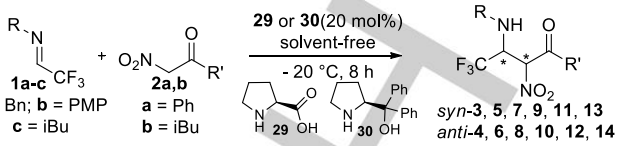
Organocatalysed Mannich-type additions

To exclude a possible competitive nitro-Mannich pathway, Mannich-type additions were performed at −20 °C choosing L-proline **29** or (*S*)-*α*,*α*-diphenylprolinol **30** as suitable organocatalysts. As known, catalyst **30** should gave *anti* isomers due to steric hindrance effects,[19] while catalyst **29** should favour the *syn* isomers thanks to a hydrogen bond in the key transition state.[20] However, recently the temperature influence on the selective additions on *C*-CF_3 substituted aldimines has been highlighted by us.[7a] In fact, only *anti*-Mannich trifluoromethyl adducts can be obtained working under solvent-free conditions at low temperature even in the presence of L-proline as catalyst.

Then, the synthesis of β-amino α-nitro β-trifluoromethyl ketones already obtained under self-catalysed nitro-Mannich conditions were now attempted under organocatalysed Mannich-type additions (Table 4).

Strangely, no influence of organocatalyst was observed comparing the *syn*/*anti* ratios reported in Table 4 with those of Table 2. However, considering the reaction temperature (−20 °C), the catalyst involvement can be invoked. Moreover, enamine intermediates were clearly observed (NMR spectra) in the crude reactions performed with catalyst **30** and successfully purified from the corresponding crude mixtures as *E* isomers **31a-c**.[21]

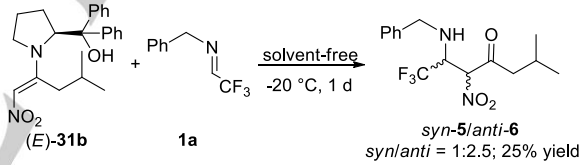
Table 4. Catalysed Mannich-type additions of α-nitromethyl ketones **2a**,**b**.



Entry	1	2	Product	*syn*/*anti*[a]	Yield[b] (%) Catalyst **29**	Yield[b] (%) Catalyst **30**
1	a	a	*syn*-**3**/*anti*-**4**	1:1	53	55
2		b	*syn*-**5**/*anti*-**6**	1:2.5	55[c]	60[c]
3	b	a	*syn*-**7**/*anti*-**8**	1:1	45	45
4		b	*syn*-**9**/*anti*-**10**	1:2.5	50[c]	55[c]
5	c	a	*syn*-**11**/*anti*-**12**	1:1	60	65
		b	*syn*-**13**/*anti*-**14**	1:2.5	56[c]	60[c]

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. [b] After flash chromatography on silica gel. [c] Obtained as 1:1 diastereomeric mixtures due to isomerisation during the purification step.

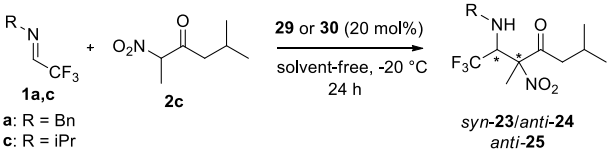
As a possible confirmation of the enamine involvement, purified **31b** (see SI) was reacted with imine **1a** (Scheme 2) and the *syn*-**5**/*anti*-**6** products were obtained with the same ratio reported in Table 4, entry 2 but in lower yield.



Scheme 2. Addition of purified nitro enamine **31b** to **1a**.

Continuing our studies on the Mannich-type reaction, the addition of α-nitroethyl ketones **2c**,**d** to achiral trifluoromethyl aldimines **1a**,**c** was considered (Table 5). Once again, phenyl α-nitroethyl ketone **2d** leads only to deacylation compounds while starting from isobutyl α-nitroethyl ketone **2c**, the best results were achieved by using catalyst **30**. In fact only *anti*-**24** and *anti*-**25** isomers were observed, although in moderate ees (see SI).

Table 5. Catalysed Mannich-type additions of α-nitroethyl ketone **2c** on **1a**,**c**.



Catalyst **29**

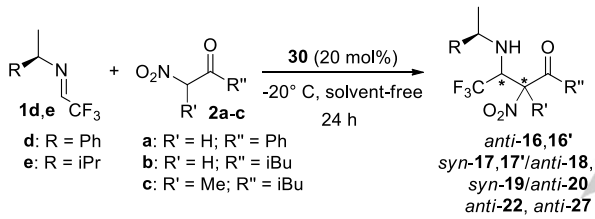
Entry	1	Product	*syn*/*anti*[a]	ee[b] (%)	Yield[c] (%)

1	**a**	*syn*-**23**/*anti*-**24**	1:1	<5	32
2	**c**	*anti*-**25**	1:49	<5	25
			Catalyst **30**		
3	**a**	*anti*-**24**	1:49	nd[d]	30
4	**c**	*anti*-**25**	1:49	15	28

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. [b] Enantiomeric excesses were detected by chiral HPLC analyses (see SI). [c] After flash chromatography on silica gel. [d] See SI.

Finally, a good geometric and/or stereofacial induction was successfully obtained performing the additions of **2a-c** on optically pure trifluoromethyl aldimines **1d**,**e** in the presence of catalyst **30** (Table 6).

