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Synthesis of α-Keto-Imides via Oxidation of Ynamides

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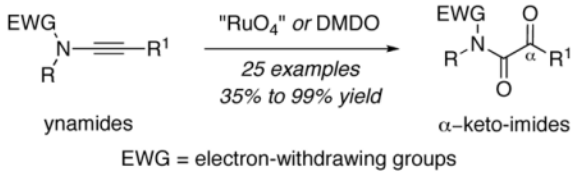
Abstract



A *de novo* preparation of α-keto-imides via ynamide oxidation is described. With a number of alkyne oxidation conditions screened, a highly efficient RuO_2-$NaIO_4$ mediated oxidation and a DMDO oxidation have been identified to tolerate a wide range of ynamide types. In addition to accessing a wide variety of α-keto-imides, the RuO_2-$NaIO_4$ protocol provides a novel entry to the vicinal tricarbonyl motif via oxidation of push-pull ynamides, and imido acylsilanes from silyl-substituted ynamides. Chemoselective oxidation of ynamides containing olefins can be achieved using DMDO, while the RuO_2-$NaIO_4$ protocol is not effective. These studies provide further support for the synthetic utility of ynamides.

Introduction

In our efforts to explore the reactivity of ynamides and to establish their utility as versatile synthons, [1–4] we arrived at α-keto-imides[5] [see **1a** in Scheme 1], a hitherto underrepresented chemical entity. Literature precedents on the engagement of α-keto-imides towards diastereoselective outcomes,[6] as well as a significant body of literature surrounding the structurally related α-keto-amides [**1b**] and esters [**1c**],[7–11] prompted us to pursue an optimized entry to these molecules. Ynamide preparation via copper-mediated amidation of bromoalkynes[2c–i] along with the recently reported amidations of terminal acetylenes[2b] have tolerated a variety of amide types and alkyne functionality,[2e,2g,3,12] providing access to a wide variety of ynamides. Building on this versatile synthon, we pursued a highly efficient oxidative protocol transforming a range of ynamide types to access a structurally diverse array of α-keto-imides.

The limited literature involving α-keto-imides confirms their utility as synthons with the potential of incorporating elements of stereocontrol. Some examples are successes in *hetero*-Diels Alder reactions,[6a] an intriguing divergent diastereoselective allylation,[6b]

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SUPPORTING INFORMATION AVAILABLE. Experimental procedures, characterization data for all new compounds, ^1H NMR, ^{13}C NMR spectra, and X-ray structural data are available free of charge via Internet at http://pubs.acs.org.

diastereoselective cyanation,[6c] and Grignard additions.[6d] In these reports, preparations of α-keto-imides were accomplished by amidation of α-keto-acids, or by ozonolytic or osmium mediated oxidative cleavage of acrylimides. Although there is a compelling parallel between α-keto-imides **1a** and the related α-keto-amides [**1b**] and esters [**1c**], the latter has attracted much more synthetic interest as evident from an array of elegant solutions to their construction, [8] including seminal work on oxidations of ynamines[7a–d] that is related to the efforts to be described herein as well as advances in their applications as synthons,[9] and a greater understanding of their role as pharmacophores.[10]

The underlying reactivity of α-keto-amides [**1b**] and esters [**1c**] stems from the enhanced electrophilicity of their respective keto carbonyl group. Transformations of these compounds have involved the addition of nucleophiles[9a] with particular interest placed on attaining stereochemical control through a chirality-inducing element substituted on the oxygen or nitrogen atom. It is noteworthy that α-keto-amides **1b** have also been engaged in pinacol-type couplings[9b] as well as photocyclizations leading to β-lactams.[9c] In the biological setting, this reactivity is implicated in the engagement of key cysteine and lysine residues important to protease,[10a–d] lipase,[10e] and histone deacetylase activity.[10f] Facile hydrate formation of the α–keto carbonyl, which serves as a transition state mimic of the tetrahedral intermediates associated with amide and ester hydrolysis, has also been associated with enzyme inhibitory activity.[10b] Given the close analogy between α-keto-imides **1a** and α-keto-amides or esters [**1b** or **1c**], access to α-keto-imides should prove to be of significance in organic synthesis and medicinal chemistry. We wish to report here highly efficient oxidative transformations of ynamides to novel α-keto-imides.

Results and Discussion

Our first experiences with α–keto-imides arose from studies aimed at the preparation of benzofurans via a Rh(I)-catalyzed demethylation-cyclization of *o*-anisole-substituted ynamides such as **2** [Scheme 2].[4c] While not highly reproducible, α–keto-imide **3**[5] could be obtained in 45% yield by exposure of ynamide **2** to the action of Wilkinson's catalyst and $AgBF_4$, and an X-ray structure of α–keto-imide **3**[5] was also attained [see Supporting Information]. Although we have not identified the stoichiometric oxidant involved, α–keto-imide formation has been correlated with the use of contaminated/decomposed samples of Wilkinson's catalyst containing triphenylphosphine oxide.

A more consistent entry to α–keto-imides from ynamides became apparent during our exploration of the dimethyldioxirane (DMDO) oxidation of ynamides **4** [Scheme 3].[5] We were interested in probing the possibility of arriving at push-pull carbenes **5** derived from the oxidation of **1** through the rearrangement of presumed oxirenes **A**. This event was confirmed by the isolation of push-pull carbene-derived cyclopropanes **6**. The formation of α–keto-imides **7** was often a competing outcome of these reactions, presumably resulting from a second oxidation of the carbenes **5**, although oxidation of oxirenes **A** to 1,3-dioxabicyclobutanes **8** followed by rearrangement to α–keto-imides **7** cannot be ruled out.

