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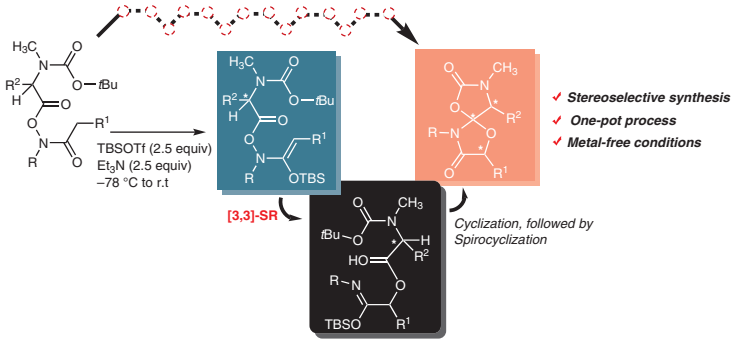
A Cascade Process of Hydroxamates Renders 1,6-Dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones

Zohreh Nazarian*
Craig M. Forsyth*

School of Chemistry, Monash University, Victoria, Melbourne, 3800, Australia
nazarianzohreh@yahoo.com.au
craig.forsyth@monash.edu



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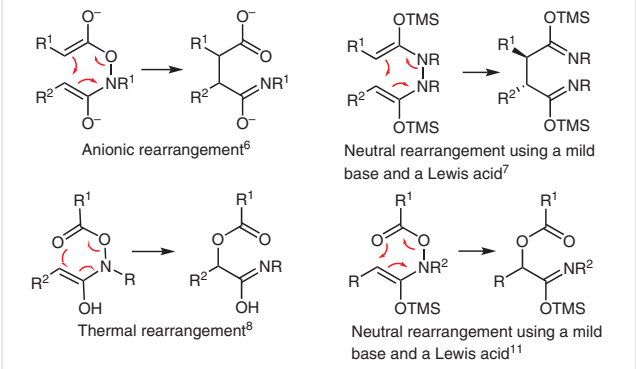
Abstract A cascade route to 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones from *N*,*O*-diacyl hydroxylamines consisting of a two-step procedure is described. The key transformation is a [3,3]-sigmatropic rearrangement of *N*,*O*-diacyl hydroxylamines promoted by formation of a silylketenaminal followed by an intramolecular cyclization and a final spirocyclization. The optimum reaction conditions employ a one-fold excess of each reagent and are utilized to prepare a range of structurally diverse examples of this class of compound.

Key words [3,3]-sigmatropic rearrangement, cascade process, *N*,*O*-diacyl hydroxylamines, 3-azaspirocyclic orthoamides, 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones



Scheme 1 Some examples of previous work on [3,3]-SRs of *N*,*O*-diacyl hydroxylamines and *N*,*N*-diacyl hydrazine

The utility of [3,3]-sigmatropic rearrangement ([3,3]-SR) in systems containing a heteroatom is reasonably well understood.[1–3] However, less well-known are [3,3]-SRs of systems comprising bis-enolates or their analogues. In fact, only a few studies have focused on this subject (Scheme 1).[4–11]

Conventional methods for enolate coupling typically use a strong base followed by metal salts such as $Cu(OAc)_2$ or $TiCl_4$. However, these harsh conditions often result in poor yields and diastereoselectivities and limit the range of substrates.[12–14] On the other hand, [3,3]-SR has emerged as a reliable approach for the coupling of enolates and C–C bond formation. Recently, the generation of α-acyloxyamides, in addition to cyclic orthoamides, via [3,3]-SR of *N*,*O*-diacyl hydroxylamines[11] has been disclosed. The reported methodology described the attempted stereoselective synthesis of α-acyloxyamides using a chiral auxiliary at the *O*-acyl moiety to be rather ineffective to build diastereoselectivity during the rearrangement.

Accordingly, in connection with this previous research, the current study was directed towards controlling the stereochemical outcome of these rearrangements, and to construct stereoselectivity during rearrangement of *N*,*O*-diacyl hydroxylamines. Although this aim was achieved, the process resulted in the serendipitous formation of 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones rather than the expected acyloxyamides or cyclic orthoamides. The first report on the synthesis of this class of compounds was published in 2016.[15]

Initially, it was sought to prepare chiral *N*,*O*-diacyl hydroxylamine substrates. Thus, *N*,*O*-diacyl hydroxylamines were readily prepared via coupling of the appropriate hydroxamic acid **2** (1.0 equiv) with the corresponding *N*-Boc-*N*-methyl amino acid **3** mediated by EDCI (1.6 equiv) in the presence of a catalytic amount of DMAP (0.1 equiv). The desired α-amino acid substituted analogs **4a–m** were obtained in modest to excellent yields (46–95%) (Table 1).

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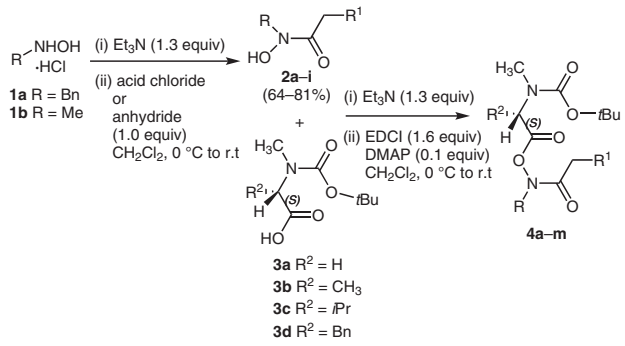
Table 1 Synthesis of *N*,*O*-Diacyl Hydroxylamines



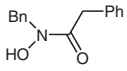
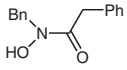
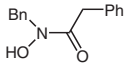
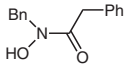
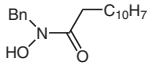
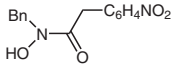
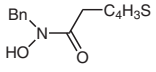
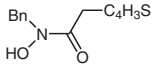
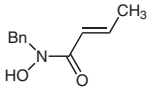
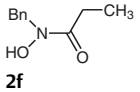
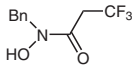
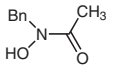
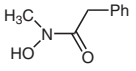
Entry	2	3	Product	Yield (%)
1	 **2a**	**3a**	**4a**	88
2	 **2a**	**3b**	**4b**	92
3	 **2a**	**3c**	**4c**	90
4	 **2a**	**3d**	**4d**	93
5	 **2b**	**3b**	**4e**	95
6	 **2c**	**3a**	**4f**	46
7	 **2d**	**3a**	**4g**	70
8	 **2d**	**3b**	**4h**	74
9	 **2e**	**3a**	**4i**	80
10	 **2f**	**3a**	**4j**	86

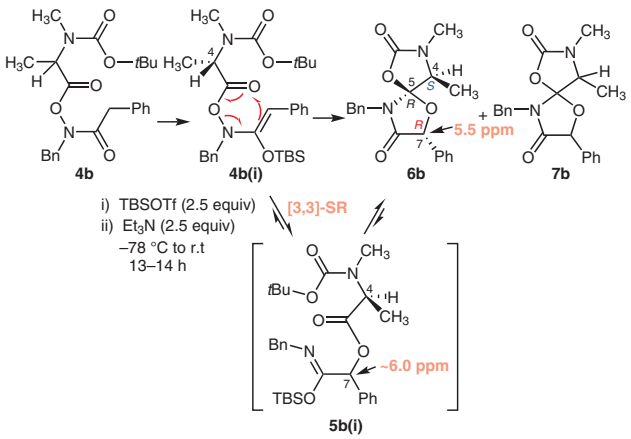
Table 1 (continued)

Entry	2	3	Product	Yield (%)
11	 **2g**	**3a**	**4k**	80
12	 **2h**	**3a**	**4l**	85
13	 **2i**	**3a**	**4m**	88

The majority of these compounds were isolated as a mixture of two rotamers, resulting from restricted rotation in *N*,*O*-diacyl hydroxylamine systems.[16] As a result, in the proton NMR spectra of these compounds a pair of signals could be assigned to a single proton. Similarly, in their carbon NMR spectra, more than one peak could be attributed to a single carbon. However, elevation of the temperature from 25 °C to 50 °C during the ^{1}H NMR and ^{13}C NMR experiments overcame restricted rotation.

