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Sequential [3,3]-Sigmatropic Rearrangement/Nucleophilic Arylation of *N*-(Benzoyloxy)enamides towards the Preparation of Cyclic β-Aryl-β-amino Alcohols

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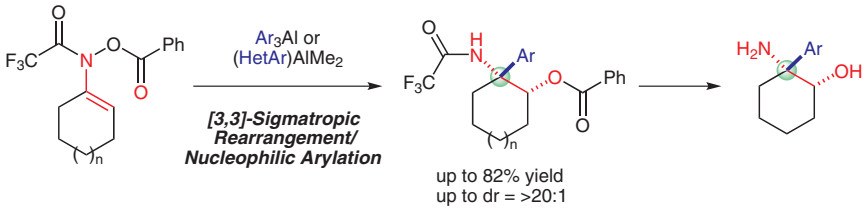

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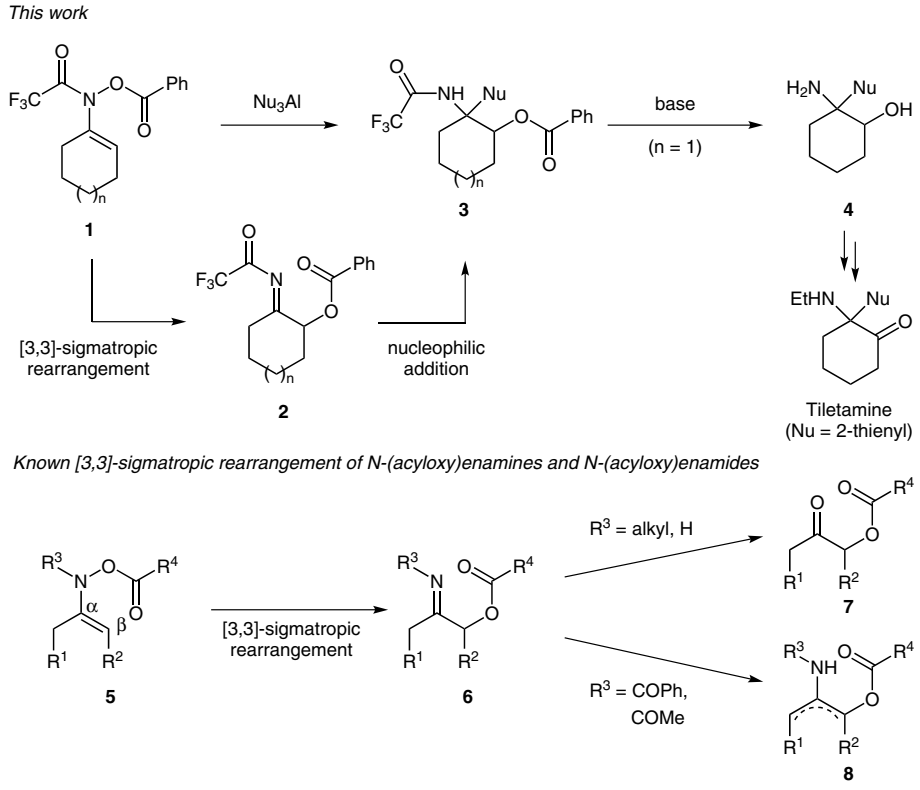
Abstract A new method has been developed for the efficient synthesis of cyclic β-aryl-β-amino alcohol derivatives bearing a tetrasubstituted carbon center via the [3,3]-sigmatropic rearrangement of *N*-(benzoyloxy)enamides followed by nucleophilic arylation reaction with a range of triarylaluminum reagents. The resulting products were converted into the corresponding sterically congested cyclic β-amino alcohols, as well as the dissociative anesthetic agent Tiletamine.

Key words β-amino alcohols, enamides, sigmatropic rearrangement, imines, nucleophilic addition, organoaluminum reagents

β-Amino alcohols are an important group of building blocks that have been used extensively for the preparation of a wide range of complex molecules, including natural products and biologically active compounds.[1] Although a variety of different methods have been developed for the preparation of β-amino alcohols, the synthetic methodologies for β-aryl-β-amino alcohols bearing a tetrasubstituted carbon center are relatively scarce. Therefore, the development of novel and useful methods for their synthesis is desirable because compounds bearing this structural motif are key intermediates in the synthesis of several biologically active molecules, including the opioid drug fedotozine[2] and a β-secretase (BACE) inhibitor.[3] Among the few methods published in this area, the addition of aryl or alkyl metal reagents (RLi, RMgBr) to *N*-sulfinyl alkyl- or arylketimines carrying α-alkoxy and α-silyloxy substituents is a powerful method for the construction of tetrasubstituted carbon centers bearing a nitrogen-based substituent.[3a,4] Furthermore, Feng and co-workers recently reported the rhodium-catalyzed addition of arylboronates to cyclic *N*-sulfamidate alkylketimine as an efficient method for the preparation of β-aryl-β-amino alcohols bearing a tetrasubstituted carbon center.[5] However, in most cases, these synthetic methods are only suitable for acyclic β-amino alcohols containing a tetrasubstituted carbon center bearing a nitrogen,[3a,4–7] with the synthesis of the corresponding cyclic β-amino alcohols remaining a significant challenge. Herein, we report a new process for the sequential [3,3]-sigmatropic rearrangement/nucleophilic addition of *N*-(benzoyloxy)enamides **1** as a strategy for the synthesis of β-aryl-β-amino alcohol derivatives **3** bearing a tetrasubstituted carbon center (Scheme 1, top). Notably, this new process provides facile access to a series of sterically congested β-amino alcohols **4**, as well as the dissociative anesthetic agent Tiletamine.

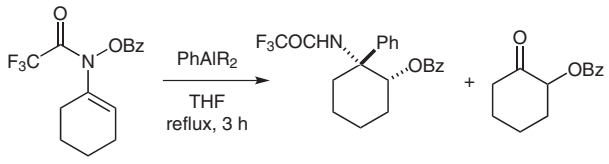
The synthesis of β-amino alcohols from enamines or enamides requires the introduction of an oxygenated functional group at the β-position.[8,9] The [3,3]-sigmatropic rearrangement of *N*-(acyloxy)enamines is a reliable method for the β-oxygenation of enamine derivatives (Scheme 1, bottom).[10] However, the carbon–carbon bond-forming reactions of the imines **6** (R^3 = H, alkyl) produced by the rearrangement of suitably functionalized enamines **5** (R^3 = H, alkyl) have not been studied in detail. Furthermore, these imines **6** are mainly used to provide the corresponding carbonyl compounds **7** (e.g., ketones).[11] During the [3,3]-sigmatropic rearrangement of *N*-(acyloxy)enamide **5** (R^3 = COPh, COMe) for the β-oxygenation of the enamide moiety, the resulting *N*-acylketimine **6** (R^3 = COPh, COMe) can undergo a tautomerization process to give the stable enamide **8**.[12] However, to the best of our knowledge, there are no reports of intermolecular nucleophilic addition to the resulting *N*-acylketimine **6** after rearrangement of enamide **5**. With this in mind, it was envisioned that the addition of a suitable nucleophile to the tautomerizable *N*-(trifluoroacetyl)ketimine **2** would provide to access the β-aryl-β-amino alcohol derivatives **3** bearing a tetrasubstituted carbon center.[13]



Scheme 1 [3,3]-Sigmatropic rearrangement of *N*-(acyloxy)enamines and *N*-(acyloxy)enamides