Persuing the purposeful preparation of α-keto-imides, we examining a number of alkyne oxidation conditions of ynamide **9** [Table 1]. In addition to DMDO oxidation,[5,13] α–keto-imide **10** formation could be achieved by the action of ozone,[7b–d] *m*-CPBA,[14] and RuO_4 generated *in situ* from either RuO_2 or $RuCl_3$.[7a,15] We also examined the action of I_2 in DMSO,[16] as well as $CuCl_2$ in DMSO[17] at elevated temperatures (150 °C), however, no evidence of α–keto-imide **10** was found, with complete consumption of the starting ynamide **9** [entries 6 and 7]. Oxidation by DMDO[18] provided the α–keto-imide in 86% isolated yield [entry 1] with ~5% yield of what appears to be the corresponding α–keto-carboxylic acid accompanied by the free Evans' oxazolidinone auxiliary. The stability of α–keto-imides in wet acetone suggests that the

formation of α–keto-carboxylic acid does not occur by a simple event of hydrolyzing the respective imide motif.[5] We are currently still investigating this mechanistic issue. *m*-CPBA oxidation provided only trace amounts of **10** [entry 3].[19] The RuO_4 mediated oxidation quickly became the method of choice, yielding **10** in quantitative yields [entries 4 and 5].

We proceeded to examine the scope of RuO_2-$NaIO_4$ mediated oxidation varying ynamide electronic properties [Table 2]. The ynamides examined varied in the nature of the electron withdrawing group on nitrogen, as well as the electron withdrawing or donating ability of the alkyne substituent [entries 4–6]. All oxidations proceeded in moderate to high yield, and the resulting α-keto-imides tolerated routine laboratory handling such as purification and storage. In addition to facile preparation of a variety of α-keto-imides, this method provides ready access to the vicinal tricarbonyl motif as in **20** and **21** [entries 4 and 5] with long standing chemical and biological intrigue,[20] and these preparations also showcase the synthetic utility of so called push-pull ynamides **14** and **15**. Imido acylsilanes such as **22** [entry 6] should be poised for umpolung chemistry elegantly demonstrated by Johnson's tandem alkylation-aldolizations of silylglyoxylates.[11]

We then examined the preparation of α-keto-imides from ynamides with varied alkyne substitution and compared DMDO and RuO_2-$NaIO_4$ conditions [Table 3]. Throughout this series, the RuO_2-$NaIO_4$ mediated oxidation provided higher yields of the doubly oxidized products. Increasing steric bulk surrounding the alkyne [from entries 1–4] was well tolerated by both methods, and is accompanied by increased yields under DMDO oxidation conditions (remainder of the material is hydrolyzed). Both the TBS-silyl ether and THP acetal protecting groups, as well as the *N*-tosyl group are tolerated under reaction conditions [see **27**→**37** and **28**→**38** in respective entries 5 and 6]. The yield of α-keto-imide **38** suffers from elimination of the *O*-THP group [entry 6].[21] High yields of triethylsilyl imido acylsilanes **39** and **40** were obtained employing the RuO_2-$NaIO_4$ conditions [entries 7 and 8]. The preparation of these less hindered silanes [relative to tri-isopropylsilane **22** in Table 2] was pursued due to their added susceptibility towards engagement of the acylsilane.[11] In contrast, the DMDO oxidation of silylated ynamides **29** and **30** did not provide any trace of imido acylsilanes **39** and **40**.[22] DMDO oxidation of both *N*-sulfonyl-substituted ynamides **31** and **32** also did not yield the respective α-ketoimides **41**[23] and **42**.[22]

The last class of ynamides examined were those containing a tethered olefin [Table 4]. Ynamide oxidation employing RuO_2-$NaIO_4$ led to the formation of a large number of higher polarity products [SiO_2 TLC analysis], attributed to alkene dihydroxylation and further cleavage reactions,[24] as well as the potential for ketal and hemi-ketalization of the resulting dihydroxy-keto-imides. In these cases, DMDO oxidation proceeded with chemoselective oxidation of the ynamide moeity. All the olefinic motifs in these substrates were stable to DMDO oxidation except for the relatively more electron rich styryl group in **45** [entry 3], which suffered from competitive epoxidation. In addition, for entries 1–4 and 6, we observed a noticeable amount of the free oxazolidinone auxiliary, thereby suggesting the formation of the corresponding α–keto-carboxylic acid.[5] Intramolecular cyclopropanation through intermediate push-pull carbenes **5**[5] [Scheme 3] was not oberved in any of these reactions.

CONCLUSION

We have described here efficient preparations of α-keto-imides through oxidations of ynamides. Both RuO_2-$NaIO_4$ and DMDO oxidations tolerate a wide range of ynamide types and substituents. In addition to facile preparation of a variety of α-keto-imides, the RuO_2-$NaIO_4$ mediated oxidation provides ready access to the vicinal tricarbonyl motif via the oxidation of push-pull ynamides as well as imido acylsilanes via the oxidation of silylated ynamides. The RuO_2-$NaIO_4$ protocol does however lead to complex mixtures during the

oxidation of olefin containing ynamides. In these cases, the chemoselective oxidation of such ynamides can be achieved employing DMDO. We believe these protocols provide practical access to a class of building blocks that will be significant in synthesis.