Table 6. Catalysed Mannich-type additions of α-nitroethyl ketone **2a-c** on **1d**,**e**.



Entry	1	2	Product	*syn*/*anti*[a]	dr[a]	Yield[b] (%)
1	d	**a**	*anti*-**16**,**16'**	1:49	50:50	38
2		**b**	*syn*-**17**/*anti*-**17'** *syn*-**18**/*anti*-**18'**	1:2.5	50:50	54
3	e	**a**	*syn*-**19**/*anti*-**20**	1:1	>95:5	55[c]
4		**b**	*anti*-**22**	1:49	>95:5	20[c]
5		**c**	*anti*-**27**	1:49	>95:5	25

[a] Determined by ^{1}H and ^{19}F NMR spectra performed on the crude mixtures. [b] After flash chromatography on silica gel. [c] Obtained as 1:1 diastereomeric mixtures due to isomerisation during the purification step.

The reaction of **2a** with chiral aldimine **1d** has allowed us to obtain only the *anti*-**16**,**16'** (Table 6, entry 1), through the formation of only the two transition states **TSI** and **TSII** (Figure 3) probably favoured by steric effects but, above all, by π interaction of the phenyl residues present both on the electrophilic and the nucleophilic species. In fact, lacking the phenyl group in nucleophilic or electrophilic partner, a different selectivity outcome was observed: a decreasing of relative configuration was observed when the same aldimine **1d** reacts with nitro ketone **2b** (Table 6, entry 2).

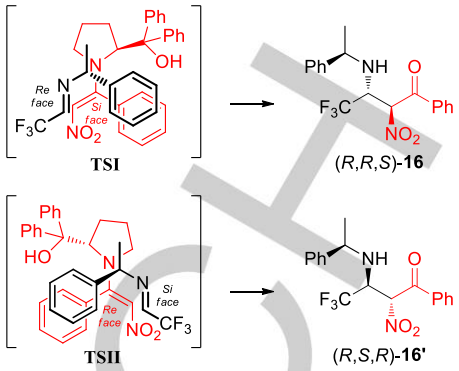


Figure 3. Proposed transition states for geometric selectivity.

On the contrary, when an isopropyl group is present on the imine chiral centre (Table 6, entry 3), proposed **TSIII** and **TSIV** (Figure 4) justify the complete stereofacial induction observed, coupled with the total loss of *syn*/*anti* selectivity.

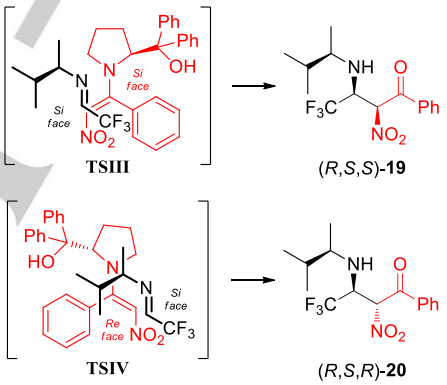


Figure 4. Proposed transition states for stereofacial selectivity.

Finally, a complete diastereoselective control was obtained when the more sterically hindered aldimine **1e** reacted with alkyl nitro ketones **2b**,**c** leading to *anti*-**22** and *anti*-**27** (Table 6, entries 4 and 5) as pure diastereomers through **TSV** (Figure 5).

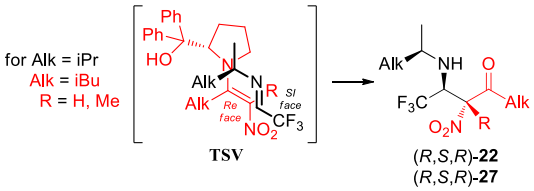


Figure 5. Proposed transition states for the complete geometric and facial diastereoselective control.

Conclusions

In conclusion, a first comparison between nitro-Mannich and Mannich-type reactions of trifluoromethyl aldimines with aryl or alkyl α-nitro alkyl ketones, compounds very difficult to handle,[22] was here reported. We were able to control the addition reactions obtaining first encouraging results working at low temperatures in the presence of (*S*)-α,α-diphenylprolinol (**30**) as catalyst. The major difficulty was found in the purification of obtained chiral β-amino α-nitro trifluoromethyl ketones, because of the fast epimerisation of both newly formed chiral centres.

A key role on the complete selective reaction control was played by the structure of either α-nitro ketone or chiral trifluoromethyl aldimine. Only the steric effects due to alkyl residues present both on the chiral imine centre and on the α-nitro ketone allow to obtain a complete diastereoselective control, leading to only *anti* isomers as pure diastereomers. Finally, also the construction of a quaternary chiral centre was successfully obtained in the synthesis of new small, but highly functionalised molecules.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 1600 Series 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 on a Varian-Mercury 300 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 Bruker Avance III at 400 MHz using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard and used to assist in structure elucidation.[23] 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 with a JASCO DIP-370 polarimetry at a wavelength of 589 nm, using a quartz cell of 1 cm length. Enantiomeric excess were determined using analytical high performance liquid chromatography (HPLC) performed on Varian 9001 instrument (column and solvent conditions are given with the compound). Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel plates. Silica gel 230-400 mesh was used for column chromatography. Trifluoromethyl aldimines **1a**-**e** were synthesised by reaction of trifluoroacetaldehyde ethyl hemiacetal and an opportune primary amine following the reported procedure.[24] **1a**,**b**,**d**,**e** are known compounds.[24] Alkyl substituted α-nitro ketones **2c**,[16a] **d**[17] are known compounds and were synthesised following the procedure reported in the literature. Isolated amide is a known compound.[25] The data of *syn*/*anti*-β-amino nitro compounds (Figure 2) are reported in the supporting information.

