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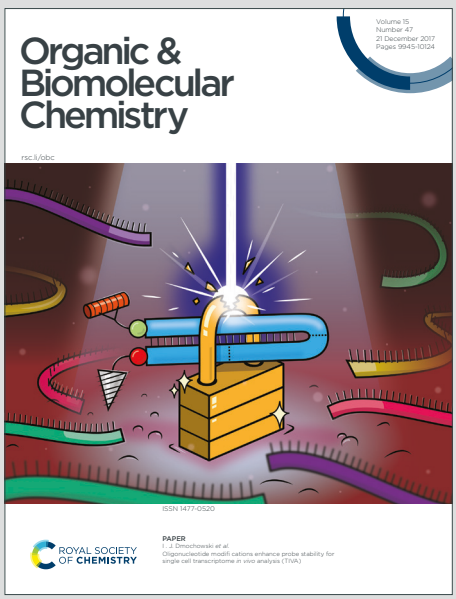

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ARTICLE

Synthesis of α-Aminooxy Amides through [3+3] Cycloaddition and $Sc(OTf)_3$-Catalyzed Double C-N Bond Cleavage in One-Pot Reaction

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Various α-aminooxy amides bearing a quaternary carbon at the α-position were prepared in good to excellent yields under mild reaction conditions from *N*-vinyl nitrones and α-bromohydroxamates. The *N*-vinyl nitrones tolerate a wide range of *N*-vinyl fluorenone nitrones and *N*-vinyl isatin nitrones. Mechanistic studies show that the reaction initially undergoes [3+3] cycloaddition between *N*-vinyl nitrones and aza-oxyallyl cations generated from α-bromohydroxamates to afford six-membered N,O-heterocycles, and then take place double C-N bond cleavage in the presence of $Sc(OTf)_3$ catalyst. A selective N-O bond cleavage of the obtained α-aminooxy amides is also realized by Fe/NH_4Cl conditions. Furthermore, gram scalable preparations of α-aminooxy amides are easily achieved.

Introduction

The introduction of an aminooxy functional group to the α-position of a carbonyl compound has attracted great attention in synthetic chemistry and medicine because the formation of C-O-NR_2 linkage is an important and useful building block in various natural products and pharmaceuticals.[1] The α-aminooxy carbonyl compounds can be not only converted to α-hydroxy ketones and 1,2-diols by reduction, but also extensively served as an efficient tool for various applications in carbohydrates and glycoconjugates due to their unusual conformational properties of N-O bonds.[2] Peptides containing an aminooxy group, namely α-aminooxy peptides, usually show a great biological activities due to their novel secondary structure including hydrogen-bonded turns or N-O turns.[3] In particular, the oxime ether group offers very attractive approaches for drug design in a variety of pharmaceutical preparation and pesticides, which exhibit excellent anticancer and anti-inflammatory activities, and larvicidal activities against pest (Figure 1).[4] Therefore, development of new methods toward the introduction of an aminooxy group to the α-position of a carbonyl compound will be desirable.

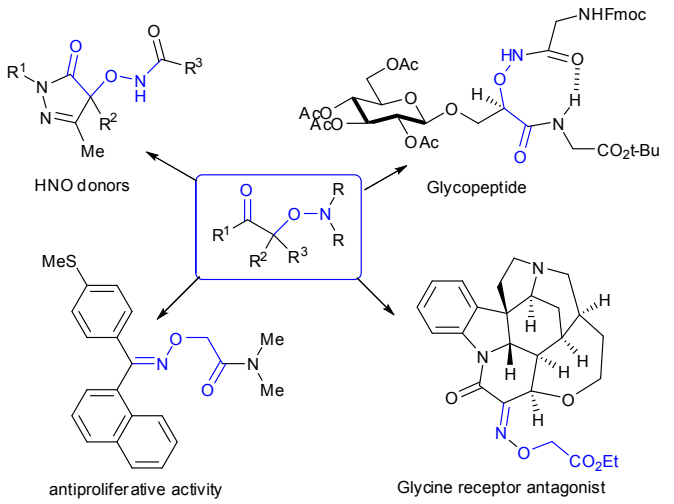

Figure 1. Selected examples containing α-aminooxy carbonyl groups

Methods for the preparation of α-aminooxy carbonyl compounds have been extensively developed in the last decades.[5] For examples, nucleophilic substitution of α-halocarbonyl compounds with *N*-hydroxyphthalimides or oximes was the one of the most used strategies to prepare α-aminooxy carbonyl compounds (Scheme 1-A).[6] However, This conventional method was always favorable to no substituent or one subsituent at the α-position of the α-halocarbonyl compounds. The α-halocarbonyl compounds bearing a quaternary carbon at the α-position usually failed and occured elimination reaction of halides in some cases. Recently, Yamamoto and coworkers found that a Lewis acid-catalyzed regioselective synthesis of α-aminooxy ketones by *N*-nitroso aldo reaction of enolate compounds while α-hydroxyamino ketones were obtained without adding catalyst (Scheme 1-B).[7] Although it figured out the preparation of α-aminooxy carbonyl compounds containing α-quaternary carbons at the

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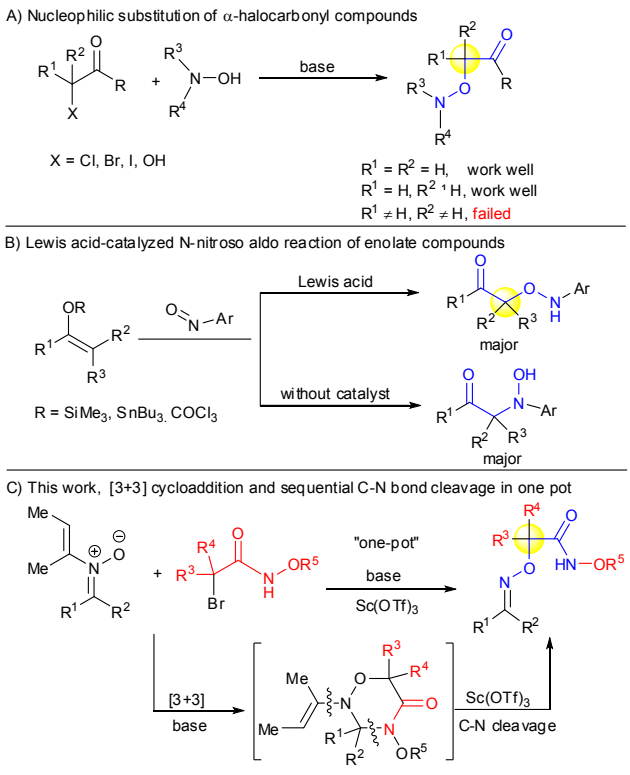
α-position, it still suffered from the addition regioselectivity of *N*-nitrosobenzene in some enantioselective catalytic systems.[8] From the above examples we can see, some elegant methods toward the preparation of α-aminooxy carbonyl compounds have been developed, but the development of novel and mild methods is still required, especially for the preparation of α-aminooxy carbonyl compounds containing a quaternary carbon at the α-position because the 3D structure of the quaternary carbon sometimes improves the biological activies.

