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Chemoselective *N*-Acylation via Condensations of *N*-(Benzoyloxy)amines and α-Ketophosphonic Acids under Aqueous Conditions

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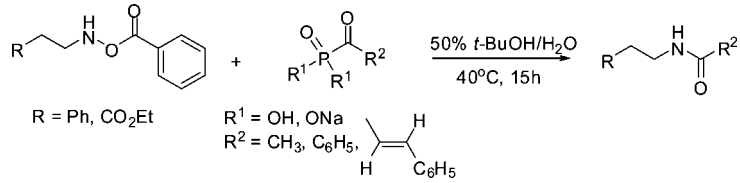

A new amide-forming reaction with *N*-benzoyloxyamines and α-ketophosphonic acids was investigated. A mixed solvent of *t*-BuOH/water (1:1) at 40 °C provided the desired amide in high yield (71−96%). Both phosphonic acids (**9**, **12**, or **13**) and their disodium salts (e.g., **10**) were shown to react with the respective *N*-benzoyloxyamines (**1b** and **4**) in excellent yields. The phosphonic acid methyl ester monosodium salt **11** did not react under these conditions. However, compound **11** did provide the desired amide in 22% yield upon addition of 2 equiv of TFA. The *N*-acylation reaction is highly chemoselective for *N*-benzoyloxyamines as both aliphatic amines and *N*-hydroxylamines were shown not to react productively with the α-ketophosphonic acids under the conditions tested. Moreover, the α-ketophosphonic acids are more selective than the related α-ketocarboxylic acid systems, which react with both the *N*-hydroxylamines and *N*-benzoyloxyamines. In this regard, this novel phosphonic acid methodology provides a new high-yielding, chemoselective acylating reagent for further study.

Introduction

Amides are the fundamental connections within protein architectures and as such represent an important synthetic target. Classically, the amide functional group (aka the peptide bond) is made via the dehydrative coupling of carboxylic acids and amines. A multitude of reagents have been developed to facilitate amide bond formation in peptides in high yield via this dehydrative approach. The vast majority of these methodologies involve the coupling of activated carboxylic acid esters and amines in the presence of other additives, which ensure the maintenance of chiral integrity (e.g., hydroxybenzotriazole) or assist in the sequestration of water.

While numerous alternative approaches to amides have recently been reviewed,[1] opportunities still exist to develop new reagents, which arrive at the amide target by molecular mechanisms other than the traditional dehydrative approach. Indeed, a success in this area could lead to a variety of benefits for chemists including the development of novel chemoselective acylating agents which react with amine derivatives by alternative mechanisms, improvements in peptide coupling reaction conditions, and changing the nature of the byproducts and waste-streams generated during peptide manufacture. Moreover, a nondehydrative pathway allows for new reactions to be conducted in aqueous media, a potential green alternative to dimethylformamide, DMF.

The present work was inspired by recent publications by the Bode group, who described a novel oxidative decarboxylation process involving hydroxylamines **1a** and α-ketoacids **2b** and their conversion to amides **3b** (Scheme 1).[2,3] Since our group

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SCHEME 1. Amide-Forming Reactions with α-Ketoacids

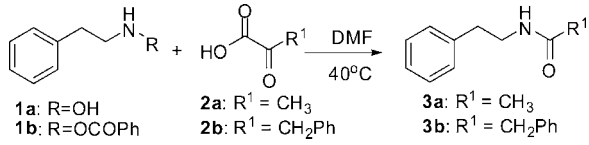
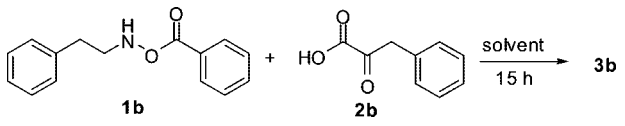


TABLE 1.[a]



entry	1b	2b	yield of 3b (%)	temp (°C)	solvent
1	1	1	92	40	50% aq *t*-BuOH
2	1	2	96	40	50% aq *t*-BuOH

[a] Relative molar equivalents of substrate (reactions conducted at 0.05 M **1b** with a 0.1 mmol scale).

had previously developed in 1997 an improved entry into *N*-(benzoyloxy)amines[4,5] (i.e., *O*-acylated hydroxylamines), e.g. **1b**, and demonstrated that these could be converted to amides and incorporated into α,*β*-peptides in 2000,[6] we speculated that these materials could also react with α-ketoacids (**2a** and **2b**) to yield amides (**3a**[7] and **3b**, respectively). Indeed, *N*-(benzoyloxy)amines can also undergo the Bode α-ketoacid chemistry (Table 1).