EXPERIMENTAL SECTION

General Procedure For RuO_2-$NaIO_4$ Mediated Oxidation of Ynamides

To a solution of ynamide **29** (377.0 mg, 1.670 mmol, 1 equiv) in CH_2Cl_2 (5 mL) and CH_3CN (5 mL) was added $NaIO_4$ (1.07 g, 5.02 mmol, 3 equiv) in H_2O (7.5 mL), and then $RuO_2•H_2O$ (11.2 mg, 0.0840 mmol, 5 mol%). The reaction mixture was stirred vigorously at rt, and the reaction progress was followed by thin layer chromatography. The sides of the reaction flask were rinsed with CH_3CN (~1 mL) at 2 h, and the reaction stirred for another 2 h. The reaction mixture was then filtered through a plug of SiO_2 rinsing with CH_2Cl_2. Further purification was accomplished by silica gel flash column chromatography [gradient elution: 17–50% EtOAc in hexanes] to afford α–keto-imide **39** as a bright yellow oil (386.0 mg, 90% yield). R_f = 0.41 [50% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (q, 6H, *J* = 8.0 Hz), 1.03 (t, 9H, *J* = 8.0 Hz), 4.02 (m, 2H), and 4.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.3, 7.1, 41.1, 64.7, 154.2, 171.5, and 232.8; IR (neat) cm^{-1} 2958w, 2914w, 2879w, 1780s, 1681s, 1642m, 1478w, 1390s, 1361m, 1335m, 1226s, 1117m, 1028m, and 967m; mass spectrum (APCI): m/e (% relative intensity) 258 (10) $(M+1)^+$, 202 (90), 172 (100), and 128 (25); HRMS (ESI) m/e calcd for $C_{11}H_{20}NO_4Si^+$ $(M+H^+)$ 258.1156, found 258.1146.