Recently, nitrone served as 1,3-dipole, has attracted great interest due to its efficient transformations in the cycloaddition reaction in organic synthesis.[9] The [3+3] cycloaddition of nitrones with aza-oxyallyl cations has been successfully developed to prepare 1,2,4-oxadiazinan-5-ones before.[10,11] During the studies of cycloaddition of *N*-vinyl fluorenone nitrones in our group,[12] we found that *N*-vinyl nitrones and aza-oxyallyl cations underwent [3+3] cycloaddition to afford various spirofluorenyl-1,2,4-oxadiazinan-5-ones under the metal-free conditions in good yields.[12b] Further studies showed that the [3+3] cycloaddition and sequential $Sc(OTf)_3$ catalyzed double C-N bond cleavage of six-membered heterocyclic adducts could afford α-aminooxy carbonyl compounds bearing a quaternary carbon at the α-position in a one-pot reaction (Scheme 1-C). The *N*-vinyl nitrones were easily prepared by the copper-mediated cross-coupling reaction of oximes with vinylboronic acids under mild reaction conditions.[13] Herein, we report a novel method toward the synthesis of α-aminooxy amides through [3+3] cycloaddition and $Sc(OTf)_3$-catalyzed double C-N bond cleavage in a one-pot reaction under mild reaction conditions.

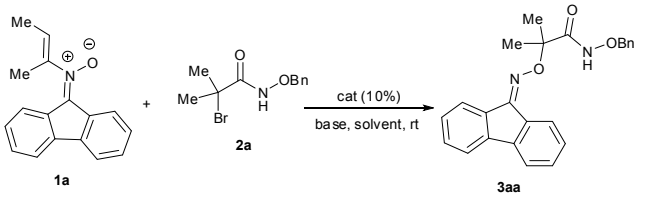


Scheme 1. Strategies for preparing α-aminooxy carbonyl compounds

Results and discussion

Initially, *N*-vinyl fluorenone nitrone **1a** and α-bromohydroxamate **2a** were chosen as model substrates. As shown in Table 1, nitrone **1a** reacting with **2a** under K_2CO_3 as base in MeCN at room temperature did not afford α-(9-fluorenylideneaminooxy)amide **3aa** in the absence of catalyst and only the [3+3] cycloadduct was obtained (Table 1, entry 1). Adding $PdCl_2$ and $RhCl_3$ delivered **3aa** in 59% and 65% yields, respectively (Table 1, entries 2-3). But product **3aa** was not observed when CuI, AgOTf, and $Mn(OAc)_2$ were used as catalysts (Table 1, entries 4-6). Pleasingly, Adding 10 mol% of $Sc(OTf)_3$ as the catalyst afforded **3aa** in 93% yield (Table 1, entry 7). Solvent screening showed that DCE gave **3aa** in 64% yield while lower yields were obtained in toluene, THF, and DMF (Table 1, entries 8-11). To our surprise, the most used hexafluoroisopropanol (HFIP) solvent in aza-oxyallyl cation chemistry only delivered **3aa** in 10% yield owing to the easy decomposition of *N*-vinyl fluorenone nitrone to 9-fluorenone in HFIP (Table 1, entry 12). The effect of base was also tested. Good yields of **3aa** were obtained with inorganic bases, such as Na_2CO_3, Cs_2CO_3, and KOH, while organic base such as NEt_3 gave **3aa** only in 14% yield (Table 1, entries 13-16). The reaction temperature was also evaluated. Increasing the temperature to 60 °C and 80 °C decreased the yield of **3aa** to 83% and 81%, respectively, and further decreased to 58% at 100 °C (Table 1, entries 17-19). When **2a** was decreased to 1.0 equiv., product **3aa** was only obtained in 80% yield and nitrone **1a** was recovered perhaps owing to the *β*-elimination of **2a** to form α,β-unsaturated amide in the presence of base (Table 1, entry 20). Therefore, the optimal conditions for preparing **3aa** was $Sc(OTf)_3$ (10 mol%) as catalyst and K_2CO_3 as base in MeCN at room temperature.

Table 1. Optimization of the Reaction Conditions.[a]



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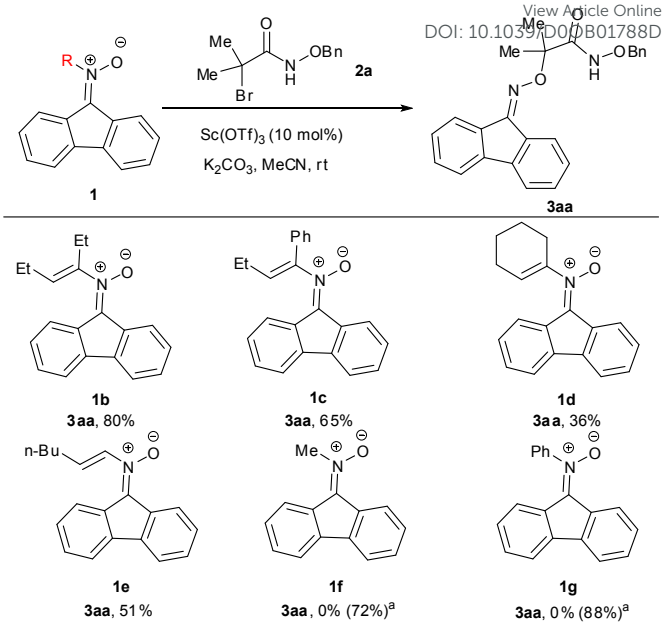
entry	cat	base	solvent	**3aa**%[b]
1	-	K_2CO_3	MeCN	-
2	$PdCl_2$	K_2CO_3	MeCN	59
3	$RhCl_3$	K_2CO_3	MeCN	65
4	CuI	K_2CO_3	MeCN	<5
5	AgOTf	K_2CO_3	MeCN	<5
6	$Mn(OAc)_2$	K_2CO_3	MeCN	<5
7	$Sc(OTf)_3$	K_2CO_3	MeCN	93
8	$Sc(OTf)_3$	K_2CO_3	DCE	64
9	$Sc(OTf)_3$	K_2CO_3	toluene	31
10	$Sc(OTf)_3$	K_2CO_3	THF	21
11	$Sc(OTf)_3$	K_2CO_3	DMF	<5
12	$Sc(OTf)_3$	K_2CO_3	HFIP	10
13	$Sc(OTf)_3$	Na_2CO_3	MeCN	78
14	$Sc(OTf)_3$	Cs_2CO_3	MeCN	56
15	$Sc(OTf)_3$	KOH	MeCN	64
16	$Sc(OTf)_3$	NEt_3	MeCN	14
17	$Sc(OTf)_3$	K_2CO_3	MeCN	83[c]
18	$Sc(OTf)_3$	K_2CO_3	MeCN	81[d]
19	$Sc(OTf)_3$	K_2CO_3	MeCN	58[e]
20	$Sc(OTf)_3$	K_2CO_3	MeCN	80[f]

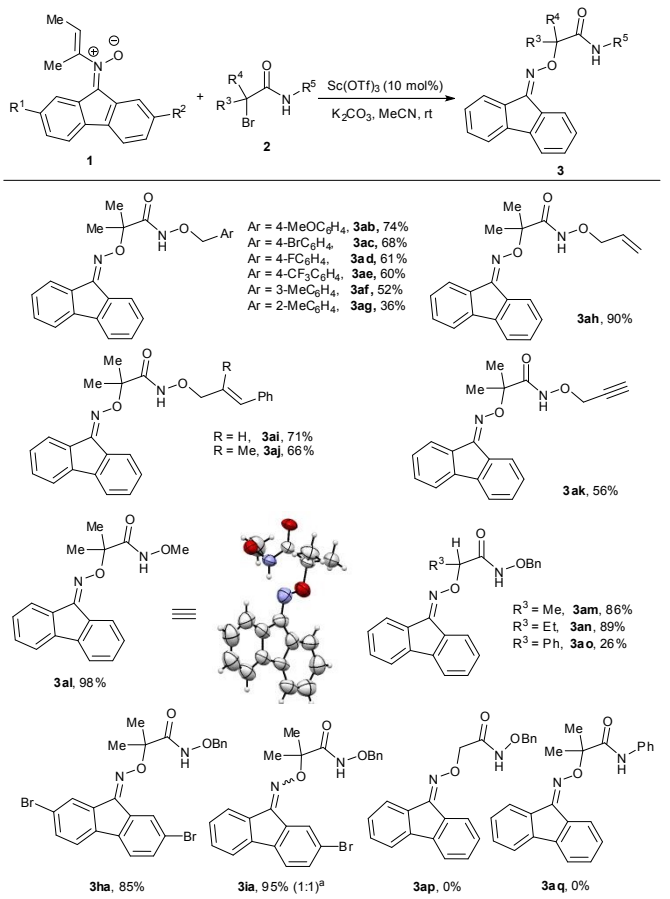
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), catalyst (10 mol%), base (0.4 mmol, 2.0 equiv.), solvent (2.0 mL), 12−24 h; [b] isolated yield; [c] ran at 60 °C; [d] ran at 80 °C; [e] ran at 100 °C; [f] **2a** (0.2 mmol, 1.0 equiv.).