With *N*,*O*-diacyl hydroxylamines **4** in hand, compound **4b** was initially exposed to the previously reported conditions for the preparation of acyloxy amides and cyclic orthoamides.[10] However, with this precursor, the reported conditions led to significant recovery of the starting material. Upon changing the Lewis acid from TMSOTf to TBSOTf, the conversion of the starting *N*,*O*-diacyl hydroxylamine increased significantly. Under the optimized conditions, **4b** was allowed to react with different ratios of the Lewis acid and base. Employing 1.0 equivalent of the reagent mainly resulted in no identifiable product, whereas using a one-fold excess of the reagent furnished a compound which did not have the expected scaffold of the rearranged product. Indeed, NMR studies revealed the serendipitous formation of a 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-dione (Scheme 2).

The appearance of a singlet at 5.53 ppm in the ^{1}H NMR spectrum of **6b** was assigned to the C*H*^{7} proton, suggesting that substrate **4b(i)** had initially undergone a [3,3]-SR[17] to form silyl iminoether **5b(i)**, followed by a cyclization and subsequent spirocyclization to generate spirocyclic compounds **6b** and **7b** (Scheme 2). The ^{1}H NMR data also matched the values previously reported for the spirocyclic compound **6b**, with further spectroscopic data (i.e., ^{13}C NMR, COSY, HSQC, HMBC and HRMS) corroborating the proposed structure. Assignment of relative stereochemistry to the product was confirmed by a crystal structure analysis of **6b**, which revealed the absolute configuration of the newly formed stereogenic centers at C5 and C7 to be *R*, in accord with a previous assignment made from X-ray crystal



Scheme 2 Formation of a spirocyclic orthoamide via silylketenaminal **4b(i)**

structure analysis of the same compound generated from the double cyclization of (*R*)-2-(benzylamino)-2-oxo-1-phenylethyl (*S*)-2-[(*tert*-butoxycarbonyl)(methyl)amino]-propanoate (Figure 1).[15]

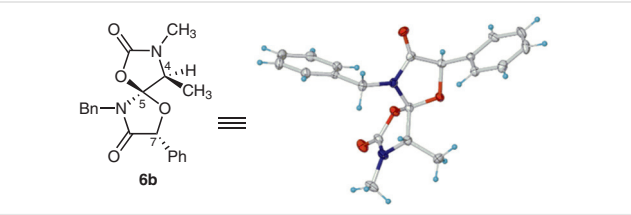


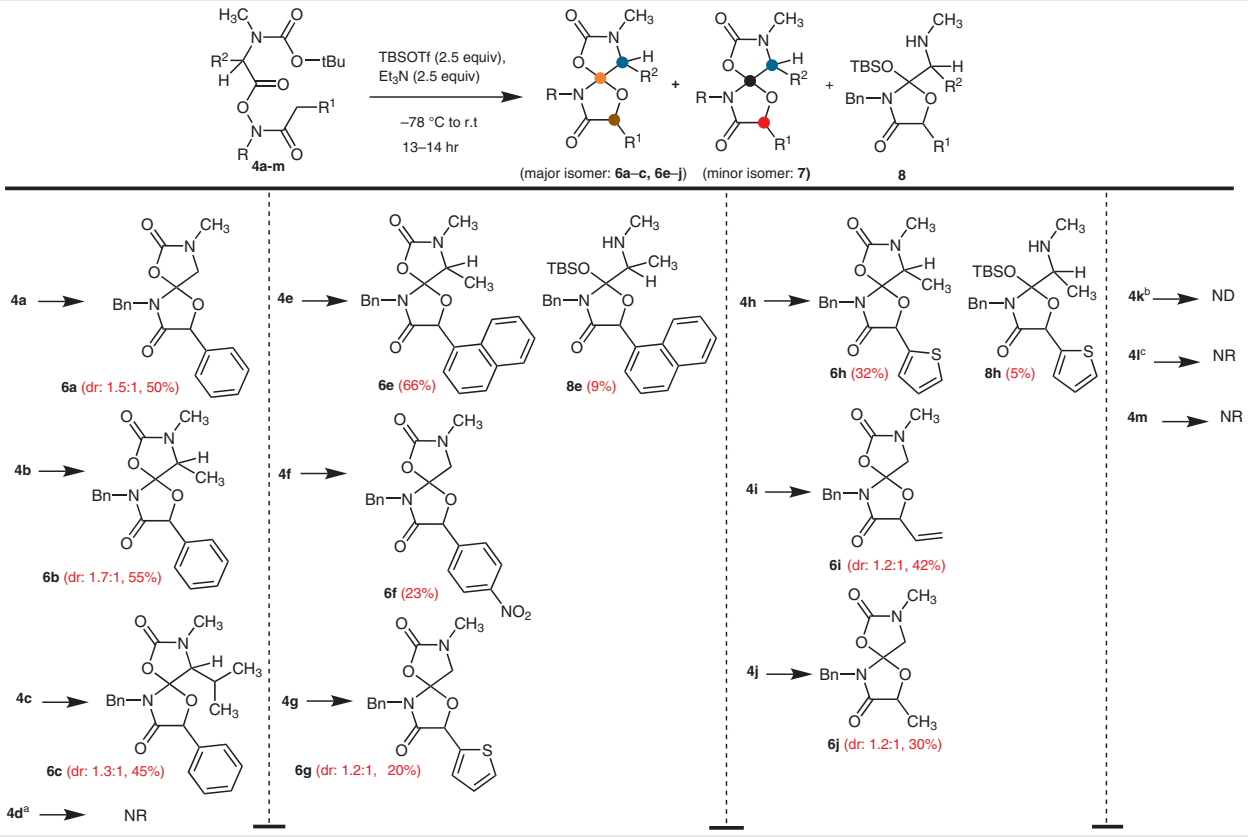
Figure 1 Crystal structure of (4*S*,5*R*,7*R*)-9-benzyl-3,4-dimethyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (**6b**) (see the Supporting Information)

Identification of the second diastereomer was not possible, as it was separated either as a mixture of two diastereomers or as a liquid diastereomer, which was obtained in insufficient quantity for a 2D NMR experiment (i.e., a NOESY experiment). Nevertheless, determination of the ratio was carried out by using the integral ratio of diagnostic signals in the ^{1}H NMR spectrum of the crude mixture.

A similar analysis carried out for other compounds based upon the observed configuration of the major diastereomer of **6b** enabled proposition of the configuration of the major isolated diastereomer (see below). To investigate the generality of the process, various *N*,*O*-diacyl hydroxylamines were subjected to the above conditions.

Upon subjecting **4a** to the optimized conditions, two diastereomers, **6a** and **7a**, were formed in 50% combined yield and a dr of 1.5:1 (Scheme 3). It is notable that attempted crystallization of **6a** in hot EtOH resulted in isomerization and formation of crystals of the racemic (*R*,*R*/*S*,*S*) diastereomers,[18] presumably due to the thermal instability of the spirocyclic nonane and a subsequent change in the configuration profile during crystal growth. A trivial increase in yield was noticed when instead of H, a CH_3 group was employed at R^2 in substrate **4b**. Purification via column chromatography on silica gel afforded two diastereomers, **6b** and **7b**, in 55% combined yield and 1.7:1 dr. When the bulky amino acid derivative **4c** was employed, the reaction occurred with 100% conversion, giving spirocyclic **6c** and **7c** in 45% total yield and 1.3:1 dr. The observed lower yield compared to **6b** is possibly due to the increased steric hindrance of isopropyl versus methyl at R^2 in precursor **4c**. The failure of the reaction with substrate **4d**, where Boc-protected phenylalanine was used at the *O*-acyl moiety, confirms that steric hindrance at R^2 is a determining factor in inhibiting the reaction. Precursor **4e**, bearing a 2-naphthyl substituent at R^1, performed well under the standard conditions leading to an improved 66% yield of spirocyclic **6e**; this represents the highest yield in this series of compounds. In this case, a small amount of cyclic orthoamide **8e** was also isolated in 9–10% yield. Unfortunately, due to the instability of the isolated compound **8e**, assignment of the configuration was not possible. The use of precursor **4f** led to a marked drop in yield (23%), presumably due to the presence of an electron-withdrawing NO_2 group at the *para* position of the phenyl substituent at R^1. Purification of the crude product via flash chromatography on silica gel gave solely the spirocycle **6f**. Most of the spirocyclic orthoamides were stable in $CDCl_3$, however, compound **6f** proved to be unstable and isomerized fairly rapidly, giving a 50:50 isomeric mixture when stored in a solution of $CDCl_3$. Which stereocenter of the spirocycle isomerized remained ambiguous. Our attempts to prevent isomerization by using basified $CDCl_3$ were unsuccessful. As a result, we switched to C_6D_6 as an alternative solvent. Surprisingly, we found that isomerization of **6f** did not occur, even when left overnight in a solution of C_6D_6. This is presumably due to the inability of C_6D_6 to coordinate with the spirocycle through H-bonding or dipole–dipole interactions that would facilitate isomerization.