General procedure for the synthesis of β-amino α-nitro β-trifluoromethyl ketones.

Nitro-Mannich addition reactions. An equimolar solution of (*E*)-aldimines (1 mmol) and α-nitro ketones were stirred at room temperature (1-3 h) under solvent-free conditions. The crude mixtures were purified by flash chromatography on silica gel.

Mannich type addition reactions. To an equimolar solution of (*E*)-aldimines (1 mmol) and α-nitro ketones, (*S*)-α,α-diphenylprolinol (**30**) (20 mol%) was added under solvent-free conditions. The reactions were stirred at –20 °C and then purified by flash chromatography on silica gel.

(*E*)-2-Methyl-*N*-(2,2,2-trifluoroethylidene)propan-1-amine (1c). Colorless oil. (0.459 g, 60%). ν_{max} cm^{-1} 1698. ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.58 (m, 1H), 3.43 (d, *J* = 7.8 Hz, 2H), 2.10–1.97 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.71 (q, *J* = 36.3 Hz), 121.65 (q, *J* = 282.8 Hz), 64.75, 28.61, 20.14 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.0 (d, *J* = 2.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_6H_{11}F_3N$ 154.0844, found 154.0853.

3-(Benzylamino)-4,4,4-trifluoro-2-nitro-1-phenylbutan-1-one (*syn*-3/*anti*-4). Yellow orange oil. (0.246 g, 70%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:20). ν_{max} cm^{-1} 3353, 1748, 1565. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–6.20 (m, 20H), 6.24 (d, *J* = 7.5 Hz, 1H), 6.21 (d, *J* = 8.2 Hz, 1H), 4.63–4.43 (m, 1H), 4.39–4.18 (m, 1H), 3.86 (dd, *J* = 63.2, 12.8 Hz, 2H), 3.83 (dd, *J* = 46.8, 13.0 Hz, 2H), 2.16 (br, 1H), 1.72 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 185.0, 135.0, 134.8, 129.3 (4C), 129.2 (2C), 128.7 (4C), 128.3 (4C), 128.2 (2C), 128.1 (2C), 127.5 (2C), 127.5 (2C), 125.2 (q, *J* = 285.3 Hz), 124.8 (q, *J* = 286.4 Hz), 87.6, 84.0, 60.0 (q, *J* = 29.4 Hz), 59.0 (q, *J* = 29.1 Hz), 53.0, 52.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.01 (d, *J* = 6.5 Hz), –72.92 (d, *J* = 6.7 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{17}H_{16}F_3N_2O_3$ 353.1113, found 353.1136.

2-(Benzylamino)-1,1,1-trifluoro-6-methyl-3-nitroheptan-4-one (*syn*-5/*anti*-6). Yellow oil. (0.249 g, 75%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:20). ν_{max} cm^{-1} 3358, 1750, 1565. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 10H), 5.37 (d, *J* = 5.9 Hz, 1H), 5.28 (d, *J* = 8.0 Hz, 1H), 4.45–4.32 (m, 1H), 4.19–4.06 (m, 1H), 3.96 (dd, *J* = 89.8, 13.0 Hz, 2H), 3.94 (dd, *J* = 75.5, 13.7 Hz, 2H), 2.59–2.28 (m, 4H), 2.25–2.10 (m, 2H), 1.82 (br, 1H), 1.56 (br, 1H), 0.98–0.89 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 195.0, 137.9, 137.8, 128.6, 128.5 (4C), 128.4 (2C), 127.8, 127.7 (2C), 125.0 (q, *J* = 285.9 Hz), 124.8 (q, *J* = 287.1 Hz), 92.2, 89.1, 59.4 (q, *J* = 29.2 Hz), 59.0 (q, *J* = 29.1 Hz), 52.9, 52.3, 51.4, 48.6, 29.6, 23.9, 23.9, 22.2, 22.1, 22.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ –70.15 (d, *J* = 7.2 Hz), –72.29 (d, *J* = 6.7 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{20}F_3N_2O_3$ 333.1426, found 333.1446.

4,4,4-Trifluoro-3-[(4-methoxyphenyl)amino]-2-nitro-1-phenyl butan-1-one (*syn*-7/*anti*-8). Orange oil (0.269 g, 73%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:25). ν_{max} cm^{-1} 3358, 1752, 1565. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.27 (m, 10H), 6.73–6.48 (m, 8H), 6.33 (d, *J* = 7.3 Hz, 1H), 6.31 (d, *J* = 7.9 Hz, 1H), 5.32–5.08 (m, 1H), 5.08–4.88 (m, 1H), 4.08 (d, *J* = 11.3 Hz, 1H), 3.85 (d, *J* = 10.6 Hz, 1H), 3.64 (s, 3H), 3.63 (s, *J* = 9.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.7, 182.9, 138.4, 138.3, 135.2, 135.1, 134.6, 134.4, 130.0, 129.4, 129.3, 128.8, 128.7 (2C), 128.5 (q, *J* = 283.4 Hz), 128.3, 127.3, 125.5 (q, *J* = 284.2 Hz), 121.8, 118.2, 117.6, 116.8, 116.4, 115.1 (2C), 114.8, 114.8 (2C), 86.9, 82.8, 59.2 (q, *J* = 30.0 Hz) 58.52 (q, *J* = 30.2 Hz), 55.5 (2C). ^{19}F NMR (282 MHz, CDCl3) δ –72.94 (d, *J* = 6.4 Hz), –73.89 (d, *J* = 6.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{17}H_{16}F_3N_2O_4$ 369.1062, found 369.1076.