Since the *N*-vinyl group of nitrone **1a** was dropped after the reaction completed, various *N*-substituted groups of nitrones **1** were explored to study the effect on the yield of **3aa** under the optimal conditions. As shown in Scheme 2, *N*-vinyl groups of nitrone, including monosubstituted, linear and cyclic disubstituted vinyl groups (**1b-1e)**, all these *N*-vinyl moieties delivered desired product **3aa** in good yields under the standard conditions. However, nitrones **1f** bearing *N*-methyl group and **1g** bearing *N*-phenyl group did not afford **3aa** even after 48 h, and only delivered their [3+3] cycloadducts in 72% and 88% yields in the presence of $Sc(OTf)_3$, respectively. These results suggested that only the *N*-vinyl groups of [3+3] cycloadducts from *N*-vinyl nitrones smoothly underwent C-N bond cleavage.



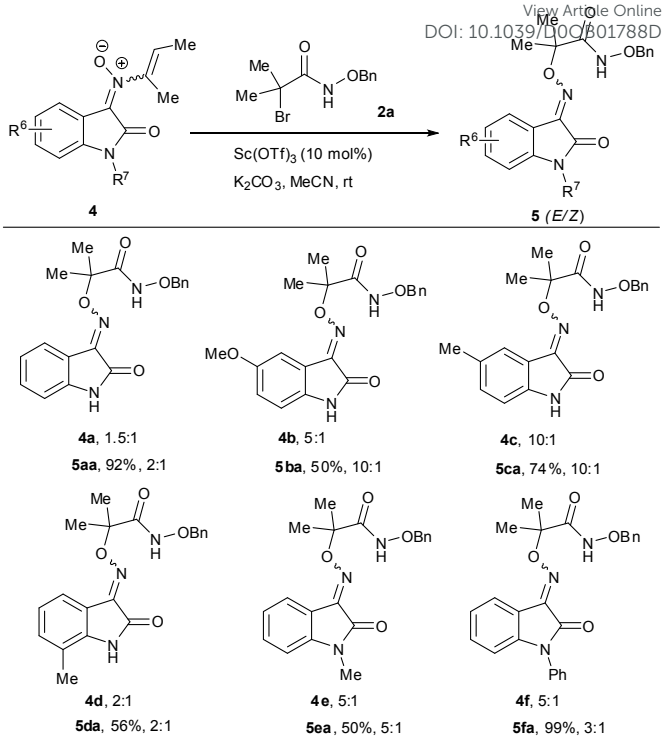
Scheme 2. The *N*-substituent effect of nitrones **1** on the formation of **3aa**. (Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), $Sc(OTf)_3$ (10 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), 12-48 h, isolated yield; [a] the yield of its [3+3] cycloadduct.)

Next, the substrate scope of nitrones **1** and α-bromohydroxamates **2** was evaluated to prepare α-aminooxyamides **3** (Scheme 3). It was found that a wide range of α-bromohydroxamates **2** reacting with nitrone **1a** were smoothly converted to α-(9-fluorenylideneaminooxy)amides **3ab-3ao** in moderate to excellent yields under the standard conditions. The structure of compound **3** was confirmed by X-ray diffraction analysis of compound **3al**.[14] The R^5 group could be present with different alkyloxy and aryloxy groups. Pleasingly, the R^5 group was compatible with vinyl and alkynyl groups (**3ah-3ak**). When the R^3 group was methyl or ethyl substituent and the R^4 group was hydrogen, *N*-benzyloxy α-bromoamides (**2m** and **2n**) produced **3am** and **3an** in 86% and 89% yields, respectively, while **2o** with a phenyl in R^3 group gave **3ao** only in 26% yield. The 9-fluorenone nitrones also tolerated bromo group in the both aryl groups of fluorenone and afforded **3ha** and **3ia** in 85% and 95% yields, respectively. However, a 1:1 *E/Z* ratio of *N*-vinyl fluorenone nitrone **1h** with only one bromo group afforded product **3ha** with 1:1 *E/Z* isomer ratio of the C=N bond, which might be owing to the 1:1 diastereomers of its cycloaddition product suggesting that the diastereoselectivity of cycloaddition product had a great impact on the *E/Z* ratio of α-aminooxy amides. To our surprise, **2p** bearing R^3 and R^4 groups with hydrogen and **2q** with a *N*-phenyl group did not deliver the desired product **3ap** and **3aq** under the standard conditions because these two substrates did not produce their [3+3] cycloaddition intermediates, which might be owing to these substituted groups cannot stabilize the aza-oxyallyl cations. This method provides a good approach to access α-aminooxy hydroxamates bearing two or three substituents at the α-position of a carbonyl group.



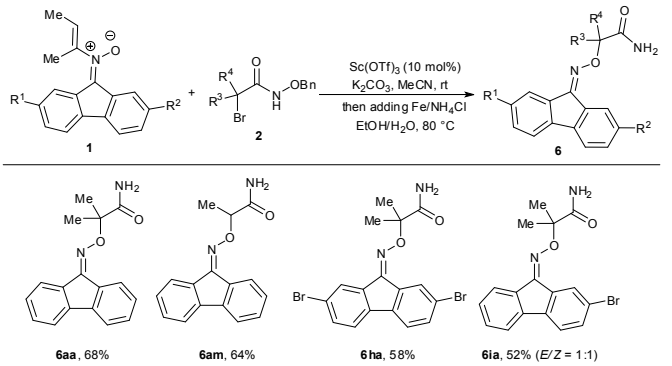
Scheme 3. Substrate scope of nitrones **1** and α-bromohydroxamates **2** for the preparation of compounds **3**. (Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Sc(OTf)_3$ (10 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), 12-18 h, isolated yield; [a] *E/Z* ratio of the C=N bond.)

In addition to *N*-vinyl fluorenone nitrones, *N*-vinyl isatin nitrones **4** were also tested. As shown in Scheme 4, aryl moiety of isatin nitrones bearing methoxy and methyl groups (**4b-4d**) were applicable to this cascade reaction, affording the corresponding α-aminooxy hydroxamates in moderate yields (**5ba-5da**). The R^7 group was compatible with both free NH and N-protecting groups. For examples, nitrones bearing N-R^7 with Me and Ph groups, resulted in **5ea** and **5fa** in 50% and 99% yields, respectively. The *E/Z* ratios of C=N bond of compounds **5** were ranging from 2:1 to 10:1, which might have correlations with the nitrone *E/Z*-geometry. For examples, a 1.5:1 *E/Z* ratio of **4a** delivered **5aa** with a 2:1 *E/Z* ratio, however, **4b** with 5:1 *E/Z* ratio afforded **5ba** with 10:1 *E/Z* ratio.



Scheme 4. Scope of *N*-vinyl isatin nitrone **4** for the preparation of **5**. (Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), $Sc(OTf)_3$ (10 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), 12-18 h, isolated yield, *E/Z* ratio of the C=N bond.)