We initially examined the reaction of *N*-(benzoyloxy)enamide **1a**, which was prepared from cyclohexanone oxime via a two-step sequence, with various organoaluminum reagents (Table 1). To accomplish the desired sequential reaction process for the synthesis of the sterically congested cyclic β-amino alcohol derivatives, we initially confirmed the [3,3]-sigmatropic rearrangement of *N*-(benzoyloxy)enamide **1a**, which is the first step in the proposed reaction process. Heating a solution of *N*-(benzoyloxy)enamide **1a** in refluxing tetrahydrofuran for three hours gave α-benzoyloxy ketone **10** in 88% yield (entry 1). Encouraged by this result, we proceeded to investigate the sequential [3,3]-sigmatropic rearrangement/phenylation reaction of **1a** in the presence of an organoaluminum reagent. The reaction of **1a** with triphenylaluminum in refluxing tetrahydrofuran proceeded smoothly to give the β-phenyl-β-amino alcohol derivatives **9aA** as a separable 9.5:1 mixture of *cis*/*trans* isomers in a combined yield of 74% (entry 2). The relative configuration of *cis*-**9aA** and *trans*-**9aA** were determined by NMR analysis. Dimethyl(phenyl)aluminum and diethyl(phenyl)aluminum also worked well in this reaction to give the desired product **9aA** in 67 and 65% yields, respectively, albeit with lower diastereoselectivities than triphenylaluminum (entries 3 and 4).[14] In contrast, the use of phenyllithium, phenylmagnesium bromide, or phenylzinc iodide instead of an aluminum reagent afforded a complex mixture of products, and **9aA** was not detected (not shown). These results, therefore, demonstrate that organoaluminum reagents are the optimal nucleophiles for this reaction.

Table 1 Optimization of the Sequential Reaction Using an Aluminum Reagent[a]

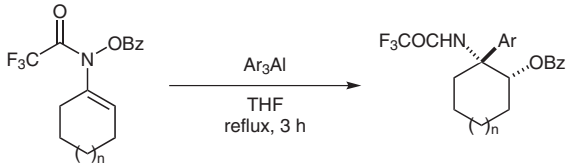


1a **9aA** **10**

Entry	Aluminum reagent	Product	Yield[b] (%)	Ratio[c] *cis*/*trans*
1	none	**10**	88	–
2	Ph_3Al , R = Ph	**9aA**	74	9.5:1
3	$PhAlMe_2$, R = Me	**9aA**	67	4.5:1
4	$PhAlEt_2$, R = Et	**9aA**	65	7.5:1

[a] General conditions: *N*-(benzoyloxy)enamide **1a** (0.20 mmol), $PhAlR_2$ (0.40 mmol), THF, reflux, 3 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.

Table 2 Sequential Reaction of Several *N*-(Benzoyloxy)enamides with Triarylaluminum Reagents[a]



1a: n = 1
1b: n = 2
1c: n = 0

9

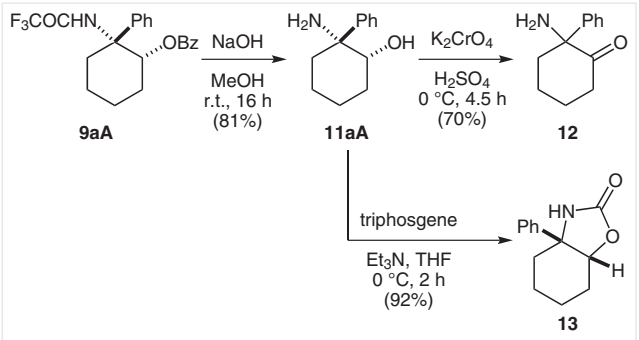
Entry	Substrate	Aluminum reagent	Product	Yield[b] (%)	Ratio[c] *cis*/*trans*
1	**1a**	$(4\text{-MeOC}_6\text{H}_4)_3\text{Al}$	**9aB**: Ar = $4\text{-MeOC}_6\text{H}_4$	69	17.5:1
2	**1a**	$(4\text{-MeC}_6\text{H}_4)_3\text{Al}$	**9aC**: Ar = $4\text{-MeC}_6\text{H}_4$	54	10.5:1
3	**1a**	$(4\text{-FC}_6\text{H}_4)_3\text{Al}$	**9aD**: Ar = $4\text{-FC}_6\text{H}_4$	13	>20:1
4	**1a**	$(2\text{-MeOC}_6\text{H}_4)_3\text{Al}$	**9aE**: Ar = $2\text{-MeOC}_6\text{H}_4$	70	10.5:1
5	**1a**	$[3,4\text{-(MeO)}_2\text{C}_6\text{H}_3]_3\text{Al}$	**9aF**: Ar = $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$	51	>20:1
6	**1b**	Ph_3Al	**9bA**: Ar = Ph	50	2:1
7	**1c**	Ph_3Al	**9cA**: Ar = Ph	41	>20:1

[a] General conditions: *N*-(benzoyloxy)enamide **1** (0.20 mmol), Ar_3Al (0.40 mmol), THF, reflux, 3 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.

With the optimal conditions in hand for the sequential reaction, we proceeded to examine the scope of the reaction with a range of different triarylaluminum reagents (Table 2).[15] The results show that triarylaluminum reagents containing an electron-donating group such as tris(4-methoxyphenyl)aluminum and tris(4-methylphenyl)aluminum perform well under the optimized reaction conditions to give the desired products **9aB** and **9aC** in moderate to good yields with high diastereoselectivities (entries 1 and 2). However, a triarylaluminum reagent containing a halogen atom [e.g., $(4\text{-FC}_6\text{H}_4)_3\text{Al}$] performed poorly giving the desired product **9aD** in only 13% yield (entry 3). Notably, triarylaluminum reagents bearing a methoxy group at the *ortho* position of their phenyl ring [e.g., $(2\text{-MeOC}_6\text{H}_4)_3\text{Al}$] or two methoxy groups on their phenyl ring [e.g., $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3)_3\text{Al}$] also performed well to give the corresponding products **9aE** and **9aF** in moderate to good yields with high diastereoselectivities (entries 4 and 5). We subsequently explored the substrate scope of this reaction using triphenylaluminum.

To evaluate the effect of the ring size of cyclic *N*-(benzoyloxy)enamides, enamide **1b** with a seven-membered ring and **1c** with a five-membered ring were subjected to the optimized reaction conditions. Interestingly, the sequential reaction of **1b** produced the desired product **9bA** with low diastereoselectivity, while the reaction of **1c** afforded *cis*-**9cA** as a single diastereomer (entries 6 and 7).

To demonstrate the utility of **9aA**, we investigated its conversion into a variety of other interesting compounds (Scheme 2). For example, the treatment of **9aA** with sodium hydroxide in methanol allowed the simultaneous removal of its trifluoroacetyl and benzoyl groups to afford the β-amino alcohol **11aA** in 81% yield. Notably, the oxidation of **11aA** with potassium chromate in sulfuric acid provided 2-amino-2-phenylcyclohexanone (**12**), which is the basic pharmacophore of the dissociative anesthetic drug ketamine.[16,17] Moreover, the cyclization of *cis*-amino alcohol **11aA** with triphosgene furnished the sterically congested oxazolidinone **13** in high yield.

