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TFA-PROTECTED α-AMINO ACID *N*-HYDROXYSUCCINIMIDE ESTER: APPLICATION FOR INTER- AND INTRAMOLECULAR ACYLATION

Zetryana Puteri Tachrim,[a] Kazuhiro Oida,[a] Fumina Ohashi,[a] Haruna Wakasa,[a] Haruka Ikemoto,[a] Natsumi Kurokawa,[a] Yasuko Sakihama,[a] Yasuyuki Hashidoko,[a] Takeyuki Suzuki,[b] and Makoto Hashimoto [a,*]

[a]Division of Applied Bioscience, Graduate School of Agriculture, Hokkaido University, Kita 9, Nishi 9, Kita-ku, Hokkaido, Japan. [b]Division of Applied Science, The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan
*Correspondence: hasimoto@abs.agr.hokudai.ac.jp; Tel./Fax: +81-11-706-3849

Abstract – The utilization of *N*-trifluoroacetyl (TFA)-α-amino acid *N*-hydroxysuccinimide ester (OSu) derivatives, a promising acylating agent with high storage stability, is reported for Friedel–Crafts acylation into arenes and *N*-heterocycles. The reaction between TFA-Phe-OSu derivatives and arenes afforded inter- and intramolecular products. TFA-Tyr-OSu derivatives, which possess hydroxyl substituent in the aromatic moiety of phenylalanine, afforded only intermolecular product with benzene. The heterocyclic TFA-Pro-OSu also shows relatively high reactivity toward acylation.

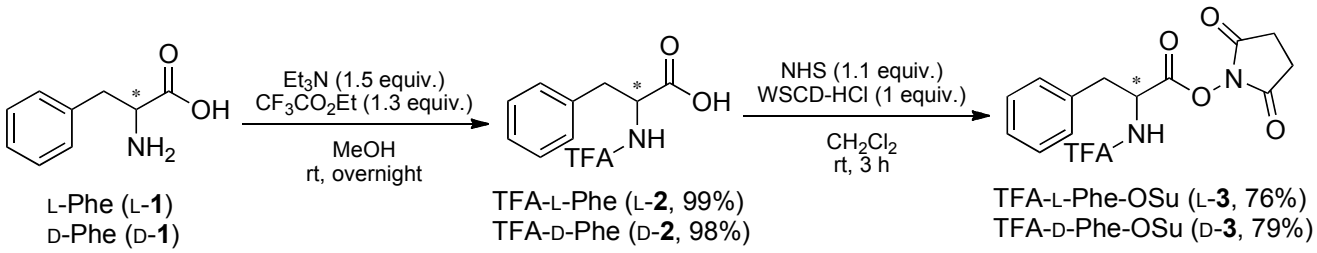
INTRODUCTION

Enantiomerically pure *N*-protected α-amino-aryl ketones are important building blocks to construct various biologically active compounds.[1,2] The most popular method for its synthesis, Weinreb amide,[3] is considerably less efficient due to the limitations of Grignard or organolithium reagents that apparently are non-commercially available and under a strong base condition that might hamper synthesis of the base sensitive *N*-protecting group of α-amino-aryl ketones. The Friedel–Crafts reaction[1,4-8] becomes a favorable method for synthesis of *N*-protected α-amino ketones,[9,10] since direct acylation can be underwent with convenient optically pure α-amino acid derivatives into various substrates with a satisfactory product yield. The drawback of a Friedel–Crafts reaction is the utilization of a commonly used acyl donor of unstable α-amino acid chloride[1,7,8] that should be used directly due to its instability for

This paper is dedicated to Prof. Dr. Kiyoshi Tomioka on the occasion of his 70th birthday.

storage. The study of Uto et al. showed that the imide carbonyl group of *N*-hydroxyphthalimide was easily reacted with benzene in the presence of $AlCl_3$.[11] On the other hand, *N*-hydroxysuccinimide derivatives can act as good leaving group for electrophilic aromatic substitution into benzene in the presence of $AlCl_3$. Recently we described the advantageous utilization of optically active *N*-trifluoroacetyl (TFA)-protected α-amino acid succinimide ester (OSu) for synthesis of *N*-protected α-amino aryl-ketone with a conventional Friedel–Crafts condition catalyzed by $AlCl_3$.[12] Moreover, the *N*-TFA branched and non-branched aliphatic of α-amino acid-OSu is convenient for storage and shows high reactivity to undergo direct acylation without loss of chirality.

To our knowledge, there is less attention to the study of *N*-TFA non-aliphatic α-amino acid ketones. This might be caused by difficulties in the reactive precursor synthesis. *N*-Protected phenylalanine acid chloride[13] previously was synthesized and known to be prolonged to racemization in peptide synthesis.[14] The azlactones utilization in phenylalanine also is known for rapid racemization under strong acidic condition.[13] Anhydro-*N*-carboxyphenylalanine[15] was previously reported to be prepared by using a toxic gas of phosgene[16] and is considerably less effective due to the existence of two possible acyl donors in the structure. The current *N*-protected phenylalanine benzotriazole[6] is reported to be more convenient to handle compared to α-amino acid chloride, but the preparation was conducted under in situ conditions that indicate the isolation takes more effort. Here in this study, we introduce the first utilization of aromatic α-amino acid, such as phenylalanine and tyrosine, or a cyclized aliphatic α-amino acid of proline for direct acylation into arenes and *N*-heterocycles via an active intermediate of OSu which is expected to have high reactivity for acylation and availability for storage.



Scheme 1. Synthesis of *N*-TFA- L-/D-phenylalanine succinimide ester derivatives (TFA- L-/D-Phe-OSu, L-/D-**3**)

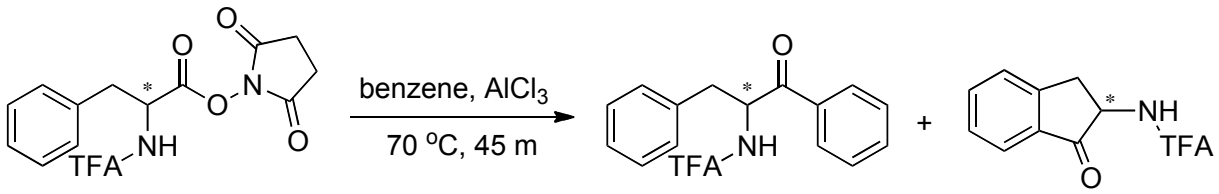
RESULTS AND DISCUSSION

Initially, the optical active L-/D-phenylalanine (L-/D-Phe, L-/D-**1**) underwent *N*-TFA protection by using ethyl trifluoroacetate in the presence of triethylamine in methanol to generate TFA-L-/D-Phe (L-/D-**2**, Scheme 1, See Supporting Information). The optically active L-/D-**2** was then transformed into

TFA-L-/D-Phe-OSu (L-/D-**3**) within 3 h at room temperature by utilization of 1.1 equivalents NHS (*N*-hydroxysuccinimide) and 1 equivalent of WSCD-HCl in CH_2Cl_2 (Scheme 1). The resulting TFA-L-/D-Phe-OSu (L-/D-**3**) was ready to use for acylation and could be stored at –20 °C for more than 3 months.

The corresponding TFA-L-/D-Phe-OSu (L-/D-**3**) was tested for acylation into benzene by activation with a conventional Friedel–Crafts catalyst of $AlCl_3$. Increasing the proportion of $AlCl_3$ (Table 1, Entries 1–4 and 7–8) or increasing the proportion of benzene (Table 1, Entries 5–6, See Supporting Information for details) resulted in the yield of desired intermolecular product TFA-L-/D-Phe-Ph (L-/D-**4**) not improving. This phenomena was caused by the formation of an intramolecular cyclization product of TFA-L-/D-cPhe (L-/D-**5**)[6] in moderate yield (Table 1). The competing intramolecular reaction specifically occurred on aromatic α-amino acid[6,7] which suggests that, presumably, the generation of benzyl carbonium ion[13] is faster to react with an aromatic side chain of phenylalanine rather than into benzene. The typical phenylalanine as acyl donor reaction with CH_2Cl_2 in the absence of benzene that results in intramolecular acylation is known[6,13,16] and investigation of TFA-L-/D-Phe-OSu (L-/D-**3**) under this condition (Table 1, Entries 9–10) showed similar intramolecular cyclization formation. Both the inter- and intramolecular product is known to preserve the chirality supported by identical optical rotation with the opposite sign.