General Procedure For DMDO Oxidation of Ynamides

To a solution of ynamide **49** (45.4 mg, 0.167 mmol) in acetone (12 mL) was added DMDO (6.0 mL, 0.11 M in acetone, 4 equiv)[18,25] at rt. The resulting reaction mixture was stirred for 2.5 h before it was filtered through Celite™ rinsing with CH_2Cl_2 and concentrated *in vacuo*. The crude residue was purification by silica gel flash column chromatography [gradient elution: 17–67% EtOAc in hexanes] to provide α–keto-imide **56** as a yellow crystalline solid (44.6 mg, 88% yield). R_f = 0.33 [67% EtOAc in hexanes]; mp = 152.0 – 153.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (m, 2H), 2.52 (br s, 2H), 3.83 (t, 2H, *J* = 7.5 Hz), 3.85 (s, 3H), 4.49 (ddd, 2H, *J* = 6.0, 1.0, 1.0 Hz), 5.33 (ddt, 1H, *J* = 10.5, 1.0, 1.0 Hz), 5.39 (ddt, 1H, *J* = 17.5, 1.5, 1.5 Hz), 5.96 (ddt, 1H, *J* = 17.5, 10.5, 6.0 Hz), 6.39 (d, 1H, *J* = 2.0 Hz), 6.63 (dd, 1H, *J* = 9.0, 2.5 Hz), and 8.04 (d, 1H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 32.1, 43.6, 55.9, 70.1, 99.2, 107.1, 116.4, 119.7, 132.3, 132.8, 161.1, 166.5, 168.1, 175.7, and 186.1; IR (film) cm^{-1} 3079w, 2938w, 2899w, 2852w, 1738m, 1673m, 1656m, 1595s, 1575m, 1504m, 1447m, 1421m, 1363s, 1286m, 1251s, 1231s, 1204s, 1175m, 1115m, 993s, 909m, and 837m; mass spectrum (APCI): m/e (% relative intensity) 304 (65) $(M+1)^+$, and 191 (100); HRMS (MALDI) m/e calcd for $C_{16}H_{17}NO_5Na^+$ $(M+Na^+)$ 326.0999, found 326.0998.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. Further Baeyer-Villiger type oxidation of 1,2-dicarbonyls is known to occur under ozone and peroxyacid oxidation conditions [see references 7b-d and 14]. Although inconclusive, the presence of byproduct benzoyl and phenyl ester-type aromatic proton resonances in the crude ^{1}H-NMR spectra resulting from the oxidation of ynamide 9 under these conditions suggests this course of action.
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21. Minor amounts of the corresponding enone i apparent by ^{1}H-NMR.
22. Silicon *d*-orbital overlap with the carbene may result a silyl-push-pull carbene [see 5 in Scheme 3 with R = SiR_3] that is susceptible to undergo Wolff rearrangement and subsequent transformations through the resulting silyl ketene intermediate. Further studies are underway.
23. We observed loss of the *N*-sulfonyl group during DMDO oxidations of *N*-sulfonyl-substituted ynamides such as 31 [also observed for 11 shown in Table 2].
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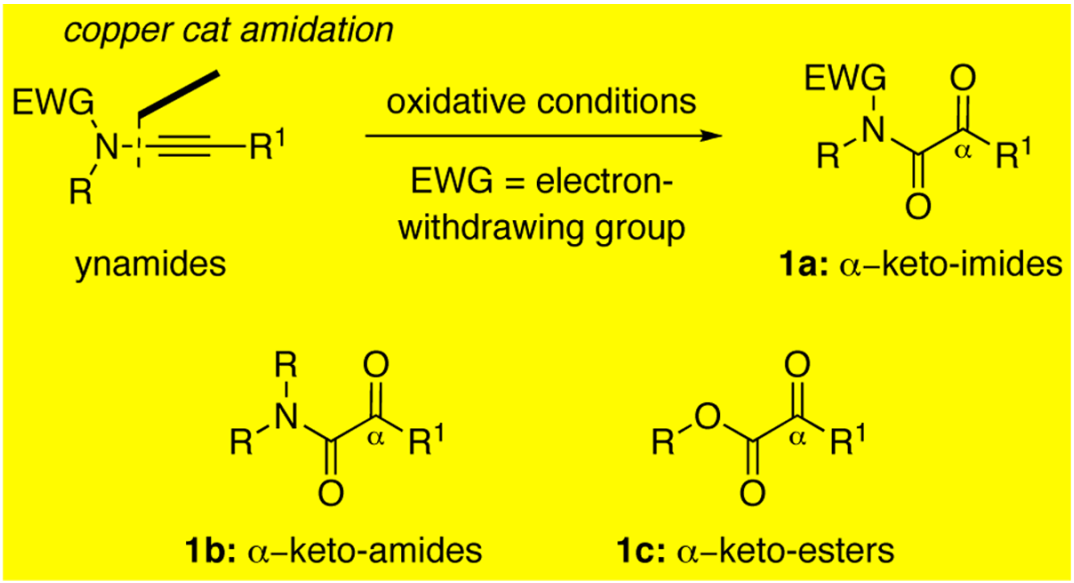
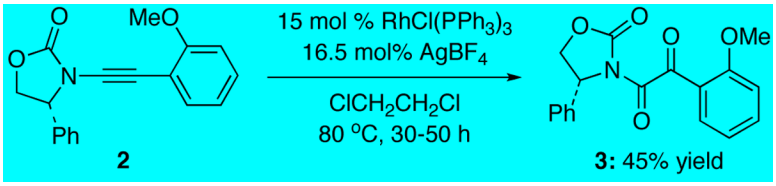
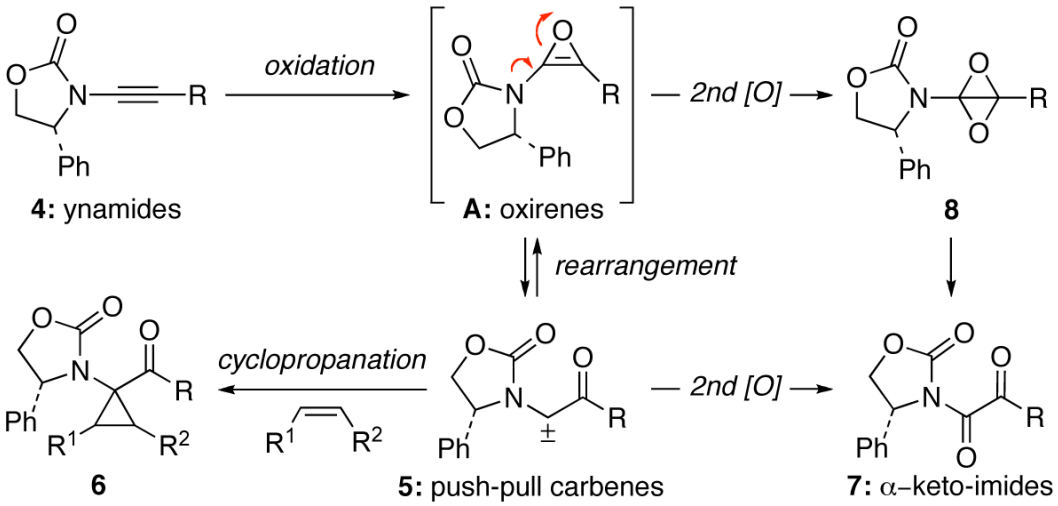


Scheme 1.
Ynamide-Derived α-Keto-Imides.



Scheme 2.
α-Keto-Imide Formation $RhCl(PPh_3)_3$-$AgBF_4$.



Scheme 3.
DMDO Oxidation of Ynamides.

Table 1

Conditions for α-Keto-Imide Formation.

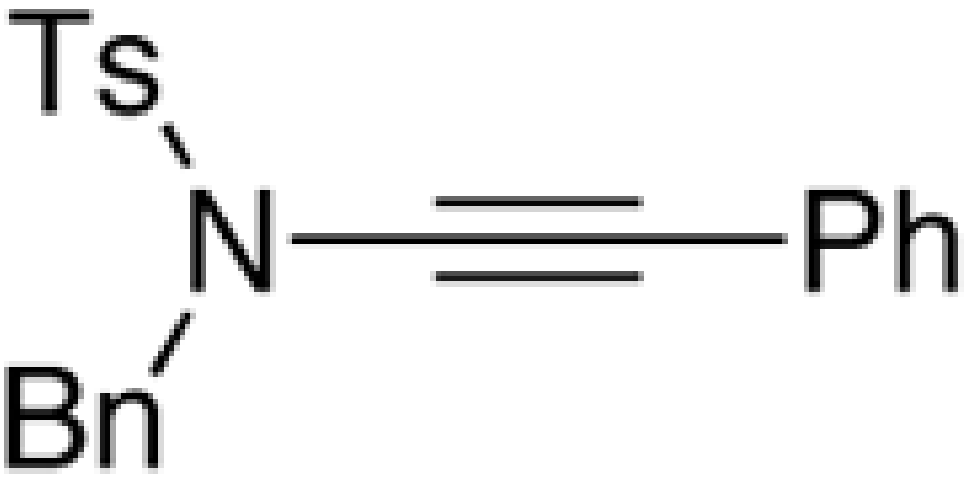
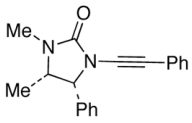
entry	conditions	yield [%][a]
1	***DMDO, acetone, rt, 2.5 h***	***86%***
2	1) O_3, CH_2Cl_2, −78 °C to rt, 2 h; 2) DMS	70%
3	*m*-CPBA, CH_2Cl_2, rt, 2.5 h	trace
4	***RuO_2•H_2O, $NaIO_4$ CH_2Cl_2, CH_3CN, H_2O, rt, 4 h***	***96%***
5	***$RuCl_3$•H_2O, $NaIO_4$, CH_2Cl_2, CH_3CN, H_2O, rt, 4 h***	***99%***
6	I_2, DMSO, 150°C, 1 h	nd[b]
7	$CuCl_2$, DMSO, 150°C, 24 h	nd