Interestingly, treating *N*-vinyl nitrone **1a** with **2a** for 12 h under the optimal conditions and then adding with Fe powder and NH_4Cl in a mixed solvent of EtOH and H_2O at 80 °C smoothly afforded α-(9-fluorenylideneaminooxy)amide **6aa** in 68% yield.[15] The structure of **6aa** was determined by its X-ray diffraction analysis.[14] As shown in Scheme 5, different types of nitrones and α-bromohydroxamates produced the corresponding amides (**6am**, **6ha**, and **6ia**) in moderate yields. These results showed that the reaction underwent both C-N and N-OBn bond cleavage, while the N-O bond of nitrone remained, showing that the adjacent acyl group allows the N-OBn bond to be more labile in cleavage.



Scheme 5. Scope of nitrone **1** for the preparation of **6** in two steps in one pot. (Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Sc(OTf)_3$ (10 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), 12 h; Then, adding Fe/NH_4Cl and EtOH/H_2O, 80 °C for 3-6 h; isolated yield.)

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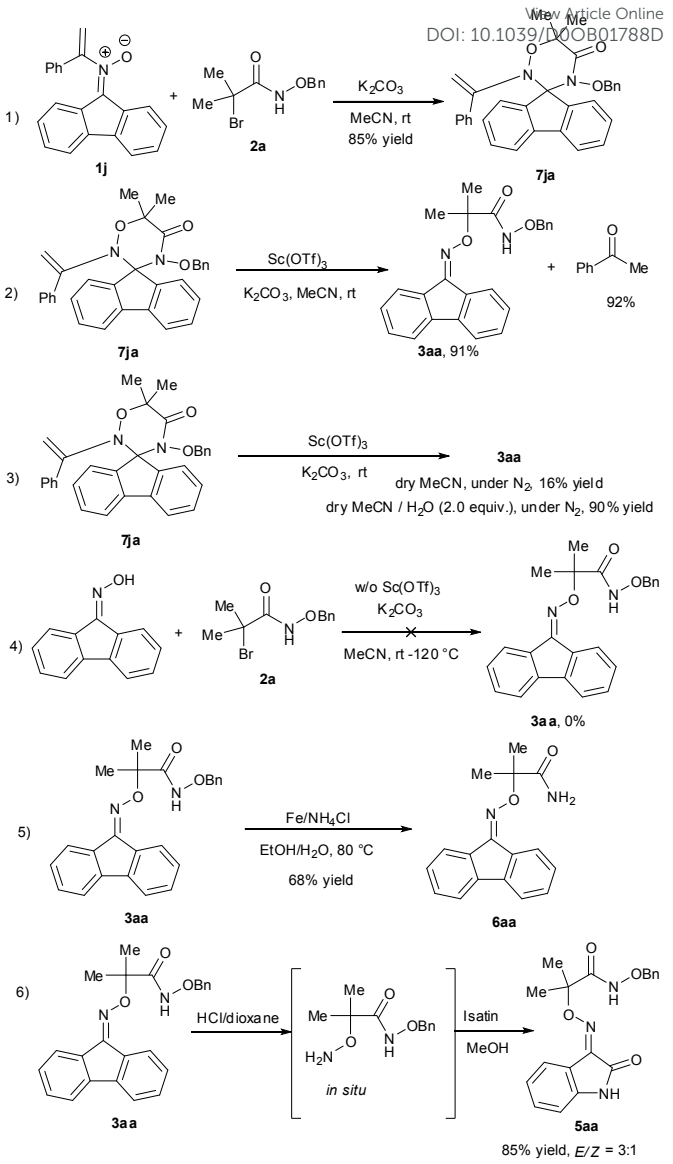
To better understand the mechanism for the formation of α-(9-fluorenylideneaminooxy) hydroxamates, control experiments were performed (Scheme 6). When *N*-vinyl nitrone **1j** and **2a** were carried out in the absence of $Sc(OTf)_3$ catalyst, [3+3] cycloadduct **7ja** was obtained in 85% yield, which was then conducted under the $Sc(OTf)_3$-catalyzed conditions affording **3aa** in 91% yield accompanied by acetophenone in 92% yield (Scheme 6-1 and 6-2). These results indicated that the vinyl group of compound **7ja** was converted to ketone by hydrolysis. Interestingly, when compound **7ja** was performed in dry MeCN under N_2 atmosphere, **3aa** was only obtained in 16% yield while 90% yield was obtained by adding additional 2.0 equiv. of water (Scheme 6-3). These results showed that water promoted the C-N bond clveage step. However, the additional water in one-pot reaction was not required because the water was produced during the formation of aza-oxyallyl cation in the presence of K_2CO_3. When 9-fluoreone oxime and **2a** were subjected to the standard conditions, product **3aa** was not observed, even though the temperature was increased to 120 °C (Scheme 6-4), suggesting that the nucleophilic substitution of α-bromohydroxamate **2** with oxime is difficult. Treating **3aa** with Fe/NH_4Cl reduction conditions afforded **6aa** in 68% yield, which indicated that **6aa** was generated from **3aa** by N-O bond reduction (Scheme 6-5). To know more about the formation of *E/Z* ratio of compound **5** in Scheme 4, we performed the hydrolysis of **3aa** with HCl in dioxane to generate α-aminooxy amides *in situ*, then condensation with isatin to afford compound **5aa** in 85% yield with a 3:1 *E/Z* ratio (Scheme 6-6). This easy hydrolysis also offers a method to prepare other types of α-aminooxy amides by condensation with various ketones.



Scheme 6. Control experiments

Based on the above experimental results, a possible mechanism for the formation of **3aa** from *N*-vinyl nitrone **1a** and α-bromohydroxamate **2a** was proposed (Scheme 7). α-Bromohydroxamate **2a** produced aza-oxyallyl cation **A** accompanied by water in the presence of K_2CO_3, which underwent [3+3] cycloaddition with nitrone **1a** to provide six-membered N,O-heterocycle **7**. Then, compound **7** took place C-N bond cleavage in the presence of Lewis acid catalyst $Sc(OTf)_3$ and water to afford intermediate **B** and *N*-vinyl moiety was converted to the corresponding ketone by hydrolysis. Finally, C-N bond cleavage of **B** and sequential H-migration via intermediate **C** gave product **3aa**.

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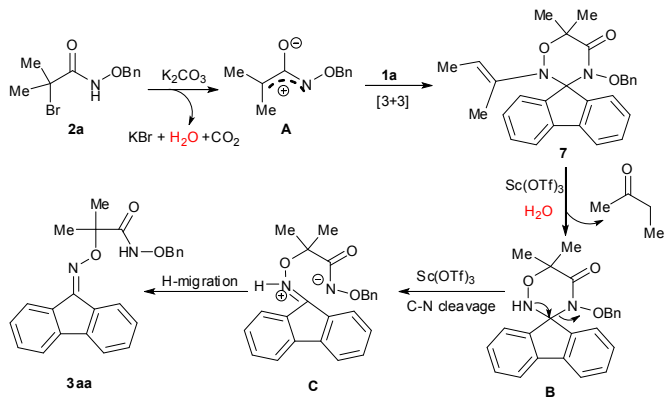
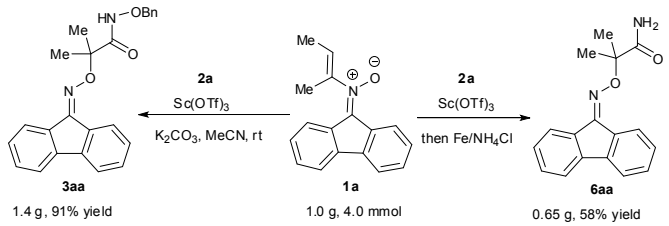


Scheme 7. Proposed mechanism

The scalability of this $Sc(OTf)_3$-catalyzed cascade reaction was then evaluated (Scheme 8). When 1.0 g of nitrone **1a** was reacted with **2a** under $Sc(OTf)_3$ conditions, product **3aa** was obtained in 91% yield (1.4 g). Treating 1.0 g of nitrone **1a** with **2a** and sequential reduction by Fe/NH_4Cl conditions, delivered **6aa** in 58% yield (0.65 g). These easy gram scale performances allow these compounds more potential applications in organic synthesis and their biological activity studies.