Table 1. Friedel–Crafts reaction of TFA- L-/D-Phe-OSu, L-/D-**3** into benzene catalyzed by $AlCl_3$[a]



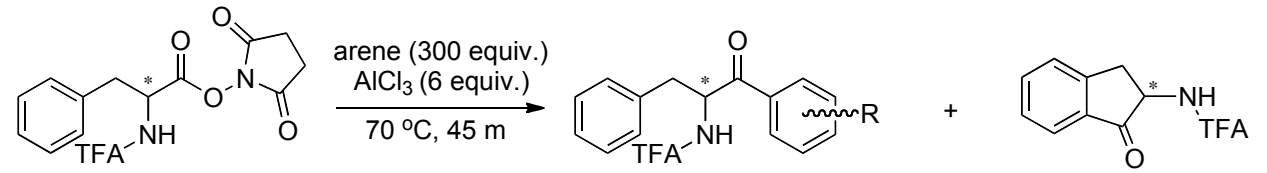
TFA-L-/D-Phe-OSu (L-/D-**3**) TFA-L-/D-Phe-Ph (L-/D-**4**) TFA-L-/D-cPhe (L-/D-**5**)

Entry	Material	$AlCl_3$ (equiv.)	Benzene (equiv.)	%Yield TFA-L-/D-Phe-Ph (L-/D-**4**)	%Yield TFA- L-/D-cPhe (L-/D-**5**)
1	L-**3**	3	300	9%	45%
2	D-**3**	3	300	8%	44%
3	L-**3**	6	300	38%	50%
4	D-**3**	6	300	43%	52%
5	L-**3**	6	600	31%	58%
6	D-**3**	6	600	34%	61%
7	L-**3**	12	300	26%	55%
8	D-**3**	12	300	33%	50%
9	L-**3**	6	–[b]	–	64%
10	D-**3**	6	–[b]	–	69%

[a]Proportion was determined by ^{1}H NMR in acetone-d_6. [b]Utilization with 300 equivalents CH_2Cl_2 under reflux condition

Based on Table 1, utilization of TFA-L-/D-Phe-OSu (L-/D-**3**) showed relatively high reactivity toward acylation into benzene under activation by $AlCl_3$ to result in *N*-TFA α-amino ketones. Conversely, anhydro-*N*-carboxy-DL-phenylalanine,[16] as previously reported, did not result in any α-amino ketones. Since utilization with more excess benzene showed TFA-L-/D-cPhe (L-/D-**5**) considerably favored formation, TFA-L-/D-Phe-OSu (L-/D-**3**) also was tested into various arenes. The treatment of TFA-L-/D-Phe-OSu (L-/D-**3**) with 300 equivalents of benzene and 6 equivalents of $AlCl_3$ (Table 1, Entries 3–4) show relatively efficient acylation, thus this condition was utilized for acylation into various arenes.

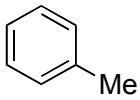
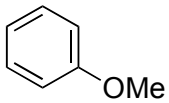
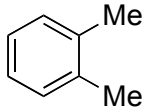
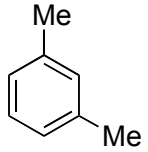
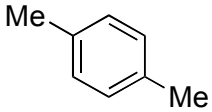
Table 2. Friedel–Crafts reaction of TFA-L-/D-Phe-OSu, L-/D-**3** into various arenes catalyzed by $AlCl_3$



TFA-L-/D-Phe-OSu (L-/D-**3**)

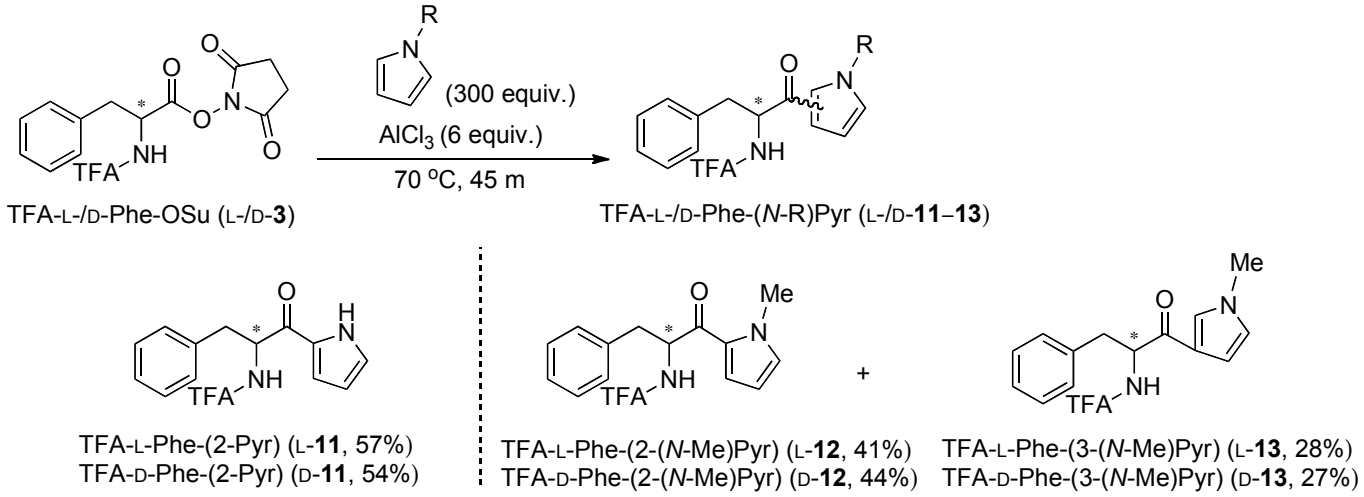
TFA-L-/D-Phe-Ph(4-Me) (L-/D-**6**)
TFA-L-/D-Phe-Ph(4-OMe) (L-/D-**7**)
TFA-L-/D-Phe-Ph(3,4-Me) (L-/D-**8**)
TFA-L-/D-Phe-Ph(2,4-Me) (L-/D-**9**)
TFA-L-/D-Phe-Ph(2,5-Me) (L-/D-**10**)

TFA-L-/D-cPhe (L-/D-**5**)

Entry	Material	Arene	Product (%Yield)	
1	L-**3**		L-**6** (52%)	L-**5** (21%)
2	D-**3**		D-**6** (58%)	D-**5** (26%)
3	L-**3**		L-**7** (68%)	L-**5** (–)
4	D-**3**		D-**7** (66%)	D-**5** (–)
5	L-**3**		L-**8** (70%)	L-**5** (15%)
6	D-**3**		D-**8** (69%)	D-**5** (10%)
7	L-**3**		L-**9** (49%)	L-**5** (36%)
8	D-**3**		D-**9** (44%)	D-**5** (33%)
9	L-**3**		L-**10** (31%)	L-**5** (54%)
10	D-**3**		D-**10** (36%)	D-**5** (43%)

The introduction of reaction between TFA-L-/D-Phe-OSu (L-/D-**3**) and toluene (Table 2, Entries 1–2) shows intermolecular reaction is preferred, which resulted in TFA-L-/D-Phe-Ph(4-Me) (L-/D-**6**) in moderate yield (52–58%), rather than when reaction between TFA-L-/D-Phe-OSu (L-/D-**3**) and benzene (Table 1). The methyl substituent act as an electron donating group in aromatic moiety of toluene which might suppress intramolecular formation. The occurrence of TFA-L-/D-Phe-Ph(4-OMe) (L-/D-**7**) was relatively in high yield (66–68%, Table 2, Entries 3–4) supporting the role of the electron donating group

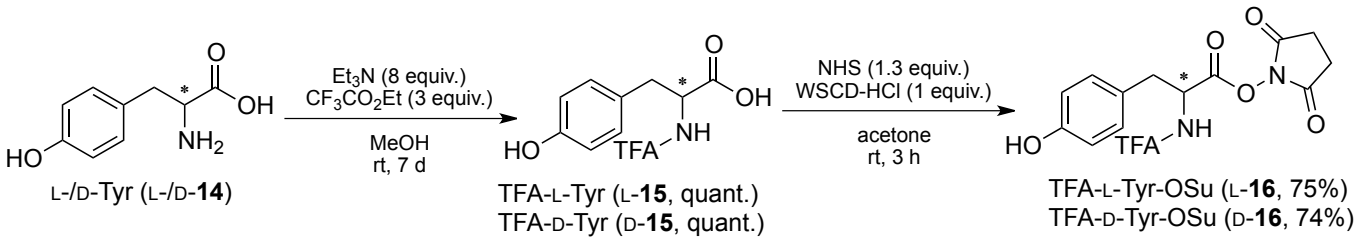
effect that activated aromatic moiety for fast electrophilic aromatic substitution under a conventional Friedel–Crafts acylation. The methoxy group of anisole might play an important role for the suppression of intramolecular cyclization since no TFA-L-/D-cPhe (L-/D-**5**) was detected by ^{1}H-NMR. The acylation mostly occurs at a less hindered position of toluene and anisole (ratio *p*-:*o*- 17:1 and 13:1, respectively). Regarding xylene (Table 2, Entries 5–10), each of the dimethyl group substituent might induce inter- and intramolecular reactions. The high reactivity was shown by *o*-xylene that resulted in approximately a 70% yield of TFA-L-/D-Phe-Ph(3,4-Me) (L-/D-**8**) which suppressed intramolecular cyclization up to a 15% yield. All the TFA-L-/D-Phe-arenes synthesized from TFA-L-/D-Phe-OSu retained their chirality and the reaction was easier to handle compared to phenylalanine acid chloride.[13]