Reaction of **4g**, where R = benzyl, R^1 = thienyl and R^2 = H, gave two diastereomers, **6g** and **7g**, in 20% combined yield and a dr of 1.2:1. Separation of the diastereomers was successfully achieved via flash chromatography on silica gel. The effect of adding a methyl substituent at R^2 in **4h** improved the overall yield, mirroring the observations for the R^1 = Ph series above. Chromatography on silica gel afforded a single diastereomer of **6h** in 32% yield along with relatively impure cyclic orthoamide **8h** in 5–6% yield. Similar to **8e**, compound **8h** was highly unstable and decomposed within a few hours at room temperature. The presence of an alkenyl substituent at R^1 in **4i** provided spirocyclic compounds **6i** and **7i** in a 1.2:1 dr and a combined yield of 42%, with a trivial drop in yield compared to the corresponding phenyl-substituted starting material. Less polar spirocyclic compound **6i** was isolated as a single isomer, whereas more polar spirocycle **7i** was isolated as a mixture of two isomers. Upon changing R^1 from phenyl (**4a–f**) to CH_3 (**4j**), the overall



Scheme 3 Scope of the 1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-diones. [a] Starting material was recovered (NR: no reaction). [b] Spirocyclic compounds were not detected (ND: not detected). [c] Starting material was recovered. Stereocenters in structures **6** & **7** are tagged with different colors to differentiate them in their stereochemistries.

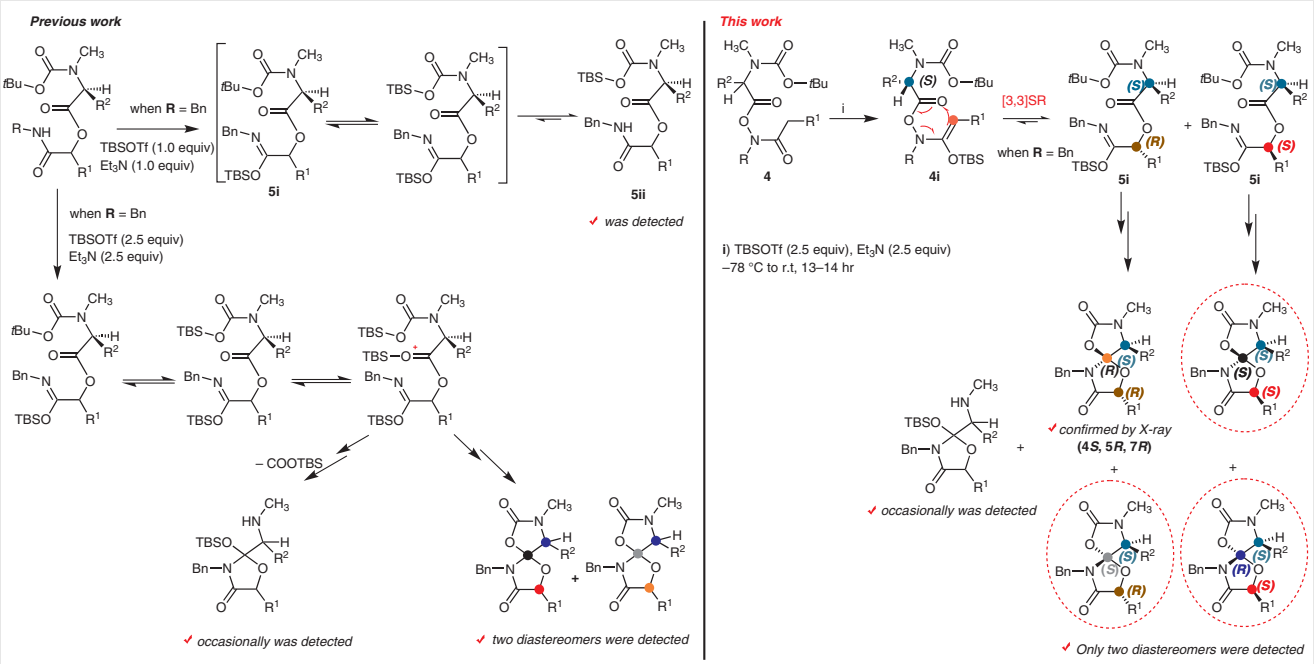
yield of the two spirocyclic orthoamides **6j** and **7j** dropped to 30% with a dr of 1.2:1. Two of the substrates, namely **4k** and **4l** with CF_3 and H substituents at R^1, respectively, did not furnish spirocyclic products despite the starting materials being consumed completely.

For **4l**, forcing thermal conditions or using an increased amount of the reagents was also ineffective. These results highlight the need for a readily enolizable proton next to the carbonyl of the amide in the transition state.

In determining the effect of the *N*-acyl substituent on the reaction, *N*,*O*-diacyl hydroxylamine **4m** was evaluated to see whether an *N*-methyl substituent would be tolerated. The results showed that in this case the reaction failed to produce any of the desired product. In general, the above results indicate that the process tolerates a wide spectrum of variations at R^1 and R^2, but not at R.

As is shown in Scheme 4, it is postulated that the transformation proceeds via a cascade route, where initially hydroxamate **4(i)** undergoes a [3,3]-SR to give Boc-protected acyloxyamides **5(i)**, forming two possible diastereomers as a result of the rearrangement. In theory each of these diastereomers can form two spirocyclic isomers. Consequently, the cyclization and ultimate spirocyclization of **5(i)** can generate spirocyclic compounds with four possible stereochemistries. In practice, however, only two spirocyclic isomers were isolated, indicating that only some stereoselectivities are involved in the process (Scheme 4). Whilst the stereochemistry of one of the spirocyclic products was unambiguously established by X-ray crystal structure analysis, the stereochemistry of the second spirocyclic product remained undefined. Nonetheless, it may have adopted one of the three possibilities shown in dashed circles in Scheme 4.

From the mechanism point of view, it can be postulated that Boc-protected silyl iminoether **5(i)** converts into the corresponding *tert*-butyldimethylsilyloxy carbonyl derivative **5(ii)** upon using 1.0 equivalent each of the reagents as discussed previously.[15] In the presence of an excess amount of the reagents, the silyl carbamate can further proceed to generate spirocyclic orthoamides. Alternatively, loss of the *tert*-butyldimethylsilyloxy carbonyl group (COOTBS) results in the cyclized products (i.e., **8e** and **8h**). It appears that a similar intermediate is responsible for the generation of the spirocyclic compound and the cyclic product, since in cases where the cyclic product was detected, only a single spiro-



Scheme 4 The structures of the four possible stereochemistries of 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones formed via [3,3]-SR. The mechanism for the formation of the spirocycles using this procedure mainly relies on the recent mechanism reported for synthesis of these compounds via Boc-protected α-acyloxyamide derivatives.

cyclic compound was isolated. Overall, the proposed mechanism in this work mainly relies on the recently reported mechanism[15] (see previous work in Scheme 4).

In summary, a new synthetic approach towards the preparation of 1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-diones has been disclosed. The process reveals that a [3,3]-SR occurs as a crucial step in the construction of a carbon–heteroatom bond. Apart from reducing the number of required manipulations, this cascade process allows several transformations via a simple synthetic route. Thus, this pathway represents a relatively short procedure for preparing a series of structurally diverse 3-azaspirocyclic orthoamides. Additionally, the formation of two of the four possible diastereomers offers the potential to generate these products in stereochemically enriched forms.[18]

All reactions were performed under N_2 or Ar unless otherwise stated. All solvents were distilled from appropriate drying agents prior to use. Unless otherwise noted, commercially available chemicals were used as received. Melting points were measured on a Reichert hot stage melting point apparatus. Optical rotations were obtained at 20 °C using a 1 dm cell at a wavelength of 589 nm (sodium D line), quoted as: $[\alpha]_D$, concentration *c* (g/100 mL), solvent. ^{1}H NMR spectra were recorded at 300, 400 or 600 MHz and chemical shifts are reported in ppm relative to internal tetramethylsilane (TMS, δ 0.0) or with the solvent reference relative to TMS employed as the internal standard [$CDCl_3$, δ 7.26; $(CD_3)_2CO$, δ 2.09; C_6D_6, δ 7.16]. ^{13}C NMR spectra were recorded at 75, 100 or 150 MHz and chemical shifts are reported in parts per million downfield relative to the center line of the triplet of $CDCl_3$ at δ 77.0 and/or $(CD_3)_2CO$ at δ 205.1 and δ 30.1. ^{19}F NMR spectra were determined at 377 MHz with trichlorofluoromethane as the internal reference (δ 0.00). Accurate mass determinations were made on an Agilent G6220A LC-TOF system.