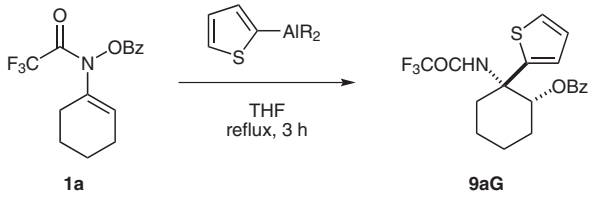


Scheme 2 Various transformations of **9aA**

Nucleophilic heteroarylation is an important reaction in synthetic chemistry because heteroaromatic units can be found in a wide range of important biologically active compounds and functional materials.[18] With this in mind, we examined the synthesis of β-heteroaryl-β-amino alcohol derivatives via the sequential [3,3]-sigmatropic rearrangement/nucleophilic heteroarylation of *N*-(benzoyloxy)enamide **1a** (Table 3). The introduction of a 2-thienyl group was initially investigated as a model heteroarylation reaction

because several thiophene-containing medicines, including Duloxetine,[18c,19] Tiotropium,[20] Clopidogrel,[18c,21] Prasugrel,[22] and Rivaroxaban,[18c,23] are already widely used in a wide range of clinical applications. Our initial studies of the nucleophilic heteroarylation of the *N*-(trifluoroacetyl)ketimine intermediate unexpectedly showed that the reaction of *N*-(benzoyloxy)enamide **1a** with tri-2-thienylaluminum under the optimized conditions developed for the sequential rearrangement/nucleophilic phenylation of **1a** in Table 1 yielded the desired product **9aG** in low yield (entry 1). Pleasingly, however, when the sequential reaction was conducted with dimethyl(2-thienyl)aluminum instead of tri-2-thienylaluminum, the yield of the desired product **9aG** dramatically increased (entry 2). Similarly, the use of diethyl(2-thienyl)aluminum afforded **9aG** in moderate yield (entry 3). These results, therefore, demonstrate that dimethyl(2-thienyl)aluminum is superior to tri-2-thienylaluminum for the sequential rearrangement/2-thienylation of **1a** with regards to both the yield of the product and atom economy of the reaction.

Table 3 Optimization for Sequential Rearrangement/2-Thienylation Reaction[a]

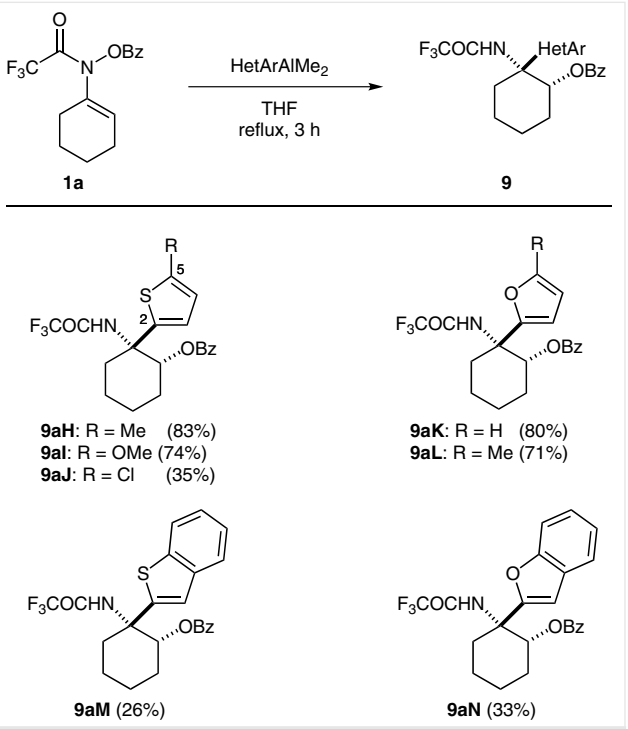


1a **9aG**

Entry	Aluminum reagent	Yield[b] (%)	Ratio[c] *cis*/*trans*
1	$(2\text{-thienyl})_3Al$ R = 2-thienyl	7	>20:1
2	$(2\text{-thienyl})AlMe_2$ R = Me	71	>20:1
3	$(2\text{-thienyl})AlEt_2$ R = Et	62	>20:1

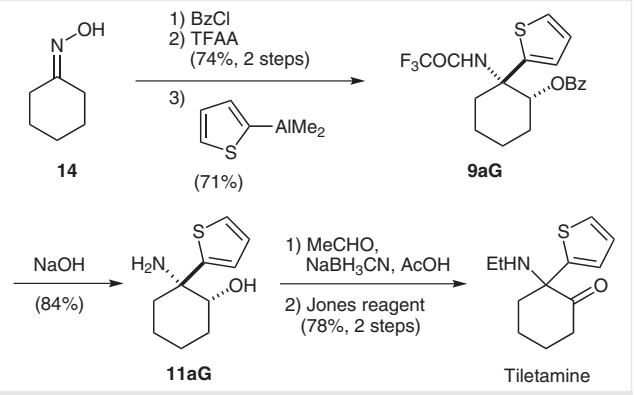
[a] General conditions: *N*-(benzoyloxy)enamide **1a** (0.20 mmol), (2-thienyl)AlR_2 (0.40 mmol), THF, reflux, 3 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.

Encouraged by this result, we proceeded to evaluate the scope of this reaction by investigating the introduction of a variety of different heteroaryl groups into the *N*-(trifluoroacetyl)ketimine intermediate (Scheme 3). For the dimethyl(5-substituted 2-thienyl)aluminum reagents, which were derived from the corresponding 5-substituted thiophenes containing a methyl, methoxy, or chloro group, the reactions proceeded at the 2-position of the thiophene to afford the desired products **9aH** and **9aI** in good yields, whilst **9aJ** was obtained in a much lower yield. Similarly, the reactions of **1a** with dimethyl(2-furyl)aluminum and dimethyl(5-methyl-2-furyl)aluminum proceeded smoothly to give the corresponding α-furylated products **9aK** and **9aL** in good yields. To further explore the scope of this transformation, we also examined the introduction of heteroaryl groups fused to a benzene ring, such as benzothiophene and benzofuran. However, desired products **9aM** and **9aN** were obtained in unsatisfactory yields.



Scheme 3 Introduction of various heteroaryl groups using $HetArAlMe_2$. *Reagents and conditions*: *N*-(benzoyloxy)enamide **1a** (0.20 mmol), $HetArAlMe_2$ (0.40 mmol), THF, reflux, 3 h; isolated yields are given. Diastereomeric ratios were determined by ^1H NMR analysis. Ratio *cis*/*trans* >20:1 in all cases except **9aM** *cis*/*trans* 13.5:1 and **9aN** *cis*/*trans* 5.5:1.

To demonstrate the synthetic value of this developed sequential rearrangement/heteroarylation reaction, we developed an efficient process for the synthesis of the dissociative anesthetic agent Tiletamine (Scheme 4), which is also classified as an NMDA receptor antagonist.[24] The deprotection of **9aG** with sodium hydroxide in methanol afforded β-(2-thienyl)-β-amino alcohol **11aG** in good yield. Subsequent *N*-ethylation of **11aG** under reductive amination conditions, followed by Jones oxidation of the resulting alcohol, provided Tiletamine in an overall yield of 35% over six steps from commercially available cyclohexanone oxime (**14**). The ^1H NMR spectrum of the synthetic Tiletamine hydrochloride salt[25] was found to be identical to that of the commercially available Tiletamine hydrochloride provided by Toronto Research Chemicals Inc.



Scheme 4 Synthesis of Tiletamine

In conclusion, we have successfully developed an alternative synthetic method for the construction of cyclic β-aryl-β-amino alcohols containing a tetrasubstituted carbon center bearing a nitrogen via the sequential [3,3]-sigmatropic rearrangement/nucleophilic arylation of *N*-(benzoyloxy)enamides. The sequential reaction of *N*-(benzoyloxy)enamides proceeds with high diastereoselectivity to give sterically congested *cis*-β-aryl-β-amino alcohol derivatives in moderate to good yields. The extension of this methodology to other systems, as well as the synthesis of biologically active compounds, is currently underway in our laboratory.

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Silicycle silica gel (SiliaFlash® F60, 40–63 μm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60 F_{254}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, or a Varian VNS AS 500 MHz operating at 300 MHz/75 MHz or 500 MHz/125 MHz for ^{1}H and ^{13}C acquisitions, respectively, with the solvent resonance or TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer SpectrumOne A spectrophotometer. HRMS were obtained by ESI method on Thermo Fisher Scientific Exactive Instrument. Melting points (uncorrected) were determined on Büchi M-565 apparatus. The following reagents were purchased: Ph_3Al (1.0 M in Bu_2O; Aldrich), ArMgBr (Aldrich), Me_2AlCl (1.0 M in hexane; Aldrich), and BuLi (2.6 M in hexane; Kanto).