Scheme 2. Friedel–Crafts reaction of TFA- L-/D-Phe-OSu, L-/D-**3** into *N*-pyrrole and *N*-methylpyrrole catalyzed by $AlCl_3$

To broaden the application of *N*-hydroxysuccinimide ester, TFA-L-/D-Phe-OSu (L-/D-**3**) was utilized into *N*-heterocycles of *N*-pyrrole and *N*-methylpyrrole (Scheme 2). Previously, *N*-TFA-L-phenylalanine-benzotriazole was reported as the only *N*-pyrrole and *N*-methylpyrrole acylation product observed, with no intramolecular cyclization product.[6] Similarly, when the optical active TFA-L-/D-Phe-OSu (L-/D-**3**) were treated with *N*-pyrrole, TFA-L-/D-Phe-(2-Pyr) (L-/D-**11**)[6] resulted with a moderate yield in which acylation occurred specifically at the C-2 position. Regarding acylation into *N*-methylpyrrole, we found two isomers of C-2 position acylated product of TFA-L-/D-Phe-(2-(*N*-Me)Pyr) (L-/D-**12**)[6] as the major product and C-3 position acylated product of TFA-L-/D-Phe(3-(*N*-Me)Pyr) (L-/D-**13**) that can be detected by TLC. Further acylation at C-3 position might be caused by the low reactivity of 2-position due to steric hindrance of *N*-methyl protecting group. Based on ^{1}H-NMR, the occurrence of overlap of two protons at 3- and 5-position of *N*-methylpyrrole[6] at 6.62 ppm (d, J = 2.0 Hz) was observed for C-2 position acylated product L-/D-**12**. Meanwhile, the proton of 2-position of *N*-methylpyrrole for L-/D-**13**

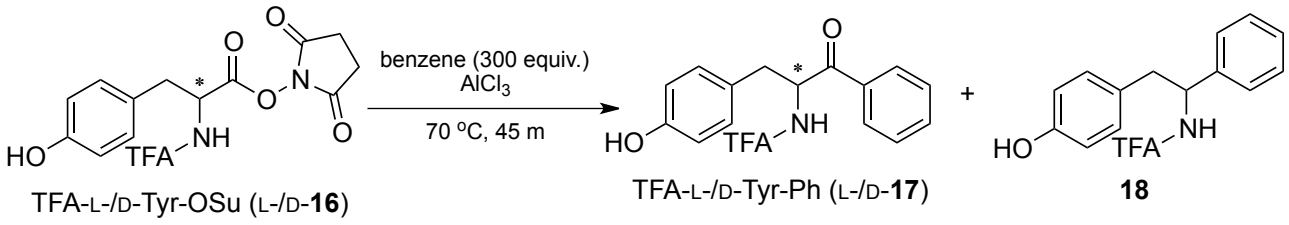
was shown as singlet at 6.93 ppm and the proton of 5-position of *N*-methylpyrrole for L-/D-**13** appeared at slightly upfield region at 6.20 (dd, J = 4.3, 2.3 Hz). The ^{13}C-NMR supports the assignment demonstrated by the observation of C=O signal of the C-2 position acylated product L-/D-**12**[6] which showed at 189.8 ppm. Meanwhile, the C-3 position acylated product L-/D-**13** showed slightly upperfield at 185.0 ppm (see Supporting Information). Both utilization of optical active TFA-L-/D-Phe-OSu (L-/D-**3**) into *N*-pyrrole and *N*-methylpyrrole showed no detection of intramolecular adduct, thus indicating that these acyl acceptor react faster with the active intermediate to result in TFA-α-amino-heterocycles ketones.



Scheme 3. Synthesis of *N*-TFA-L-/D-tyrosine succinimide ester derivatives (TFA- L-/D-Tyr-OSu, L-/D-**16**)

The *N*-hydroxysuccinimide ester (OSu) utilization as a potential acyl donor for aryl-ketones synthesis was extended by introduction of tyrosine derivatives. Following the optical active L-/D-tyrosine (L-/D-Tyr, L-/D-**14**) underwent *N*-TFA protection, then the resultant TFA-L-/D-Tyr (L-/D-**15**, Scheme 3, See Supporting Information) directly transformed into TFA-L-/D-Tyr-OSu (L-/D-**16**) within 3 h at room temperature by utilization of 1.3 equivalents NHS and 1 equivalent of WSCD-HCl in acetone (Scheme 3, See Supporting Information). Table 3 shows the Friedel–Crafts reaction of TFA-L-/D-Tyr-OSu (L-/D-**16**) into benzene catalyzed by $AlCl_3$. The hydroxyl group in an aromatic moiety of TFA-L-/D-Tyr-OSu (L-/D-**16**) was not hampered in its reactivity to undergo acylation into benzene. Unlike TFA-L-/D-Phe-OSu (L-/D-**3**) utilization into benzene (Table 1), the TFA-L-/D-Tyr-Ph (L-/D-**17**, Table 3) utilization showed no appearance of intramolecular product. When 6 equivalents $AlCl_3$ was used, the lower yield of TFA-L-Tyr-Ph (L-**17**, Table 3, Entry 1) was due to the formation of decarbonylated compound **18**. A higher proportion of $AlCl_3$ (24 equivalent, Table 3, Entry 3–4) suppressed **18** formation and the resultant TFA-L-/D-Tyr-Ph (L-/D-**17**) was in satisfactory yield without loss of chirality. Under an acidic condition offered by this system, hydroxyl substituent in an aromatic moiety of tyrosine skeleton unnecessary to be protected, and utilization of TFA-L-/D-Tyr-OSu (L-/D-**16**) was considerably more effective for direct synthesis of TFA-L-/D-Tyr-Ph (L-/D-**17**). The aromatic α-amino acids might exibits intramolecular acylation due to attachable aromatic moiety in their side chain that was preferable to react with the active intermediate.

Table 3. Friedel–Crafts reaction of *N*-TFA-L-/D-tyrosine succinimide ester derivatives (TFA-L-/D-Tyr-OSu, L-/D-**16**) into benzene catalyzed by $AlCl_3$

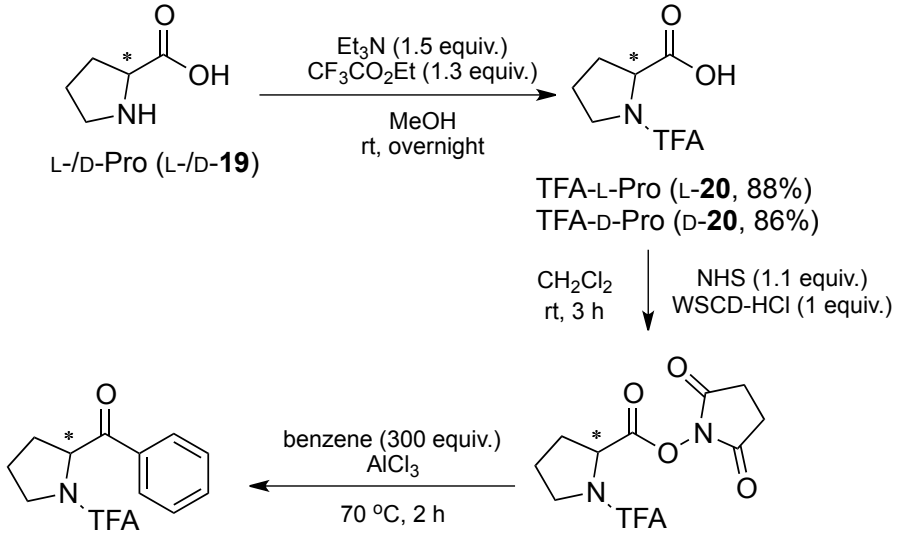


TFA-L-/D-Tyr-OSu (L-/D-**16**) TFA-L-/D-Tyr-Ph (L-/D-**17**) **18**

Entry	Material	$AlCl_3$ (equiv.)	17 (%Yield)	Ratio of 17 : 18[a]
1	L-**16**	6	49%	1.00:0.45
2	L-**16**	12	56%	1.00:0.21
3	L-**16**	24	78%	1.00:0.13
4	D-**16**	24	79%	1.00:0.10

[a]Observed by ^{1}H-NMR

Next, proline derivatives, the only cyclized aliphatic α-amino acid, was then tested for the inter- and intramolecular reaction via *N*-hydroxysuccinimide ester (OSu) utilization. L-/D-Proline (L-/D-**19**) first was *N*-TFA-protected to result in TFA-L-/D-Proline (L-/D-**20**, Scheme 4, See Supporting Information), before transforming into TFA-L-/D-Pro-OSu (L-/D-**21**) within 3 h at room temperature by utilization of 1.1 equivalents NHS and 1 equivalent of WSCD-HCl in CH_2Cl_2 (Scheme 4).