1,1,1-Trifluoro-2-[(4-methoxyphenyl)amino]-6-methyl-3-nitro heptan-4-one (*syn*-9/*anti*-10). Yellow orange oil. (0.292 g, 84%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:20). ν_{max} cm^{-1} 3357, 1747, 1559. ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 24.6, 8.9 Hz, 8H), 5.49 (d, *J* = 5.2 Hz, 1H), 5.40 (d, *J* = 7.5 Hz, 1H), 5.10–4.90 (m, 1H), 4.91–4.71 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 3.99 (d, *J* = 10.7 Hz, 1H), 3.68 (s, *J* = 5.6 Hz, 6H), 2.65–2.28 (m, 4H), 2.14–1.98 (m, 2H), 1.04–0.74 (m, 12H). ^{13}C NMR (101 MHz, CDCl3) δ 195.7, 194.9, 154.2, 154.1, 138.4, 138.2, 125.0 (q, *J* = 284.7 Hz), 124.0 (q, *J* = 285.8 Hz), 116.3 (2C), 116.3 (2C), 114.8 (2C), 114.8 (2C), 91.3, 87.7, 58.5 (q, *J* = 30.4 Hz), 58.0 (q, *J* = 30.5 Hz), 55.4 (2C), 51.7, 48.3, 23.8, 23.6, 21.8 (2C), 21.8 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.46 (d, *J* = 6.8 Hz), –73.60 (d, *J* = 6.2 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{20}F_3N_2O_4$ 349.1375, found 349.1321.

4,4,4-Trifluoro-3-(isobutylamino)-2-nitro-1-phenylbutan-1-one (*syn*-11/*anti*-12). Yellow orange oil. (0.254 g, 80%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 90:10). ν_{max} cm^{-1} 3353, 1752, 1568. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05–7.93 (m, 4H), 7.76–7.48 (m, 6H), 6.27 (d, *J* = 8.6 Hz, 1H), 6.26 (d, *J* = 8.2 Hz, 1H), 4.52–4.40 (m, 1H), 4.40–4.26 (m, 1H), 2.88–2.68 (m, 2H), 2.45–2.32 (m, 2H), 1.70–1.53 (m, 1H), 1.62 (br, 2H), 1.53–1.39 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7, 3H), 0.71 (d, *J* = 6.7 Hz, 3H), 0.69 (d, *J* = 6.7 Hz 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9, 185.0, 135.0 (2C), 134.7 (2C), 129.3 (2C), 129.2 (2C), 128.8 (2C), 128.7 (2C), 125.3 (d, *J* = 285.2 Hz), 124.9 (d, *J* = 286.0 Hz), 87.6, 84.1, 61.1 (q, *J* = 29.1 Hz), 60.4 (q, *J* = 28.7 Hz), 57.4, 57.1, 29.0, 28.7, 20.0, 20.0, 20.0, 19.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.74 (d, *J* = 7.0 Hz), –73.67 (d, *J* = 6.9 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{18}F_3N_2O_3$ 319.1270, found 319.1293.

1,1,1-Trifluoro-2-(isobutylamino)-6-methyl-3-nitroheptan-4-one (*syn*-13/*anti*-14). Pale yellow oil. (0.253 g, 85%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 90:10). ν_{max} cm^{-1} 3353, 1755, 1566. ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (d, J = 4.1 Hz, 1H), 4.59 (d, J = 4.1 Hz, 1H), 4.04–3.88 (m, 2H), 2.76–2.66 (m, 4H), 2.51–2.39 (m, 4H), 1.71–1.55 (m, 2H), 1.45–1.21 (m, 4H), 0.88 (d, *J* = 6.7 Hz, 12H), 0.87 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 189.3, 127.5 (d, *J* = 268.9 Hz), 125.4 (d, *J* = 285.7 Hz), 83.3, 80.8,

63.0 (q, *J* = 27.9 Hz), 62.3 (q, *J* = 27.9 Hz), 57.2, 56.6, 29.2 (2C), 22.6 (2C), 22.5 (2C), 20.2 (4C), 16.7 (2C), 12.7 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.56 (d, *J* = 7.1 Hz), −71.97 (d, *J* = 6.8 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{12}H_{22}F_3N_2O_3$ 299.1583, found 299.1580.