Having shown for the first time that *N*-benzoyloxyamines can undergo this chemistry, we recently extended this discovery to include the related α-ketophosphonic acids and their salts. Indeed, we found that α-ketophosphonic acids (and their salts) are highly chemoselective acylating agents. This report describes our findings with these novel phosphonic acid reagents and demonstrates their unprecedented degree of chemoselectivity in *N*-acylation.

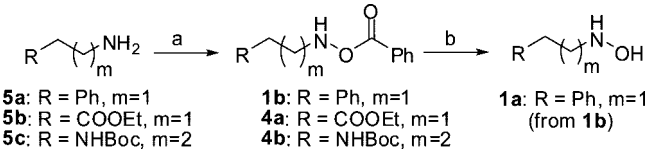
Results and Discussion

To survey this new chemistry, several *N*-benzoyloxyamines and α-ketophosphonates were prepared.

Synthesis. Three hydroxylamine derivatives were prepared for comparisons. Compound **1b** was prepared by published methods in 72% yield.[4] For comparison the *N*-hydroxy system **1a** was prepared from **1b**, using MeOH/THF and LiOH in 84% yield. Since our *N*-benzoyloxylation process[4,5] provided ready access to *β*-*N*-(benzoyloxy)amino acids (i.e., good models for *β*-peptide synthesis), *β*-alanine derivative **4a** and Boc-protected benzoyloxyamine **4b** were also prepared and screened along with the other N−O containing models, **1a** and **1b** (Scheme 2).

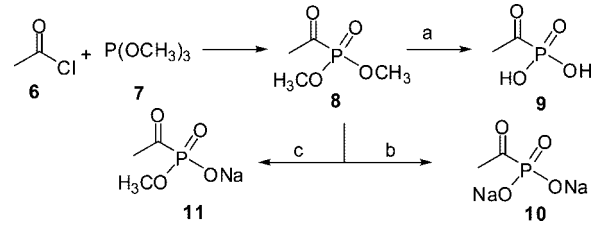
A variety of routes are available for the synthesis of phosphonic acids and their precursors.[8–12] α-Ketophosphonate esters can be synthesized either by the reaction of acid chorides[8] and trialkylphosphites or by the coupling[10] of aldehydes and trialkyl phosphites to form α-hydroxyphosphonates followed by oxidation.[11]

SCHEME 2. Synthesis of 1a, 1b, 4a, and 4b[a]



[a] Reagents: (a) BPO, pH 10.5 aq. buffer; (b) LiOH/CH_3OH/THF.

SCHEME 3. Synthesis of α-Ketophosphonic Acid Derivatives[a]



[a] Reagents: (a) (i) $(CH_3)_3SiBr$, (ii) CH_3OH, 56%; (b) (i) $(CH_3)_3SiBr$, (ii) $NaHCO_3$, 77%; (c) NaI, Acetone, 85%.

As shown in Scheme 3, the α-ketophosphonate dimethyl ester (e.g., **8**) can be readily converted to either the phosphonic acid **9**[8] or the disodium salts **10**[9] in good yields. For example, acetyl phosphonic acid **9** was prepared by the reaction of acetyl chloride **6** with trimethyl phosphite **7** (to give **8**[12b]) followed by dealkylation with trimethylsilyl bromide (TMSBr) and methanol to give **9** (56%).[8] Alternatively, treatment of **8** with TMSBr followed by aqueous sodium bicarbonate gave the disodium salt **10** (77%) as reported.[9] The selective deprotection of **8** to the monoester monosodium salt **11** (85%) was accomplished via the literature method[8] using NaI and acetone. In this regard, the flexibility associated with the chemoselective phosphonate ester cleavage steps provided rapid entry into a variety of diacid (**9**), diacid salts (**10**), and monoacid ester (**11**) derivatives for evaluation in this new chemistry.

