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Full Paper

Amide Activation

β-Lactams as Formal Dipoles through Amide-Bond Activation

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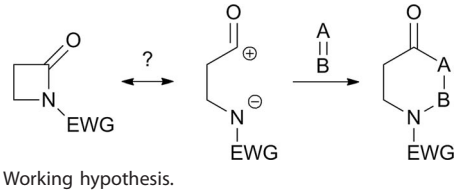
Abstract: Activation of β-lactams can be achieved by simple Lewis-base catalysis to trigger an unprecedented reaction based on the formal dipolar behaviour of a strained amide bond. A new synthetic route for 1,3-oxazinan-6-ones is presented by reaction of β-lactams with ethylglyoxylate, which after methodological optimizations identified 4-pyrrolidinopyridine as the catalyst of choice in aprotic polar solvents. Mechanistic details are also discussed in light of the intrinsic limitations identified for this transformation.

Introduction

The amide bond occupies a prominent, if not a peculiar, place in the realm of organic chemistry. Many reports focus on the tremendously important challenge of making such bonds, but we were intrigued by the new synthetic opportunities created by employing reactive intermediates obtained by breaking an amide bond. More specifically, we wanted to explore the reactivity pathways that can be followed when an amide bond is viewed as a synthetic equivalent of an acylium/anionic-nitrogen pair. In short, this area falls into the rarely explored domain of amide-bond activation. A very limited number of reports explore such processes, all of which rely on the activating properties of electron-withdrawing groups at the nitrogen atom.[1] An interesting combination of activating conditions can be found in β-lactams with sulfonyl or carbonyl *N*-substituents. In these compounds the electron-withdrawing properties of the *N*-substituent are exalted by the inherent ring tension, which results in a high propensity to ring-open, as shown by the number of articles that deal with the alcoholysis or aminolysis of *N*-sulfonyl, or *N*-acyl or *N*-carbamate β-lactams.[2] Only two examples exploit both the electrophilicity of the carbonyl moiety and the nucleophilic character of the nitrogen atom with electrophiles other than a proton.[3]

We thus decided to investigate the reactivity of azetidinones toward dipolarophiles under activation with nucleophilic catalysts as presented in Scheme 1 .



Scheme 1. Working hypothesis.

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Results and Discussion

Initially, we tried to identify the type of dipolarophiles and catalysts that could be employed in the hypothesized transformation. As presented in Figure 1, among the small library of reactants tested in combination with four Lewis basic catalysts, which exhibited contrasting nucleophilicity/basicity balances,[4] activated aldehydes stood out. All experiments were carried out in NMR spectroscopic tubes with $CDCl_3$ as solvent and catalyst (10 mol-%).

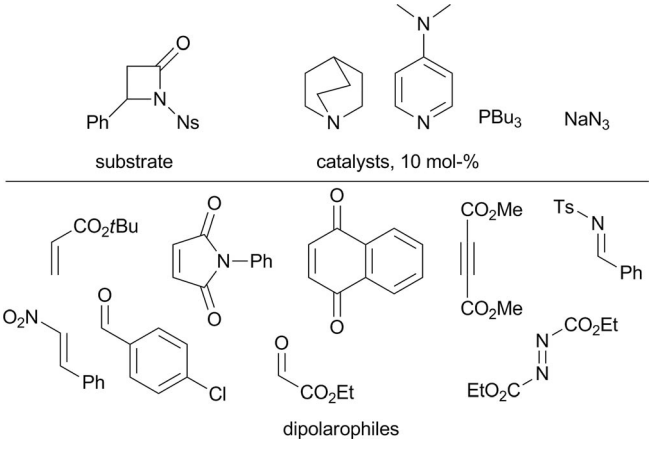


Figure 1. Dipolarophiles screened and catalysts tested.

From the eight dipolarophiles treated with lactam **1a** only ethyl glyoxylate **2**, in conjunction with 4-(dimethylamino)pyridine (DMAP) gave rise to the expected reaction to deliver 1,3-oxazinan-6-one **3a** as the product in 91 % yield (Scheme 2). All other experiments that used less-activated substrates, left β-lactams unreacted, which degraded under more forcing conditions (Scheme 5).

Scheme 2. Oxazinanone synthesis from an azetidinone.

This reaction is remarkable at exemplifying the formal dipolar character of an azetidinone, and it gives easy access to a class of particular heterocycles, 1,3-oxazinan-6-ones, for which few methods of preparation are known, despite important applications in the synthesis of enantiopure β-amino acids.[5–7] After having found a candidate for such β-lactam activation reactions in 4–6-member ring expansions, we performed optimization studies to delineate the best reaction conditions. After having verified that 4-pyrrolidinopyridine (PPY) was more effective than DMAP in this transformation, as observed for other organocatalyzed reactions because it is more nucleophilic and Lewis basic.[8] Various solvents were tested as media and the conversion at different times was followed by ^{1}H NMR spectroscopy as shown in Table 1.

Table 1. Conversion rates at different times in various solvents. All experiments were performed in duplicate with 10 mol-% of PPY and followed by ^{1}H NMR spectroscopy with 1,3,5-triisopropylbenzene as internal standard.

	dr	15 min	30 min	1 h	24 h	Isolated yield
$CHCl_3$	75:25	35	45	57	100	67
ACN	75:25	48	57	67	100	91
THF	80:20	50	72	85	100	73
DMSO	90:10	85	85	85	100	69
DMF	85:15	85	92	100	100	76

The polarity of the solvent clearly influences both the reaction rate and the final diastereomeric ratio, but in all cases reactions went to completion after one day at room temperature. Trials performed at lower catalyst loadings, 5 or 2 mol-%, resulted in incomplete conversion even after this time. If dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and tetrahydrofuran (THF) are the favoured media in terms of conversion and *dr*, isolated yields were eroded by practical difficulties with purification because the 1,3-oxazinan-6-ones produced are sensitive to both heat, during evaporation, and silica gel, during chromatography. Overall, optimal yields were obtained by using acetonitrile as solvent.