Hydroxamic Acids 2; General Procedure (GP1)

To a magnetically stirred solution of *N*-alkyl hydroxylamine hydrochloride (3.0 mmol) in dry CH_2Cl_2 (20 mL) under N_2 was added Et_3N (7.5 mmol, 1.0 mL) dropwise via a syringe at 0 °C. While in an ice bath, the reaction was stirred for 20 min. Next, the freshly prepared corresponding acid chloride or acid anhydride (3.0 mmol) in dry CH_2Cl_2 (30 mL) was added slowly over a 10 min period. The resulting mixture was then warmed to room temperature and allowed to stir for a further 4–5 h. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 and washed with HCl (1.0 M) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure.[19] Purification of the crude residue was accomplished by flash column chromatography with an appropriate solvent system (EtOAc/hexanes) to afford the desired hydroxamic acids **2a–i**.

N-Benzyl-*N*-hydroxy-2-phenylacetamide (2a)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and phenylacetyl chloride (3.0 mmol, 0.40 mL), in accordance with GP1.

Yield: 0.58 g (80%); off-white solid; mp 94–95 °C (Lit.[19] 96–97 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 10 H), 4.81 (s, 2 H), 3.85–3.76 (br s, 2 H).

ESI-MS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{15}NO_2Na$: 264.09; found: 264.1.

N-Benzyl-N-hydroxy-2-(naphthalene-2-yl)acetamide (2b)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and 2-(naphthalen-2-yl)acetyl chloride (3.0 mmol, 0.61 mL), in accordance with GP1.

Yield: 0.73 g (78%); off-white crystalline solid; mp 140–141 °C.

IR (Diamond-ATR, neat): 3059, 3030, 2923, 2853, 1641, 1495, 1453, 1422, 1144, 1078, 1029, 939, 804, 755, 731, 691 cm^{-1}.

^1H NMR (600 MHz, acetone-d_6): δ (mixture of two rotamers) = 8.17 (br s, 1 H), 7.80–7.66 (m, 3 H), 7.44–7.26 (m, 9 H), 5.92 and 4.83 (2 × s, 2 H), 3.99–3.92 (m, 2 H).

^{13}C NMR (150 MHz, acetone-d_6): δ (mixture of two rotamers) = 171.96, 137.74, 135.43, 134.19, 134.09, 132.87, 132.09, 130.15, 129.52, 128.89, 128.81,128.73, 128.71, 128.54, 128.51, 128.32, 128.03, 127.98, 127.70, 126.35, 125.88, 52.48, 52. 57, 40.01.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1333.

N-Benzyl-N-hydroxy-2-(4-nitrophenyl)acetamide (2c)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and 2-(4-nitrophenyl)acetyl chloride (3.0 mmol, 0.6 mL) in accordance with GP1.

Yield: 0.67 g (79%); off-white crystalline solid.

IR (Diamond-ATR, neat): 3169, 1606, 1518, 1495, 1453, 1346 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 9.17 (br s, 1 H), 8.17 (d, *J* = 8.7 Hz, 2 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.30 (s, 5 H), 4.81 (s, 2 H), 4.04 (s, 2 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 170.7, 147.2, 144.3, 137.3, 131.1, 128.6, 127.7, 123.4, 52.1, 39.0.

HRMS (ESI-TOF): *m*/*z* [M – H]$^+$ calcd for $C_{15}H_{13}N_2O_4$: 285.0881; found: 285.0888.

N-Benzyl-N-hydroxy-2-(thiophen-2-yl)acetamide (2d)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.5 mmol, 0.56 g) and 2-(thiophen-2-yl)acetyl chloride (3.5 mmol, 0.43 mL) in accordance with GP1.

Yield: 0.70 g (81%); off-white crystalline solid; mp 95–96 °C (Lit.[19] 97–98 °C); R_f = 0.34 (35% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 7 H), 6.96–6.92 (m, 2 H), 4.84 (br s, 2 H), 3.97 (br d, *J* = 14.8 Hz, 2 H).

(*E*)-N-Benzyl-N-hydroxybut-2-enamide (2e)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g), crotonic anhydride (3.0 mmol, 0.44 mL) and Et_3N (7.5 mmol, 1.0 mL) in accordance with GP1.

Yield: 0.44 g (77%), off-white solid; mp 83–86 °C; R_f = 0.37 (50% EtOAc/hexanes).

IR (Diamond-ATR, neat): 2359, 2341, 1683, 1602, 1455, 1228, 1155, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 7.00 (dq, *J* = 13.9, 6.9 Hz, 1 H), 6.24 (br s, 1 H), 4.86 (s, 2 H), 1.90 (dd, *J* = 7.0, 1.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 135.4, 128.8, 128.0, 52.2, 18.3; signals corresponding to *C*O and *C*OCH were not observed.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NO_2$: 192.1019; found: 192.1020.

N-Benzyl-N-hydroxypropionamide (2f)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and propionyl chloride (3.0 mmol, 0.3 mL) in accordance with GP1.

Yield: 0.39 g (65%); off-white crystalline solid; mp 60–61 °C; R_f = 0.37 (35% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3179, 2978, 2939, 2361, 2336, 1615, 1453, 1232 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.92–7.10 (m, 5 H), 4.79 (s, 2 H), 2.52–2.34 (br m, 2 H), 1.25–1.08 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 175.6, 168.5, 136.2, 134.5, 128.5, 128.0, 127.6, 127.0, 52.5 and 52.1, 25.6 and 24.7, 9.3 and 8.8.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}NO_2Na$: 202.0838; found: 202.0831.

N-Benzyl-3,3,3-trifluoro-N-hydroxypropanamide (2g)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and 3,3,3-trifluoropropanoyl chloride (3.0 mmol, 0.44 mL) in accordance with GP1.

Yield: 0.51 g (67%); off-white crystalline solid; mp 99–100 °C; R_f = 0.47 (35% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3221, 1648, 1625, 1452, 1271, 1243, 1142, 1114, 726, 697 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 9.31 (s, 1 H), 7.35–7.27 (m, 5 H), 4.80 (s, 2 H), 3.64 (q, J_{H-F} = 10.8 Hz, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 163.6, 135.9, 127.7, 126.8, 125.7, 122.9, 50.8, 36.1 (q, J_{C-F} = 28.9 Hz).

^{19}F NMR (377 MHz, acetone-d_6): δ = –58.0 (t, *J* = 10.8 Hz, 3 F).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}F_3NO_2Na$: 256.0556; found: 256.0556.

N-Benzyl-N-hydroxyacetamide (2h)

Prepared using *N*-benzyl hydroxylamine hydrochloride (**1a**) (3.0 mmol, 0.48 g) and acetyl chloride (3.0 mmol, 0.21 mL) in accordance with to the GP1.

Yield: 0.39 g (78%); off-white crystalline solid; mp 105 °C (Lit.[20] 108–109 °C); R_f = 0.2 (50% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H), 3.75 (s, 2 H), 3.31 (s, 3 H); a signal due to O*H* was not observed.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}NO_2Na$: 188.06; found: 188.1.

N-Hydroxy-N-methyl-2-phenylacetamide (2i)

Prepared using *N*-methylhydroxylamine hydrochloride (**1b**) (3.0 mmol, 0.25 g) and phenylacetyl chloride (3.0 mmol, 0.4 mL) in accordance with GP1.

Yield: 0.32 g (64%); off-white crystalline solid; mp 54 °C (Lit.[19] 54–55 °C).

^1H NMR (300 MHz, $CDCl_3$, 60 °C): δ = 7.36–7.26 (m, 5 H), 3.73 (s, 2 H), 3.31 (s, 3 H); signal due to O*H* was not observed.