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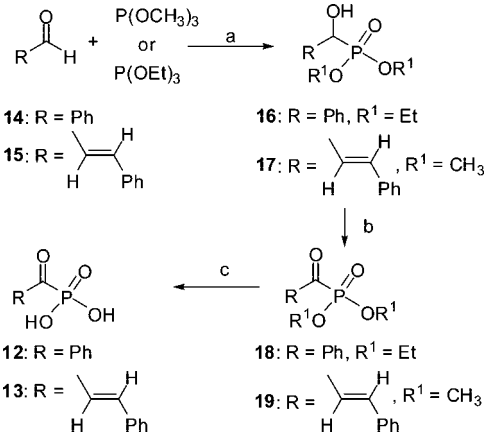
SCHEME 4. Synthesis of 12 and 13[a]



[a] Reagents: (a) TFA/0°C to rt, 60–70%; (b) PCC/CH_2Cl_2; (c) (i) $(CH_3)_3SiBr$, (ii) CH_3OH.

As shown in Scheme 4, the α-ketophosphonic acids **12** and **13** were synthesized by the coupling of their precursory aldehydes **14** and *trans*-**15** with trimethyl phosphite to give α-hydroxyphosphonates **16** and **17**, respectively.[10] Subsequent oxidation with PCC[11a] gave **18** and **19** in 49% and 58% yield, respectively. The α-ketophosphonic acids **12** and **13** were synthesized in good yields by *O*-dealkylation of **18**[8a] and **19**[13] with TMSBr and MeOH.

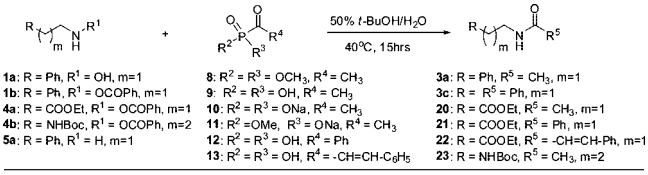
With the necessary reagents in hand, the reaction was explored as a function of the phosphonate functionality. The results are shown in Table 2. This study revealed for the first time that amides can be formed in high yield by α-ketophosphonic acid derivatives and *N*-benzoyloxyamines.

There were several significant findings from our study. First, the hydroxylamine derivative **1a** did not acylate upon reaction with the phosphonic acid **9** (with or without TFA added), and the disodium salt **10** (Table 2, entries 1−3). In contrast, the *N*-benzoyloxyamines **1b**, **4a**, and **4b** provided the expected amides in good to excellent yields with **9** and **10** (Table 2, entries 5, 6, 11, 12, and 17). Second, the phosphonate diester **8** and monoester **11** were unreactive with **1b** and **4a** (Table 2, entries 4, 7, 10, and 13). Interestingly, the monoester **11** could be converted to the desired amide, albeit in low yield, upon the addition of TFA (Table 2, entries 8 and 14). Third, this technology seems to be general as both the benzoylphosphonate **12** and the *trans*-cinnamoyl derivative **13** were converted to their respective amide products in ≥75% yield (Table 2, entries 9, 15 and 16).

As shown in Table 2, the α-ketophosphonic acids and salt forms (**9**, **10**, **11**, **12**, and **13**) were all reactive to **1b**, **4a**, or **4b**, while the α-ketophosphonate dimethyl ester **8** was not.