By using DMSO as solvent, good diastereoselectivities (90:10) could be achieved and we thus wanted to determine the relative configuration within the major diastereomer. For nosyl-protected oxazinanone **3**, a crystal suitable for X-ray crystallographic analysis revealed a *cis*-relationship between the 2,4 substituents as shown in Figure 2.

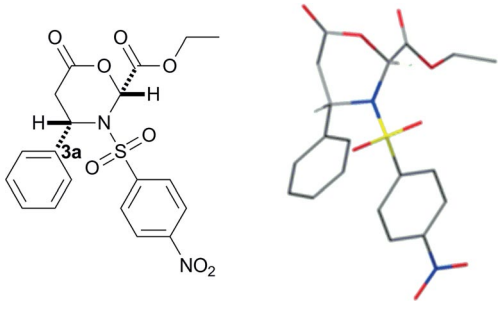
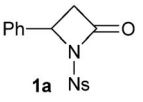
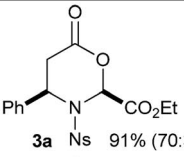
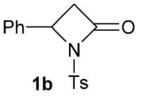
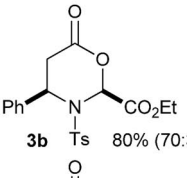
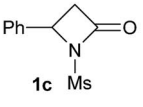
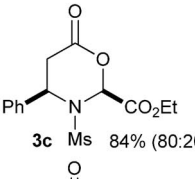
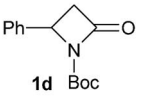
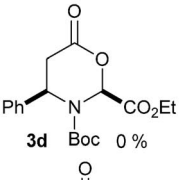
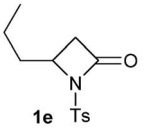
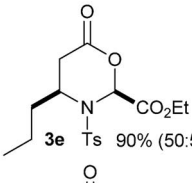
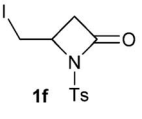
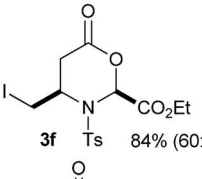
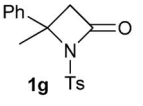
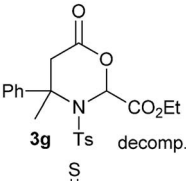
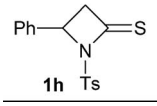
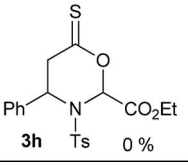


Figure 2. Relative configuration of major isomer *cis*-**3a**.

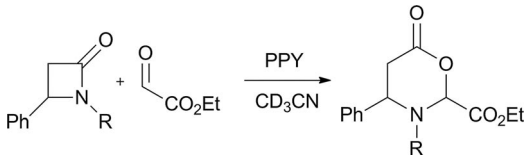
We considered the modest levels of diastereoselectivity as inconsequential because in most of the reported transformations of 1,3-oxazinan-6-ones the authors describe the generation of iminium-carboxylate intermediates in which the final product is not affected by the use of a starting material composed by a mixture of isomers.[5b,5d,5e,6a] We next investigated the scope of this transformation by using various azetidinones under optimized reaction conditions, the results are shown in Tables 2, 3, and 4.

Table 2. 4-Substituted oxazinanones.

Reactant	Product, yield, (*dr*)
 **1a** Ns	 **3a** Ns 91% (70:30)
 **1b** Ts	 **3b** Ts 80% (70:30)
 **1c** Ms	 **3c** Ms 84% (80:20)
 **1d** Boc	 **3d** Boc 0 %
 **1e** Ts	 **3e** Ts 90% (50:50)
 **1f** Ts	 **3f** Ts 84% (60:40)
 **1g** Ts	 **3g** Ts decomp.
 **1h** Ts	 **3h** Ts 0 %

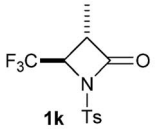
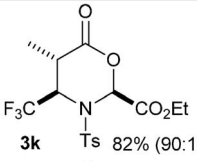
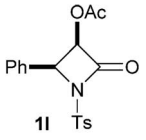
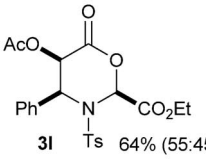
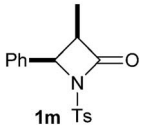
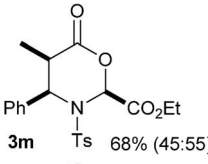
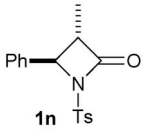
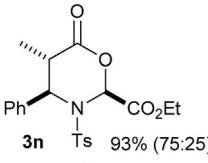
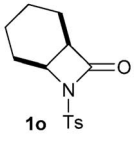
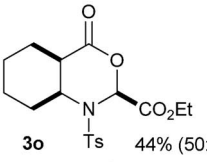
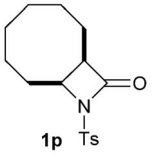
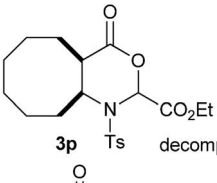
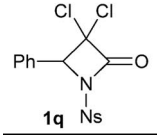
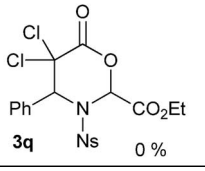
For lactams **1a**–**1h** it appears that the electron-withdrawing ability of the N-substituent is of utmost importance in this reaction, with sulfonyl-based activating groups being favourable, even though reactant stability issues can bring complications, as for triflamide **3i**, which is very prone to premature ring-opening by traces of water. However, amide or *tert*-butoxycarbonyl

Table 3. Influence of the activating group. All experiments were performed in duplicate with PPY (10 mol-%) in CD_3CN at room temperature for 24 h.