Scheme 8. Gram scale preparations

Conclusions

We have developed an efficient method for the synthesis of α-aminooxy amides in good to excellent yields through [3+3] cycloaddition and $Sc(OTf)_3$-catalyzed double C-N bond cleavage in one pot reaction from *N*-vinyl nitrones and α-bromohydroxamates. The present method features mild reaction coniditions, broad substrate scope, easily available starting materials, new application of *N*-vinyl nitrones, and preparation of α-aminooxy carbonyl group bearing a quaternary carbon at the α-position.

Experimental

^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 400 MHz and 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Chromatography was performed using with 300-400 mesh silica gel (SiO_2). Unless otherwise noted, all reagents and solvents were obtained from commercial sources and, where appropriate, purified prior to use. *N*-Vinyl fluorenone nitrones **1a-1j**[13a], N-vinyl nitrones **4a-4f**[13b], α-bromohydroxamates **2a-2q**[16], and **7ja**[12b], were prepared according to the literature methods and their spectral data matched literature values.

General procedure for the synthesis of α-(9-fluorenylideneaminooxy) amides 3: In a 25 mL round-bottom flask was charged with $Sc(OTf)_3$ (10 mol%), *N*-vinyl fluorenone nitrones **1** (0.2 mmol), α-bromohydroxamates **2** (0.4 mmol, 2.0 equiv.), and K_2CO_3 (0.4 mmol, 2.0 equiv.). Then, MeCN (2.0 mL) was added. The resulting mixture was stirred vigorously at room temperature for 12−24 h (monitored by TLC). At this time, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded with silica gel, 1/4 to 1/2, ethyl acetate/petroleum ether) to provide α-aminooxy amides **3**.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(benzyloxy)-2-methylpropanamide (3aa). A white solid, 0.072 g, 93% yield. Mp: 90−91 °C; ^1H NMR (400 MHz, DMSO): *δ* 11.20 (s, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.55−7.52 (m, 1H), 7.49−7.45 (m, 1H), 7.41−7.32 (m, 4H), 7.28−7.24 (m, 3H), 4.78 (s, 2H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, DMSO): *δ* 170.5, 152.4, 141.3, 140.2, 136.3, 135.2, 132.0, 130.9, 130.1, 130.0, 129.6, 128.9, 128.8, 128.7, 128.6, 121.9. 121.1, 120.9, 83.8, 77.2, 24.7; IR (thin film) 3456, 3022, 2924, 1494, 1448, 1363, 1187, 964 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_3$ $(M+H)^+$ 387.1703, found 387.1693.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(4-methoxybenzyloxy)-2-methylpropanamide (3ab). A white solid, 0.062 g, 74% yield. Mp: 81−82 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.59−7.54 (m, 3H), 7.39−7.33 (m, 2H), 7.23−7.19 (m, 2H), 7.16 (d, *J* = 8.0, 2H), 6.54 (d, *J* = 8.5, 2H), 4.76 (s, 2H), 3.56 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 159.8, 153.6, 141.8, 140.3, 135.1, 131.5, 130.9, 130.4, 130.0, 129.1, 128.3, 128.1, 127.0, 122.0, 120.0, 119.9, 113.7, 84.7, 77.8, 55.0, 24.6, 24.5; IR (thin film) 3454, 2926, 1637, 1451, 1098, 961 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_4$ $(M+H)^+$ 417.1809, found 417.1806.

2-(((9H-Fluoren-9-ylidene)amino)oxy)-*N*-((4-bromobenzyl) oxy)-2-methylpropanamide (3ac). A white solid, 0.064 g, 68% yield. Mp: 94−95 °C; ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.71 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.67−7.60 (m, 3H), 7.47−7.40 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.83 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.2, 153.7, 141.8, 140.3, 134.9, 133.9, 131.6, 131.5, 130.6, 130.5, 129.9, 129.0, 128.3, 128.1, 122.8. 121.8, 120.2, 120.1, 84.6, 24.5; IR (thin film) 3404, 2924, 1680, 1450, 1164, 960 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}BrN_2O_3$ $(M+H)^+$ 465.0808, found 465.0807.

2-(((9H-Fluoren-9-ylidene)amino)oxy)-*N*-((4-fluorobenzyl) oxy)-2-methylpropanamide (3ad). A white solid, 0.049 g, 61%

yield. Mp: 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.68−7.62 (m, 3H), 7.48−7.40 (m, 2H), 7.29−7.26 (m, 4H), 6.79−6.74 (m, 2H), 4.85 (s, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.2, 164.0 (d, *J* = 245.8 Hz), 153.7, 141.9, 140.3, 135.0, 131.7, 131.1, 131.0, 130.8 (d, *J* = 3.6 Hz), 130.6, 130.0, 129.1, 128.3, 128.1, 121.9. 120.2, 120.1, 115.5, 115.2, 84.6, 24.6; IR (thin film) 3672, 2924, 1510, 1259, 1038, 971 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{22}FN_2O_3$ $(M+H)^+$ 405.1609, found 405.1608.

2-(9H-Fluoren-9-ylideneaminooxy)-2-methyl-*N*-(4-(trifluoromethyl)benzyloxy)propanamide (3ae). A white solid, 0.054 g, 60% yield. Mp: 101−102 °C; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 11.05 (s, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.89−7.83 (m, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.60−7.50 (m, 5H), 7.48 (t, *J* = 14.8 Hz, 1H), 7.39−7.31 (m, 2 H), 4.88 (s, 2 H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 170.7, 152.5, 141.3, 141.1, 140.2, 135.1, 132.0, 131.0, 130.1, 130.0, 129.9, 129.3, 128.9, 128.7, 128.6 (q, *J* = 269.7 Hz), 126.0, 125.4 (q, *J* = 3.6 Hz), 123.3, 121.9, 121.1, 121.0, 120.6, 83.8, 76.2, 24.6; IR (thin film) 3451, 2928, 1659, 1481, 1167, 964 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{22}F_3N_2O_3$ $(M+H)^+$ 455.1577, found 455.1575.

2-(((9H-Fluoren-9-ylidene)amino)oxy)-2-methyl-*N*-((3-methylbenzyl)oxy)propanamide (3af). A yellow oil, 0.042 g, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.62−7.59 (m, 2H), 7.47−7.38 (m, 2H), 7.28−7.26 (m, 2H), 7.14 (s, 1H), 7.10 (d, *J* = 6.4 Hz, 1H), 7.00−6.97 (m, 2H), 4.87 (s, 2H), 2.16 (s, 3H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 153.6, 141.9, 140.3, 138.2, 135.0, 134.8, 131.5, 130.4, 130.0, 129.7, 129.4, 129.1, 128.3, 128.1, 126.2, 122.0, 120.1, 119.9, 84.6, 24.6, 21.1; IR (thin film) 3317, 2926, 1678, 1452, 1264, 960 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3$ $(M+H)^+$ 401.1860, found 401.1859.