L-/D-Pro (L-/D-**19**)

TFA-L-Pro (L-**20**, 88%)
TFA-D-Pro (D-**20**, 86%)

TFA-L-Pro-OSu (L-**21**, 91%)
TFA-D-Pro-OSu (D-**21**, 94%)

TFA-L-Pro-Ph (L-**22**, 84%)
TFA-D-Pro-Ph (D-**22**, 81%)

Scheme 4. Synthesis and utilization of *N*-TFA-L-/D-proline succinimide ester derivatives (TFA-L-/D-Pro-OSu, L-/D-**21**)

Direct acylation of TFA-L-/D-Pro-OSu (L-/D-21) with 300 equivalents of benzene which was activated by 6 equivalents $AlCl_3$ can generate TFA-L-/D-Pro-Ph (L-/D-22)[1,8,17] within excellent yield (81–84%, Scheme 4). There was no observation of intramolecular cyclization in these proline derivatives. Based on NMR (Supporting Information), *cis*- and *trans*- *N*-TFA-proline derivatives were observed. Hence, it also suggested that all *N*-TFA-proline derivatives exhibit no loss of chirallity.

CONCLUSION

To summarize, utilizing TFA-α-amino acid-OSu derivatives having an aromatic moiety side chain for Friedel–Crafts acylation reaction activated by $AlCl_3$ might introduce an intermolecular reaction with arenes and heterocycles. Rapid intramolecular cyclization is possible in the reaction for TFA-L-/D-Phe-OSu (L-/D-**3**). The OSu derivatives for tyrosine, that possess hydroxyl substituent in an aromatic moiety of phenylalanine, or proline, the only cyclized α-amino acid, can contribute as an acyl donor for Friedel–Crafts acylation without loss of chirality. These characteristics might play an important role in further study to broaden the application of synthesis bioactive compounds.

EXPERIMENTAL

General Remarks. All reagents used were of analytical grade. FT-IR spectra were recorded on a FT-IR 4100 spectrometer (JASCO, Tokyo, Japan). NMR spectra were measured by an EX 270 spectrometer (JEOL, Tokyo, Japan). Optical rotations were measured at 23 ^{o}C on a JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). HRMS-ESI spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA).

General Procedure for the Preparation of TFA-a-Amino Acid. The corresponding amino groups of α-amino acid underwent TFA protection by using ethyl trifluoroacetate in the presence of triethylamine in MeOH to generate TFA-α-amino acid (L-/D-2, L-/D-15, L-/D-20, see Supplementary Information).

General Procedure for Preparation of TFA-α-Amino Acid N-Hydroxysuccinimide Ester. *N*-Hydroxysuccinimide (1.1 or 1.3 equivalents) was added to a solution of TFA-α-amino acid (L-/D-2, L-/D-15, L-/D-20, 1.0 mmol) in pre-cooled solvent (10 mL). The suspension of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride (WSCD-HCl, 1.0 equivalent) in solvent (10 mL) was added drop-wise at 0 °C and the reaction was stirred for 3 h. The solvent was removed by rotary evaporation. The residue that remained was dissolved in EtOAc; washed with water, sat. $NaHCO_3$, sat. NaCl, dried over $MgSO_4$, and then evaporated. The product was washed with hexane to be used for further reaction.

(*S*)-2,5-Dioxopyrrolidin-1-yl 3-phenyl-2-(2,2,2-trifluoroacetamido)propanoate (TFA-L-Phe-OSu,

L-3). Colorless amorphous mass. $[\alpha]_D$ –34 (*c* 1.0, MeOH). IR (neat) ν : 3310, 3109, 3033, 2947, 1826, 1818, 1785, 1762, 1737, 1723 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.34–7.27 (5H, m, Ar-H), 6.87 (1H, br d, *J* = 5.9 Hz, N*H*), 5.27 (1H, q, *J* = 5.9 Hz, C*H*NH), 3.42 (1H, dd, *J* = 14.3, 5.9 Hz, CH_2CH), 3.28 (1H, dd, *J* = 14.3, 5.9 Hz, CH_2CH), 2.85 (4H, s, 2 x CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 168.5 (2 x CO), 166.1, 156.6 (q, $^2J_{CF}$ = 38.0 Hz), 133.4, 129.5 (2 x CH), 128.9 (2 x CH), 127.9, 115.3 (q, $^1J_{CF}$ = 287.2 Hz), 51.5, 37.2, 25.5 (2 x CH_2) ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{15}H_{14}F_3N_2O_5$ 359.0855, found 359.0857.

(*R*)-2,5-Dioxopyrrolidin-1-yl 3-phenyl-2-(2,2,2-trifluoroacetamido)propanoate (TFA-D-Phe-OSu, D-3). Colorless amorphous mass. $[\alpha]_D$ +34 (*c* 1.0, MeOH). IR (neat) ν : 3308, 3111, 3033, 2946, 1826, 1816, 1785, 1761, 1735, 1721 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.35–7.28 (5H, m, Ar-H), 6.79 (1H, br d, *J* = 5.9 N*H*), 5.28 (1H, q, *J* = 5.9 Hz, C*H*NH), 3.42 (1H, dd, *J* = 14.3, 5.9 Hz, CH_2CH), 3.30 (1H, dd, *J* = 14.3, 5.9 Hz, CH_2CH), 2.86 (4H, s, 2x CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 168.5 (2 x CO), 166.1, 156.6 (q, $^2J_{CF}$ = 38.4 Hz), 133.3, 129.5 (2 x CH), 128.9 (2 x CH), 127.9, 115.3 (q, $^1J_{CF}$ = 288.1 Hz), 51.5, 37.2, 25.5 (2 x CH_2) ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{15}H_{14}F_3N_2O_5$ 359.0855, found 359.0856.

(*S*)-2,5-Dioxopyrrolidin-1-yl 3-(4-hydroxyphenyl)-2-(2,2,2-trifluoroacetamido)propanoate (TFA-L-Tyr-OSu, L-16). Yellowish amorphous mass. $[\alpha]_D$ –29 (*c* 1.0, MeOH). IR (neat) ν : 3324, 1820, 1792, 1755 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.86 (1H, d, *J* = 8.6 Hz, N*H*), 8.15 (1H, br s, O*H*), 7.10 (2H, d, *J* = 8.2 Hz, Ar-H), 6.67 (2H, d, *J* = 8.2 Hz, Ar-H), 5.03 (1H, td, *J* = 10.2, 4.6 Hz, C*H*NH), 3.28 (1H, dd, *J* = 14.2, 4.6 Hz, CH_2CH), 3.04 (1H, dd, *J* = 14.2, 10.2 Hz, CH_2CH), 2.73 (4H, s, 2 x CH_2) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 170.2 (2 x CO), 167.2, 157.6 (q, $^2J_{CF}$ = 38.0 Hz), 157.3, 131.2 (2 x CH), 126.9, 116.6 (q, $^1J_{CF}$ = 287.2 Hz), 116.2 (2 x CH), 53.2, 36.3, 26.2 (2 x CH_2) ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{13}F_3N_2O_6Na$ 397.0623, found 397.0625.