R =	Tf **3i**	4-Ns **3a**	Ts **3b**	Ms **3c**	$COCF_3$ **3j**	Boc **3d**
Yield %	decomp.	91	80	84	0	0

Table 4. 4,5-Substituted oxazinanones.

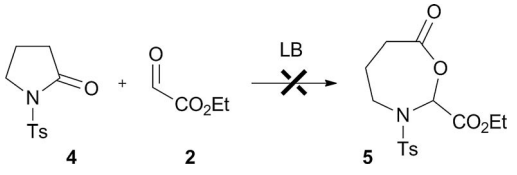
Reactant	Product, yield, (*dr*)
 **1k**	 **3k** 82% (90:10)
 **1l**	 **3l** 64% (55:45)
 **1m**	 **3m** 68% (45:55)
 **1n**	 **3n** 93% (75:25)
 **1o**	 **3o** 44% (50:50)
 **1p**	 **3p** decomp.
 **1q**	 **3q** 0 %

(Boc) substituents **3j** and **3d** bring too weak an activation to allow the transformation of the azetidinone to proceed, see Table 3.

The use of elevated temperatures in more polar solvents like DMF gave no trace of expected oxazinanone **3**. Trials with super-DMAP,[9] a very strong nucleophilic/basic catalyst that has proven superior abilities in some reactions, resulted in no conversion under these very hard conditions.

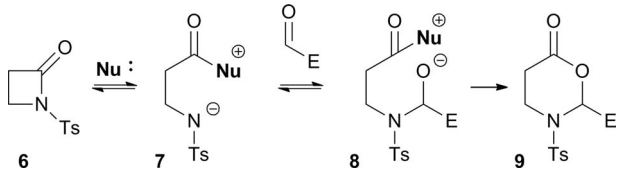
By examining the other position of substitution on the lactam ring, one sees that alkyl and halogenoalkyl-substituted lactams **1e**–**1f** are transformed smoothly. The diastereomeric ratios obtained in these cases reveal, in negative, the crucial role played by putative π–π interactions in the stereo-determining step; 4-disubstituted azetidinone **1g** was inert, as was thiolactam **1h**. Gratifyingly, 3,4-disubstituted lactams **1k**–**1n** were adequate substrates for the ring expansion as presented in Table 4. Interestingly, for lactams **1m** and **1n**, *trans*-isomer **1n** reacted significantly faster than corresponding *cis*-isomer **1m** over the same time. This information, together with the absence of formation of oxazinanone **3p** from bicyclic lactam **1p**, could indicate the importance of the last ring-closure step in the postulated mechanism.

The reaction is sensitive to steric crowding, because disubstitution at the 3-position of azetidinone **1q** precludes reactivity. We were curious to know whether the ring-tension present in azetidinones was a requirement for the reaction, so treated pyrrolidinone **4** with the ring-enlargement procedure (Scheme 3).



Scheme 3. Requirement of ring-tension.

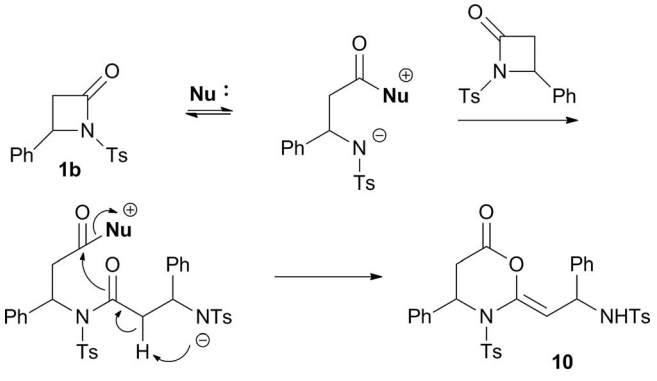
Despite forcing conditions, by using polar solvents, high temperature, and high loading of very nucleophilic catalysts, no 1,3-oxazepan-7-one **5** was detected. The failed reactions of various substrates, which proved inert to ring expansion, can inform the mechanism. If we consider the most plausible reaction pathway for this transformation, depicted in Scheme 4, three steps are identified: (1) ring opening, (2) addition to the carbonyl group, and (3) final ring closure. For Boc-protected lactam **1d**, thiolactam **1h**, dichlorolactam **1q**, and pyrrolidinone **4**, step 1 does not proceed. This was verified by performing hydrolysis/methanolysis reactions under the same forced conditions, but by replacing ethylglyoxylate **2** by three equivalents of water or methanol. Should a substantial amount of acylpyridinium be formed in step 1, rapid formation of the corresponding open-chain acid or methyl ester would be observed, but this was not the case after 24 h.



Scheme 4. Oxazinanone formation pathway.

Alcoholysis of β-lactams by using a very strong nucleophile/base azide anion as catalyst is well documented,[2,10] which does not promote ring expansion in our case. A first important

energetic barrier must be passed in this transformation with the cleavage of the N–CO bond. This step requires both strong electronic activation and release of ring strain inherent to β-lactams. A second bottleneck must be passed with the final ring-closure of the oxazinanone cycle. We did not expect this step to be problematic, but for certain substrates, like **1g** and **1p**, the expected products were not observed and a side reaction took place (Scheme 5). This parasitic pathway in the case of lactam **1b** with PPY in the absence of electrophile gave homodimerisation adduct **10**.



Scheme 5. Homodimerisation side-product.

Characteristic ethylenic protons were also found in the NMR spectra of reaction mixtures of experiments that failed to give desired products **3g** and **3p**. We hypothesized that, with these substrates, the ring closure of pyridinium alcoholate **8** is slowed by conformational constrains and that the zwitterion is then left with no other option than to attack a second lactam to give *exo*-ethylenic compounds of type **10**.