N,O-Diacyl Hydroxylamines Bearing N-Boc-N-methyl α-Amino Acid; General Procedure (GP2)

To a stirring solution of *N*-hydroxy-*N*-alkyl acetamide **2a–i** (1.0 equiv) in dry CH_2Cl_2 (10 mL) at 0 °C were added *N*-Boc-*N*-methyl α-amino acid **3a–d** (1.0 equiv), EDCI·HCl (1.6 equiv) and DMAP (0.1 equiv) un-

der an atmosphere of N_2. To the resulting suspension was added Et_3N (1.3 equiv) dropwise via a syringe, after which the mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with CH_2Cl_2, washed with HCl (1.0 M) and water, and then dried over $MgSO_4$. The crude residue was purified via flash chromatography to yield products **4a–m**.

***tert*-Butyl {2-[(*N*-Benzyl-2-phenylacetamido)oxy]-2-oxoethyl}(methyl)carbamate (4a)**

Yield: 0.60 g (88%); colorless liquid; R_f = 0.25 (20% EtOAc/hexanes).

IR (Diamond-ATR, neat): 2976, 1791, 1682, 1496, 1455, 1389, 1366, 1153, 1060, 731, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.34–7.26 (m, 10 H), 4.81 (s, 2 H), 3.84 (d, *J* = 11.4 Hz, 2 H), 3.69 (s, 2 H), 2.81 (s, 3 H), 1.36 and 1.30 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 171.24, 167.96 and 167.60, 155.86 and 154.86, 134.81 and 134.56, 133.79 and 133.44, 129.33, 129.16, 128.68, 128.60, 128.56, 128.16, 128.02, 127.22, 127.00, 80.81 and 80.69, 52.24, 49.08 and 48.89, 39.90 and 39.74, 35.66 and 35.33, 28.25.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{28}N_2O_5Na$: 435.1890; found: 435.1894.

(*S*)-*tert*-Butyl {1-[(*N*-Benzyl-2-phenylacetamido)oxy]-1-oxopropan-2-yl}(methyl)carbamate (4b)

Yield: 0.77 g (92%); colorless liquid; R_f = 0.42 (35% EtOAc/hexanes); $[\alpha]_D^{20}$ –28 (*c* 1.0, CH_2Cl_2).

IR (Diamond-ATR, neat): 2976, 2931, 1789, 1682, 1455, 1389, 1153, 1060, 872, 731, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.30–7.24 (m, 10 H), 4.87 (ABq, *J* = 15.6 Hz, 1 H), 4.76 (ABq, *J* = 15.6 Hz, 1 H), 4.62 (br m, 1 H), 3.58 (s, 2 H), 2.63 (s, 3 H), 1.34 (br s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 170.32, 155.67, 154.71, 134.86, 133.83, 129.40, 129.01, 128.90, 128.54, 127.97, 126.77, 80.60, 53.07, 52.69, 39.52, 30.70, 30.08, 29.69, 28.28, 15.29,14.59.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{30}N_2O_5Na$: 449.2047; found: 449.2042.

***tert*-Butyl {1-[(*N*-Benzyl-2-phenylacetamido)oxy]-3-methyl-1-oxobutan-2-yl}(methyl)carbamate (4c)**

Yield: 0.59 g (90%); colorless liquid; R_f = 0.5 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –54.5 (*c* 1.0, CH_2Cl_2).

IR (Diamond-ATR, neat): 3332, 3032, 2971, 2932, 1786, 1692, 1455, 1391, 1368, 1161 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.32–7.23 (m, 10 H), 4.97–4.79 (m, 2 H), 4.47 and 4.19 (2 × d, *J* = 11.2 Hz, 1 H), 3.69–3.63 (m, 2 H), 2.66 (s, 3 H), 2.24–2.11 (m, 1 H), 1.42 and 1.41 (2 × s, 9 H), 0.91–0.80 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 170. 96, 168.97 and 168.29, 155.90 and 154.88, 134.78 and 134.57, 133.68 and 133.49, 129.49, 129.25, 128.58, 128.51, 128.06, 127.93, 127.12, 127.02, 80.85, 80.63, 63.15 and 61.67, 52.18, 39.20 and 30.12, 28.27 and 27.27, 19.59 and 19.36 and 19.12, 18.55 and 18.36.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{34}N_2O_5Na$: 477.2360; found: 477.2367.

(*S*)-*tert*-Butyl {1-[(*N*-Benzyl-2-phenylacetamido)oxy]-1-oxo-3-phenylpropan-2-yl}(methyl)carbamate (4d)

Yield: 0.58 g (93%); colorless liquid; R_f = 0.35 (0.35% EtOAc/hexanes); $[\alpha]_D^{20}$ –34.8 (*c* 1.0, CH_2Cl_2).

IR (Diamond-ATR, neat): 3244, 2977, 2933, 1790, 1688, 1480, 1392, 1367, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.28–7.10 (m, 15 H), 4.88–4.80 (m, 3 H), 3.57 (ABq, *J* = 12.8 Hz, 2 H), 3.10–2.82 (m, 2 H), 2.62 and 2.56 (2 × s, 3 H), 1.36 and 1.27 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 169.07, 168.58, 155.45, 136.31, 136.14, 134.88, 133.77, 129.41, 129.18, 129.02, 128.90, 128.60, 128.52, 127.93, 126.97, 80.67, 58.86, 52.30, 39.82 and 39.45, 35.13 and 34.83, 32.29, 28.19.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{34}N_2O_5Na$: 525.2360; found: 525.2364.

(*S*)-*tert*-Butyl (1-{[*N*-Benzyl-2-(naphthalen-2-yl)acetamido]oxy}-1-oxopropan-2-yl)(methyl)carbamate (4e)

Yield: 0.54 g (95%); colorless liquid; R_f = 0.44 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –131.7 (*c* 1.0, CH_2Cl_2).

IR (Diamond-ATR, neat): 3337, 3057, 3030, 2975, 2932, 1789, 1681, 1478, 1454, 1388, 1366, 1153, 1060, 986, 860, 804, 777, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.74–7.58 (m, 4 H), 7.43–7.12 (m, 8 H), 4.89 (ABq, *J* = 15.6 Hz, 1 H), 4.78 (ABq, *J* = 15.4 Hz, 1 H), 4.68–4.57 (m, 1 H), 3.76 and 3.65 (2 × s, 2 H), 2.62 (s, 3 H), 1.34 (s, 9 H), 1.21 (d, *J* = 3.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.36, 155.70, 134.85, 133.47, 133.40, 132.48, 131.36, 128.84, 128.57, 128.47, 128.45, 128.29, 128.10, 127.98, 127.79, 127.69, 127.62, 127.14, 126.78, 126.44, 126.08, 125.99, 125.68, 124.73, 80.64, 52.79, 52.79, 52.28, 39.69, 39.11, 30.75, 30.14, 28.29, 15.29, 14.58.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{32}N_2O_5Na$: 499.2203; found: 499.2214.

(*S*)-*tert*-Butyl (2-{[*N*-Benzyl-2-(4-nitrophenyl)acetamido]oxy}-2-oxoethyl)(methyl)carbamate (4f)

Yield: 0.24 g (46%); yellow oil.

IR (Diamond-ATR, neat): 3032, 1795, 1680, 1518, 1366, 1344, 1238, 1151, 1095, 733, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 8.15 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.28 (m, 5 H), 4.90 (s, 2 H), 3.96 (ABq, *J* = 13.6 Hz, 2 H), 3.76 (ABq, *J* = 18.2 Hz, 2 H), 2.85 (s, 3 H), 1.45 and 1.38 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 168.20 and 167.75, 156.00, 147.29 and 147.14, 141.45 and 140.84, 134.43 and 134.16, 130.57, 128.70, 128.42, 128..25, 123.78, 123.62, 80.95, 52.16, 49.19, 38.95, 35.96 and 35.44, 28.24. The signal corresponding to carbon in NCH_2PhOC was not observerd.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{27}N_3O_7Na$: 480.1741; found: 480.1746.