(*R*)-2,5-Dioxopyrrolidin-1-yl 3-(4-hydroxyphenyl)-2-(2,2,2-trifluoroacetamido)propanoate (TFA-D-Tyr-OSu, D-16). Yellowish amorphous mass. $[\alpha]_D$ +29 (*c* 1.0, MeOH). IR (neat) ν : 3323, 1820, 1788, 1732 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.87 (1H, d, *J* = 8.6 Hz, N*H*), 8.15 (1H, br s, O*H*), 7.10 (2H, d, *J* = 8.6 Hz, Ar-H), 6.67 (2H, d, *J* = 8.6 Hz, Ar-H), 5.03 (1H, td, *J* = 9.9, 4.8 Hz, C*H*NH), 3.28 (1H, dd, *J* = 14.3, 4.8 Hz, CH_2CH), 3.04 (1H, dd, *J* = 14.2, 9.9 Hz, CH_2CH), 2.74 (4H, s, 2 x CH_2) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 170.1 (2 x CO), 167.2, 157.6 (q, $^2J_{CF}$ = 37.4 Hz), 157.4, 131.2 (2 x CH), 127.0, 116.7 (q, *J* = 287.7 Hz), 116.2 (2 x CH), 53.3, 36.3, 26.2 (2 x CH_2) ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{13}F_3N_2O_6Na$ 397.0623, found 397.0636.

(*S*)-2,5-Dioxopyrrolidin-1-yl 1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (TFA-L-Pro-OSu, L-21). Colorless amorphous mass. $[\alpha]_D$ –85 (*c* 1.0, $CHCl_3$); Lit.[18] $[\alpha]_D$ –98 (*c* 1.0, CH_3OH). IR (neat) ν :

3376, 2988, 1830, 1786, 1758 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.89 (1H, t, *J* = 6.3 Hz, CH_2CH), 3.95–3.70 (2H, m, CH_2), 2.84 (4H, s, 2 x CH_2), 2.45–2.35 (2H, m, CH_2), 2.30–2.04 (2H, m, CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 168.6, 166.9, 166.4, 155.9 (q, $^2J_{CF}$ = 38.2 Hz), 115.9 (q, $^1J_{CF}$ = 286.8 Hz), [57.9 & 57.4], [48.0 & 47.1], [32.1 & 28.7], 25.5, [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{11}H_{12}F_3N_2O_5$ 309.0698, found 309.0708.

(*R*)-2,5-Dioxopyrrolidin-1-yl 1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (TFA-D-Pro-OSu, D-21). Colorless amorphous mass. $[\alpha]_D$ +85 (*c* 1.0, $CHCl_3$). IR (neat) ν : 3376, 2987, 1827, 1785, 1758 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.88 (1H, t, *J* = 6.1 Hz, CH_2CH), 3.92–3.68 (2H, m, CH_2), 2.84 (4H, s, 2 x CH_2), 2.47–2.35 (2H, m, CH_2), 2.26–2.11 (2H, m, CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 168.5, 166.8, 166.4, 155.9 (q, $^2J_{CF}$ = 38.2 Hz), 115.9 (q, $^1J_{CF}$ = 287.0 Hz), [58.0 & 57.4], [48.0 & 47.1], [32.1 & 28.7], 25.5, [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{11}H_{12}F_3N_2O_5$ 309.0698, found 309.0725.

General Procedure for Friedel-Crafts acylation. TFA-α-amino acid-OSu (0.1–0.5 mmol) was suspended in arenes or N-heterocycles. Into the suspension, pulverized $AlCl_3$ was added and then stirred at a temperature of 70 °C. The reaction was monitored by the consumption of starting material on TLC. The solvent was reduced by rotary evaporation, then the mixture was poured into an EtOAc-H_2O two-phase system. The organic layer was washed with H_2O, sat. NaCl, dried over $MgSO_4$, and then evaporated. The crude product was purified by silica column chromatography (EtOAc/hexane 1:3 for L-/D-**4**, L-/D-**5**, L-/D-**11**–L-/D-**13**, L-/D-**17**, L-/D-**22** and Et_2O/hexane 1:5 for L-/D-**6**–L-/D-**10**).

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-1,3-diphenylpropan-2-yl)acetamide (TFA-L-Phe-Ph, L-4). Colorless needles; $[\alpha]_D$ +14.0 (*c* 1.0, MeOH). IR (neat) ν : 3326, 3065, 3032, 1728, 1686 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.96 (2H, d, *J* = 7.4 Hz, Ar-H), 7.66 (1H, t, *J* = 7.4 Hz, Ar-H), 7.52 (2H, t, *J* = 7.4 Hz, Ar-H), 7.31 (1H, br d, *J* = 6.3 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.92 (2H, dd, *J* = 6.4, 2.8 Hz, Ar-H), 5.82 (1H, q, *J* = 6.3, 6.3, 6.3 Hz, C*H*NH), 3.37 (1H, dd, *J* = 14.2, 6.3 Hz, CH_2CH), 3.12 (1H, dd, *J* = 14.2, 6.3 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.9, 156.5 (q, $^2J_{CF}$ = 37.6 Hz), 134.4, 134.2, 133.8, 129.4 (2 x CH), 129.1 (2 x CH), 128.8 (2 x CH), 128.5 (2 x CH), 127.4, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 55.3, 38.2 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{17}H_{15}F_3NO_2$ 322.1055, found 322.1065.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-1,3-diphenylpropan-2-yl)acetamide (TFA-D-Phe-Ph, D-4). Colorless needles; $[\alpha]_D$ –14.0 (*c* 1.0, MeOH). IR (neat) ν : 3326, 3066, 3032, 1720, 1684 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.96 (2H, d, *J* = 7.3 Hz, Ar-H), 7.65 (1H, t, *J* = 7.3 Hz, Ar-H), 7.52 (2H, t, *J* = 7.3 Hz, Ar-H), 7.40 (1H, br d *J* = 5.9 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.92 (2H, dd, *J* = 6.3, 3.0 Hz, Ar-H), 5.82 (1H, q, *J* = 5.9, 5.9, 5.9 Hz, C*H*NH), 3.37 (1H, dd, *J* = 14.2, 5.9 Hz, CH_2CH), 3.11 (1H, dd, *J* = 14.2, 5.9 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.9, 156.5 (q, $^2J_{CF}$ = 37.4 Hz), 134.4, 134.2, 133.8,

129.4 (2 x CH), 129.1 (2 x CH), 128.7 (2 x CH), 128.5 (2 x CH), 127.4, 115.6 (q, $^1J_{CF}$ = 287.7 Hz), 55.3, 38.2 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{17}H_{15}F_3NO_2$ 322.1055, found 322.1065.

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetamide (TFA-L-cPhe, L-5).[6] Colorless amorphous mass; $[\alpha]_D$ –1.4 (*c* 1.0, acetone); –3.1 (*c* 1.6, DMF); Lit.[6] $[\alpha]_D$ –3.2 (*c* 1.6, DMF). IR (neat) ν : 3301, 3108, 2954, 1733, 1700 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.97 (1H, br d, *J* = 5.4 Hz, N*H*), 7.75–7.68 (2H, m, Ar-H), 7.58 (1H, d, *J* = 7.4 Hz, Ar-H), 7.47 (1H, t, *J* = 7.4 Hz, Ar-H), 4.74 (1H, ddd, *J* = 8.6, 5.4, 5.4 Hz, C*H*NH), 3.68 (1H, dd, *J* = 16.8, 8.6 Hz, CH_2CH), 3.20 (1H, dd, *J* = 16.8, 5.4 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 201.2, 157.7 (q, $^2J_{CF}$ = 36.9 Hz), 152.1, 136.3, 135.9, 128.7, 127.6, 124.4, 117.0 (q, $^1J_{CF}$ = 287.7 Hz), 56.0, 33.2 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{11}H_9F_3NO_2$ 244.0585, found 244.0586.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetamide (TFA-D-cPhe, D-5). Colorless amorphous mass; $[\alpha]_D$ +1.6 (*c* 1.0, acetone); +3.1 (*c* 1.6, DMF). IR (neat) ν : 3300, 3109, 2955, 1733, 1699 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.94 (1H, br d, *J* = 5.3 Hz, N*H*), 7.75–7.68 (2H, m, Ar-H), 7.58 (1H, d, *J* = 7.4 Hz, Ar-H), 7.47 (1H, t, *J* = 7.4 Hz, Ar-H), 4.74 (1H, ddd, *J* = 8.4, 5.3, 5.3 Hz, C*H*NH), 3.68 (1H, dd, *J* = 16.8, 8.4 Hz, CH_2CH), 3.20 (1H, dd, *J* = 16.8, 5.3 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 201.2, 157.7 (q, $^2J_{CF}$ = 36.3 Hz), 152.1, 136.3, 135.9, 128.7, 127.6, 124.4, 117.0 (q, $^1J_{CF}$ = 287.7 Hz), 56.0, 33.2 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{11}H_9F_3NO_2$ 244.0585, found 244.0588.