Conclusions

An experimental illustration of the formal dipolar behaviour of activated β-lactams was realised by a new 4–6-member ring-expansion reaction, which employed Lewis base organocatalysis with a very electrophilic aldehyde partner. Insights into the important requirements of this unprecedented reaction were studied, which revealed that only very electrophilic dipolarophiles could be employed because with less-activated substrates a dimerisation side-reaction occurred. We therefore moved our attention toward other cyclic substrates that could illustrate more efficiently a similar type of reactivity. This work is currently under investigation and will be reported in due course.

Experimental Section

General: Electrospray ionization (ESI) mass spectra were recorded with a Q-TOF instrument. Samples (solubilized in CH_3CN at 1 mg/mL and then diluted by 1000) were introduced into the mass spectrometer by an UPLC system and a Leucine Enkephalin solution was co-injected by a micro pump. Thin-layer chromatography was carried out on aluminium sheets pre-coated with silica gel 60 F254 (Merck). Tetrahydrofuran and dichloromethane were dried immediately before use by distillation from standard drying agents. All one-pot reactions were set up under air with non-distilled chloroform without any precautions to exclude moisture.

Starting racemic β-lactams (NH unsubstituted) were prepared following procedures reported in the literature: cyclooctyl and propyl;[11] cyclohexyl;[12] and phenyl and thiolactam.[13] Disubstituted Me,Ph[14] was sulfonylated by following General Procedure 1.

Starting racemic β-lactams with *N*-Ts and *N*-Ns substitutions **1f**,[15] **1k**,[16] **1l**,[17] and **1q**,[18] were directly prepared by following procedures reported in the literature.

***cis*-2-Oxo-4-phenyl-1-tosylazetidin-3-yl Acetate (1l):** Synthesized from acetoxyacetyl chloride (0.94 mL, 8.78 mmol, 1.2 equiv.) and *N*-benzylidene-4-methylbenzenesulfonamide (1.88 g, 7.26 mmol, 1.0 equiv.) by means of Vitaliy's procedure.[17] White solid, 1.74 g (67 % yield). M.p. 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.4 Hz, 2 H), 7.49–7.24 (m, 5 H), 7.24–7.10 (m, 2 H), 5.90 (d, J = 5.7 Hz, 1 H), 5.47 (d, J = 5.7 Hz, 1 H), 2.46 (s, 2 H), 1.65 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.11, 161.53, 145.91, 134.83, 131.38, 129.73, 128.63, 128.00, 127.84, 127.08, 76.15, 63.26, 20.38, 18.58 ppm. IR: $\tilde{\nu}$ = 3065, 3035, 2990, 1797, 1755, 1593, 1493, 1451, 1364, 1195, 1167, 1126, 915, 812, 729, 676 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{18}H_{17}NO_5NaS$ [M + Na]$^+$ 382.0725; found 382.0732.

General Procedure 1, *N*-Tosylation of β-Lactams: Under an inert atmosphere, β-lactams (NH) (1 equiv.) and dry THF (0.15 M) were placed in a dry round-bottom flask and cooled to –78 °C. A solution of *n*Buli (1.6 M in hexanes, 1.4 equiv.) was added dropwise at the same temperature and the mixture was stirred for 15–20 min. Then toluenesulfonyl chloride (4 equiv.) was added in one-pot. After 2 h at –78 °C, the solution was quenched by the addition of brine at 0 °C. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate).

(1,8-*cis*)-9-Tosyl-9-azabicyclo[6.2.0]decan-10-one (1p): White solid, 3.7 g (81 % yield). M.p. 100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.0 Hz, 2 H), 7.3 (d, J = 8.0 Hz, 2 H), 4.18–3.99 (m, 1 H), 3.19–3.00 (m, 1 H), 2.45 (d, J = 2.9 Hz, 3 H), 1.95 (m, 1 H), 1.77–1.57 (m, 4 H), 1.55–1.13 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.54, 145.05, 136.42, 129.99, 127.22, 61.12, 53.78, 28.59, 27.29, 26.74, 25.87, 25.36, 21.58 ppm. IR: $\tilde{\nu}$ = 3045, 2914, 2852, 1777, 1594, 1462, 1444, 1361, 1168, 1140, 1085, 808, 667 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{16}H_{21}NO_3NaS$ [M + Na]$^+$ 330.1140; found 330.1136.

4-Propyl-1-tosylazetidin-2-one (1e): Yellow solid, 1.02 g (48 % yield). M.p. 70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H), 4.12–3.96 (m, 1 H), 3.05 (dd, J = 15.9, 6.0 Hz, 1 H), 2.66 (dd, J = 15.9, 3.3 Hz, 1 H), 2.45 (s, 3 H), 2.23–2.03 (m, 1 H), 1.60–1.52 (m, 1 H), 1.44–1.23 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.54, 145.05, 136.42, 129.99, 127.22, 61.12, 53.78, 28.59, 27.29, 26.74, 25.87, 25.36, 21.58 ppm. IR: $\tilde{\nu}$ = 3045, 2959, 2852, 1780, 1596, 1361, 1168, 1361, 1167, 1123, 1088, 814, 669 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{13}H_{18}NO_3S$ [M + H]$^+$ 268.1007; found 268.1010.

(1,6-*cis*)-7-Tosyl-7-azabicyclo[4.2.0]octan-8-one (1o): White solid, 1.89 g (56 % yield). M.p. 68–70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.2 Hz, 2 H), 4.28–4.15 (m, 1 H), 3.25 (td, J = 6.7, 4.5 Hz, 1 H), 2.44 (s, 3 H), 2.19–2.02 (m, 1 H), 1.88–1.59 (m, 3 H), 1.59–1.22 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.70, 145.09, 136.11, 129.98, 127.18, 54.46, 47.43, 23.39, 21.67, 19.22, 18.28, 16.09 ppm. IR: $\tilde{\nu}$ = 3045, 2931, 2866, 1783, 1600 1444, 1351, 1289, 1137, 1088, 808, 714 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{14}H_{18}NO_3S$ [M + H]$^+$ 280.1007; found 280.1009.