***tert*-Butyl (2-{[*N*-Benzyl-2-(thiophen-2-yl)acetamido]oxy}-2-oxoethyl)(methyl)carbamate (4g)**

Yield: 0.55 g (70%); yellow oil; R_f = 0.39 (35% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3307, 2975, 2930, 1757, 1671, 1538, 1481, 1454, 1391, 1366, 1297, 1244, 1179, 1148 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.49–7.26 (m, 5 H), 7.24–7.17 (m, 1 H), 7.02–6.97 (m, 1 H), 6.44 (s, 1 H), 4.62–4.34 (m, 2 H), 4.19 and 3.80 (ABq, *J* = 17.6 Hz, 2 H), 2.94 and 2.91 (2 × s, 3 H), 1.62 and 1.36 and 1.33 (3 × s, 9 H), a signal corresponding to the CH_2 protons of NCH_2Ph was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.29, 167.36, 156.90, 137.85, 137.02, 128.83, 128.76, 128.55, 127.84, 127.65, 127.35, 126.92, 126.63, 126.16, 80.88, 71.98, 71.43, 51.35, 51.05, 43.66, 43.40, 36.41, 35.57, 28.23, 28.11. The signal corresponding to the methylene carbon of NCH_2Ph was not observed.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}N_2O_5SNa$: 441.1455; found: 441.1457.

(*S*)-*tert*-Butyl (1-{[*N*-Benzyl-2-(thiophen-2-yl)acetamido]oxy}-1-oxopropan-2-yl)(methyl)carbamate (4h)

Yield: 0.52 g (74%); yellow oil; R_f = 0.22 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –37.6 (*c* 1.3, CH_2Cl_2).

IR (Diamond-ATR, neat): 3297, 2975, 2930, 1746, 1662, 1537, 1453, 1390, 1366, 1149, 1087, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.74–7.69 and 7.54–7.51 (2 × m, 1 H), 7.33–7.27 and 7.22–7.16 (2 × m, 5 H), 6.42 and 6.32 (2 × s, 1 H), 4.70 and 4.16 (br q, *J* = 6.8 Hz, 1 H), 4.60–4.36 (m, 2 H), 2.92 and 2.78 (2 × s, 3 H), 1.48–1.43 (m, 3 H), 1.34 (s, 9 H); a signal corresponding to the CH_2 protons of NCH_2Ph was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 170.97 and 170.48, 167.7 and 167.64, 156.94 and 156.25, 138.02 and 137.91, 137.43, 128.68, 128.53, 128.45, 127.79, 127.75, 127.42, 127.31, 127.19, 126.87, 126.85, 126.38, 80.79 and 80.70, 72.56 and 71.89, 56.57 and 54.41, 43.37, 33.82 and 31.10, 28.27, 14.60 and 14.15. The signal corresponding to the CH2 carbon of NCH_2Ph was not observed.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{28}N_2O_5SNa$: 455.1611; found: 455.1602.

(*E*)-*tert*-Butyl {2-[(*N*-Benzylbut-2-enamido)oxy]-2-oxoethyl}-(methyl)carbamate (4i)

Yield: 0.54 g (80%); colorless liquid; R_f = 0.53 (35% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3031, 2975, 1793, 1690, 1699, 1635, 1445, 1387, 1366, 1236, 1151, 1095, 1055, 963, 921, 881, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.33–7.27 (m, 5 H), 7.07 (dt, *J* = 14.5, 6.9 Hz, 1 H), 6.16 and 6.05 (2 × d, *J* = 15.2 Hz, 1 H), 4.93 (s, 2 H), 3.97 (ABq, *J* = 12.8 Hz, 2 H), 2.82 (s, 3 H), 1.89 and 1.87 (dd, *J* = 7.0, 1.6 Hz, 3 H), 1.44 and 1.40 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 168.13 and 167.67, 166.41 and 166.09, 155.87 and 154.86, 145.19 and 144.97, 135.05 and 134.81, 128.64, 128.55, 128.53, 128.30, 128.03, 127.89, 119.68 and 119.34 , 80.69 and 80.65, 52.42 and 52.12, 49.17 and 49.00, 35.66 and 35.30, 28.23 and 28.19, 18.28 and 18.25.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}N_2O_5Na$: 385.1734; found: 385.1737.

***tert*-Butyl {2-[(*N*-Benzylpropionamido)oxy]-2-oxoethyl}(methyl)carbamate (4j)**

Yield: 0.59 g, 86%, colorless liquid; R_f = 0.4 (35% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3089, 3064, 1793, 1685, 1453, 1389, 1366, 1306, 1237, 1150, 1099, 806, 633 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.35–7.27 (m, 5 H), 4.88 and 4.81 (2 × s, 2 H), 3.96 (d, *J* = 15.9 Hz, 2 H), 2.82 (s, 3 H), 2.32 (q, *J* = 7.5 Hz, 2 H), 1.45 and 1.40 (2 × s, 9 H), 1.14 (ddd, *J* = 13.4, 9.2, 5.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 174.00, 168.07 and 167.78, 155.82 and 154.84, 135.03 and 134.80, 128.65, 128.58, 128.38, 128.07, 127.94, 80.76 and 80.66, 52.10, 49.20 and 48.91, 35.61 and 35.37, 28.19, 25.71, 8.38.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}N_2O_5Na$: 373.1734; found: 373.1742.

(*S*)-*tert*-Butyl {1-[(*N*-Benzyl-3,3,3-trifluoropropanamido)oxy]-1-oxopropan-2-yl}(methyl)carbamate (4k)

Yield: 0.37 g (80%); colorless liquid; R_f = 0.22 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –10.4 (*c* 0.5, CH_2Cl_2).

IR (Diamond-ATR, neat): 3225, 2980, 1796, 1684, 1453, 1393, 1368, 1329, 1259, 1155 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.36–7.27 (m, 5 H), 4.90 (s, 2 H), 4.61 and 4.41–4.37 (br s and m, 1 H), 3.29–3.22 (m, 2 H), 2.75 (s, 3 H), 1.42 (s, 9 H), 1.30 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 158.4, 134.3, 128.9, 128.7, 128.3, 125.2, 122.4, 81.0, 53.6 and 53.0, 51.6, 37.2 (q, J_{C-F} = 117.2 Hz), 31.5, 28.2, 14.4; the signal corresponding to *C*O in NCH_2PhOCO was not observed.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{25}F_3N_2O_5Na$: 441.1608; found: 441.1612.

***tert*-Butyl {2-[(*N*-Benzylacetamido)oxy]-2-oxoethyl}(methyl)carbamate (4l)**

Yield: 0.47 g (85%); colorless liquid.

IR (Diamond-ATR, neat): 2976, 2932, 1795, 1685, 1452, 1389, 1367, 1242, 1151, 1100, 1058, 1032, 879, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.34–7.30 (m, 5 H), 4.88 and 4.82 (2 × s, 2 H), 3.96 (d, *J* = 11.8 Hz, 2 H), 2.94 and 2.83 (2 × s, 3 H), 2.08 (s, 3 H), 1.42 and 1.40 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 171.80, 168.08 and 167.73, 155.85 and 154.84, 134.91 and 134.66, 128.69, 128.61, 128.14, 128.00, 80.80 and 80.70, 51.93, 49.16 and 48.95, 35.68 and 35.36 , 28.23, 20.49.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{24}N_2O_5Na$: 359.1577; found: 359.1581.

***tert*-Butyl Methyl{2-[(*N*-Methyl-2-phenylacetamido)oxy]-2-oxoethyl}carbamate (4m)**

Yield: 0.56 g (88%); colorless liquid.

IR (Diamond-ATR, neat): 3222, 2927, 1770, 1625, 1490, 1434, 1395, 1192, 1105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two rotamers) = 7.31–7.23 (m, 5 H), 4.02 (d, *J* = 18.4 Hz, 2 H), 3.66 (s, 2 H), 3.33 and 3.32 (2 × s, 3 H), 2.92 (s, 3 H), 1.47 and 1.43 (2 × s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of two rotamers) = 167.88 and 167.64, 155.91 and 154.91, 133.86 and 133.50, 129.20, 129.05, 128.72, 128.61, 127.19, 127.01, 80.89 and 80.81, 49.32 and 49.00, 39.83 and 39.70, 35.86 and 35.67, 28.27.

HRMS (ESI-TOF): *m*/*z* [M – H]$^+$ calcd for $C_{17}H_{23}N_2O_5$: 335.1607; found: 335.1971.

1,6-Dioxa-3,9-diazaspiro[4.4]nonane-2,8 diones 6 and 7; General Procedure (GP3)

To an oven-dried round-bottomed flask containing dry CH_2Cl_2 at –78 °C was added *N*,*O*-diacyl hydroxylamine **4a–m** (1.0 equiv) under an atmosphere of N_2. To this solution was added TBSOTf (2.5 equiv) dropwise via a microsyringe through a septum, followed after 5 min by Et_3N (2.5 equiv). The reaction was maintained at –78 °C for about 15–20 min while stirring vigorously and was then removed from the dry ice bath and allowed to stir at room temperature for an additional 13–14 h. After the reaction was deemed complete (via TLC), the solvent was evaporated under reduced pressure and the crude product was then applied directly to a silica gel column and eluted with the appropriate solvent system.