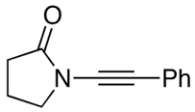
[a] Isolated yields.

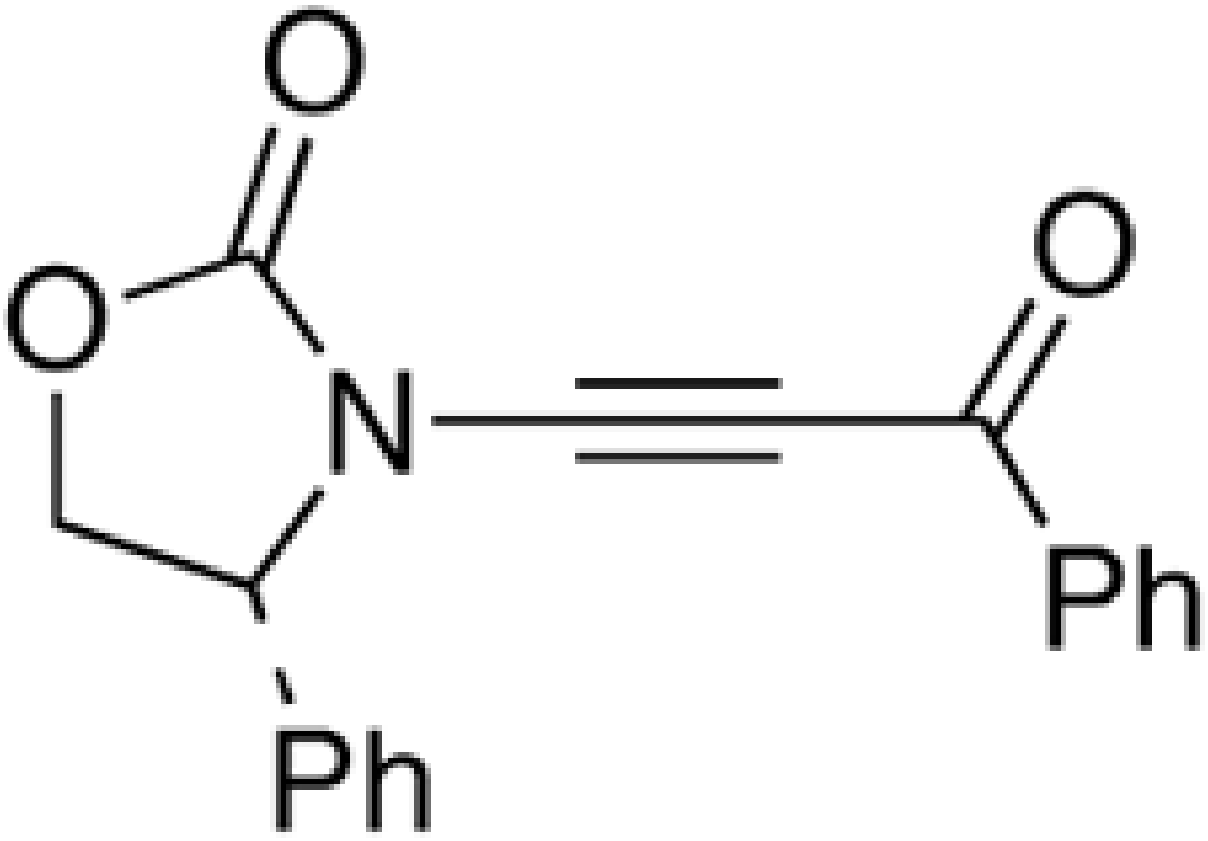
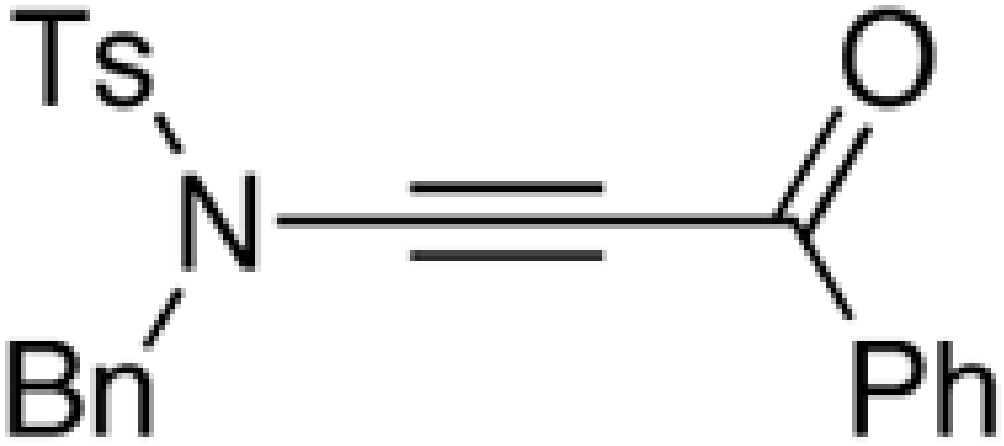
[b] Not detected.