4,4,4-Trifluoro-2-nitro-1-phenyl-3-[(*R*)-(1-phenylethyl)amino] butan-1-one (*syn*-15/15'; *anti*-16/16'). Yellow orange oil. (0.230 g, 63%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:20). v_{max} cm^{-1} 3357, 1748, 1568. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–6.96 (m, 40H), 6.32 (d, *J* = 7.7 Hz, 1H), 6.30 (d, *J* = 6.6 Hz, 1H), 6.27 (d, *J* = 6.1 Hz, 1H), 6.15 (d, *J* = 6.9 Hz, 1H), 4.68–3.85 (m, 8H), 2.61 (br, 2H), 2.34 (br, 2H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.26 (d, *J* = 5.1 Hz, 3H), 1.24 (d, *J* = 5.1 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9, 186.6, 186.1, 185.2, 143.8, 143.7, 143.1, 141.9, 135.1, 134.9, 134.8, 134.6, 134.3 (2C), 133.2 (2C), 130.9 (2C), 129.5 (2C), 129.4 (2C), 129.3 (2C), 129.2 (2C), 128.7 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.5, 128.4, 128.3 (2C), 128.3 (2C), 127.8 (2C), 127.5 (2C), 127.2 (2C), 127.0, 126.8 (q, *J* = 285.2 Hz), 126.7 (2C), 126.6, 125.9, 125.7 (q, *J* = 284.3 Hz), 125.5, 125.2 (q, *J* = 284.7 Hz), 124.9 (q, *J* = 283.4 Hz), 88.3, 87.6, 84.6, 84.4, 57.9 (q, *J* = 22.8 Hz), 57.9 (q, *J* = 29.4 Hz), 57.0, 57.0 (q, *J* = 29.4 Hz), 56.7, 56.6 (q, *J* = 28.4 Hz), 56.5, 56.1, 24.6, 24.1, 22.7, 22.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.61 (d, *J* = 6.8 Hz), −72.12 (d, *J* = 6.9 Hz), −72.67 (d, *J* = 6.9 Hz), −73.65 (d, *J* = 7.3 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{18}H_{18}F_3N_2O_3$ 367.1270, found 367.1289.

1,1,1-Trifluoro-6-methyl-3-nitro-2-[(*R*)-(1-phenylethyl)amino] heptan-4-one (*syn*-17/17'; *anti*-18/18'). Yellow orange oil. (0.225 g, 65%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 90:10). v_{max} cm^{-1} 3354, 1750, 1563. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.07 (m, 20H), 5.31 (d, *J* = 5.5 Hz, 1H), 5.26 (d, *J* = 7.3 Hz, 1H), 5.23 (d, *J* = 4.9 Hz, 1H), 5.11 (d, *J* = 7.0 Hz, 1H), 4.43–3.56 (m, 8H), 2.63–1.89 (m, 8H), 2.25–1.80 (m, 8H), 1.40–1.17 (m, 12H), 1.02–0.75 (m, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3 (2C), 194.7 (2C), 143.9, 143.5, 142.0, 141.8, 128.7, 128.7 (2C), 128.6 (2C), 128.6 (2C), 128.0 (2C), 127.8, 127.7 (q, *J* = 275.6 Hz), 127.7, 127.5 (4C), 127.3, 126.7 (4C), 125.1 (q, *J* = 287.6 Hz), 124.9 (q, *J* = 288.7 Hz), 124.7 (q, *J* = 271.6 Hz), 92.3, 92.0, 89.4, 89.1, 57.7 (q, *J* = 29.2 Hz), 57.3 (q, *J* = 29.1 Hz), 57.0 (q, *J* = 29.6 Hz), 57.0 (q, *J* = 28.7 Hz), 50.5, 52.0, 50.8, 48.8, 47.9 (2C), 46.2, 42.2, 29.6, 26.2, 24.4 (2C), 24.0 (2C), 23.9, 23.9, 22.7, 22.2, 22.1 (4C), 22.1, 21.6. ^{19}F NMR (282 MHz, CDCl3) δ −70.89 (d, *J* = 6.7 Hz), −71.43 (d, *J* = 6.9 Hz), −71.95 (d, *J* = 7.1 Hz), −72.94 (d, *J* = 7.4 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{16}H_{22}F_3N_2O_3$ 347.1583, found 347.1569.

4,4,4-Trifluoro-3-[(*R*)-(3-methylbutan-2-yl)amino]-2-nitro-1-phenylbutan-1-one (*syn*-19/19'; *anti*-20/20'). Yellow orange oil. (0.212 g, 64%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:25). v_{max} cm^{-1} 3355, 1751, 1565. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–7.39 (m, 20H), 6.29 (d, *J* = 8.5 Hz, 1H), 6.28 (d, *J* = 8.5 Hz, 1H), 6.25 (d, *J* = 7.7 Hz, 1H), 6.23 (d, *J* = 8.1 Hz, 1H), 4.99–4.35 (m, 8H), 2.90–2.61 (m, 4H), 1.72–1.43 (m, 4H), 1.02–0.51 (m, 36H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4 (2C), 185.1 (2C), 135.1, 135.0, 134.7, 134.5, 132.4 (q, *J* = 278.0 Hz), 131.8 (q, *J* = 284.3 Hz), 129.5 (q, *J* = 274.7 Hz), 129.3 (2C), 129.3 (2C), 129.2 (2C), 129.1 (q, *J* = 277.8 Hz), 128.8, 128.8, 128.7 (2C), 128.6, 128.1, 88.1, 87.7, 84.6, 84.40, 59.3 (q, *J* = 28.6 Hz), 58.3 (q, *J* = 28.7 Hz), 58.1, 58.0 (q, *J* = 23.8 Hz), 56.8 (q, *J* = 28.6 Hz), 56.8, 56.2, 53.5, 33.2, 32.8, 31.8, 31.6, 18.7, 18.6, 18.4 (2C), 18.2 (2C), 17.3, 16.9 (2C), 16.6 (2C), 16.3 (2C), 16.2, 15.9, 15.1, 14.6 (2C), 14.4 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.54 (d, *J* = 5.7 Hz), −72.15 (d, *J* = 6.2 Hz), −73.64 (d, *J* = 6.2 Hz), −73.81 (d, *J* = 6.5 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{15}H_{20}F_3N_2O_3$ 333.1426, found 333.1447.