4-Methyl-4-phenyl-1-tosylazetidin-2-one (1g): White solid, 1.2 g (61 % yield). M.p. 132–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.59 (m, 2 H), 7.52–7.11 (m, 7 H), 3.27–3.03 (m, 2 H), 2.45 (s, 3 H), 2.11 (d, J = 1.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.03, 145.01, 140.15, 136.56, 129.66, 128.65, 128.19, 127.56, 125.46, 65.86, 53.57, 24.49, 21.68 ppm. IR: $\tilde{\nu}$ = 3090, 3052, 2983, 2952, 1783, 1589, 1496, 1440, 1357, 1199, 1147, 1085, 808, 770, 673 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{14}H_{18}NO_3S$ [M + H]$^+$ 316.1007; found 316.1003.

(3,4-*trans*)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (1n): White solid, 0.42 g (29 % yield). M.p. 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.52 (m, 2 H), 7.49–7.08 (m, 7 H), 4.62 (d, J = 2.9 Hz, 1 H), 3.18 (dd, J = 7.4, 3.0 Hz, 1 H), 2.45 (s, 3 H), 1.37 (d, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.66, 145.08, 136.10, 135.68, 129.76, 128.92, 128.83, 127.45, 126.60, 64.99, 54.68, 21.69, 12.55 ppm. IR: $\tilde{\nu}$ = 3066, 3032, 2969, 2928, 1787, 1593, 1489, 1451, 1358, 1244, 1164, 1137, 1081, 798, 748, 659 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{17}H_{17}NO_3NaS$ [M + Na]$^+$ 338.0827; found 338.0424.

(3,4-*cis*)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (1m): White solid, 0.42 g (29 % yield). M.p. 131–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.2 Hz, 2 H), 7.33 (dd, J = 6.9, 4.7 Hz, 5 H), 7.15 (dd, J = 6.3, 2.7 Hz, 2 H), 5.24 (d, J = 6.7 Hz, 1 H), 3.61 (p, J = 7.4 Hz, 1 H), 2.47 (s, 3 H), 0.83 (d, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.78, 145.32, 135.70, 133.78, 129.91, 128.54, 128.48, 127.66, 127.08, 61.04, 50.16, 21.73, 9.56 ppm. IR: $\tilde{\nu}$ = 3066, 3032, 2969, 2928, 1787, 1593, 1489, 1451, 1358, 1244, 1164, 1137, 1081, 798, 748, 659 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{17}H_{17}NO_3NaS$ [M + Na]$^+$ 338.0827; found 338.0424.

4-Phenyl-1-tosylazetidine-2-thione (1h): Brown solid, 0.24 g (15 % yield). M.p. 122–125 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.3 Hz, 2 H), 7.48–7.03 (m, 7 H), 5.56 (dd, J = 5.7, 2.7 Hz, 1 H), 3.38 (dd, J = 16.6, 5.7 Hz, 1 H), 2.95 (dd, J = 16.6, 2.7 Hz, 1 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.02, 145.94, 136.22, 133.70, 129.31, 128.76, 128.43, 127.78, 126.61, 64.27, 48.73, 20.41 ppm. IR: $\tilde{\nu}$ = 3062, 3026, 1785, 1712, 1592, 1492, 1450, 1411, 1366, 1310, 1291, 1277, 1165, 1129, 1109, 1087, 805, 758 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{16}H_{15}NO_2S_2$ [M + H]$^+$ 318.0622; found 318.0608.

Procedure for Side Reaction Study, Product 10: To a stirred solution of β-lactam (**1a**; 45.8 mg, 0.152 mmol) in CD_3CN (0.5 mL), was added a solution of PPY in $CDCl_3$ (30 µL, 0.505 M, 10 mol-%). Conversion rate to form product was monitored by NMR spectroscopy after 1 d. Product (**10**). ^{1}H NMR (300 MHz, CD_3CN): δ = 7.95–7.03 (m, H arom.), 6.80–6.49 (m, 2 H), 4.60 (t, J = 7.1 Hz, 1 H), 2.74 (dd, J = 15.4, 7.2 Hz, 1 H), 2.60 (dd, J = 15.4, 7.0 Hz, 1 H), 2.42 (s, 3 H), 2.33 (s, 3 H) ppm. HRMS (ESI, TOF): m/z calcd. for $C_{32}H_{30}N_2O_6S_2Na$ [M + Na]$^+$ 625.1437; found 625.1451.

General Procedures for Oxazinanones Synthesis. General Procedure 2, Condition A: To a stirred solution of β-lactams (0.303 mmol), ethyl glyoxalate (50 % in toluene, Alfa Aesar; 60 µL, 0.303 mmol, 1 equiv.) in CD_3CN (1 mL), was added a solution of PPY in $CDCl_3$ (60 µL, 0.505 M, 10 mol-%). After 3 h at room temperature, the solvent was removed under reduced pressure and the residue purified by silica-gel (60–120 mesh) column chromatography (EtOAc, R_f = 1) to afford the resulting oxazinone product.