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-3-phenyl-1-(*p*-tolyl)propan-2-yl)acetamide (TFA-L-Phe-Ph(4-Me), L-6). Colorless needles; $[\alpha]_D$ +16 (*c* 1.0, MeOH). IR (neat) ν : 3304, 3091, 3034, 2932, 1708, 1680 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.87 (2H, d, *J* = 8.2 Hz, Ar-H), 7.33 (4H, d, *J* = 8.2 Hz, Ar-H), 7.23–7.20 (1H, m, Ar-H), 6.92–6.88 (2H, m, Ar-H), 5.77 (1H, ddd, *J* = 5.9, 5.9, 5.9 Hz, C*H*NH), 3.38 (1H, dd, *J* = 14.2, 5.9 Hz, CH_2CH), 3.11 (1H, dd, *J* = 14.2, 5.9 Hz, CH_2CH), 2.46 (3H, s, CH_3) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.4, 156.4 (q, $^2J_{CF}$ = 37.4 Hz), 145.6, 134.4, 131.2, 129.7 (2 x CH), 129.4 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 127.3, 115.6 (q, $^1J_{CF}$ = 287.7 Hz), 55.1, 38.2, 21.6 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_2$ 336.1211, found 336.1180.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-3-phenyl-1-(*p*-tolyl)propan-2-yl)acetamide (TFA-D-Phe-Ph(4-Me), D-6). Colorless needles; $[\alpha]_D$ –16 (*c* 1.0, MeOH). IR (neat) ν : 3301, 3090, 3034, 2931, 1708, 1680 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.87 (2H, d, *J* = 8.2 Hz, Ar-H), 7.33 (4H, d, *J* = 8.2 Hz, Ar-H), 7.23–7.20 (1H, m, Ar-H), 6.93–6.89 (2H, m, Ar-H), 5.78 (1H, ddd, *J* = 5.8, 5.8, 5.8 Hz, C*H*NH), 3.37 (1H, dd, *J* = 14.0, 5.8 Hz, CH_2CH), 3.11 (1H, dd, *J* = 14.0, 5.8 Hz, CH_2CH), 2.45 (3H, s, CH_3) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.3, 156.5 (q, $^2J_{CF}$ = 38.0 Hz), 145.7, 134.3, 131.2, 129.8 (2 x CH), 129.4 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 127.4, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 55.1, 38.3, 21.7 ppm. HRMS-ESI

(*m*/*z*) $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_2$ 336.1211, found 336.1186.

(*S*)-2,2,2-Trifluoro-*N*-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-Ph(4-OMe), L-7). Colorless amorphous mass; $[\alpha]_D$ +27 (*c* 1.0, MeOH). IR (neat) ν : 3300, 3089, 3033, 2961, 2934, 1712, 1671 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.94 (2H, d, *J* = 8.9 Hz, Ar-H), 7.40 (1H, br d, *J* = 5.6 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.98 (2H, d, *J* = 8.9 Hz, Ar-H), 6.95–6.91 (2H, m, Ar-H), 5.75 (1H, ddd, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.90 (3H, s, OCH_3), 3.35 (1H, dd, *J* = 14.0, 5.6 Hz, CH_2CH), 3.11 (1H, dd, *J* = 14.0, 5.6 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 194.1, 164.6, 156.4 (q, $^2J_{CF}$ = 37.4 Hz), 134.4, 131.2 (2 x CH), 129.4 (2 x CH), 128.5 (2 x CH), 127.3, 126.6, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 114.3 (2 x CH), 55.6, 54.9, 38.6 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_3$ 352.1161, found 352.1158.

(*R*)-2,2,2-Trifluoro-*N*-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-Ph(4-OMe), D-7). Colorless amorphous mass; $[\alpha]_D$ –27 (*c* 1.0, MeOH). IR (neat) ν : 3352, 3090, 3033, 2944, 2926, 1727, 1671 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.94 (2H, d, *J* = 8.9 Hz, Ar-H), 7.37 (1H, br d, *J* = 5.6 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.98 (2H, d, *J* = 8.9 Hz, Ar-H), 6.94–6.90 (2H, m, Ar-H), 5.74 (1H, ddd, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.91 (3H, s, OCH_3), 3.35 (1H, dd, *J* = 14.0, 5.6 Hz, CH_2CH), 3.11 (1H, dd, *J* = 14.0, 5.6 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 194.1, 164.5, 156.4 (q, $^2J_{CF}$ =37.6 Hz), 134.5, 131.1 (2 x CH), 129.3 (2 x CH), 128.3 (2 x CH), 127.2, 126.5, 115.7 (q, $^1J_{CF}$ = 287.3 Hz), 114.2 (2 x CH), 55.4, 54.8, 38.4 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_3$ 352.1161, found 352.1169.

(*S*)-*N*-(1-(3,4-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-Phe-Ph(3,4-Me), L-8). Colorless needles; $[\alpha]_D$ +16 (*c* 1.0, MeOH). IR (neat) ν : 3326, 3031, 2945, 2935, 1732, 1685 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.71 (2H, d, *J* = 6.9 Hz, Ar-H), 7.46 (1H, br d, *J* = 5.9 Hz, N*H*), 7.28–7.19 (4H, m, Ar-H), 6.93 (2H, d, *J* = 7.8 Hz, Ar-H), 5.79 (1H, ddd, *J* = 4.9, 5.9, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH), 3.10 (1H, dd, *J* = 13.8, 4.9 Hz, CH_2CH), 2.33 (3H, s, CH_3), 2.32 (3H, s, CH_3) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.5, 156.4 (q, $^2J_{CF}$ = 37.4 Hz), 144.4, 137.6, 134.4, 131.5, 130.2, 129.8, 129.4 (2 x CH), 128.4 (2 x CH), 127.2, 126.5, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 55.1, 38.3, 20.0, 19.6 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1356.

(*R*)-*N*-(1-(3,4-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-D-Phe-Ph(3,4-Me), D-8). Colorless needles; $[\alpha]_D$ –16 (*c* 1.0, MeOH). IR (neat) ν : 3329, 3031, 2946, 2925, 1735, 1687 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.71 (2H, d, *J* = 6.9 Hz, Ar-H), 7.45 (1H, br d, *J* = 5.9 Hz, N*H*), 7.28–7.19 (4H, m, Ar-H), 6.93 (2H, d, *J* = 7.8 Hz, Ar-H), 5.79 (1H, ddd, *J* = 4.9, 5.9, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH), 3.10 (1H, dd, *J* = 13.8, 4.9 Hz, CH_2CH), 2.34 (3H, s,

C*H*$_3$), 2.32 (3H, s, C*H*$_3$) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 195.5, 156.4 (q, $^2J_{CF}$ =37.2 Hz), 144.4, 137.6, 134.4, 131.5, 130.2, 129.8, 129.4 (2 x CH), 128.4 (2 x CH), 127.3, 126.5, 115.7 (q, $^1J_{CF}$ = 288.3 Hz), 55.1, 38.3, 20.0, 19.7 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1362.

(*S*)-*N*-(1-(2,4-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-Phe-Ph(2,4-Me), L-9). Colorless needles; $[\alpha]_D$ +11 (*c* 1.0, MeOH). IR (neat) ν : 3301, 3090, 3032, 2931, 1706, 1675 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.69 (1H, d, *J* = 8.6 Hz, Ar-H), 7.48 (1H, br d, *J* = 5.4 Hz, N*H*), 7.21–7.18 (3H, m, Ar-H), 7.15–7.11 (2H, m, Ar-H), 6.87–6.83 (2H, m, Ar-H), 5.74 (1H, ddd, *J* = 5.4, 5.4, 5.4 Hz, C*H*NH), 3.32 (1H, dd, *J* = 14.0, 5.4 Hz, C*H*$_2$CH), 3.04 (1H, dd, *J* = 14.0, 5.4 Hz, C*H*$_2$CH), 2.40 (6H, s, 2 x C*H*$_3$) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 197.3, 156.5 (q, $^2J_{CF}$ = 37.8 Hz), 144.0, 140.9, 134.4, 133.7, 130.5, 129.6, 129.3 (2 x CH), 128.5 (2 x CH), 127.3, 126.8, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 56.3, 37.8, 21.6, 21.5 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1375.