N-(Benzoyloxy)enamides 1; General Procedure

To a solution of corresponding oxime (20 mmol) in *n*-hexane–CH_2Cl_2 (66 mL, 10:1) was added pyridine (1.62 mL, 20 mmol) and benzoyl chloride (2.32 mL, 20 mmol) dropwise at r.t. The mixture was stirred at r.t. for 4 h, and then it was diluted with H_2O (40 mL). The organic layer was washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to afford corresponding *O*-benzoyloxime ether. The *O*-benzoyloxime ether was used to next reaction without further purification. To the solution of *O*-benzoyloxime ether in CH_2Cl_2 (30 mL) was added TFAA (13.8 mL, 100 mmol) dropwise at 0 °C. The mixture was stirred at r.t. overnight, and then it was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 50:1) to give *N*-(benzoyloxy)enamide **1**.

N-(Benzoyloxy)-*N*-(cyclohex-1-enyl)-2,2,2-trifluoroacetamide (1a)

Prepared according to the general procedure using cyclohexanone oxime (2.26 g, 20 mmol) to give **1a** as a white solid; yield: 4.6 g (74%, 2 steps); mp 34–36 °C.

IR ($CHCl_3$): 1776, 1721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (2.5:1 mixture of rotamers) = 8.08 (d, *J* = 7.5 Hz, 2 H), 7.66 (tm, *J* = 7.0 Hz, 1 H), 7.51 (tm, *J* = 7.5 Hz, 2 H), 6.36 (br m, 5/7 H), 6.21 (br m, 2/7 H), 2.37–2.21 (m, 4 H), 1.79–1.71 (m, 2 H), 1.66–1.58 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (2.5:1 mixture of rotamers) = 163.4, 162.7, 152.4 (q, *J* = 36.0 Hz), 136.0, 135.2, 134.7, 134.4, 133.6, 130.1, 129.8, 128.8, 127.8, 126.4, 126.0, 116.1 (q, *J* = 286.0 Hz), 115.9 (q, *J* = 286.0 Hz), 26.4, 25.3, 25.0, 24.4, 22.1, 21.1, 21.0, 20.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_3F_3$: 314.0999; found: 314.0998.

N-(Benzoyloxy)-*N*-(cyclohept-1-enyl)-2,2,2-trifluoroacetamide (1b)

Prepared according to the general procedure using cycloheptanone oxime[26] (2.54 g, 20 mmol) to give **1b** as a pale yellow oil; yield: 2.2 g (33%, 3 steps).

IR (neat): 1776, 1722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (1.5:1 mixture of rotamers) = 8.07 (d, *J* = 8.0 Hz, 2 H), 7.66 (tm, *J* = 7.0 Hz, 1 H), 7.51 (tm, *J* = 7.0 Hz, 2 H), 6.46 (br m, 3/5 H), 6.33 (br m, 2/5 H), 2.50 (br m, 2 H), 2.24 (br m, 2 H), 1.79–1.61 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (1.5:1 mixture of rotamers) = 163.4, 162.6, 152.6 (q, *J* = 36.0 Hz), 141.7, 139.6, 139.3, 134.7, 134.4, 133.2, 130.1, 129.8, 128.9, 128.8, 126.5, 126.1, 116.1 (q, *J* = 286.5 Hz), 115.8 (q, *J* = 286.5 Hz), 31.6, 31.2, 30.6, 27.0, 26.1, 25.7, 25.6, 25.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}NO_3F_3$: 328.1155; found: 328.1153.

N-(Benzoyloxy)-*N*-(cyclopent-1-enyl)-2,2,2-trifluoroacetamide (1c)

Prepared according to the general procedure using cyclopentanone oxime[26] (1.98 g, 20 mmol) to give **1c** as a pale yellow oil; yield: 2.3 g (39%, 2 steps).

IR (neat): 1782, 1724 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (4.5:1 mixture of rotamers) = 8.10 (dm, *J* = 8.5 Hz, 2 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.54 (t, *J* = 7.5 Hz, 2 H), 6.22 (br m, 2/11 H), 5.84 (br m, 9/11 H), 2.77 (br m, 2 H), 2.48–2.43 (m, 2 H), 1.99 (quint, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (4.5:1 mixture of rotamers) = 163.3, 153.3 (q, *J* = 36.0 Hz), 138.3, 135.0, 130.2, 129.0, 125.4, 118.6, 115.7 (q, *J* = 286.5 Hz), 31.7, 30.4, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}NO_3F_3$: 300.0842; found: 300.0846.

Sequential [3,3]-Sigmatropic Rearrangement/Nucleophilic Phenylation; General Procedure A (GPA)

To a solution of *N*-(benzoyloxy)enamide **1a** (63 mg, 0.20 mmol) in THF (3.0 mL) was added Ph_3Al (1.0 M in Bu_2O, 0.40 mL, 0.40 mmol) dropwise at r.t. under an argon atmosphere. The mixture was stirred at reflux for 3 h, and then it was quenched with 1.3 M aq Rochelle's salt (10 mL) at r.t. The resulting suspension was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane–EtOAc, 5:1) to give *cis*-**9aA** (52 mg, 67%) and *trans*-**9aA** (6 mg, 7%).

(1*R,2*R**)-2-Phenyl-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (*cis*-9aA)**

White crystals; mp 114–116 °C (hexane–EtOAc).

IR ($CHCl_3$): 3427, 1736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.81 (dm, *J* = 8.5 Hz, 2 H), 7.55 (tm, *J* = 7.5 Hz, 1 H), 7.41 (tm, *J* = 7.5 Hz, 2 H), 7.34 (dm, *J* = 8.5 Hz, 2 H), 7.28 (tm, *J* = 7.5 Hz, 2 H), 7.20 (tm, *J* = 7.5 Hz, 1 H), 6.91 (br s, 1 H), 5.38 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.13 (dm, *J* = 14.5 Hz, 1 H), 2.16 (ddm, *J* = 13.5, 4.5 Hz, 1 H), 2.08 (td, *J* = 14.5, 3.5 Hz, 1 H), 1.95–1.90 (m, 1 H), 1.79–1.71 (m, 2 H), 1.66–1.57 (m, 1 H), 1.52–1.43 (m, 1 H); NOE was observed between 1-H (δ = 5.38) and 3-H_{ax} (δ = 2.08) in NOESY spectroscopy.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8, 156.3 (q, *J* = 36.0 Hz), 140.3, 133.4, 129.4, 129.3, 128.7, 128.6, 127.8, 125.2, 115.9 (q, *J* = 288.5 Hz), 77.4, 63.8, 32.9, 28.0, 23.6, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}NO_3F_3Na$: 414.1288; found: 414.1289.

(1*R,2*S**)-2-Phenyl-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (*trans*-9aA)**

White crystals; mp 113–116 °C (hexane–EtOAc).

IR ($CHCl_3$): 3427, 1736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (dm, *J* = 8.5 Hz, 2 H), 7.55–7.49 (m, 3 H), 7.39 (tm, *J* = 8.5 Hz, 2 H), 7.28 (tm, *J* = 7.5 Hz, 2 H), 7.20 (tm, *J* = 7.5 Hz, 1 H), 6.81 (br s, 1 H), 5.70 (dd, *J* = 5.5, 3.0 Hz, 1 H), 2.69 (tm, *J* = 5.5 Hz, 2 H), 2.08–2.02 (m, 1 H), 1.94–1.87 (m, 1 H), 1.86–1.80 (m, 1 H), 1.76–1.60 (m, 3 H); NOE was observed between NH (δ = 6.81) and 6-H_{ax} (δ = 1.94–1.87) in NOESY spectroscopy.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5, 155.5 (q, *J* = 36.0 Hz), 140.6, 133.3, 129.6, 129.5, 128.41, 128.38, 127.8, 126.4, 115.5 (q, *J* = 288.5 Hz), 73.9, 61.3, 29.3, 27.2, 21.3, 20.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}NO_3F_3Na$: 414.1288; found: 414.1289.