Ethyl 3-[(4-Nitrophenyl)sulfonyl]-6-oxo-4-phenyl-1,3-oxazinane-2-carboxylate (3a): White solid, 120 mg (91 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.7 Hz, 2 H, major), 7.95 (d, J = 8.5 Hz, 2 H, minor), 7.64 (d, J = 8.6 Hz, 2 H, major), 7.42 (d, J = 8.6 Hz, 2 H, minor), 7.23–6.87 (m, 5 H, major+minor), 6.61 (s, 1 H, major), 6.29 (s, 1 H, minor), 5.21 (dd, J = 7.5, 3.8 Hz, 1 H, minor), 5.06 (t, J = 9.2 Hz, 1 H, major), 4.37 (dd, J = 7.0, 3.2 Hz, 2 H, minor), 4.30–4.10 (m, 1 H, major), 3.17 (dd, J = 16.9, 7.8 Hz,1 H, minor), 2.84 (dd, J = 16.4, 10.5 Hz, 1 H minor+2 H, major), 1.36 (t, J = 7.1 Hz, 3 H, minor), 1.25 (t, J = 7.1 Hz, 3 H, major) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.83, 166.51, 166.01, 165.44, 150.13, 149.70, 145.44, 144.36, 137.03, 136.40, 129.13, 128.87, 128.34, 127.49, 126.88, 123.78, 82.09, 81.64, 63.87, 56.71, 55.78, 36.57, 32.30, 14.01 ppm. IR: $\tilde{\nu}$ = 3118, 2983, 2900, 1780, 1749, 1534, 1347, 1171, 1081, 1050, 856 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{19}H_{18}N_2O_8NaS$ [M + Na]$^+$ 457.0682; found 457.0685.

Ethyl 3-[(4-Methyl)sulfonyl]-6-oxo-4-phenyl-1,3-oxazinane-2-carboxylate (3b): White solid, 97 mg (80 % yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.3 Hz, 2 H, major), 7.38–6.98 (m, 10 H, major+minor), 6.61 (s, 1 H, major), 6.22 (s, 1 H, minor), 5.23 (dd, J = 7.6, 4.7 Hz, 1 H, minor), 5.00 (dd, J = 10.1, 7.7 Hz, 1 H, major), 4.40 (q, J = 7.0 Hz, 2 H, minor), 4.27–3.99 (m, 2 H, major), 3.22 (dd, J = 16.8, 7.6 Hz, 1 H, minor), 3.04–2.67 (m, 2 H major+1 H minor), 2.40 +2.34 (s+s', 3 H, major+minor), 1.40 (t, J = 7.1 Hz, 3 H, minor), 1.26 (t, J = 7.2 Hz, 3 H, major) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 166.41, 166.31, 166.15, 164.71, 145.11, 144.66, 139.54, 134.01, 129.68, 129.28, 128.34, 128.20, 127.73, 127.65, 127.46, 125.91, 125.85, 81.73, 81.58, 63.17, 62.64, 55.24, 54.66, 36.41, 35.27, 20.28, 20.24, 12.95, 12.85 ppm. IR: $\tilde{\nu}$ = 3066, 3007, 2952, 1766, 1756, 1597, 1455, 1365, 1209, 1168, 1078, 1019, 818 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{20}H_{21}NO_6NaS$ [M + Na]$^+$ 426.0987; found 426.0993.

Ethyl 3-(Methylsulfonyl)-6-oxo-4-phenyl-1,3-oxazinane-2-carboxylate (3c): White solid, 83 mg (84 % yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.54–7.30 (m, 5 H), 6.45 (s, 1 H, major), 6.12 (s, 1 H, minor), 5.32 (dd, J = 7.9, 4.1 Hz, 1 H, minor), 5.19 (t, J = 9.3 Hz, 1 H, major), 4.37 (q, J = 7.1 Hz, 2 H, minor+major), 3.30 (dd, J = 16.8, 7.8 Hz, 1 H, minor), 3.01 (d, J = 9.3 Hz, 2 H, major), 2.88 (dd, J = 16.8, 4.0 Hz, 1 H, minor), 2.72 (s, 3 H, major), 2.61 (s, 3 H, minor), 1.38 (dd, J = 9.2, 5.1 Hz, 3 H, major+minor) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 166.69, 166.57, 139.81, 139.58, 128.69, 128.43, 128.12, 127.91, 125.99, 125.80, 81.55, 81.49, 63.29, 62.79, 55.36, 54.94, 40.94, 39.11, 37.12, 35.77, 12.89 ppm. IR: $\tilde{\nu}$ = 3017, 2994, 1780, 1731, 1462, 1361, 1207, 1184, 1161, 1088, 1039, 1007, 762 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{14}H_{18}NO_6S$ [M + H]$^+$ 328.0855; found 328.0847.

General Procedure 3, Condition B: To a stirred solution of β-lactams (0.303 mmol), ethyl glyoxalate (50 % in toluene, Alfa Aesar; 180 µL, 0.909 mmol, 3 equiv.) in CD_3CN (1 mL), and mesitylene as an internal reference (42 µL, 0.302 mmol, 1 equiv.) was added to a solution of PPY in $CDCl_3$ (60 µL, 0.505 M, 10 mol-%). After 1 d at 40 °C, NMR spectroscopic analysis was performed and yields were determined by using 1,3,5-mesitylene. The solvent was removed under reduced pressure and the residue purified by silica-gel (60–120 mesh) column chromatography.

Ethyl 6-Oxo-4-propyl-3-tosyl-1,3-oxazinane-2-carboxylate (3e): Yield 90 % as a mixture of isomers (50:50). ^{1}H NMR (300 MHz, CD_3CN): δ = 7.84–7.79 (m, 2 H, major+minor), 7.45–7.41 (m, 2 H, major+minor), 6.43 (s, 1 H, major), 5.85 (s, 1 H, minor), 4.47–4.20 (m, 2 H, major), 4.08–3.78 (m, 2 H, minor), 2.75–2.59 (m, 1 H minor+ 2 H major), 2.45 (s, 3 H, major+minor), 2.43–2.33 (m, 1 H, minor), 1.81–1.45 (m, 2 H, major+minor), 1.42–1.11 (m, 6 H, major+minor), 0.87 (m, 6 H, major+minor) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 166.72, 166.37, 163.90, 144.97, 135.42, 134.40, 129.73, 129.54, 127.94, 127.62, 81.15, 80.47, 63.02, 62.24, 52.26, 51.59, 38.54, 36.47, 34.47, 32.39, 20.29, 20.27, 17.68, 17.55, 12.97, 12.89, 12.58, 12.50 ppm. IR: $\tilde{\nu}$ = 2959, 2876, 1748, 1361, 1191, 1167, 1039 cm^{-1}. HRMS (ESI, TOF): m/z calcd. for $C_{17}H_{23}NO_6NaS$ [M + Na]$^+$ 392.1144; found 392.1146.