2-(((9H-Fluoren-9-ylidene)amino)oxy)-2-methyl-*N*-((2-methylbenzyl)oxy)propanamide (3ag). A yellow oil, 0.029 g, 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.67−7.61 (m, 3H), 7.47−7.39 (m, 2H), 7.30−7.26 (m, 3H), 7.21 (d, *J* = 7.6, 1H), 7.08−7.06 (m, 2H), 6.90−6.86 (m, 1H), 4.95 (s, 2H), 2.39 (s, 3H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 153.7, 141.9, 140.3, 138.1, 135.1, 132.8, 131.6, 130.6, 130.5, 130.4, 130.1, 129.1, 128.9, 128.3, 128.1, 125.6, 122.0, 120.1, 119.9, 84.7, 24.6, 18.9; IR (thin film) 3598, 2989, 1462, 1276, 1261, 750 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3$ $(M+H)^+$ 401.1860, found 401.1859.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(allyloxy)-2-methylpropanamide (3ah). A white solid, 0.060 g, 90% yield. Mp: 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.72 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.22−7.17 (m, 1H), 5.87−5.77 (m, 1H), 5.21 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.30 (d, *J* = 6.0 Hz, 1H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.1, 153.8, 141.8, 140.3, 135.0, 131.8, 131.6, 130.4, 130.0, 129.1, 128.2, 128.0, 121.9, 120.9, 120.1, 119.9, 84.6, 77.2, 24.6; IR (thin film) 3220, 2971, 1654, 1495, 1448, 963 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_3$ $(M+H)^+$ 337.1547, found 337.1535.

(*E*)-2-(((9H-Fluoren-9-ylidene)amino)oxy)-*N*-(cinnamyloxy)-2-methylpropanamide (3ai). A yellow solid, 0.058 g, 71% yield. Mp: 76−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.66−7.56 (m, 3H), 7.44−7.35 (m, 2H), 7.26−7.18 (m, 7H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.30−6.23 (m, 1H), 4.55 (d, *J* = 6.8 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 153.8, 141.8, 140.3, 136.4, 135.9, 135.0, 131.6, 130.4, 130.0, 129.1, 128.5, 128.3, 128.1, 128.0, 126.6, 122.6, 121.9, 120.1, 120.0, 84.7, 24.6; IR (thin film) 3689, 2924, 1740, 1451, 1267, 965 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{25}N_2O_3$ $(M+H)^+$ 413.1860, found 413.1858.

(*E*)-2-(((9H-Fluoren-9-ylidene)amino)oxy)-2-methyl-*N*-((2-methyl-3-phenylallyl)oxy) propanamide (3aj). A yellow oil, 0.056 g, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.64−7.59 (m, 2H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.44−7.40 (m, 1H), 7.37−7.33 (m, 1H), 7.27−7.16 (m, 5H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.45 (s, 1H), 4.43 (s, 2H), 1.91 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 153.8, 141.9, 140.3, 136.6, 134.9, 132.4, 131.5, 131.0, 130.4, 130.0, 129.1, 128.8, 128.7, 128.2, 128.0, 126.7, 121.9, 120.1, 120.0, 84.7, 82.9, 24.7, 15.8; IR (thin film) 3696, 2989, 2368, 1451, 1275, 961 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{27}N_2O_3$ $(M+H)^+$ 427.2016, found 427.2013.

2-(9H-Fluoren-9-ylideneaminooxy)-2-methyl-*N*-(prop-2-ynyloxy)propanamide (3ak). A white solid, 0.037 g, 56% yield. Mp: 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.02 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* =8.0 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.22-7.19 (m, 1H), 4.48 (d, *J* = 2.0 Hz, 2H), 2.16 (s, 1H), 1.68 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 170.6, 152.5, 141.3, 140.2, 135.2, 134.6, 132.0, 130.9,130.0, 128.9, 122.0, 121.0, 120.9, 83.8, 79.0, 78.9, 62.7, 24.7; IR (thin film) 3454, 2971, 2094, 1637, 1080, 974, 617 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_2O_3$ $(M+H)^+$ 335.1390, found 335.1389.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-methoxy-2-methyl propanamide (3al). A white solid, 0.061g, 98% yield. Mp: 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.80 (s, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.38 (t, *J* = 9.0 Hz, 1H), 7.31 (t, *J* = 8.5 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H), 7.19 (t, *J* = 9.0 Hz, 1H), 3.65 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 172.5, 153.9, 141.9, 140.3, 135.0, 131.6, 130.5， 130.1, 129.2, 128.3, 128.1, 122.0, 120.1, 120.0, 84.6, 64.3, 24.6; IR (thin film) 3264, 2929, 2805, 1921, 1661, 1482, 956 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}N_2O_3$ $(M+H)^+$ 311.1390, found 311.1389.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(benzyloxy)propan amide (3am). A white solid, 0.064g, 86% yield. Mp: 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.57 (s, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.57−7.52 (m, 3H), 7.38−7.31 (m, 2H), 7.23−7.15 (m, 4H), 7.04−7.03 (m, 3H), 4.90−4.80 (m, 3H), 1.61 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.4, 154.0, 141.8, 140.4, 134.8, 134.6, 131.6, 130.5, 130.0, 129.1, 129.0, 128.7, 128.4, 128.3, 128.1, 122.0, 120.0, 119.9, 80.9, 78.3, 17.4; IR (thin film) 3204, 2988, 1666, 1448, 1045, 974 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_2O_3$ $(M+H)^+$ 373.1547, found 373.1532.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(benzyloxy)butan amide (3an). A white solid, 0.069 g, 89% yield. Mp: 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.58−7.50 (m, 3H), 7.36−7.29 (m, 2H), 7.21−7.14 (m, 4H), 7.03−7.01 (m, 3H), 4.86−4.73 (m, 3H), 2.09−1.91 (m, 2H), 1.03 (t J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 154.0, 141.7, 140.3, 134.8, 134.7, 131.6, 130.5, 130.0, 129.1, 129.0, 128.6, 128.4, 128.3, 128.1, 122.0, 120.1, 119.9, 85.9, 78.3, 24.9, 9.6; IR (thin film) 3475, 3199, 2971, 1670, 1449, 976 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_3$ (M+H)$^+$ 387.1703, found 387.1686.

2-(9H-Fluoren-9-ylideneaminooxy)-*N*-(benzyloxy)-2-phenyl acetamide (3ao). A white solid, 0.023 g, 26% yield. Mp: 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.95 (d, J = 6.4 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.56−7.52 (m, 2H), 7.46 (d, J = 4.4 Hz, 2H), 7.35−7.33 (m, 4H), 7.22−7.18 (m, 3H), 7.16−7.12 (m, 2H), 7.07−7.06 (m, 3H), 5.80 (s, 1H), 4.85−4.82 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.3, 153.4, 141.4, 140.4, 136.3, 136.1, 134.7, 132.5, 131.3, 129.9, 129.8, 129.6, 129.4, 129.2, 129.1, 128.9. 128.8, 128.7, 127.8, 122.0, 121.2, 121.1, 84.2, 77.3; IR (thin film) 3432, 2925, 1668, 1448, 1025, 997 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{23}N_2O_3$ (M+H)$^+$ 435.1703, found 435.1694.

***N*-(Benzyloxy)-2-(2,7-dibromo-9H-fluoren-9-ylidene aminooxy)-2-methylpropanamide (3ha).** A yellow solid, 0.092 g, 85% yield. Mp: 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.13 (s, 1H), 7.64−7.63 (m, 1H), 7.51−7.32 (m, 4H), 7.24−7.23 (m, 2H), 7.08−7.07 (m, 3H), 4.85 (s, 2H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 151.6, 139.6, 138.1, 136.4, 134.8, 134.4, 133.4, 132.1, 131.0, 129.1, 128.7, 128.4, 125.2, 122.2, 122.1. 121.3, 121.2, 85.4, 78.2, 24.5; IR (thin film) 3341, 2923, 1690, 1430, 1165, 972 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}Br_2N_2O_3$ (M+H)$^+$542.9901, found 542.9902.