1,1,1-Trifluoro-6-methyl-2-[(*R*)-(3-methylbutan-2-yl)amino]-3-nitroheptan-4-one (*syn*-21/21'; *anti*-22/22'). Pale yellow oil. (0.209 g, 67%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 90:10). v_{max} cm^{-1} 3352, 1749, 1564. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (d, J = 5.9 Hz, 1H), 5.30 (d, J = 6.4 Hz, 1H), 5.28 (d, J = 8.4 Hz, 1H), 5.26 (d, J = 8.3 Hz, 1H), 4.52–4.25 (m, 2H), 4.28–4.04 (m, 2H), 2.85–2.38 (m, 16H), 2.26–2.12 (m, 4H), 1.70–1.53 (m, 4H), 1.04–0.81 (m, 60H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 195.3, 195.3, 195.2, 125.1 (q, J = 281.6 Hz, 2C), 124.9 (d, J = 282.1 Hz, 2C), 92.5, 92.4, 89.6, 89.2, 58.4 (q, J = 28.7 Hz), 57.5 (d, J = 27.9 Hz), 57.1 (q, J = 28.7 Hz), 57.0 (d, J = 27.6 Hz), 52.5 (2C), 51.9 (2C), 49.1 (2C), 48.7 (2C), 33.3, 33.1, 31.7, 31.5, 22.4, 22.3, 22.2, 22.2, 22.1 (2C), 22.1 (2C), 19.0 (2C), 18.8 (2C), 18.5, 18.4, 17.2, 17.1 (2C), 16.2, 16.2, 16.1 (2C), 15.8, 14.9, 14.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.65 (d, J = 7.1 Hz), −71.61 (d, J = 7.1 Hz), −72.88 (d, J = 6.9 Hz), −74.22 (d, J = 8.1 Hz). HRMS: m/z [M + H]+ calcd. for $C_{13}H_{24}F_3N_2O_3$ 313.1739, found 313.1765.

2-(Benzylamino)-1,1,1-trifluoro-3,6-dimethyl-3-nitroheptan-4-one (*syn*-23/*anti*-24). Yellow oil. (0.111 g, 32%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). v_{max} cm^{-1} 3358, 1750, 1566. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.14 (m, 10H), 4.71–4.47 (m, 3H), 4.39 (dq, *J* = 14.8, 7.5 Hz, 1H), 3.97 (dd, *J* = 71.3, 10.5 Hz, 2H), 3.93 (dd, *J* = 92.2, 10.9 Hz, 2H), 2.26–2.01 (m, 4H), 1.80 (s, 3H), 1.78 (s, 3H), 1.56 (br, 2H), 0.91 (d, *J* = 6.6 Hz, 6H), 0.89 (d, *J* = 6.4, 3H), 0.86 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 196.8, 138.4, 137.8, 128.6, 128.4 (2C), 128.4 (4C), 127.8, 127.6 (2C), 125.2 (q, *J* = 287.2 Hz), 125.1 (q, *J* = 287.8 Hz), 97.9, 96.2, 63.4 (q, *J* = 28.1 Hz), 62.3 (q, *J* = 27.9 Hz), 53.6, 52.9, 45.6, 45.0, 23.9, 23.7, 22.2 (2C), 22.1, 22.0, 17.2, 16.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.46 (d, *J* = 8.7 Hz), −65.77 (d, *J* = 8.1 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{16}H_{22}F_3N_2O_3$ 347.1583, found 347.1531.

2-(Benzylamino)-1,1,1-trifluoro-3,6-dimethyl-3-nitroheptan-4-one (*anti*-24). Yellow oil. (0.104 g, 30%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). v_{max} cm^{-1} 3355, 1753, 1568. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.06 (m, 5H), 4.50–4.09 (m, 1H) 3.94 (dd, *J* = 87.3, 11.6 Hz, 2H), 2.40 (d, *J* = 6.6 Hz, 2H), 2.27–2.07 (m, 2H), 2.07 (br, 1H), 1.80 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 138.4, 128.4 (2C), 128.4 (2C), 127.6, 125.2 (q, *J* = 287.3 Hz), 97.9, 63.4 (q, *J* = 28.0 Hz), 53.6, 45.6, 23.7, 22.2, 22.0, 17.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.77 (d, *J* = 8.1 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{16}H_{22}F_3N_2O_3$ 347.1583, found 347.1536.

1,1,1-Trifluoro-2-(isobutylamino)-3,6-dimethyl-3-nitroheptan-4-one (*anti*-25). Pale yellow oil. (0.087 g, 28%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). v_{max} cm^{-1} 3357, 1755, 1563. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.5 Hz, 1H), 2.82 (dd, *J* = 11.0, 7.1 Hz, 1H), 2.41 (dd, *J* = 6.6, 1.2 Hz, 2H), 2.31 (dd, *J* = 11.2, 7.1 Hz, 1H), 2.14 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.78 (s, 3H), 1.61–1.53 (m, 1H), 1.38 (br, 1H), 0.90 (d, *J* = 6.7 Hz, 6H), 0.85 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 125.2 (q, *J* = 287.1 Hz), 98.1, 64.4 (q, *J* = 28.0 Hz), 57.7, 45.7, 29.0, 23.7, 22.26, 22.0, 20.2, 17.1, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.10 (d, *J* = 7.2 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{13}H_{24}F_3N_2O_3$ 313.1739, found 313.1767.