Preparation of Triarylaluminum (0.20 M solution);[27] General Procedure

To a solution of $AlCl_3$ (200 mg, 1.5 mmol) in THF (3.0 mL) was added corresponding ArMgBr in THF solution (4.5 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at r.t. for 3 h, and then it was used directly in the following reaction.

Sequential [3,3]-Sigmatropic Rearrangement/Nucleophilic Arylation; General Procedure B (GPB)

To a solution of *N*-(benzoyloxy)enamide **1a** (0.20 mmol) in THF (3.0 mL) was added triarylaluminum (0.20 M in THF, 2.0 mL, 0.40 mmol) dropwise at r.t. under an argon atmosphere. The mixture was stirred at reflux for 3 h, and then it was quenched with 1.3 M aq Rochelle's salt (10 mL) at r.t. The resulting suspension was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane–EtOAc, 5:1) to give β-aryl-β-amino alcohol derivatives as shown in Table 2.

(1*R,2*R**)-2-(4-Methoxyphenyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aB)**

Prepared by GPB; triarylaluminum was prepared from 4-methoxyphenylmagnesium bromide (0.50 M in THF). After purification, **9aB** (58 mg, 69%, *cis*/*trans* 17.5:1) was obtained as a pale yellow oil. Further isolation gave the single diastereomer reported here.

IR (neat): 3430, 1725 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dm, *J* = 8.5 Hz, 2 H), 7.56 (tm, *J* = 7.5 Hz, 1 H), 7.42 (tm, *J* = 8.5 Hz, 2 H), 7.27 (dm, *J* = 7.5 Hz, 2 H), 6.91 (br s, 1 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 5.35 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.72 (s, 3 H), 3.08 (dm, *J* = 15.0 Hz, 1 H), 2.15–2.02 (m, 2 H), 1.93–1.89 (m, 1 H), 1.80–1.40 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 158.8, 156.1 (q, *J* = 36.0 Hz), 133.3, 132.2, 129.31, 129.27, 128.5, 126.4, 115.7 (q, *J* = 288.5 Hz), 113.9, 77.2, 63.1, 55.0, 32.7, 27.9, 23.4, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NO_4F_3Na$: 444.1393; found: 444.1390.

(1*R,2*R**)-2-(4-Methylphenyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aC)**

Prepared by GPB; triarylaluminum was prepared from *p*-tolylmagnesium bromide (1.0 M in THF). After purification, **9aC** (47 mg, 54%, *cis*/*trans* 10.5:1) was obtained as white crystals. Further isolation gave the single diastereomer reported here; mp 118–122 °C (hexane–EtOAc).

IR ($CHCl_3$): 3428, 1736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (dm, *J* = 8.5 Hz, 2 H), 7.56 (tm, *J* = 7.5 Hz, 1 H), 7.42 (tm, *J* = 8.5 Hz, 2 H), 7.22 (dm, *J* = 8.0 Hz, 2 H), 7.08 (dm, *J* = 8.0 Hz, 2 H), 6.90 (br s, 1 H), 5.37 (dd, *J* = 11.0, 4.5 Hz, 1 H), 3.10 (dm, *J* = 14.5 Hz, 1 H), 2.25 (s, 3 H), 2.16–2.12 (m, 1 H), 2.10–2.04 (m, 1 H), 1.94–1.89 (m, 1 H), 1.78–1.70 (m, 2 H), 1.64–1.55 (m, 1 H), 1.51–1.42 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8, 156.2 (q, *J* = 36.0 Hz), 137.4, 137.3, 133.4, 129.5, 129.41, 129.36, 128.6, 125.1, 115.9 (q, *J* = 288.5 Hz), 77.3, 63.6, 32.9, 28.0, 23.5, 21.2, 20.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NO_3F_3Na$: 428.1444; found: 428.1445.

(1*R,2*R**)-2-(4-Fluorophenyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aD)**

Prepared by GPB; triarylaluminum was prepared from 4-fluorophenylmagnesium bromide (1.0 M in THF). After purification, **9aD** (11 mg, 13%) was obtained as a colorless oil.

IR ($CHCl_3$): 3428, 1736 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (dm, *J* = 8.5 Hz, 2 H), 7.58 (tm, *J* = 7.5 Hz, 1 H), 7.43 (tm, *J* = 7.5 Hz, 2 H), 7.34–7.28 (m, 2 H), 6.97 (tm, *J* = 8.5 Hz, 2 H), 6.91 (br s, 1 H), 5.34 (dd, *J* = 10.5, 4.5 Hz, 1 H), 2.17–1.91 (m, 4 H), 1.81–1.40 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 162.0 (d, *J* = 245.5 Hz), 156.2 (q, *J* = 36.0 Hz), 136.1, 133.5, 129.3, 129.2, 128.6, 127.1 (d, *J* = 8.0 Hz), 115.8 (q, *J* = 288.0 Hz), 115.6 (d, *J* = 21.5 Hz), 77.2, 63.3, 32.8, 28.0, 23.5, 21.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{19}NO_3F_4Na$: 432.1193; found: 432.1193.

(1*R,2*R**)-2-(2-Methoxyphenyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aE)**

Prepared by GPB; triarylaluminum was prepared from 2-methoxyphenylmagnesium bromide (1.0 M in THF). After purification, **9aE** (59 mg, 70%, *cis*/*trans* 10.5:1) was obtained as a yellow oil. Further isolation gave the single diastereomer reported here.

IR (neat): 3429, 1728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dm, *J* = 8.5 Hz, 2 H), 7.54 (tm, *J* = 7.5 Hz, 1 H), 7.40 (tm, *J* = 7.5 Hz, 2 H), 7.27–7.19 (m, 2 H), 7.11 (br s, 1 H), 6.93–6.86 (m, 2 H), 6.09 (dd, *J* = 9.5, 4.5 Hz, 1 H), 3.84 (s, 3 H), 2.88 (dm, *J* = 14.5 Hz, 1 H), 2.80–2.70 (m, 1 H), 2.00–1.46 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 156.8, 156.1 (q, *J* = 35.5 Hz), 133.2, 129.7, 129.4, 129.3, 128.4, 127.8, 126.5, 120.7, 115.9 (q, *J* = 288.5 Hz), 112.1, 74.4, 64.0, 55.2, 29.6, 27.8, 22.7, 21.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NO_4F_3Na$: 444.1393; found: 444.1392.

(1*R,2*R**)-2-(3,4-Dimethoxyphenyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aF)**

Prepared by GPB; triarylaluminum was prepared from 3,4-dimethoxyphenylmagnesium bromide (0.50 M in THF). After purification, **9aF** (46 mg, 51%) was obtained as a pale yellow oil.

IR ($CHCl_3$): 3426, 1733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dm, *J* = 8.5 Hz, 2 H), 7.57 (tm, *J* = 7.5 Hz, 1 H), 7.43 (tm, *J* = 7.5 Hz, 2 H), 6.92 (br s, 1 H), 6.91 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.83 (d, *J* = 2.5 Hz, 1 H), 6.77 (d, *J* = 8.5 Hz, 1 H), 5.37 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.12 (dm, *J* = 14.5 Hz, 1 H), 2.17–2.08 (m, 1 H), 2.04–1.99 (m, 1 H), 1.95–1.90 (m, 1 H), 1.82–1.41 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 156.2 (q, *J* = 35.5 Hz), 148.7, 148.3, 133.5, 133.0, 129.3, 128.6, 127.6, 115.8 (q, *J* = 288.5 Hz), 111.0, 118.7, 77.1, 63.4, 55.7, 55.5, 32.9, 28.1, 23.5, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{24}NO_5F_3Na$: 474.1499; found: 474.1502.