***N*-(Benzyloxy)-2-(2-bromo-9H-fluoren-9-ylideneaminooxy)-2-methylpropanamide (3ia).** A yellow solid, 0.102 g, 95% yield. Mp: 114−115 °C; *One isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.17 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.53−7.50 (m, 2H), 7.47−7.43 (m, 2H), 7.25−7.19 (m, 6H), 4.85 (s, 2H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 152.7, 140.9, 139.4, 136.8, 134.9, 134.7, 133.2, 132.1, 130.7, 129.2, 128.7, 128.4, 125.1, 122.1, 121.8, 121.3,120.2, 85.0, 78.3, 24.5; *Another isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.66 (s, 1H), 7.57−7.55 (m, 2H), 7.41−7.33 (m, 3H), 7.09−7.03 (m, 6H), 4.85 (s, 2H), 1.64 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 152.6, 140.6, 139.1, 134.8, 134.2, 133.2, 131.7, 129.7, 129.1, 128.6, 128.4, 125.1, 122.1, 121.7, 121.2, 120.0, 85.0, 78.1, 24.5; IR (thin film) 3214, 2926, 1672, 1440, 1154, 965 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}BrN_2O_3$ (M+H)$^+$ 465.0814, found 465.0793.

General procedure for the synthesis of α-(9-isatinlideneaminooxy) amides 5: In a 25 mL round-bottom flask was charged with $Sc(OTf)_3$ (10 mol%), *N*-vinyl isatin nitrones **4** (0.2 mmol), α-bromohydroxamate **2a** (0.4 mmol, 2.0 equiv.), and K_2CO_3 (0.4 mmol, 2.0 equiv.). Then, MeCN (2.0 mL) was added. The resulting mixture was stirred vigorously at room temperature for 12−24 h (monitored by TLC). At this time, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded with silica gel, 1/4 to 1/2, ethyl acetate/petroleum ether) to provide α-aminooxy amides **5.**

***N*-(Benzyloxy)-2-methyl-2-(((2-oxoindolin-3-ylidene)amino) oxy)propanamide (5aa)**. A white solid, 0.065 g, 92% yield. (*E/Z* = 2:1), Mp: 77-78 °C ; *Major isomer:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 10.80 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.36−7.33 (m, 3H), 7.32−7.30 (m, 3H), 7.01−6.98 (m, 1H), 6.86 (d, J = 8.0 Hz, 1H), 4.78 (s, 2H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 158.5, 144.5, 143.0, 136.1, 132.4, 129.5, 128.7, 128.6, 122.4, 121.4, 119.5, 110.9, 84.8, 77.2, 24.5; *Minor isomer:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H), 10.81 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.39−7.36 (m, 3H), 7.35−7.32 (m, 3H), 7.05−7.02 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.77 (s, 2H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 164.2, 145.4, 143.9, 136.2, 133.6, 129.6, 128.8, 128.7, 128.6, 122.6, 116.3, 110.9, 84.8, 77.2, 24.6; IR (thin film) 3637, 2963, 1729, 1261, 1097, 970 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3O_4$ (M+H)$^+$ 354.1448, found 354.1449.

***N*-(Benzyloxy)-2-(((5-methoxy-2-oxoindolin-3-ylidene) amino)oxy)-2-methylpropanamide (5ba)**. (*E/Z* = 10:1), A white solid, 0.038 g, 50% yield. Mp: 155-156 °C; *Major isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.05 (s, 1H), 7.42−7.41 (m, 2H), 7.30−7.26 (m, 3H), 7.12 (d, J = 1.6 Hz, 1H), 6.90−6.87 (m, 1H), 6.77 (d, J = 8.8 Hz, 1H), 4.98 (s, 2H), 3.82 (s, 3H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 159.0, 156.0, 145.1, 135.1, 134.6, 129.2, 128.6, 128.4, 119.7, 118.5, 111.3, 106.7, 85.9, 78.2, 55.9, 24.0; IR (thin film) 3686, 2995, 1699, 1487, 1163, 980 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_3O_5$ (M+H)$^+$ 384.1554, found 384.1556.

***N*-(Benzyloxy)-2-methyl-2-(((5-methyl-2-oxoindolin-3ylidene) amino)oxy)propanamide (5ca).** (*E/Z* = 10:1), A yellow solid, 0.054 g, 74% yield. Mp: 169-170 °C; *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.48 (s, 1H), 7.41−7.40 (m, 3H), 7.28−7.27 (m, 3H), 7.13 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 4.97 (s, 2H), 2.34 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 159.2, 145.0, 138.7, 135.1, 132.6, 132.5, 129.2, 128.6, 128.4, 122.1, 119.0, 110.4, 85.7, 78.2, 24.0, 21.0; IR (thin film) 3689, 2963, 1707, 1296, 1041, 816 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_3O_4$ (M+H)$^+$ 368.1605, found 368.1604.

***N*-(Benzyloxy)-2-methyl-2-(((7-methyl-2-oxoindolin-3-ylidene)amino)oxy)propanamide (5da)**. *(E/Z* = 2:1), A yellow solid, 0.041 g, 56% yield. Mp: 114-115 °C ; *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.14 (s, 1H), 7.43−7.40 (m, 3H), 7.29−7.26 (m, 3H), 7.18 (d, J = 7.6 Hz, 1H), 7.01−6.98 (m, 1H), 4.95 (s, 2H), 2.24 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 159.0, 145.0, 139.5, 135.1, 133.2, 129.2, 128.5, 128.4, 123.0, 119.6, 119.2, 118.7, 85.9, 78.2, 24.0, 15.8; *minor isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.39 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.41−7.39 (m, 3H), 7.28−7.26 (m, 2H), 7.20−7.16 (m, 1H), 6.95−6.91 (m, 1H), 4.96 (d, J = 12.0 Hz, 2H), 2.26 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 164.3, 140.8, 134.9, 134.6, 129.4, 128.7, 128.5, 125.5, 123.1, 123.0, 119.8, 115.5, 86.3, 78.3, 24.0, 16.0; IR (thin film) 3635, 2928, 1709, 1262, 1016, 981 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_3O_4$ (M+H)$^+$ 368.1605, found 368.1609.

***N*-(Benzyloxy)-2-methyl-2-(((1-methyl-2-oxoindolin-3-ylidene)amino)oxy)propanamide (5ea)**. (*E/Z* = 5:1), A white solid, 0.037 g, 50% yield. Mp: 94-95 °C; *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.01 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.44−7.40 (m, 3H), 7.27−7.25 (m, 3H), 7.11−7.07 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.96 (s, 2H), 3.21 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.6, 162.7, 145.0, 135.0, 133.2, 131.9, 129.3, 128.6, 128.3, 127.8, 123.1, 115.2, 108.7, 86.3, 78.2, 26.1, 24.5; *minor isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.68 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.40−7.37 (m, 3H), 7.27−7.25 (m, 3H), 7.04−7.00 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.92 (s, 2H), 3.23 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.6, 162.7, 144.8, 135.0, 133.2, 131.9, 129.2, 128.4, 128.3, 127.8, 123.0, 115.2, 108.6, 86.3, 78.2, 25.8, 24.0; IR (thin film) 3406, 2984, 2314, 1601, 1164, 672 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1608.