9-Benzyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6a, 7a)

Prepared using **4a** (0.46 mmol, 0.19 g), TBSOTf (1.15 mmol, 0.31 mL) and Et_3N (1.15 mmol, 0.16 mL) in accordance with GP3.

Yield: 78 mg (50% combined yield); dr = 1.5:1.

Less polar spirocyclic **6a**[15] (major product): off-white solid; R_f = 0.32 (40% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.24 (m, 10 H), 5.46 (s, 1 H), 5.02 (d, *J* = 15.6 Hz, 1 H), 4.08 (d, *J* = 15.7 Hz, 1 H), 3.53 (d, *J* = 11.1 Hz, 1 H), 3.22 (d, *J* = 11.1 Hz, 1 H), 2.77 (s, 3 H).

The more polar isomer **7a**[15] was isolated as a mixture of two diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of **6a** and **7a**) = 7.54 (d, *J* = 6.9 Hz, 14 H),7.54–7.25 (m, 10 H), 5.52 (s, 1 H), 5.47 (s, 1 H), 5.09 (d, *J* = 15.6 Hz, 1 H), 5.03 (d, *J* = 15.5 Hz, 1 H), 4.11 (s, 1 H), 4.07 (s, 1 H), 3.33 (d, *J* = 11.1 Hz, 1 H), 3.23 (d, *J* = 11.0 Hz, 1 H), 2.79 (s, 3 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.42, 169.72, 154.55, 154.49, 135.42, 135.25, 134.21, 133.90, 129.11, 129.05, 128.92, 128.82, 128.71, 128.58, 128.52, 128.20, 127.90, 126.52, 124.11, 112.21, 111.75, 79.50, 79.38, 54.76, 54.25, 43.77, 43.67, 30.22, 30.18.

9-Benzyl-3,4-dimethyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6b, 7b)

Prepared using **4b** (0.47 mmol, 0.20 g), TBSOTf (1.2 mmol, 0.31 mL) and Et_3N (1.2 mmol, 0.16 mL) in accordance with GP3.

Yield: 90 mg (55% combined yield); dr = 1.7:1 dr.

Less polar spirocyclic **6b**[15] (major product): off-white solid; R_f = 0.32 (40% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.23 (m, 10 H), 5.53 (s, 1 H), 5.10 (d, *J* = 16.0 Hz, 1 H), 4.13 (d, *J* = 16.0 Hz, 1 H), 3.56 (q, *J* = 6.6 Hz, 1 H), 2.76 (s, 3 H), 1.17 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 154.3, 135.8, 133.9, 129.2, 129.1, 128.9, 128.2, 127.3, 126.8, 113.4, 77.9, 57.5, 43.7, 28.3, 12.4.

More polar spirocyclic **7b**:[15] colorless liquid; R_f = 0.18 (40% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.27 (m, 10 H), 5.45 (s, 1 H), 5.01 (d, *J* = 15.8 Hz, 1 H), 4.16 (d, *J* = 15.8 Hz, 1 H), 3.45 (q, *J* = 6.5 Hz, 1 H), 2.74 (s, 3 H), 1.18 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 154.3, 135.6, 134.4, 129.1, 129.1, 128.9, 128.4, 127.7, 126.5, 113.7, 79.7, 58.3, 43.8, 28.3, 12.2.

9-Benzyl-4-isopropyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6c, 7c)

Prepared using **4c** (0.39 mmol, 0.18 g), TBSOTf (0.97 mmol, 0.26 mL) and Et_3N (0.97 mmol, 0.14 mL) in accordance with GP3.

Yield: 66 mg (45% combined yield); dr = 1.3:1.

Less polar spirocyclic **6c**[15] (major product): off-white solid; mp 153–155 °C; R_f = 0.25 (20% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.25 (m, 10 H), 5.54 (s, 1 H), 5.12 (d, *J* = 15.9 Hz, 1 H), 4.06 (d, *J* = 15.9 Hz, 1 H), 3.32 (d, *J* = 2.3 Hz, 1 H), 2.80 (s, 3 H), 2.08 (m, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 155.0, 135.9, 133.6, 129.3, 128.9, 128.3, 127.6, 127.1, 113.8, 78.2, 66.3, 43.8, 30.7, 27.5, 19.8, 16.6.

More polar spirocycle **7c** was isolated as a mixture of two diastereomers.

9-Benzyl-3,4-dimethyl-7-(naphthalene-2-yl)-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6e)

Prepared using **4e** (0.46 mmol, 0.22 g), TBSOTf (1.1 mmol, 0.28 mL) and Et_3N (1.05 mmol, 0.146 mL) in accordance with GP3.

Yield: 120 mg (66%); off-white solid; mp 174–175 °C; R_f = 0.32 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ –75.8 (*c* 1.0, CH_2Cl_2).

IR (Diamond-ATR, neat): 3059, 3032, 2979, 2938, 1773, 1737, 1452, 1429, 1398, 922 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96–7.87 (m, 4 H), 7.56–7.52 (m, 2 H), 7.50 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.38–7.31 (m, 5 H), 5.70 (s, 1 H), 5.14 (d, *J* = 16.2 Hz, 1 H), 4.16 (d, *J* = 16.2 Hz, 1 H), 3.59 (q, *J* = 6.6 Hz, 1 H), 2.77 (s, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 154.5, 135.4, 133.8, 133.1, 131.3, 129.1, 129.0, 128.3, 127.8, 127.4, 127.0, 126.9, 126.7, 123.5, 113.5, 78.1, 57.6, 43.8, 28.3, 12.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_4$: 403.1652; found: 403.1656.

3-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-[(*S*)-1-(methylamino)ethyl]-5-(naphthalen-1-yl)oxazolidin-4-one (8e)

Yield: 20 mg (9%); yellow oil; R_f = 0.6 (40% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3326, 2953, 2928, 2855, 1714, 1434, 1413, 1359, 1252, 1165, 838 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.87–7.82 (m, 3 H), 7.72 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.50–7.49 (m, 4 H), 7.48–7.29 (m, 3 H), 5.75 (s, 1 H), 4.95 (d, *J* = 14.9 Hz, 1 H), 4.25 (d, *J* =14.9 Hz, 1 H), 2.52 (q, *J* = 6.4 Hz, 1 H), 1.86 (s, 3 H), 1.18 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.16 (s, 3 H), –0.19 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 137.4, 133.1, 133.0, 128.8, 128.6, 128.2, 128.0, 127.7, 127.7, 126.2, 126.1, 125.7, 124.7, 112.4, 79.5, 62.0, 43.5, 33.7, 25.7, 18.1, 13.3, –3.0, –4.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{39}N_2O_3Si$: 491.2724; found: 491.2727.

9-Benzyl-3-methyl-7-(4-nitrophenyl)-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6f)

Prepared using **4f** (0.47 mmol, 0.22 g), TBSOTf (1.1 mmol, 0.29 mL) and Et_3N (1.1 mmol, 0.16 mL) in accordance with GP3.

Yield: 41 mg (23%); pale yellow solid; mp 133–134 °C; $[\alpha]_D^{20}$ +1.20 (*c* 0.77, CH_2Cl_2).

IR (Diamond-ATR, neat): 3389, 1776, 1736, 1522, 1398, 1414, 1348, 978 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.83-7.79 (d, *J* = 8.9 Hz, 2 H), 7.10-7.05 (d, *J* = 8.9 Hz, 2 H), 6.97-6.94 (m, 3 H) , 6.92-6.90 (m, 2 H), 4.83 (s, 1 H), 4.66 (d, *J* = 15.6 Hz, 2 H), 3.62 (d, *J* = 15.6 Hz, 2 H), 2.70 (ABq, *J* = 11.2 Hz, 2 H), 2.15 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 168.5, 153.7, 148.2, 140.5, 135.7, 128.8, 126.3, 123.4, 111.2, 76.4, 53.3, 43.3, 29.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N_3O_6$: 384.1190; found: 384.1192.