(2*S*)-1,1,1-Trifluoro-3,6-dimethyl-2-{[(*R*)-3-methylbutan-2-yl]amino}-3-nitroheptan-4-one (*syn*-26/*anti*-27). Pale yellow oil. (0.065 g, 20%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). v_{max} cm^{-1} 3363, 1748, 1562. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (dq, *J* = 11.5, 7.3 Hz, 1H), 4.48 (dq, *J* = 11.7, 7.4 Hz, 1H), 2.91–2.67 (m, 2H), 2.44 (dd, *J* = 6.6, 2.8 Hz, 2H), 2.40 (dd, *J* = 6.5, 3.8 Hz, 2H) 2.28–2.00 (m, 4H), 1.82 (s, 3H), 1.79 (s, 3H), 1.26 (br, 2H), 1.07–0.70 (m 30H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 197.8, 126.2 (q, *J* = 283.5 Hz), 125.5 (q, *J* = 282.4 Hz), 90.2, 89.9, 65.3 (q, *J* = 27.9 Hz), 63.7 (q, *J* = 28.3 Hz), 61.3 (2C), 45.6 (2C), 29.0 (2C), 23.7, 22.2 (2C), 22.0, 20.2 (4C) 20.1 (4C), 16.6 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.97 (d, *J* = 8.4 Hz) −65.05 (d, *J* = 7.4 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{14}H_{26}F_3N_2O_3$ 327.1896, found 327.1873.

(2*S*,3*R*)-1,1,1-Trifluoro-3,6-dimethyl-2-{[(*R*)-3-methylbutan-2-yl]amino}-3-nitroheptan-4-one (*anti*-27). Pale yellow oil. (0.082 g, 25%) Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). v_{max} cm^{-1} 3361, 1751, 1559. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (q, *J* = 6.8 Hz, 1H), 2.84–2.74 (m, 1H), 2.45 (dd, *J* = 6.5, 4.5 Hz, 2H), 2.18–2.03 (m, 1H), 1.79 (s, 3H), 1.63–1.54 (m, 1H), 1.50 (br, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 125.1 (q, *J* = 288.6 Hz), 96.8, 59.8 (q, *J* = 27.6 Hz), 55.7, 45.5, 33.4, 23.9, 22.3, 22.3, 18.4, 17.1, 16.9, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.02 (d, *J* = 7.5 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{14}H_{26}F_3N_2O_3$ 327.1896, found 327.1850. $[\alpha]_D$: −14.6 (*c* = 4 g/100mL, $CHCl_3$).

***N*-Benzyl-1,1,1-trifluoro-3-nitrobutan-2-amine (28a, *syn/anti* = 1:1).** Yellow oil. (0.157 g, 60%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 80:20). v_{max} cm^{-1} 3353, 1565. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.17 (m, 10H), 4.78–4.63 (m, 2H), 4.13–4.04 (m, 1H), 4.08 (dd, *J* = 98.2, 13.0 Hz, 2H), 3.90 (dd, *J* = 84.9, 13.2 Hz, 2H), 3.62 (p, *J* = 7.4 Hz, 1H), 1.79 (br, 2H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.59 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 138.3, 128.5 (4C), 128.4 (2C), 128.3, 127.7, 127.6 (2C), 125.4 (q, *J* = 286.3 Hz), 125.3 (q, *J* = 286.0 Hz), 82.8, 80.5, 61.3 (q, *J* = 28.2 Hz), 60.6 (q, *J* = 28.0 Hz), 52.6, 52.2, 16.6, 12.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.1 (d, *J* = 7.8 Hz), −71.2 (d, *J* = 7.5 Hz). HRMS: *m/z* [M + H]$^+$ calcd. for $C_{11}H_{14}F_3N_2O_2$ 263.1007, found 263.1001.

1,1,1-Trifluoro-*N*-isobutyl-3-nitrobutan-2-amine (*syn*-28b). Pale yellow oil. (0.034 g, 15%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:25). ν_{max} cm^{-1} 3349, 1564. ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (dq, *J* = 13.7, 6.8 Hz, 1H), 3.48 (p, *J* = 7.6 Hz, 1H), 2.76 (dd, *J* = 10.9, 6.9 Hz, 1H), 2.39 (dd, *J* = 11.3, 6.9 Hz, 1H), 1.71-1.57 (m, 1H), 1.65 (d, *J* = 6.8, Hz, 3H), 1.27 (br, 1H), 0.88 (d, *J* = 2.4 Hz, 3H), 0.86 (d, *J* = 2.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 125.4 (q, *J* = 286.3 Hz), 83.2, 62.8 (q, *J* = 27.9 Hz), 56.5, 29.1, 20.1, 20.1, 16.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.47 (d, *J* = 7.0 Hz). HRMS: *m/z* $[M + H]^+$ calcd. for $C_8H_{16}F_3N_2O_2$ 229.1164, found 229.1184.