***N*-(Benzyloxy)-2-methyl-2-(((2-oxo-1-phenylindolin-3-ylidene)amino)oxy)propanamide (5fa)**. (*E/Z* = 3:1), A yellow oil, 0.085 g, 99% yield. *Major isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.88 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.59−7.55 (m, 2H), 7.49−7.45 (m, 1H), 7.42−7.38 (m, 4H), 7.35−7.31 (m, 1H), 7.27−7.26 (m, 3H), 7.15−7.11 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 2H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.5, 156.8, 144.2, 143.6, 135.0, 133.4, 131.8, 129.8, 129.2, 128.6, 128.4, 128.3, 126.5, 123.4, 121.5, 118.3, 110.0, 85.9, 78.1, 53.4, 24.0; *Minor isomer:* ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.67 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.58−7.54 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.43−7.40 (m, 4H), 7.37−7.33 (m, 1H), 7.29−7.26 (m, 3H), 7.08−7.04 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.94 (s, 2H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.6, 161.9, 144.9, 144.8, 135.0, 133.5, 133.1, 129.8, 129.5, 128.7, 128.5, 128.0, 126.5, 123.6, 115.3, 110.0, 86.4, 78.2, 53.4, 24.5; IR (thin film) 3654, 2956, 1736, 1303, 1261, 978 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}N_3O_4$ $(M+H)^+$ 430.1761, found 430.1763.

General procedure for the synthesis of compounds 6: In a 25 mL round-bottom flask was charged with $Sc(OTf)_3$ (10 mol%), *N*-vinyl fluorenone nitrones **1** (0.2 mmol), α-bromohydroxamates **2** (0.4 mmol, 2.0 equiv.), and K_2CO_3 (0.4 mmol, 2.0 equiv.). Then, MeCN (2.0 mL) was added. The resulting mixture was stirred vigorously at room temperature for 12 h (monitored by TLC). At this time, iron powder (2 mmol, 10.0 equiv.), ammonium chloride (2 mmol, 10.0 equiv.), and 4.0 mL of EtOH/H_2O (1:1) was added under air atmosphere. The reaction vessel was stirred vigorously at 80 °C for 3-6 h (monitored by TLC). The solution was then diluted with water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified flash column chromatography (the crude residue was dry loaded with silica gel, 1/4 to 1/2, ethyl acetate/petroleum ether) to provide compounds **6**.

2-(9H-Fluoren-9-ylideneaminooxy)-2-methylpropanamide (6aa). A yellow solid, 0.038 g, 68% yield. Mp: 70−71°C; ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 8.33 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.54−7.51 (m, 1H), 7.46−7.40 (m, 2H), 7.34−7.31 (m, 1H), 7.20−7.17 (m, 2H), 1.60 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 175.7, 152.2, 141.3, 140.2, 135.2, 132.0, 130.8, 130.1, 129.9, 129.0, 128.7, 121.9, 121.0, 120.9, 84.2, 24.7; IR (thin film) 3431, 2925, 1651, 1390, 1025, 997 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}N_2O_2$ $(M+H)^+$ 281.1285, found 281.1279.

2-(9H-Fluoren-9-ylideneaminooxy)propanamide (6am). A yellow solid, 0.034 g, 64% yield. Mp: 75−76 °C; ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 8.31 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.55−7.52 (m, 1H), 7.48−7.39 (m, 3H), 7.37−7.31 (m, 1H), 7.26 (s, 1H), 4.82 (q, *J* = 6.5 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 173.7, 152.5, 141.2, 140.3, 135.0, 132.1, 131.0, 130.1, 130.0, 129.1, 128.7, 121.9, 121.1, 121.0, 80.8, 17.9; IR (thin film) 3429, 2925, 1649, 1025, 996 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2O_2$ $(M+H)^+$ 267.1128, found 267.1123.

2-(2,7-Dibromo-9H-fluoren-9-ylideneaminooxy)-2-methyl propanamide (6ha). A white solid, 0.045 g, 58% yield. Mp: 80−81 °C; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 8.41 (s, 1H), 7.91−7.85 (m, 2H), 7.78 (d, *J* = 6.8 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 7.17 (s, 1H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 175.2, 150.0, 139.3, 138.3, 137.0, 134.7, 133.6, 132.2, 131.3, 124.4, 123.4, 123.1, 122.0, 122.9, 85.1, 24.5; IR (thin film) 3453, 2924, 1642, 1463, 1110, 819 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}$ $Br_2N_2O_2$ $(M+H)^+$ 436.9495, found 436.9493.

2-(2-Bromo-9H-fluoren-9-ylideneaminooxy)-2-methyl propanamide (6ia). (*E/Z* = 1:1), A white solid, 0.037 g, 52% yield. Mp: 64-65 °C; *One isomer:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.77−7.73 (m, 2H), 7.57−7.54 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.17−7.16 (m, 3H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.4, 151.1, 140.3, 139.2, 137.3, 134.8, 132.3, 131.7, 129.8, 129.4, 124.3, 123.0, 121.9, 121.4, 84.6, 24.6; *Another isomer:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, *J* = 7.6 Hz, 1H), 7.87−7.84 (m, 4H), 7.69−7.64 (m, 2H), 7.49−7.43 (m, 2H), 7.28 (s, 1H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.4, 151.1, 140.3, 139.2, 134.9, 133.4, 132.2, 131.0, 129.7, 129.1, 123.1, 121.9, 121.5, 121.3, 84.6, 24.5; IR (thin film) 3404, 2960, 1646, 1261, 1095, 801, 732 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}$ BrN_2O_2 $(M+H)^+$ 359.0390, found 359.0382.

Gram scale preparation of 3aa: $Sc(OTf)_3$ (10 mol%), *N*-vinyl fluorenone nitrone **1a** (1.0 g, 4.0 mmol), α-bromohydroxamate **2a** (8.0 mmol, 2.0 equiv.) and K_2CO_3 (8.0 mmol, 2.0 equiv.) were dissolved in MeCN (30 mL). Then stirring at room temperature for 24 h. Purification using medium pressure chromatography (1:2; ethyl acetate: petroleum ether) afforded **3aa** as a white solid (1.4 g, 91%).

Gram scale preparation of 6aa: $Sc(OTf)_3$ (10 mol%), *N*-vinyl fluorenone nitrone **1a** (1.0 g, 4.0 mmol), α-bromohydroxamate **2a** (8.0 mmol, 2.0 equiv.) and K_2CO_3 (8.0 mmol, 2.0 equiv.) were dissolved in MeCN (30 mL). Then the reaction mixture was stirring at room temperature for 24 h. Then, iron powder (40 mmol, 10.0 equiv.), ammonium chloride (40 mmol, 10.0 equiv.), and 40.0 mL of EtOH/H_2O (1:1) were added under air atmosphere. The reaction vessel was stirred vigorously at 80

℃ for 6 h. Purification using medium pressure chromatography (1:2; ethyl acetate: petroleum ether) afforded **6aa** as a white solid (0.65 g, 58%).

Conflicts of interest

There are no conflicts to declare

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14 CCDC: 1938292 (**3al**) and 1938293 (**6aa**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

15 Other reductive conditions were also tested to form **6aa**. The results are listed below: Zn/HOAc (**6aa**, 0%), Zn/NH_4Cl (**6aa**, 25%).

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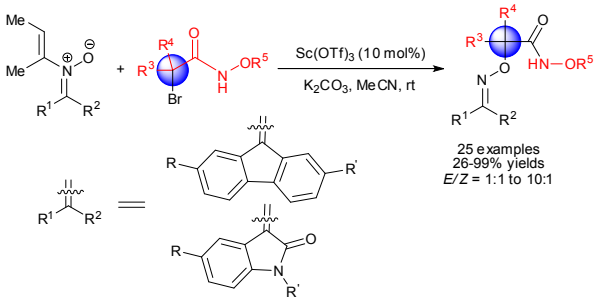
Graphic Abstract



A [3+3] cycloaddition and $Sc(OTf)_3$-catalyzed double C-N bond cleavage to synthesize various α-aminooxy amides bearing a quaternary carbon in one pot has been achieved from *N*-vinyl nitrones and α-bromohydroxamates.