It is interesting to note that the phenylethylamine **5a** was not *N*-acetylated with either the phosphonic acid **9** or its disodium salt **10** (Table 2, entries 19 and 20) under the conditions studied. For example, with **5a** and **10** only trace quantities of the acetamide product **3a** were observed (<0.9%). However, the amine **5a** did react with diester **8** to give the desired amide **3a** in 24% yield after heating in 50% *t*-BuOH/water at 40 °C for 15 h (Table 2, entry 18). Indeed, it has been reported previously by Hata et al. that amines can react directly with diethyl acetylphosphonate to give amides.[14] However, this reaction is solvent dependent and is sensitive to substituent effects.

TABLE 2.



no.	amine derivative	α-ketophosphonate derivative[a]a	expected Amide	yield (%)
1	**1a**	**9**	**3a**	0
2	**1a**	**9** + TFA (2 equiv)[b]	**3a**	0
3	**1a**	**10**	**3a**	0
4	**1b**	**8**	**3a**	0
5	**1b**	**9**	**3a**	71
6	**1b**	**10**	**3a**	71
7	**1b**	**11**	**3a**	0
8	**1b**	**11** + TFA (2 equiv)[b]	**3a**	22
9	**1b**	**12**	**3c**	79
10	**4a**	**8**	**20**	0
11	**4a**	**9**	**20**	96
12	**4a**	**10**	**20**	95
13	**4a**	**11**	**20**	0
14	**4a**	**11** + TFA (2 equiv)[b]	**20**	13
15	**4a**	**12**	**21**	79
16	**4a**	**13**	**22**	75
17	**4b**	**10**	**23**	98
18	**5a**	**8**	**3a**	24
19	**5a**	**9**	**3a**	0
20	**5a**	**10**	**3a**	<1

[a] All reactions were run with 2 equiv of the α-ketophosphonate derivative and 1 equiv of the amine derivative, [b] 2 equiv of trifluoroacetic acid, TFA, with respect to the amine derivative.

Contributions from this amine reaction may be problematic as it may require protection of reactive amine side chains from lysine or other amine functionalities, etc. However, one can envision that this issue may be overcome by the future design of bulky phosphonate esters, which retard this amine reaction pathway, or the use of other reaction conditions (e.g., short reaction times or at different pH values), which may minimize this undesired amine reaction.

While simple acid−base chemistry (i.e., protonation of the amine by the phosphonic acid) could explain the nonreactivity of amines with the phosphonic acid, we specifically looked for the fate of the amine in the reaction of **5a** and the phosphonic acid salt, **10**. One could clearly see unreacted **5a** on the TLC plate (R_f 0.2; 7% $MeOH/CH_2Cl_2$/0.5% NH_4OH) after 15 h (after workup). However, upon workup with aq. Na_2CO_3, only trace quantities of **5a** (2.7% recovery) were detected in the ^1H NMR ($CDCl_3$) of the crude product mixture (derived from the organic layer) and only 0.85% of the amide **3a** was detected. A repeat of this experiment, where the product mixture was partitioned between chloroform and water, allowed for inspection of the water phase. Indeed, a water-soluble α-iminophosphonic acid salt, **5b**, was formed in 60% yield with EtOH as an internal standard (by ^1H NMR, Scheme 5). This was likely formed by addition of the amine **5a** to the keto group of **10**. This intermediate was unstable and readily reverted back to the amine **5a** on the normal phase silica TLC plate (7% MeOH/0.5% NH_4OH in CH_2Cl_2) or with 1 M NaOH for 30 min at rt.

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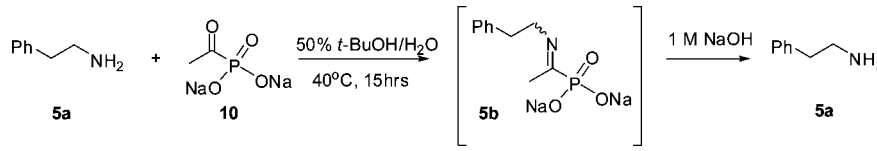
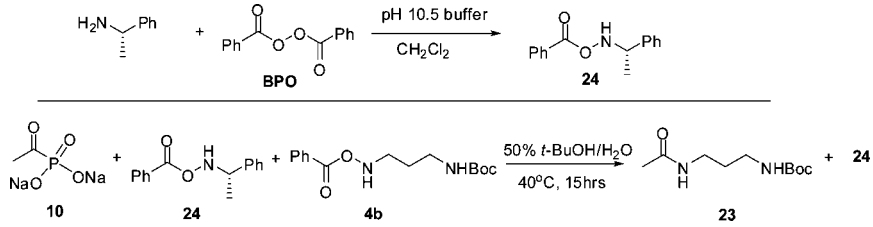
SCHEME 5. Formation of 5b