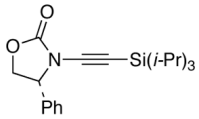
Table 2

RuO_2-$NaIO_4$ Mediated Oxidation.

entry	ynamides
1	 **11**
2	 **12**

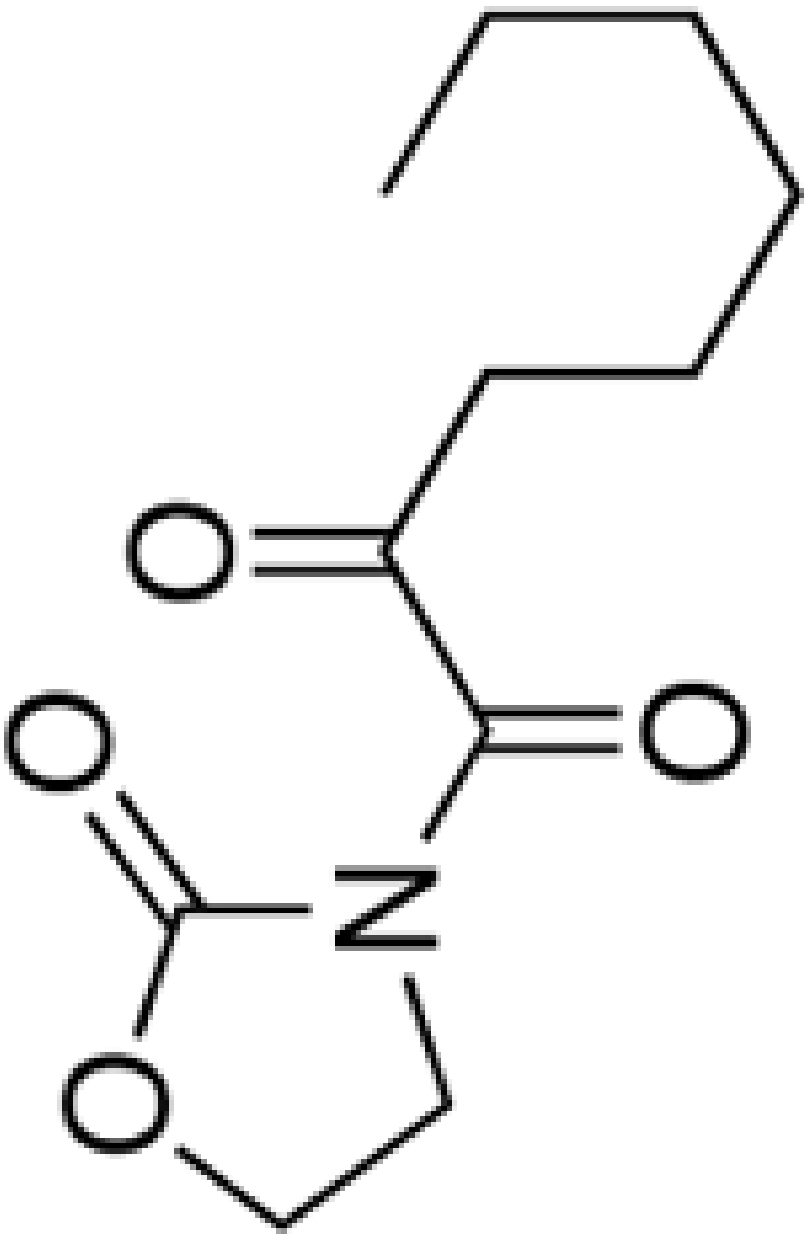
entry	ynamides
3	 **13**

entry	ynamides
4	 **14**
5	 **15**

entry	ynamides
6	 **16**

[a] 5 mol% $RuO_2 \cdot H_2O$, 3 equiv $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$, rt, 4 h.

[b] Isolated yields.