Ethyl 4-(Iodomethyl)-6-oxo-3-tosyl-1,3-oxazinane-2-carboxylate (3f): Yield 84 % as a mixture of isomers (60:40). ^{1}H NMR

(300 MHz, CD_3CN): δ = 7.86–7.81 (m, 2 H, major+minor), 7.48–7.43 (m, 2 H, major+minor), 6.39 (s, 1 H, major), 5.92 (s, 1 H, minor), 4.51–4.14 (m, 2 H, major+minor), 3.98–3.93 (m, 1 H, minor), 3.92–3.80 (m, 1 H, major), 3.58–3.37 (m, 2 H, major+minor), 2.87–2.78 (m, 1 H, major+minor), 2.75–2.56 (m, 1 H, major+minor), 2.46+2.45 (s+s′, 3 H, major+minor), 1.38–1.29 (m, 3 H, major+minor) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 166.16, 166.06, 166.04, 163.13, 145.42, 145.28, 134.51, 133.38, 129.85, 129.58, 128.06, 127.71, 81.33, 80.88, 63.28, 62.38, 52.18, 51.92, 34.80, 33.33, 20.31, 12.90, 12.84, 9.87, 8.62 ppm. IR: $\tilde{\nu}$ = 2993, 1773, 1748, 1593, 1361, 1157, 1019 cm^{-1}. HRMS (ESI, TOF): *m/z* calcd. for $C_{15}H_{18}INO_6NaS$ $[M + Na]^+$ 489.9797; found 489.9803.

Ethyl (4,5-*trans*)-5-Methyl-6-oxo-4-phenyl-3-tosyl-1,3-oxazinane-2-carboxylate (3n): Yield 93 % as a mixture of isomers (75:25). ^1H NMR (300 MHz, CD_3CN): δ = 7.76 (d, *J* = 8.4 Hz, 2 H, minor), 7.58 (d, *J* = 8.4 Hz, 2 H, dia major), 7.41–7.27 (m, 9 H, minor+major), 6.60 (s, 1 H, major), 6.18 (s, 1 H, minor), 4.50 (d, *J* = 11.9 Hz, 1 H major+minor), 4.35 (qd, *J* = 7.2, 2.4 Hz, 2 H, major+minor), 3.15 (dq, *J* = 13.3, 6.7 Hz, 1 H, minor), 2.92 (dq, *J* = 13.0, 6.6 Hz, 1 H, major), 2.42 (s, 3 H, major+minor), 1.37 (t, *J* = 7.2 Hz, 3 H, minor), 1.30 (t, *J* = 9.1 Hz, 3 H, major), 1.04 (d, *J* = 6.6 Hz, 3 H, minor), 0.89 (d, *J* = 6.6 Hz, 3 H, major) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 169.57, 167.01, 144.97, 144.69, 138.15, 134.72, 134.45, 134.20, 81.17, 80.95, 63.25, 62.42, 62.33, 61.92, 40.53, 38.88, 20.27, 20.22, 12.95, 12.89, 12.02 ppm. IR: $\tilde{\nu}$ = 3054, 2983, 1748, 1593, 1360, 1162, 1071, 1014, 802 cm^{-1}. HRMS (ESI, TOF): *m/z* calcd. for $C_{21}H_{23}NO_6NaS$ $[M + Na]^+$ 440.1144; found 440.1146.

(4,5-*cis*)-Ethyl 5-Methyl-6-oxo-4-phenyl-3-tosyl-1,3-oxazinane-2-carboxylate (3m): Yield 68 % as a mixture of isomers (45:55). ^1H NMR (300 MHz, CD_3CN): δ = 7.87 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 1 H), 7.35–7.28 (m, 5 H), 7.24–7.12 (m, 5 H), 7.06 (m, 1 H), 6.86 (d, *J* = 7.4 Hz, 1 H), 6.61 (s, 1 H), 6.52 (s, 1 H), 6.21 (s, 1 H), 5.29 (d, *J* = 6.8 Hz, 1 H), 5.23 (d, *J* = 7.4 Hz, 1 H), 5.19 (d, *J* = 6.4 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.42–4.28 (m, 1 H), 4.06–3.80 (m, 1 H), 3.74–3.60 (m, 1 H), 3.32 (p, *J* = 6.6 Hz, 1 H), 2.97–2.82 (m, 1 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.32 (s, 1 H), 1.40–1.25 (m, 1 H), 1.20–1.10 (m, 1 H), 0.99 (d, *J* = 6.9 Hz, 1 H), 0.90 (d, *J* = 6.5 Hz, 1 H), 0.75 (d, *J* = 7.6 Hz, 1 H), 0.68 (d, *J* = 6.6 Hz, 1 H) ppm. IR: $\tilde{\nu}$ = 3054, 2983, 1748, 1593, 1360, 1162, 1071, 1014, 802 cm^{-1}. HRMS (ESI, TOF): *m/z* calcd. for $C_{21}H_{23}NO_6NaS$ $[M + Na]^+$ 440.1144; found 440.1146.