(*R*)-*N*-(1-(2,4-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-D-Phe-Ph(2,4-Me), D-9). Colorless needles; $[\alpha]_D$ –11 (*c* 1.0, MeOH). IR (neat) ν : 3302, 3091, 3019, 2931, 1708, 1676 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.69 (1H, d, *J* = 8.9 Hz, Ar-H), 7.45 (1H, br d, *J* = 5.4 Hz, N*H*), 7.21–7.19 (3H, m, Ar-H), 7.16–7.12 (2H, m, Ar-H), 6.86–6.83 (2H, m, Ar-H), 5.74 (1H, ddd, *J* = 5.4, 5.4, 5.4 Hz, C*H*NH), 3.32 (1H, dd, *J* = 14.2, 5.4 Hz, C*H*$_2$CH), 3.05 (1H, dd, *J* = 14.2, 5.4 Hz, C*H*$_2$CH), 2.40 (6H, s, 2 x CH_3) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 197.3, 156.5 (q, $^2J_{CF}$ = 37.6 Hz), 144.0, 140.9, 134.4, 133.7, 130.5, 129.6, 129.3 (2 x CH), 128.5 (2 x CH), 127.3, 126.8, 115.7 (q, $^1J_{CF}$ = 287.3 Hz), 56.3, 37.8, 21.5, 21.5 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1371.

(*S*)-*N*-(1-(2,5-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-Phe-Ph(2,5-Me), L-10). Colorless needles; $[\alpha]_D$ +10 (*c* 1.0, MeOH). IR (neat) ν : 3303, 3033, 2927, 1708, 1679 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.45–7.38 (2H, m, Ar-H), 7.17–7.05 (4H, m, Ar-H), 6.80–6.74 (2H, m, Ar-H), 5.63 (1H, ddd, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.16 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*$_2$CH), 2.93 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*$_2$CH), 2.25 (3H, s, C*H*$_3$), 2.23 (3H, s, C*H*$_3$) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 198.2, 156.5 (q, $^2J_{CF}$ = 37.6 Hz), 137.1, 135.7, 134.5, 133.6, 133.3, 132.5, 129.7, 129.2 (2 x CH), 128.4 (2 x CH), 127.2, 115.7 (q, $^1J_{CF}$ = 287.0 Hz), 56.6, 37.6, 20.7, 20.7 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1366.

(*R*)-*N*-(1-(2,5-Dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (TFA-D-Phe-Ph(2,5-Me), D-10). Colorless needles; $[\alpha]_D$ –10 (*c* 1.0, MeOH). IR (neat) ν : 3325, 3031, 2928, 1726, 1685 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.45–7.38 (2H, m, Ar-H), 7.16–7.05 (4H, m, Ar-H), 6.79–6.74 (2H, m, Ar-H), 5.63 (1H, ddd, *J* = 5.8, 5.8, 5.8 Hz, C*H*NH), 3.16 (1H, dd, *J* = 14.2, 5.8 Hz, C*H*$_2$CH), 2.93

(1H, dd, J = 14.2, 5.8 Hz, CH_2CH), 2.25 (3H, s, CH_3), 2.23 (3H, s, CH_3) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 198.2, 156.5 (q, $^2J_{CF}$ = 37.2 Hz), 137.1, 135.6, 134.5, 133.6, 133.3, 132.4, 129.6, 129.2 (2 x CH), 128.4 (2 x CH), 127.2, 115.7 (q, $^1J_{CF}$ = 286.8 Hz), 56.6, 37.6, 20.7, 20.7 ppm. HRMS-ESI (*m*/*z*) $[M+H]^+$ calcd for $C_{19}H_{19}F_3NO_2$ 350.1368, found 350.1373.

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-3-phenyl-1-(1*H*-pyrrol-2-yl)propan-2-yl)acetamide (TFA-L-Phe-(2-Pyr), L-11).[6] Colorless amorphous mass; $[\alpha]_D$ +40 (*c* 1.0, $CHCl_3$). Lit.[6] $[\alpha]_D$ +44.3 (*c* 1.6, $CHCl_3$). IR (neat) ν : 3308, 1701, 1654 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.49 (1H, br s, N*H*), 7.24–7.20 (3H, m, Ar-H), 7.13-7.11 (1H, m, Ar-H), 7.03–6.95 (3H, m, Ar-H & C*H*), 6.34 (1H, dd, *J* = 6.4, 2.5 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH), 3.17 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 184.8, 156.4 (q, $^2J_{CF}$ = 37.4 Hz), 134.7, 129.4 (2 x CH), 129.0, 128.5 (2 x CH), 127.4, 126.6, 118.3, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 111.8, 55.3, 39.8 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{13}F_3N_2O_2Na$ 333.0821, found 333.0824.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-3-phenyl-1-(1*H*-pyrrol-2-yl)propan-2-yl)acetamide (TFA-D-Phe-(2-Pyr), D-11). Colorless amorphous mass; $[\alpha]_D$ –40 (*c* 1.0, $CHCl_3$). IR (neat) ν : 3309, 1701, 1655 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.50 (1H, br s, N*H*), 7.24–7.20 (3H, m, Ar-H), 7.13–7.10 (1H, m Ar-H), 7.02–6.98 (3H, m, Ar-H & C*H*), 6.34 (1H, dd, *J* = 6.4, 2.5 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH), 3.17 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 184.8, 156.4 (q, $^2J_{CF}$ = 38.0 Hz), 134.7, 129.4 (2 x CH), 129.0, 128.5 (2 x CH), 127.4, 126.6, 118.3, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 111.8, 55.2, 39.8 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{15}H_{13}F_3N_2O_2Na$ 333.0821, found 333.0821.

(*S*)-2,2,2-Trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-(2-(*N*-Me)Pyr), L-12). Yellowish amorphous mass; $[\alpha]_D$ +53 (*c* 1.0, $CHCl_3$); Lit.[6] $[\alpha]_D$ +43.6 (*c* 1.6, $CHCl_3$). IR (neat) ν : 3289, 3123, 3088, 1724 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.36 (1H, br s, N*H*), 7.26–7.20 (4H, m, Ar-H), 7.04–6.99 (2H, m, Ar-H & C*H*), 6.62 (2H, d, *J* = 2.0 Hz, C*H*), 5.32 (1H, dd, *J* = 13.8, 6.3 Hz, C*H*NH), 3.67 (3H, s, CH_3), 3.31 (1H, dd, *J* = 13.8, 6.3 Hz, CH_2CH), 3.15 (1H, dd, *J* = 13.8, 6.3 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 189.8, 156.4 (q, $^2J_{CF}$ = 37.4 Hz), 135.1, 129.5 (2 x CH), 128.3 (2 x CH), 128.0, 127.1, 124.1, 122.3, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 109.8, 56.2, 39.2, 36.7 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{16}H_{15}F_3N_2O_2Na$ 347.0978, found 347.0975.

(*R*)-2,2,2-Trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-(2-(*N*-Me)Pyr), D-12). Yellowish amorphous mass; $[\alpha]_D$ –53 (*c* 1.0, $CHCl_3$). IR (neat) ν : 3264, 3123, 3088, 1725 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.37 (1H, br s, N*H*), 7.26–7.20 (4H, m, Ar-H), 7.03–6.99 (2H, m, Ar-H & C*H*), 6.62 (2H, d, *J* = 2.0 Hz, C*H*), 5.33 (1H, dd, *J* = 13.8, 6.4 Hz, C*H*NH), 3.67 (3H, s, CH_3), 3.31 (2H, dd, *J* = 13.8, 6.4 Hz, CH_2CH), 3.15 (1H, dd, *J* = 13.8, 6.4 Hz, CH_2CH) ppm.

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 189.8, 156.4 (q, $^2J_{CF}$ = 37.6 Hz), 135.1, 129.5 (2 x CH), 128.3 (2 x CH), 128.0, 127.1, 124.1, 122.3, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 109.8, 56.2, 39.2, 36.7 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{16}H_{15}F_3N_2O_2Na$ 347.0978, found 347.0976.

(*S*)-2,2,2-Trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-3-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-(3-(*N*-Me)Pyr), L-13). Yellowish amorphous mass; $[\alpha]_D$ +48 (*c* 1.0, $CHCl_3$). IR (neat) ν : 3307, 1704, 1654 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.25–7.21 (3H, m, Ar-H), 7.03 (1H, d, *J* = 4.3 Hz, Ar-H), 7.00–6.96 (2H, m, Ar-H & C*H*), 6.93 (1H, s, C*H*), 6.20 (1H, dd, *J* = 4.3, 2.3 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.6 Hz, C*H*NH), 3.90 (3H, s, CH_3), 3.34 (1H, dd, *J* = 13.8, 5.6 Hz, CH_2CH), 3.13 (1H, dd, *J* = 13.8, 5.6 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 185.0, 156.3 (q, $^2J_{CF}$ = 37.1 Hz), 135.0, 133.0, 129.4 (2 x CH), 128.4 (2 x CH), 127.8, 127.3, 120.9, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 109.2, 55.4, 40.0, 37.6 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{16}H_{15}F_3N_2O_2Na$ 347.0978, found 347.0979.