2-Phenyl-2-(2,2,2-trifluoroacetamido)cycloheptyl Benzoate (9bA)

Prepared by GPA; *N*-(benzoyloxy)enamide **1b** (66 mg, 0.20 mmol) was used as starting material. The residue was purified by PTLC (hexane–EtOAc, 5:1) to give *cis*-**9bA** (27 mg, 33%) and *trans*-**9bA** (14 mg, 17%).

(1*R,2*R**)-2-Phenyl-2-(2,2,2-trifluoroacetamido)cycloheptyl Benzoate (*cis*-9bA)**

White crystals; mp 130–133 °C (hexane–EtOAc).

IR ($CHCl_3$): 3430, 1736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (dm, *J* = 8.5 Hz, 2 H), 7.55 (tm, *J* = 7.5 Hz, 1 H), 7.42 (tm, *J* = 7.5 Hz, 2 H), 7.30 (dm, *J* = 7.5 Hz, 2 H), 7.25 (tm, *J* = 7.5 Hz, 2 H), 7.17 (tm, *J* = 7.0 Hz, 1 H), 7.16 (br s, 1 H), 5.32 (dd, *J* = 10.0, 4.5 Hz, 1 H), 2.74–2.69 (m, 1 H), 2.59–2.53 (m, 1 H), 2.03–1.70 (m, 6 H), 1.67–1.58 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5, 156.4 (q, *J* = 36.0 Hz), 140.2, 133.4, 129.4, 129.3, 128.6, 127.6, 125.1, 116.0 (q, *J* = 288.5 Hz), 81.4, 65.8, 34.0, 30.1, 26.8, 22.9, 21.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NO_3F_3Na$: 428.1444; found: 428.1443.

(1*R,2*S**)-2-Phenyl-2-(2,2,2-trifluoroacetamido)cycloheptyl Benzoate (*trans*-9bA)**

Colorless oil.

IR ($CHCl_3$): 3427, 1732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (br s, 1 H), 7.69 (dm, *J* = 8.0 Hz, 2 H), 7.53 (tm, *J* = 7.5 Hz, 1 H), 7.36–7.23 (m, 7 H), 5.40 (dd, *J* = 9.5, 1.5 Hz, 1 H), 3.09 (dd, *J* = 15.0, 8.5 Hz, 1 H), 2.38 (dd, *J* = 15.0, 9.5 Hz, 1 H), 2.26–2.17 (m, 1 H), 1.99–1.84 (m, 3 H), 1.78–1.74 (m, 1 H), 1.70–1.51 (m, 3 H); NOE was observed between NH (δ = 7.95) and 1-H (δ = 5.40) in NOESY spectroscopy.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 155.8 (q, *J* = 36.0 Hz), 138.9, 133.4, 129.6, 129.2, 128.4, 128.3, 127.6, 126.1, 115.7 (q, *J* = 288.5 Hz), 81.0, 67.5, 33.0, 30.4, 29.2, 26.1, 22.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NO_3F_3Na$: 428.1444; found: 428.1444.

(1*R,2*R**)-2-Phenyl-2-(2,2,2-trifluoroacetamido)cyclopentyl Benzoate (9cA)**

Prepared by GPA; *N*-(benzoyloxy)enamide **1c** (60 mg, 0.20 mmol) was used as starting material. The residue was purified by PTLC (hexane–EtOAc, 5:1) to give *cis*-**9cA** (31 mg, 41%) as a colorless oil.

IR ($CHCl_3$): 3429, 1730 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (dm, *J* = 8.5 Hz, 2 H), 7.63 (tm, *J* = 7.5 Hz, 1 H), 7.55 (br s, 1 H), 7.50 (tm, *J* = 7.0 Hz, 2 H), 7.47–7.44 (m, 2 H), 7.36 (tm, *J* = 7.5 Hz, 2 H), 7.29 (tm, *J* = 7.5 Hz, 1 H), 5.51 (dd, *J* = 7.0, 5.5 Hz, 1 H), 2.76 (t, *J* = 7.5 Hz, 2 H), 2.28–2.22 (m, 1 H), 2.12–2.02 (m, 1 H), 1.97–1.84 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 156.1 (q, *J* = 36.0 Hz), 140.1, 133.8, 129.6, 129.3, 128.84, 128.77, 128.1, 125.7, 115.7 (q, *J* = 288.5 Hz), 82.5, 67.8, 32.9, 28.9, 20.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}NO_3F_3Na$: 400.1131; found: 400.1130.

(1*R,2*R**)-2-Amino-2-phenylcyclohexanol (11aA)**

β-Phenyl-β-amino alcohol derivatives *cis*-**9aA** (39 mg, 0.10 mmol) was stirred in 5% NaOH in MeOH solution (2.0 mL) at r.t. The mixture was stirred at r.t. for 16 h, and then it was concentrated. The residue was dissolved in $CHCl_3$ (15 mL) and washed with H_2O (2 × 10 mL) and brine (10 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by PTLC (hexane–EtOAc, 2:1) to give β-amino alcohol **11aA** (15 mg, 81%) as white crystals; mp 115–116 °C (hexane–EtOAc).

IR (KBr): 3187 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dm, *J* = 8.5 Hz, 2 H), 7.37 (tm, *J* = 7.0 Hz, 2 H), 7.28–7.22 (m, 1 H), 3.94 (dd, *J* = 10.0, 4.0 Hz, 1 H), 1.98 (br s, 3 H), 1.85–1.71 (m, 4 H), 1.68–1.51 (m, 3 H), 1.48–1.32 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 128.5, 126.7, 125.6, 74.2, 58.2, 38.2, 29.4, 23.8, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO$: 192.1383; found: 192.1384.

2-Amino-2-phenylcyclohexanone (12)[28]

To a solution of β-amino alcohol **11aA** (57 mg, 0.30 mmol) in 30% aq H_2SO_4 (6.0 mL) was added K_2CrO_4 (117 mg, 0.60 mmol) at 0 °C. The mixture was stirred at r.t. for 4.5 h, then it was filtered through a pad of Celite (Et_2O, 20 mL) and solvent was removed under reduced pressure. The residue was basified with 2.0 M NaOH and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$–MeOH, 10:1) to give α-amino ketone **12** (15 mg, 70%) as a colorless oil.

IR ($CHCl_3$): 3375, 3297, 1712 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.25 (m, 5 H), 2.92–2.86 (m, 1 H), 2.50–2.34 (m, 2 H), 2.14 (br s, 2 H), 2.02–1.95 (m, 1 H), 1.82–1.60 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.5, 141.7, 129.2, 127.7, 126.1, 66.5, 39.8, 39.3, 28.2, 22.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO$: 190.1226; found: 190.1224.

(3a*R,7a*R**)-3a-Phenylhexahydrobenzoxazol-2(3*H*)-one (13)**[29]

To a solution of β-amino alcohol **11aA** (38 mg, 0.20 mmol) in THF (5.0 mL) was added triphosgene (59 mg, 0.20 mmol) and Et_3N (0.07 mL, 0.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, then it was diluted with EtOAc (15 mL). The organic layer was washed with 1.0 M HCl (15 mL), 1.0 M NaOH (15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$–MeOH, 20:1) to give oxazolidin-2-one **13** (40 mg, 92%) as a colorless oil.

IR ($CHCl_3$): 3440, 1748 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.27 (m, 5 H), 6.64 (br s, 1 H), 4.68 (t, *J* = 4.0 Hz, 1 H), 2.25–2.17 (m, 1 H), 2.10–2.03 (m, 1 H), 1.92–1.54 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 143.3, 128.7, 127.7, 125.3, 82.2, 61.9, 34.8, 25.7, 19.5, 17.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}NO_2Na$: 240.0995; found: 240.0995.

Dimethyl(heteroaryl)aluminum (0.30 M solution);[30] General Procedure

To a solution of heteroarene (1.5 mmol) in THF (3.0 mL) was added BuLi (2.6 M in hexane, 0.60 mL, 1.5 mmol) dropwise at –78 °C under an argon atmosphere. The mixture was stirred at 0 °C for 30 min, and then Me_2AlCl (1.0 M in hexane, 1.5 mL, 1.5 mmol) was added to the mixture. The resulting mixture was stirred at r.t. for 30 min and was used directly in the following reaction.