9-Benzyl-3-methyl-7-(thiophen-2-yl)-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6g, 7g)

Prepared using **4g** (0.52 mmol, 0.22 g), TBSOTf (1.3 mmol, 0.34 mL) and Et_3N (1.3 mmol, 0.18 mL) in accordance with GP3.

Yield: 35 mg (20% combined yield); dr = 1.2:1.

Less polar isomer **6g** (major product): pale yellow solid; mp 142–143 °C; R_f = 0.32 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ +1.47 (*c* 0.44, CH_2Cl_2).

IR (Diamond-ATR, neat): 3348, 2928, 1773, 1736, 1414, 1398, 1362, 1291, 977 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 6 H), 7.25–7.23 (m, 1 H), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1 H), 5.78 (s, 1 H), 5.11 (d, *J* = 15.8 Hz, 1 H), 4.10 (d, *J* = 15.7 Hz, 1 H), 3.54 (d, *J* = 11.2 Hz, 1 H), 3.30 (d, *J* = 11.2 Hz, 1 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 154.4, 136.4, 135.2, 128.9, 128.2, 127.5, 127.4, 127.1, 127.0, 111.5, 75.0, 54.3, 43.8, 30.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_4S$: 345.0904; found: 345.0900.

More polar spirocyclic **7g**: yellow liquid; R_f = 0.18 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ –3.69 (*c* 0.26, CH_2Cl_2).

IR (Diamond-ATR, neat): 3345, 2966, 1771, 1735, 1671, 1496, 1400, 1396, 1292, 976 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 7 H), 7.01 (dd, *J* = 5.0, 3.6 Hz, 1 H), 5.68 (s, 1 H), 5.06 (d, *J* = 15.5 Hz, 1 H), 4.12 (d, *J* = 15.5 Hz, 1 H), 3.52 (d, *J* = 11.1 Hz, 1 H), 3.21 (d, *J* = 11.1 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 154.4, 136.2, 135.1, 129.1, 128.6, 128.2, 127.3, 127.2, 127.1, 112.1, 75.5, 54.5, 44.0, 30.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_4S$: 345.0904; found: 345.0899.

9-Benzyl-3,4-dimethyl-7-(thiophen-2-yl)-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6h)

Prepared using **4h** (0.46 mmol, 0.20 g), TBSOTf (1.1 mmol, 0.28 mL) and Et_3N (1.1 mmol, 0.02 mL) in accordance with GP3.

Yield: 53 mg (32%); light yellow solid; mp 159–160 °C; R_f = 0.32 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ –4.81 (*c* 0.022, CH_2Cl_2).

IR (Diamond-ATR, neat): 3346, 3064, 3032, 2935, 1774, 1739, 1432, 1399, 1338, 925 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 7 H), 7.00 (dd, *J* = 5.1, 3.6 Hz, 1 H), 5.72 (s, 1 H), 5.03 (d, *J* = 16.0 Hz, 1 H), 4.06 (d, *J* = 16.0 Hz, 1 H), 3.45 (q, *J* = 6.8 Hz, 1 H), 2.74 (s, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 154.2, 136.3, 135.6, 129.1, 128.3, 128.0, 127.3, 127.1, 113.3, 74.7, 57.6, 43.8, 28.3, 12.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_4S$: 359.1060; found: 359.1054.

3-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-[1-(methylamino)ethyl]-5-(thiophen-2-yl)oxazolidin-4-one (8h)

Yield: 12 mg (5%); yellow oil; R_f = 0.6 (20% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.26 (m, 7 H), 7.01 (m, 1 H), 5.78 (s, 1 H), 4.91 (d, *J* = 14.8 Hz, 1 H), 4.20 (d, *J* = 15.6 Hz, 1 H), 2.44 (q, *J* = 6.4 Hz, 1 H), 1.81 (s, 3 H), 1.12 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.12 (s, 3 H), –0.14 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 137.2, 128.9, 127.9, 127.0, 126.6, 126.5, 126.0, 125.6, 112.5, 61.7, 43.6, 33.7, 25.7, 18.0, 14.1, –3.2, –4.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{35}N_2O_3SSi$: 447.2132; found: 447.2128.

9-Benzyl-3-methyl-7-vinyl-1,6-dioxa-3,9-diazaspiro[4.4]nonane-2,8-dione (6i, 7i)

Prepared using **4i** (0.49 mmol, 0.18 g), TBSOTf (1.3 mmol, 0.32 mL) and Et_3N (1.3 mmol, 0.17 mL) in accordance with GP3.

Yield: 60 mg (42% combined yield); dr = 1.2:1.

Less polar diastereomer **6i** (major product); off-white solid; R_f = 0.32 (40% EtOAc/hexanes).

IR (Diamond-ATR, neat): 3353, 3063, 3031, 2927, 1773, 1726, 1393, 1362, 1311, 986 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 5.96 (ddd, *J* = 17.1, 10.5, 5.8 Hz, 1 H), 5.61 (ddd, *J* = 17.1, 1.5, 0.9 Hz, 1 H), 5.42 (ddd, *J* = 10.5, 1.5, 0.9 Hz, 1 H), 5.01 (d, *J* = 15.6 Hz, 1 H), 4.93 (dt, *J* = 5.8, 1.5 Hz, 1 H), 4.03 (d, *J* = 15.6 Hz, 1 H), 3.46 (d, *J* = 11.2 Hz, 1 H), 3.18 (d, *J* = 11.2 Hz, 1 H), 2.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 154.5, 135.3, 130.7, 129.0, 128.5, 128.1, 127.9, 120.1, 112.1, 78.6, 54.4, 43.7, 30.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_4$: 289.1183; found: 289.1182.

More polar isomer **7i** was isolated as a mixture of two diastereomers.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of **6i** and **7i**) = 7.51–7.23 (m, 10 H), 6.00–5.89 (m, 2 H), 5.63–5.53 (m, 2 H), 5.46–5.41 (m, 2 H), 5.04 (m, 1 H), 5.00 (d, *J* = 4.4 Hz, 2 H), 4.93 (m, 1 H), 4.06 (d, *J* = 4.4 Hz, 1 H), 4.02 (d, *J* = 4.4 Hz, 1 H), 3.48 (d, *J* = 4.8 Hz, 1 H), 3.45 (d, *J* = 4.4 Hz, 1 H), 3.24 (ABq, *J* = 11.2 Hz, 1 H), 3.19 (ABq, *J* = 11.2 Hz, 1 H), 2.78 (s, 3 H), 2.76 (s, 3 H).

9-Benzyl-3,7-dimethyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (6j, 7j)

Prepared, using **4j** (0.57 mmol, 0.20 g), TBSOTf (1.43 mmol, 0.38 mL) and Et_3N (1.43 mmol, 0.20 mL) in accordance with GP3.

Yield: 47 mg (30% combined yield); dr = 1.2:1.

Less polar isomer **6j**[15] (major product): off-white solid; R_f = 0.51 (50% EtOAc/hexanes).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 5.00 (d, *J* = 16.0 Hz, 1 H), 4.61 (q, *J* = 12.0 Hz, 1 H), 4.03 (d, *J* = 16.0 Hz, 1 H), 3.40 (d, *J* = 12.0 Hz, 1 H), 3.22 (d, *J* = 12.0 Hz, 1 H), 2.76 (s, 3 H), 1.50 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 154.8, 135.5, 129.0, 129.0, 128.4, 127.8, 123.3, 111.6, 101.7, 54.1, 43.5, 30.2, 17.2.

More polar isomer **7j** was isolated as a mixture of two diastereomers.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of **6j** and **7j**) = 7.38–7.30 (m, 5 H), 7.29–7.21 (m, 5 H), 5.01 (d, *J* = 7.6 Hz, 1 H), 4.97 (d, *J* = 7.7 Hz, 1 H), 4.62 (q, *J* = 6.8 Hz, 1 H), 4.55 (q, *J* = 7.0 Hz, 1 H), 4.04 (d, *J* = 3.8 Hz, 1 H),

4.00 (d, *J* = 3.7 Hz, 1 H), 3.41 (d, *J* = 3.0 Hz, 1 H), 3.38 (d, *J* = 3.0 Hz, 1 H), 3.22 (d, *J* = 11.1 Hz, 1 H), 3.16 (d, *J* = 11.0 Hz, 1 H), 2.75 (s, 3 H), 2.74 (s, 3 H), 1.54 (d, *J* = 7.0 Hz, 3 H), 1.50 (d, *J* = 6.8 Hz, 3 H).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706660.

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