(*R*)-2,2,2-Trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-3-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-(3-(*N*-Me)Pyr), D-13). Yellowish amorphous mass; $[\alpha]_D$ –48 (*c* 1.0, $CHCl_3$). IR (neat) ν : 3302, 1703, 1649 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.25–7.22 (3H, m, Ar-H), 7.03 (1H, d, *J* = 4.0 Hz, Ar-H), 7.00–6.96 (2H, m, Ar-H & C*H*), 6.93 (1H, s, C*H*), 6.20 (1H, dd, *J* = 4.3, 2.3 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.6 Hz, C*H*NH), 3.90 (3H, s, CH_3), 3.34 (1H, dd, *J* = 13.8, 5.6 Hz, CH_2CH), 3.13 (1H, dd, *J* = 13.8, 5.6 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 185.0, 156.3 (q, $^2J_{CF}$ = 37.4 Hz), 135.0, 133.0, 129.4 (2 x CH), 128.4 (2 x CH), 127.8, 127.3, 120.9, 115.7 (q, $^1J_{CF}$ = 287.7 Hz), 109.2, 55.4, 40.0, 37.6 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{16}H_{15}F_3N_2O_2Na$ 347.0978, found 347.0980.

(*S*)-2,2,2-Trifluoro-*N*-(3-(4-hydroxyphenyl)-1-oxo-1-phenylpropan-2-yl)acetamide (TFA-L-Tyr-Ph, L-17). Colorless amorphous mass. $[\alpha]_D$ +45 (*c* 1.0, MeOH). IR (neat) ν : 3464, 3311, 1713, 1682 cm^{-1}. ^{1}H-NMR (270 MHz, ACETONE-D_6) δ: 8.65 (1H, br d, *J* = 7.3 Hz, N*H*), 8.25 (1H, s, O*H*), 8.07 (2H, d, *J* = 7.4 Hz, Ar-H), 7.67 (1H, t, *J* = 7.4 Hz, Ar-H), 7.56 (2H, t, *J* = 7.4 Hz, Ar-H), 7.11 (2H, d, *J* = 8.2 Hz, Ar-H), 6.76 (2H, d, *J* = 8.2 Hz, Ar-H), 5.77 (1H, ddd, *J* = 8.9, 7.3, 5.2 Hz, C*H*NH), 3.26 (1H, dd, *J* = 14.2, 5.2 Hz, CH_2CH), 3.00 (1H, dd, *J* = 14.2, 8.9 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, ACETONE-D_6) δ: 197.4, 157.2, 157.2 (q, $^2J_{CF}$ = 36.9 Hz), 135.8, 134.6, 131.2 (2 x CH), 129.7 (2 x CH), 129.3 (2 x CH), 127.8, 116.9 (q, $^1J_{CF}$ = 287.7 Hz), 116.1 (2 x CH), 57.0, 36.9 ppm. HRMS-ESI (*m*/*z*) $[M+Na]^+$ calcd for $C_{17}H_{14}F_3NO_3Na$ 360.0818, found 360.0820.

(*R*)-2,2,2-Trifluoro-*N*-(3-(4-hydroxyphenyl)-1-oxo-1-phenylpropan-2-yl)acetamide (TFA-D-Tyr-Ph, D-17). Colorless amorphous mass. $[\alpha]_D$ –45 (*c* 1.0, MeOH). IR (neat) ν : 3464, 3309, 1710, 1677 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.64 (1H, br d, *J* = 7.6 Hz, N*H*), 8.24 (1H, s, O*H*), 8.07 (2H, d, *J* = 7.4 Hz, Ar-H), 7.67 (1H, t, *J* = 7.4 Hz, Ar-H), 7.56 (2H, t, *J* = 7.4 Hz, Ar-H), 7.11 (2H, d, *J* = 8.6 Hz, Ar-H), 6.76 (2H, d, *J* = 8.6 Hz, Ar-H), 5.77 (1H, ddd, *J* = 8.6, 7.6, 5.1 Hz, C*H*NH), 3.26 (1H, dd, *J* = 14.3, 5.1

Hz, CH_2CH), 3.00 (1H, dd, J = 14.3, 8.6 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 197.4, 157.2, 157.2 (q, $^2J_{CF}$ = 37.4 Hz), 135.8, 134.6, 131.2 (2 x CH), 129.7 (2 x CH), 129.4 (2 x CH), 127.8, 116.9 (q, $^1J_{CF}$ = 287.2 Hz), 116.1 (2 x CH), 57.0, 36.9 ppm. HRMS-ESI (m/z) $[M+Na]^+$ calcd for $C_{17}H_{14}F_3NO_3Na$ 360.0818, found 360.0814.

2,2,2-Trifluoro-*N*-(2-(4-hydroxyphenyl)-1-phenylethyl)acetamide (18). Yellowish amorphous mass. IR (neat) ν : 3329, 1693 cm^{-1}. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 8.82 (1H, br d, J = 8.6 Hz, NH), 8.18 (1H, s, OH), 7.44 (2H, d, J = 7.9 Hz, Ar-H), 7.38–7.24 (3H, m, Ar-H), 7.09 (2H, d, J = 8.6 Hz, Ar-H), 6.74 (2H, d, J = 8.6 Hz, Ar-H), 5.24 (1H, ddd, J = 8.6, 8.6, 6.9 Hz, CHNH), 3.15 (1H, d, J = 8.6 Hz, CH_2CH), 3.12 (1H, d, J = 6.9 Hz, CH_2CH) ppm. ^{13}C-NMR (67.5 MHz, acetone-d_6) δ: 156.9, 156.8 (q, $^2J_{CF}$ = 36.3 Hz), 142.3, 131.0 (2 x CH), 129.4 (2 x CH), 129.3 (2 x CH), 128.3, 127.7, 117.1 (q, $^1J_{CF}$ = 288.3 Hz), 115.9 (2 x CH), 56.8, 41.5 ppm.

(*S*)-1-(2-Benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethanone (TFA-L-Pro-Ph, L-22).[1,8,17] Colorless needles. $[\alpha]_D$ –81 (c 1.0, $CHCl_3$). IR (neat) ν : 3361, 3136, 1776, 1711, 1695 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 7.9 Hz, Ar-H), 7.62 (1H, t, J = 7.9 Hz, Ar-H), 7.50 (2H, t, J = 7.9 Hz, Ar-H), 5.57 (1H, dd, J = 9.2, 4.0 Hz, CH_2CH), 3.99–3.77 (2H, m, CH_2), 2.42–2.29 (2H, m, CH_2), 2.18–1.98 (2H, m, CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: [195.6 & 195.3], 155.5 (q, $^2J_{CF}$ = 37.4 Hz), [134.4 & 134.0], [133.7 & 133.3], 129.0, 128.8, 128.5, 128.4, 116.3 (q, $^1J_{CF}$ = 287.2 Hz), [62.6 & 62.1], [48.3 & 47.3], [31.3 & 28.5], [24.8 & 20.8] ppm (*cis*- and *trans*- mix). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_2$ 272.0898, found 272.0898.

(*R*)-1-(2-Benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethanone (TFA-D-Pro-Ph, D-22). Colorless needles. $[\alpha]_D$ +81 (c 1.0, $CHCl_3$). IR (neat) ν : 3362, 3135, 1773, 1711, 1696 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 7.6 Hz, Ar-H), 7.62 (1H, t, J = 7.6 Hz, Ar-H), 7.50 (2H, t, J = 7.6 Hz, Ar-H), 5.58 (1H, dd, J = 9.1, 3.8 Hz, CH_2CH), 4.00–3.77 (2H, m, CH_2), 2.41–2.30 (1H, m, CH_2), 2.15–1.97 (2H, m, CH_2) ppm. ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: [195.6 & 195.3], 155.5 (q, $^2J_{CF}$ = 37.4 Hz), [134.4 & 134.0], [133.7 & 133.3], 129.0, 128.8, 128.5, 128.4, 116.3 (q, $^1J_{CF}$ = 287.2 Hz), [62.6 & 62.1], [48.3 & 47.4], [31.2 & 28.5], [24.7 & 20.8] ppm (*cis*- and *trans*- mix). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_2$ 272.0898, found 272.0916.

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