Sequential [3,3]-Sigmatropic Rearrangement/Nucleophilic Heteroarylation; General Procedure C (GPC)

To a solution of *N*-(benzoyloxy)enamide **1a** (63 mg, 0.20 mmol) in THF (3.0 mL) was added dimethyl(heteroaryl)aluminum (0.30 M in THF, 1.3 mL, 0.40 mmol) dropwise at r.t. under an argon atmosphere. The mixture was stirred at reflux for 3 h, and then it was quenched with 1.3 M aq Rochelle's salt (10 mL) at r.t. The resulting suspension was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane–EtOAc, 5:1) to give β-heteroaryl-β-amino alcohol derivatives as shown in Table 3 and Scheme 3.

(1*R,2*S**)-2-(2-Thienyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aG)**

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from thiophene. After purification, **9aG** (56 mg, 71%) was obtained as white crystals; mp 94–97 °C (hexane–EtOAc).

IR ($CHCl_3$): 3427, 1736 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dm, *J* = 8.5 Hz, 2 H), 7.59 (tm, *J* = 7.5 Hz, 1 H), 7.44 (tm, *J* = 7.0 Hz, 2 H), 7.13 (dd, *J* = 5.0, 1.5 Hz, 1 H), 7.04 (br s, 1 H), 6.99 (dd, *J* = 3.5, 1.5 Hz, 1 H), 6.86 (dd, *J* = 5.0, 3.5 Hz, 1 H), 5.29 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.28 (dm, *J* = 14.5 Hz, 1 H), 2.16–2.04 (m, 2 H), 1.89–1.67 (m, 3 H), 1.62–1.39 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 155.9 (q, *J* = 36.0 Hz), 145.1, 133.4, 129.4, 129.2, 128.5, 126.6, 124.7, 124.4, 115.5 (q, *J* = 288.0 Hz), 77.6, 61.2, 33.4, 27.8, 23.0, 20.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}NO_3F_3SNa$: 420.0852; found: 420.0852.

(1*R,2*S**)-2-(5-Methyl-2-thienyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aH)**

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from 2-methylthiophene. After purification, **9aH** (68 mg, 83%) was obtained as white crystals; mp 90–93 °C (hexane–EtOAc).

IR ($CHCl_3$): 3427, 1737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dm, *J* = 8.5 Hz, 2 H), 7.60 (tm, *J* = 7.0 Hz, 1 H), 7.47 (tm, *J* = 8.0 Hz, 2 H), 6.95 (br s, 1 H), 6.77 (d, *J* = 3.5 Hz, 1 H), 6.52 (dm, *J* = 3.5 Hz, 1 H), 5.27 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.24 (dm, *J* = 14.5 Hz, 1 H), 2.35 (s, 3 H), 2.17–2.01 (m, 2 H), 1.89–1.85 (m, 1 H), 1.78–1.39 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 156.0 (q, *J* = 36.0 Hz), 142.4, 139.2, 133.4, 129.5, 129.4, 128.6, 124.8, 124.3, 115.6 (q, *J* = 288.0 Hz), 77.6, 61.2, 33.4, 27.9, 23.0, 21.0, 15.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}NO_3F_3SNa$: 434.1008; found: 434.1009.

(1*R,2*S**)-2-(5-Methoxy-2-thienyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aI)**

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from 2-methoxythiophene. After purification, **9aI** (63 mg, 74%) was obtained as a colorless oil.

IR ($CHCl_3$): 3427, 1735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (dm, *J* = 8.5 Hz, 2 H), 7.60 (tm, *J* = 7.5 Hz, 1 H), 7.48 (tm, *J* = 7.5 Hz, 2 H), 6.89 (br s, 1 H), 6.62 (dm, *J* = 4.0 Hz, 1 H), 5.95 (d, *J* = 4.0 Hz, 1 H), 5.24 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.77 (s, 3 H), 3.20 (dm, *J* = 14.5 Hz, 1 H), 2.16–2.09 (m, 1 H), 2.08–1.97 (m, 1 H), 1.89–1.84 (m, 1 H), 1.77–1.39 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 164.8, 155.9 (q, *J* = 36.0 Hz), 133.5, 130.2, 129.5, 129.4, 128.6, 122.2, 115.6 (q, *J* = 288.0 Hz), 102.8, 77.4, 61.0, 59.9, 32.8, 27.9, 23.0, 21.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}NO_4F_3SNa$: 450.0957; found: 450.0959.

(1*R,2*S**)-2-(5-Chloro-2-thienyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aJ)**

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from 2-chlorothiophene. After purification, **9aJ** (30 mg, 35%) was obtained as a colorless oil.

IR ($CHCl_3$): 3427, 1736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dm, *J* = 8.5 Hz, 2 H), 7.62 (tm, *J* = 7.5 Hz, 1 H), 7.49 (tm, *J* = 7.5 Hz, 2 H), 6.93 (br s, 1 H), 6.77 (d, *J* = 4.0 Hz, 1 H), 6.70 (d, *J* = 4.0 Hz, 1 H), 5.23 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.26 (dm, *J* = 14.5 Hz, 1 H), 2.19–2.14 (m, 1 H), 2.04–1.87 (m, 2 H), 1.79–1.38 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 156.1 (q, *J* = 36.5 Hz), 143.5, 133.7, 129.5, 129.2, 128.7, 125.8, 124.0, 115.5 (q, *J* = 288.0 Hz), 77.4, 61.1, 33.1, 27.9, 23.1, 20.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{17}NO_3F_3SClNa$: 454.0462; found: 454.0462.

(1*R**,2*S**)-2-(2-Furyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aK)

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from furan. After purification, **9aK** (61 mg, 80%) was obtained as a yellow oil.

IR ($CHCl_3$): 3428, 1736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dm, *J* = 8.5 Hz, 2 H), 7.60 (tm, *J* = 7.5 Hz, 1 H), 7.47 (tm, *J* = 7.5 Hz, 2 H), 7.28 (dd, *J* = 2.0, 1.0 Hz, 1 H), 6.90 (br s, 1 H), 6.29–6.25 (m, 2 H), 5.47 (dd, *J* = 9.5, 4.0 Hz, 1 H), 2.96 (dm, *J* = 14.5 Hz, 1 H), 2.29–2.20 (m, 1 H), 2.04–1.96 (m, 1 H), 1.90–1.46 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 156.2 (q, *J* = 36.0 Hz), 152.5, 142.1, 133.5, 129.5, 128.6, 115.6 (q, *J* = 288.0 Hz), 110.4, 107.4, 75.1, 59.6, 30.3, 27.5, 22.5, 20.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}NO_4F_3Na$: 404.1080; found: 404.1080.

(1*R**,2*S**)-2-(5-Methyl-2-furyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aL)

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from 2-methylfuran. After purification, **9aL** (56 mg, 71%) was obtained as white crystals; mp 90–93 °C (hexane–EtOAc).

IR ($CHCl_3$): 3428, 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dm, *J* = 8.5 Hz, 2 H), 7.60 (tm, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 2 H), 6.88 (br s, 1 H), 6.14 (d, *J* = 3.5 Hz, 1 H), 5.85 (dm, *J* = 3.5 Hz, 1 H), 5.42 (dd, *J* = 9.5, 4.0 Hz, 1 H), 2.93 (dm, *J* = 14.5 Hz, 1 H), 2.27–2.18 (m, 1 H), 2.10 (s, 3 H), 2.02–1.96 (m, 1 H), 1.88–1.68 (m, 3 H), 1.60–1.45 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 156.0 (q, *J* = 36.0 Hz), 142.4, 139.2, 133.4, 129.5, 129.4, 128.6, 124.8, 124.3, 115.6 (q, *J* = 288.0 Hz), 77.6, 61.2, 33.4, 27.9, 23.0, 21.0, 15.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}NO_4F_3Na$: 418.1237; found: 418.1235.