1,1,1-Trifluoro-*N*-isobutyl-3-nitrobutan-2-amine (*anti*-28b). Pale yellow oil. (0.046 g, 20%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:25). ν_{max} cm^{-1} 3349, 1564. ^1H NMR (300 MHz $CDCl_3$) δ 4.71 (qd, *J* = 6.7, 4.2 Hz, 1H), 4.03 (qd, *J* = 7.5, 4.3 Hz, 1H), 2.74 (dd, *J* = 11.7, 6.8 Hz, 1H), 2.38 (dd, *J* = 11.6, 6.9 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.26 (s, 1H), 0.87 (d, *J* = 2.7, 2.7 Hz, 3H), 0.85 (d, *J* = 2.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.11 (q, *J* = 285.4 Hz), 82.86, 62.56 (q, *J* = 27.8 Hz), 56.25, 28.79, 19.82 (2C), 16.28. ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.9 (d, *J* = 7.1 Hz). HRMS: *m/z* $[M + H]^+$ calcd. for $C_8H_{16}F_3N_2O_2$ 229.1164, found 229.1185.

1,1,1-Trifluoro-*N*-[(*R*)-3-methylbutan-2-yl]-3-nitrobutan-2-amine (28c, *syn/anti* = 1:1, dr = 1:1). Pale yellow oil. (0.073 g, 30%). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 90:10). ν_{max} cm^{-1} 3351, 1555. ^1H NMR (400 MHz, $CDCl_3$) δ 4.80–4.59 (m, 4H), 4.12 (dq, *J* = 14.7, 7.4, 4.1 Hz, 2H), 3.65 (dq, *J* = 10.6, 7.2 Hz, 2H), 2.87–2.61 (m, 4H), 1.68–1.53 (m, 12H), 1.38 (br, 4H), 1.00–0.70 (m, 40H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 125.5 (q, *J* = 286.0 Hz), 125.4 (q, *J* = 285.9 Hz), 125.3 (q, *J* = 285.6 Hz), 125.3 (q, *J* = 285.5 Hz), 83.4, 83.3, 81.0, 80.9, 60.7 (q, *J* = 27.9 Hz), 60.2 (q, *J* = 27.6 Hz), 59.4 (q, *J* = 27.8 Hz), 58.8 (q, *J* = 27.7 Hz), 57.3 (2C), 56.3 (2C), 33.3, 33.2, 31.9, 31.7, 18.8, 18.7, 18.5, 18.4, 17.1 (2C), 17.0, 16.3, 16.2, 16.1, 16.0, 16.0, 15.4, 15.1, 12.6, 12.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.99 (d, *J* = 8.4 Hz), −71.23 (d, *J* = 10.5 Hz), −71.93 (d, *J* = 9.0 Hz), −72.16 (d, *J* = 7.1 Hz). HRMS: *m/z* $[M + H]^+$ calcd. for $C_9H_{18}F_3N_2O_2$ 243.1320, found 243.1346**.**

Acknowledgements

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Keywords: addition reactions • nitro ketones • organocatalyst • solvent-free reactions • trifluoromethyl compounds

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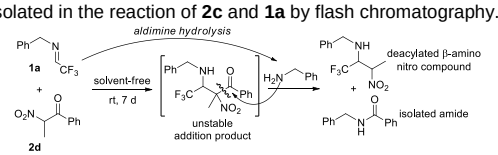
[18] Considering the long reaction times, the aldimine hydrolysis lead to the in situ formation of corresponding primary amine, which was able to promote the deacylation reaction. Actually, the following reported amide was isolated in the reaction of **2c** and **1a** by flash chromatography.



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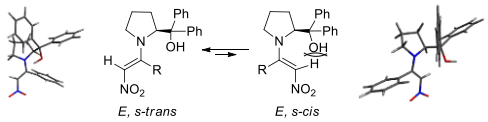
[21] The *E* enamine **31a-c** can be present in two different conformations,



the *s-trans* structure being the most favoured because of steric effects, as confirmed by optimised geometries (see SI): a) D. J. Walaszek, K. Rybicka-Jasinska, S. Smolen, M. Karczewski, D. Grykoa, *Adv. Synth. Catal.* **2015**, *357*, 2061-2070; b) B. S. Donslund T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860-13874 and references therein; c) P. Dinér, A. Kjærsgaard, M. A. Lie K. A. Jørgensen, *Chem.−Eur. J.* **2008**, *14*, 122-127; d) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041. Nitro enamines **31a-c** were also synthesised by stirring an equimolar mixture of **30** and **2a-c** at rt under solvent-free conditions (8 h) and then reacted with **1a** (see SI),

obtaining the same stereochemical results reported in Table 4 for the organocatalysed Mannich-type additions performing with **30** as catalyst.

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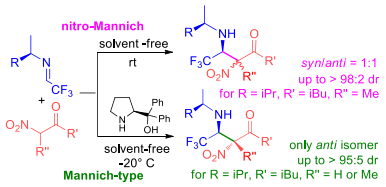
FULL PAPER

A comparison between nitro-Mannich and Mannich-type reactions of aryl and alkyl α-nitroalkyl ketones with trifluoromethyl aldimines is reported.



Solvent-free C-C coupling

*Alessia Pelagalli, Lucio Pellacani and Stefania Fioravanti**

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In pursuit of β-amino α-nitro β-trifluoromethyl ketones: nitro-Mannich *vs* Mannich-type reactions