SCHEME 6. Synthesis of 24 and Competition Experiment with 4b and 24 To Give 23 Exclusively



Rewardingly, this side reaction with amines is reversible. In short, as shown in Table 2 (entries 19 and 20), there is no *N*-acylation of amine **5a** in the presence of the free phosphonic acid or salt (**9** and **10**) beyond only trace quantities. Therefore, one can selectively N-acylate *N*-benzoyloxyamines by using reagent **9** or **10** in lieu of the diester **8**.

Moreover, no *N*-acylation was observed with Bode's hydroxylamine derivative **1a** (Table 2, entries 1−3). Indeed, we were pleased to discover that this is a highly *chemoselective reaction*, wherein only the *N*-benzoyloxyamines (**1b** and **4**) react selectively with the acylphosphonic acids to give the respective amide.

The acetyl-, cinnamoyl-, and benzoylphosphonic acids (**9**, **12**, and **13**) were all reactive and the reaction seems to be quite general (Table 2). For example, the reaction of *N*-(benzoyloxy)-phenethylamine **1b** with acetyl phosphonic acid **9** or its disodium salt **10** provided the desired amide **3a** in 71% yield. The reaction of benzoyloxyamine derivative **4a** with either **9** or **10** provided the desired amide **20** in 96% and 95% yield, respectively (Table 2, entries 11 and 12). Similarly, the reaction of benzoyloxyamine derivative **4b** with **10** gave the amide **23** in 98% yield. The benzoyl phosphonic acid **12** reacted with **1b** and **4a** to give the amides **3c** and **21** in 79% yield, respectively (Table 2). The reaction of cinnamoylphosphonic acid **13** with **4a** gave the amide **22** in 75% yield. Therefore, the aliphatic, alkenyl, and aromatic acyl groups can be used in constructing reactive α-ketophosphonates.

To investigate the influence of steric factors upon this reaction, benzoyloxyamine **24** was synthesized from α-methylbenzylamine (Scheme 6). In this case, *N*-benzoyloxyamine **24** is a regioisomer of **1b**. Even though both systems (**1b** and **24**) are primary amines, the α-branched system **24** did not react with the acetylphosphonic acid salt **10** after 24 h in 50% *t*-BuOH/water at 40 °C. In contrast, the nonbranched analogue **1b** and **10** gave 71% yield of the desired amide **3a** (Table 2, entry 6).

A competition experiment was also conducted to further illustrate the selectivity of this reaction for primary *N*-benzoyloxyamines with nonbranched α carbons. One equivalent of the nonbranched α carbon analogue **4b** and the branched system **24** were challenged to react with 2 equiv of acetylphosphonic acid salt **10** (Scheme 6). Even though the stoichiometry was sufficient to convert both systems to their respective amides, the branched system **24** again did not react. In contrast, the **4b** component of the mixture was completely converted to its respective amide **23** after 15 h in 97% yield. Therefore, this reaction is highly chemoselective and suggests that one could use an excess of the α-ketophosphonic acid to assist conversion to the amide product.

In summary, *N*-benzoyloxyamines were for the first time shown to react with both α-ketophosphonic acids and their acid salts to form amides in good to excellent yields. While numerous *N*-acylation methods exist to form amide bonds, few, if any, demonstrate this high degree of chemoselectivity. Indeed, the special chemoselectivity and reactivity observed with the *N*-benzoyloxyamines and α-ketophosphonic acids warrants further study and should provide an important new contribution to the organic synthesis "toolbox".