(1*R**,2*S**)-2-(2-Benzo[*b*]thienyl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aM)

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from benzothiophene. After purification, **9aM** (23 mg, 26%, *cis*/*trans* 13.5:1) was obtained as a colorless oil. Further isolation gave the single diastereomer reported here.

IR (neat): 3427, 1728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dm, *J* = 8.5 Hz, 2 H), 7.72–7.64 (m, 2 H), 7.59 (tm, *J* = 7.5 Hz, 1 H), 7.46 (tm, *J* = 7.5 Hz, 2 H), 7.32–7.22 (m, 4 H), 7.05 (br s, 1 H), 5.40 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.35 (dm, *J* = 14.0 Hz, 1 H), 2.22–2.14 (m, 2 H), 1.93–1.90 (m, 1 H), 1.83–1.45 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 156.2 (q, *J* = 36.0 Hz), 145.7, 139.1, 138.9, 135.5, 129.6, 129.3, 128.6, 124.5, 124.4, 123.7, 122.1, 121.4, 115.6 (q, *J* = 288.0 Hz), 77.2, 61.6, 33.5, 28.0, 23.1, 21.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}NO_3F_3SNa$: 470.1008; found: 470.1008.

(1*R**,2*S**)-2-(Benzo[*b*]furan-2-yl)-2-(2,2,2-trifluoroacetamido)cyclohexyl Benzoate (9aN)

Prepared by GPC; dimethyl(heteroaryl)aluminum was prepared from benzofuran. After purification, **9aN** (29 mg, 33%, *cis*/*trans* 5.5:1) was obtained as white crystals. Further isolation gave the single diastereomer reported here; mp 114–119 °C (hexane–EtOAc).

IR ($CHCl_3$): 3427, 1738 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dm, *J* = 8.5 Hz, 2 H), 7.60 (tm, *J* = 7.5 Hz, 1 H), 7.50–7.43 (m, 3 H), 7.33–7.30 (m, 1 H), 7.25–7.14 (m, 2 H), 7.02 (br s, 1 H), 6.67 (d, *J* = 1.0 Hz, 1 H), 5.61 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.05 (dm, *J* = 14.5 Hz, 1 H), 2.42–2.32 (m, 1 H), 2.10–2.04 (m, 1 H), 1.93–1.75 (m, 3 H), 1.68–1.54 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 156.3 (q, *J* = 36.0 Hz), 155.1, 154.6, 133.5, 129.5, 129.4, 128.6, 127.7, 124.4, 122.9, 121.2, 115.5 (q, *J* = 288.0 Hz), 111.2, 104.5, 74.9, 60.0, 30.3, 27.6, 22.5, 20.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}NO_4F_3Na$: 454.1237; found: 454.1235.

(1*R**,2*S**)-2-Amino-2-(2-thienyl)cyclohexanol (11aG)

β-(2-Thienyl)-β-amino alcohol derivative *cis*-**9aG** (40 mg, 0.10 mmol) was stirred in 5% NaOH in MeOH solution (2.0 mL) at r.t. The mixture was stirred at r.t. for 16 h and then it was concentrated. The residue was dissolved in $CHCl_3$ (15 mL) and washed with H_2O (3 × 10 mL) and brine (10 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by PTLC (EtOAc) to give β-amino alcohol **11aG** (16 mg, 84%) as a white solid.

IR ($CHCl_3$): 3392 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (dm, *J* = 5.0 Hz, 1 H), 7.02–6.98 (m, 2 H), 3.88 (dd, *J* = 9.5, 4.0 Hz, 1 H), 2.33 (br s, 3 H), 2.00–1.92 (m, 1 H), 1.86–1.73 (m, 2 H), 1.70–1.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 127.0, 124.0, 122.5, 75.0, 57.8, 38.8, 29.0, 23.1, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}NOS$: 198.0947; found: 198.0948.

2-(Ethylamino)-2-(2-thienyl)cyclohexanone (Tiletamine)

To a solution of β-amino alcohol **11aG** (53 mg, 0.27 mmol) in MeOH (5.0 mL) was added acetaldehyde (0.018 mL, 0.32 mmol), AcOH (0.016 mL, 0.27 mmol), and $NaBH_3CN$ (26 mg, 0.41 mmol) successively at 0 °C. The mixture was stirred at r.t. for 1.5 h, and then sat. aq Na_2CO_3 (10 mL) was added. The mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated in vacuo to afford (1*R**,2*S**)-2-(ethylamino)-2-(2-thienyl)cyclohexanol. This structure was confirmed by ^{1}H NMR; ethyl proton signals were observed at δ = 2.44–2.33 (m, 2 H) and 1.07 (t, *J* = 7.0 Hz, 3 H). The above amino alcohol was used in the subsequent reaction without further purification. To the solution of amino alcohol (84 mg) in acetone (20 mL) was slowly added Jones reagent (2.3 M, 0.064 mL, 0.15 mmol) at r.t. and the mixture stirred at r.t. for 30 min. After completion of the reaction, the mixture was filtered through a pad of Celite (Et_2O, 10 mL) and solvent was removed under reduced pressure. The residue was basified with 2.0 M aq NaOH and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried

($MgSO_4$) and concentrated in vacuo. The residue was purified by PTLC ($CHCl_3$–MeOH, 10:1) to give Tiletamine (61 mg, 78%) as a pale yellow oil.

IR (neat): 3329, 1713 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 5.0, 1.0 Hz, 1 H), 6.99 (dd, *J* = 5.0, 3.5 Hz, 1 H), 6.88 (dd, *J* = 3.5, 1.0 Hz, 1 H), 2.69 (dm, *J* = 13.0 Hz, 1 H), 2.48 (dd, *J* = 9.0, 5.5 Hz, 2 H), 2.38 (dq, *J* = 10.5, 7.0 Hz, 1 H), 2.25 (dq, *J* = 10.5, 7.0 Hz, 1 H), 2.06 (br s, 1 H), 2.03–1.84 (m, 4 H), 1.81–1.69 (m, 1 H), 1.04 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.6, 145.4, 126.9, 125.7, 125.2, 67.6, 39.0, 38.7, 36.8, 26.9, 22.3, 15.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NOS$: 224.1104; found: 224.1099.

2-(Ethylamino)-2-(2-thienyl)cyclohexanone Hydrochloride (Tiletamine Hydrochloride)

Tiletamine (15 mg, 0.065 mmol) was stirred in 1.0 M HCl in Et_2O (2.0 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, then it was concentrated under reduced pressure to give Tiletamine hydrochloride (17 mg, quant) as a white solid. The ^1H NMR spectrum of synthetic Tiletamine hydrochloride was found to be identical to that of commercially available Tiletamine hydrochloride by Toronto Research Chemicals Inc.; mp 182–185 °C (dec.).

IR ($CHCl_3$): 1725 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.97 (br s, 1 H), 9.30 (br s, 1 H), 7.84 (d, *J* = 4.5 Hz, 1 H), 7.21–7.18 (m, 2 H), 2.92 (dm, *J* = 13.0 Hz, 1 H), 2.68–2.64 (m, 1 H), 2.53–2.33 (m, 4 H), 1.98–1.94 (m, 1 H), 1.18 (dm, *J* = 13.0 Hz, 1 H), 1.73–1.57 (m, 2 H), 1.15 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 204.1, 134.2, 130.5, 129.8, 128.1, 68.2, 38.5, 37.2, 34.7, 26.2, 21.4, 11.2.

HRMS (ESI): *m*/*z* [M – HCl]$^+$ calcd for $C_{12}H_{18}NOS$: 224.1104; found: 224.1102.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561294.

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