α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
 33	42[d]	81

α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
34	41	85
35	95	95

α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
36	82	79

α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
37	69	85

	α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
38		52	68

α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
39	nd[e]	90

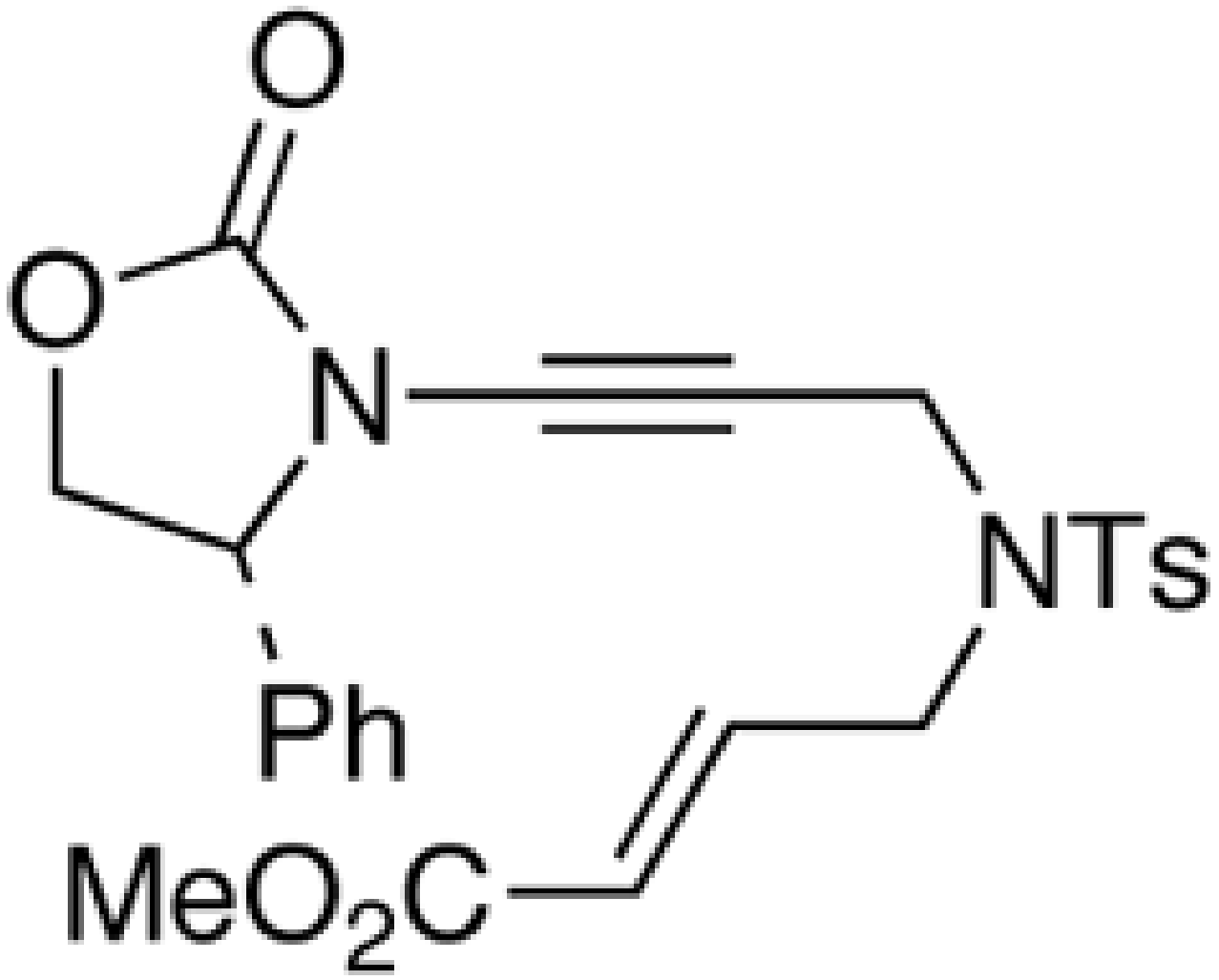
α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
40	nd	86

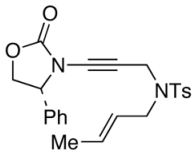
α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
41	nd	95

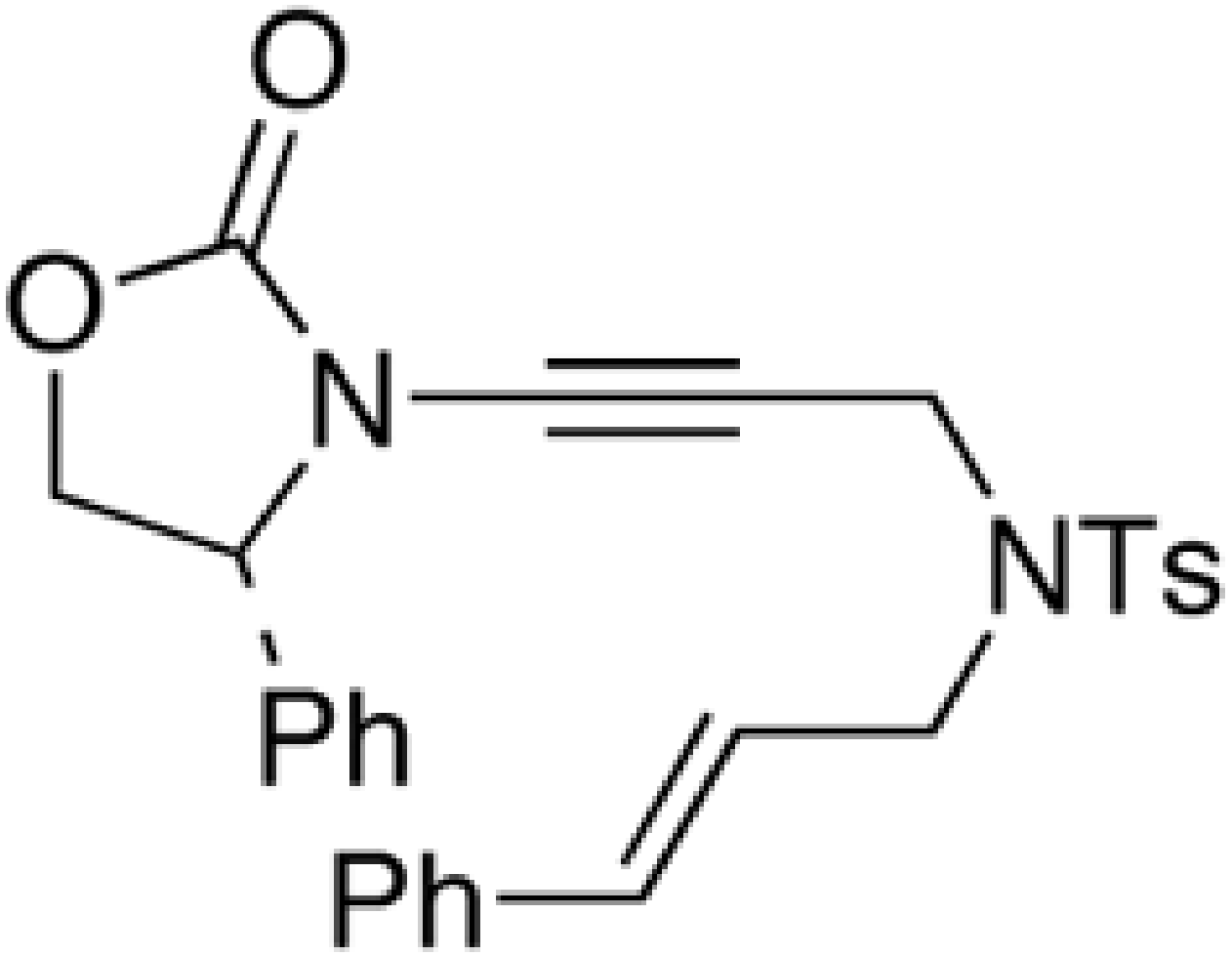
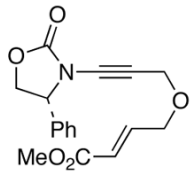
α-keto-imides	yield [%][a]:DMDO[b]	RuO_4[c]
42	nd	87