Experimental Section

α-Ketoacids **2a** and **2b** are commercially available. The synthesis of amide **3b** has been reported by Bode.[2] The syntheses of *N*-(benzoyloxy)amines **1b**,[4] **4a**,[6a] and **4b**[4] have been reported previously by our group. The *N*-OH derivative was synthesized from **1b** by the literature method[15] and the analytical data matched the reported values.[16] The monosodium salt **11**[8] and disodium salt **10**[9] were synthesized as reported. The phosphonate esters **8**,[12b] **18**,[11a] and **19**[13] are known and were synthesized as reported in the literature. The analytical data of these compounds matched those previously reported.

General Procedure for the Deprotection of Phosphonate Esters to Phosphonic Acids. TMSBr (1.26 mmol) was slowly added neat to the phosphonate ester (0.21 mmol) under nitrogen. The reaction mixture was allowed to stand at room temperature for 12 h after which the excess of TMSBr was evaporated. Methanol (5 mL) was added to the residue at 0 °C and the reaction was stirred for an additional 30 min. The solvent was evaporated to give the desired phosphonic acid.

The phosphonic acids **9**, **12**, and **13** were synthesized by using the above general method. Compounds **9**[8a] and **12**[8a] are known and their NMR spectral data matched the reported values and they were used without further purification.

(3-Phenylacryloyl)phosphonic Acid 13. Yield 79%; ^{1}H NMR (D_2O) δ 8.09 (d, J = 16 Hz, 1H, CH), 7.51 (m, 3H, ArH), 7.75 (d, 2H, ArH), 7.09 (dd, J = 16 and 4 Hz, 1H, CH); ^{13}C NMR (D_2O) δ 151.7, 137.1, 134.6, 132.1, 132.0, 128.5, 128.1; high resolution

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mass spectrum (FAB), theory for ($C_9H_9O_4P$) M + Na 235.0131, found 235.0130.

General Procedure for Coupling of α-Keto Phosphonic Acids with *N*-Benzoyloxyamines. The *N*-Benzoyloxyamine (0.13 mmol) and the α-ketophosphonic acid or its derivative (0.27 mmol) were dissolved in *tert*-butyl alcohol and water (1:1 v/v, 5 mL). The solution was heated to 40 °C for 15 h and the solvent was removed under high vacuum. The oily residue was dissolved in CH_2Cl_2 (10 mL) and washed with aq Na_2CO_3 (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the crude reaction mixture. The required amide was purified either by column chromatography or by preparative TLC.

The amides **3a**, **3b**, **20**, **21**, **22**, and **23** were synthesized by using the above method. Of these, the amides **3a**,[7] **3c**,[17] **20**,[18] and **21**[19] are known and their spectral data matched the literature values. Beyond the NMR spectra shown in the Supporting Information for **21**, a high resolution mass spectrum was obtained for compound **21**: (FAB) theory for ($C_{12}H_{15}O_3N$) M + Na 244.0944, found 244.0962. Elemental Anal. for **21**, theoretical for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.91; H, 6.93; N, 6.33.

3-Acetylaminopropionic Acid Ethyl Ester 20. ^{1}H NMR ($CDCl_3$) δ 6.15 (br s, 1H, NH), 4.15 (q, J = 7.2 Hz, 2H, OCH_2), 3.52 (q, J = 6 Hz, 2H, NCH_2), 2.53 (t, J = 6 Hz, 2H, NCH_2), 1.96 (s, 2H, $PhCH_2$), 1.27 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.5, 168.8, 59.6, 33.8, 32.9, 22.3, 13.1; IR ($CDCl_3$): 1727, 1675, 1194 cm^{-1}; high resolution mass spectrum (FAB), theory for ($C_7H_{13}N_1O_3$) M + H 160.0968, found M + 1 160.0981. Anal. Calcd. theory for ($C_7H_{13}N_1O_3 \cdot 0.2H_2O$): C, 51.65; H, 8.30; N, 8.60. Found: C, 51.55; H, 8.43; N, 8.47.