Ethyl (4,5-*cis*)-5-Acetoxy-6-oxo-4-phenyl-3-tosyl-1,3-oxazinane-2-carboxylate (3l): Yield 64 % as a mixture of isomers (55:45). ^1H NMR (300 MHz, CD_3CN): δ = 7.87 (d, *J* = 8.3 Hz, 2 H, minor), 7.49 (d, *J* = 8.1 Hz, 2 H, minor), 7.41–7.08 [m, 5 Hminor+(5+2)H major], 6.97 (d, *J* = 7.7 Hz, 2 H, major), 6.60 (s, 1 H, minor), 6.52 (s, 1 H, major), 5.97 (d, *J* = 7.5 Hz, 1 H, major), 5.53–5.46 (m, 2 H minor+1 H major), 4.35 (q, *J* = 7.1 Hz, 2 H, major), 3.90–3.71 (m, 2 H, minor), 2.49 (s, 3 H, minor), 2.36 (s, 3 H, major), 1.92 (s, 6 H, major+minor), 1.34 (t, *J* = 7.1 Hz, 3 H, major), 1.14 (t, *J* = 7.2 Hz, 3 H, minor) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 168.41, 167.94, 166.47, 164.94, 164.03, 163.53, 145.61, 144.29, 136.25, 134.21, 133.58, 132.56, 129.96, 129.11, 128.46, 128.16, 128.02, 127.84, 127.72, 127.57, 126.82, 81.71, 81.25, 66.44, 65.66, 63.35, 62.46, 58.21, 57.28 ppm. IR: $\tilde{\nu}$ = 3095, 2990, 1773, 1753, 1597, 1358, 1199, 1157, 1054, 1016, 669, 562, 662 cm^{-1}. HRMS (ESI, TOF): *m/z* calcd. for $C_{22}H_{23}NO_8NaS$ $[M + Na]^+$ 484.1042; found 484.1045.

Ethyl (4,5-*trans*)-5-Methyl-6-oxo-3-tosyl-4-(trifluoromethyl)-1,3-oxazinane-2-carboxylate (3k): Yield 82 % as a mixture of isomers (90:10). ^1H NMR (300 MHz, CD_3CN): δ = 7.86 (d, *J* = 8.3 Hz, 2 H, minor+major), 7.48 (d, *J* = 8.2 Hz, 2 H, minor+major), 6.40 (s, 1 H, major), 5.83 (s, 1 H, minor), 4.50 (dd, *J* = 9.3, 6.9 Hz, 1 H, major), 4.26 (m, 2 H minor+ 2 H major+minor), 3.09 (dd, *J* = 9.4, 6.7 Hz, 1 H, major), 2.47 (s, 3 H, major+minor), 1.43–1.10 (m, 6 H, major+minor) ppm. ^{19}F NMR (188 MHz, CD_3CN): δ = –73.10 (d, *J* = 6.8 Hz), –75.39 (d, *J* = 6.6 Hz) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 167.32, 166.74, 164.94, 162.27, 130.05, 129.78, 129.45, 128.30, 127.76, 80.98, 63.18, 62.49, 61.36, 58.17 (q, *J* = 31.8 Hz), 40.81, 34.46, 31.82, 29.29, 23.39, 20.33, 14.50, 12.72 ppm. IR: $\tilde{\nu}$ = 2986, 1752, 1596, 1372, 1282, 1254, 1182, 1140, 1085, 1064 cm^{-1}. HRMS (ESI, TOF): *m/z* calcd. for $C_{16}H_{18}NO_6F_3NaS$ $[M + Na]^+$ 432.0705; found 432.0706.

Procedure 4, Synthesis of 3o: To a stirred solution of β-lactams (**2o**; 0.303 mmol), ethyl glyoxalate (50 % in toluene, Alfa Aesar; 180 µL, 0.909 mmol, 3 equiv.) in CD_3CN (1 mL), and mesitylene as an internal reference (42 µL, 0.302 mmol, 1 equiv.) was added a solution of PPY in $CDCl_3$ (80 µL, 0.505 M, 17 mol-%). After 2 d at 70 °C, NMR spectroscopic analysis was performed and yields were determined by using 1,3,5-mesitylene. The solvent was removed under reduced pressure and the residue purified by silica gel (60–120 mesh) column chromatography.

Ethyl (4,8-*cis*)-4-Oxo-1-tosyloctahydro-1*H*-benzo[*d*][1,3]oxazine-2-carboxylate (3o): Yield 44 % as a mixture of isomers (50:50). ^1H NMR (300 MHz, CD_3CN): δ = 7.90–7.74 (m, 2 H), 7.47–7.37 (m, 2 H), 6.42 (s, 1 H), 6.25 (s, 1 H), 4.32–4.4 (m, 2 H+1 H+1 H), 2.46+2.45 (s+s′, 3 H), 1.75–0.75 (m, 3 H+8 H aliphatic) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 169.09, 167.57, 167.15, 166.99, 145.18, 144.96, 144.18, 143.12, 138.49, 138.30, 135.85, 135.48, 129.85, 129.71, 129.52, 129.34, 129.31, 127.67, 127.17, 126.68, 126.56, 126.41, 126.35, 93.06, 92.55, 81.48, 80.82, 65.46, 65.25, 62.79, 62.49, 61.57, 61.51, 57.72, 54.43, 54.32, 53.23, 51.82, 47.01, 45.14, 45.02, 41.83, 40.29, 39.08, 31.19, 28.98, 28.89, 28.70, 26.10, 24.49, 24.29, 24.07, 23.02, 22.55, 21.62, 20.82, 20.33, 20.29, 20.22, 20.17, 19.90, 18.53, 17.72, 15.58, 13.96, 12.90, 12.81 ppm. HRMS (ESI, TOF): *m/z* calcd. for $C_{18}H_{24}NO_6S$ $[M + H]^+$ 382.1324; found 382.1328.

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