3-(3-Phenylacryloylamino)propionic Acid Ethyl Ester 22. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 16 Hz, 1H, CH), 7.50 (m, 2H, ArH), 7.36 (m, 3H, ArH), 6.38 (d, J = 16 Hz, 1H, CH), 6.35 (br s, 1H, NH), 4.18 (q, J = 7 Hz, 2H, CH_2), 3.66 (q, J = 6 Hz, 2H, CH_2), 2.62 (t, J = 6 Hz, 2H, CH_2), 1.28 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.4, 163.2, 138.6, 132.2, 127.1, 126.6, 125.2, 118, 58.3, 32.4, 31.4, 11.6; IR ($CDCl_3$) 1725, 1670, 1203 cm^{-1}; high resolution mass spectrum (FAB), theory for ($C_{14}H_{17}O_3N$) M + H 248.1281, found 248.1288 (also theory for M + Na 270.1101, found 270.1116).

***tert*-Butyl 3-Acetamidopropylcarbamate 23.** ^{1}H NMR ($CDCl_3$) δ 6.57 (br t, 1H, NH), 5.14 (br t, 1H, NH), 3.27 (q, J = 6 Hz, 2H, CH_2), 3.16 (q, J = 6 Hz, 2H, CH_2), 1.99 (s, 3H, CH_3),1.61 (q, J = 6 Hz, 2H, CH_2), 1.44 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.8, 156.9, 79.4, 37.2, 36.1, 30.2, 28.4, 23.4; high resolution mass spectrum (FAB), theory for ($C_{14}H_{17}O_3N$) M + H 217.1547, found 217.1540 (also theory for M + Na 239.1366, found 239.1374).

(*S*)-*O*-Benzoyl-*N*-(1-phenylethyl)hydroxylamine 24. A solution of benzoyl peroxide (BPO, 8.25 mmol) in CH_2Cl_2 (5 mL/mmol BPO) was added quickly to a mixture of *S*-(1-phenylethyl) amine (8.25 mmol) and a pH 10.5 buffer solution (5 mL/mmol amine) at room temperature. TLC was used to monitor the consumption of starting material. After the reaction was complete, the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was subjected to flash column chromatography with 70% CH_2Cl_2/hexane. Yield 75%; R_f 0.34 (7:3; CH_2Cl_2:hexane); ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2H, CH), 7.45−7.21 (m, 8H, CH), 4.29 (q, J = 6.5 Hz, 1H, CH), 1.48 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 133.3, 129.3, 128.6, 128.5, 127.9, 127.1, 60.9, 19.8; high resolution mass spectrum (FAB), theory for ($C_{14}H_{17}O_3N$) M + H 242.1176, found 242.1176 (also theory for M + Na 264.0995, found 264.1012). Anal. Calcd. theory for ($C_{15}H_{15}NO_2$): C, 74.67; H, 6.27; N, 5.81. Found: C, 74.55; H, 6.34; N, 5.63.

Competition Experiment with 4b and 24. The *N*-Benzoyloxyamines **4b** (0.34 mmol) and **24** (0.34 mmol) and the α-ketophosphonic acid disodium salt **10** (0.68 mmol) were dissolved in *tert*-butyl alcohol and water (1:1 v/v, 5 mL). The solution was heated to 40 °C for 15 h and the solvent was removed under high vacuum. The oily residue was dissolved in CH_2Cl_2 (10 mL) and washed with aq Na_2CO_3 (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide the crude reaction mixture. Dibenzyl ether (100 μL) was added as an internal standard and the ^{1}H NMR spectrum was recorded to determine the percent yield of the product formed (via relative integration).

Supporting Information Available: ^{1}H NMR for **1a**, **1b**, **3a**, **3c**, **4**, **5b**, **8**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, and **24** in $CDCl_3$ and α-ketophosphonic acids **9**, **10**, **11**, **12**, and **13** in D_2O and ^{13}C NMR spectra of the new compounds **13** (D_2O), **22** ($CDCl_3$), **23** ($CDCl_3$), and **24** ($CDCl_3$). This material is available free of charge via the Internet at http://pubs.acs.org.

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