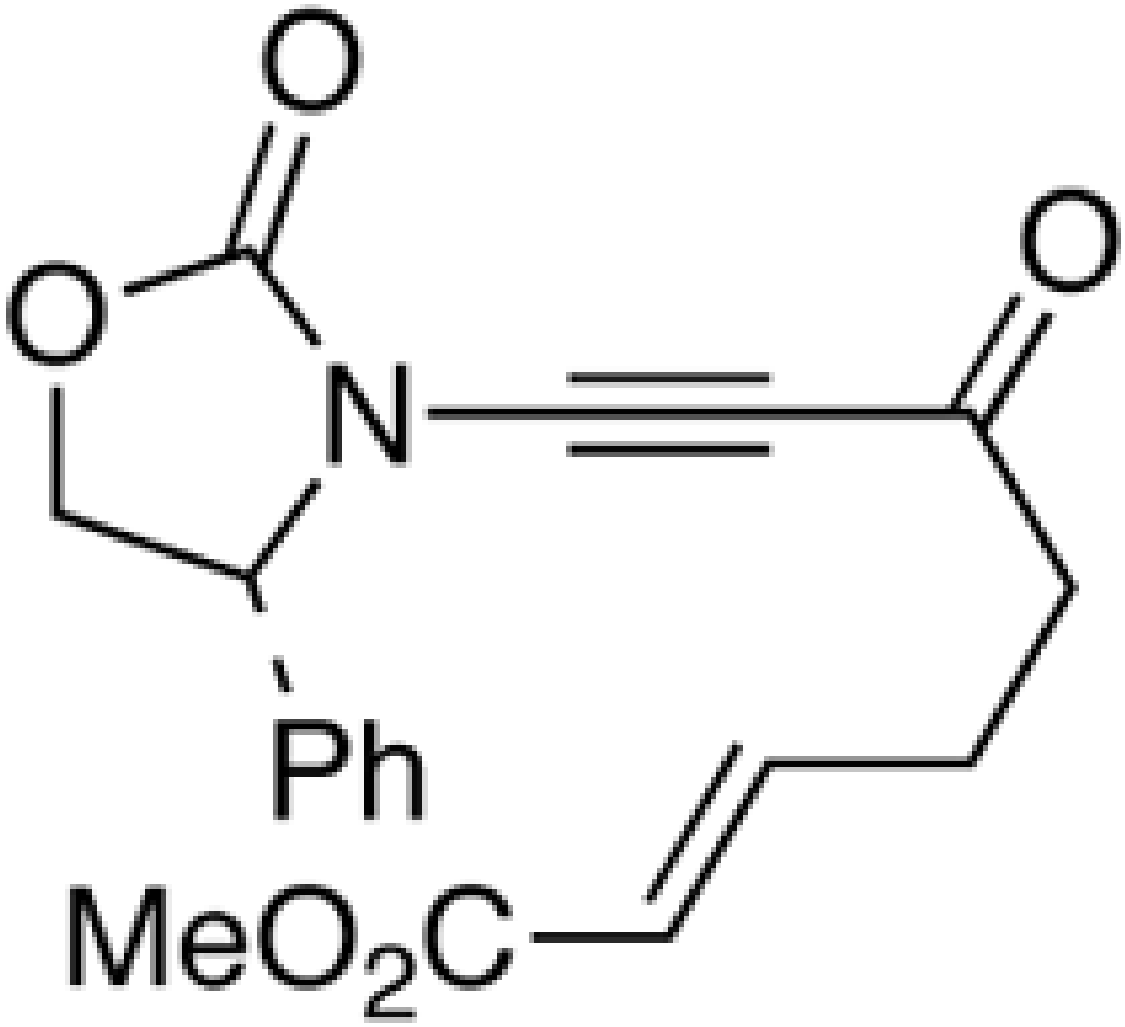
Table 4

Chemoselectivity in Oxidatively Sensitive Ynamides.

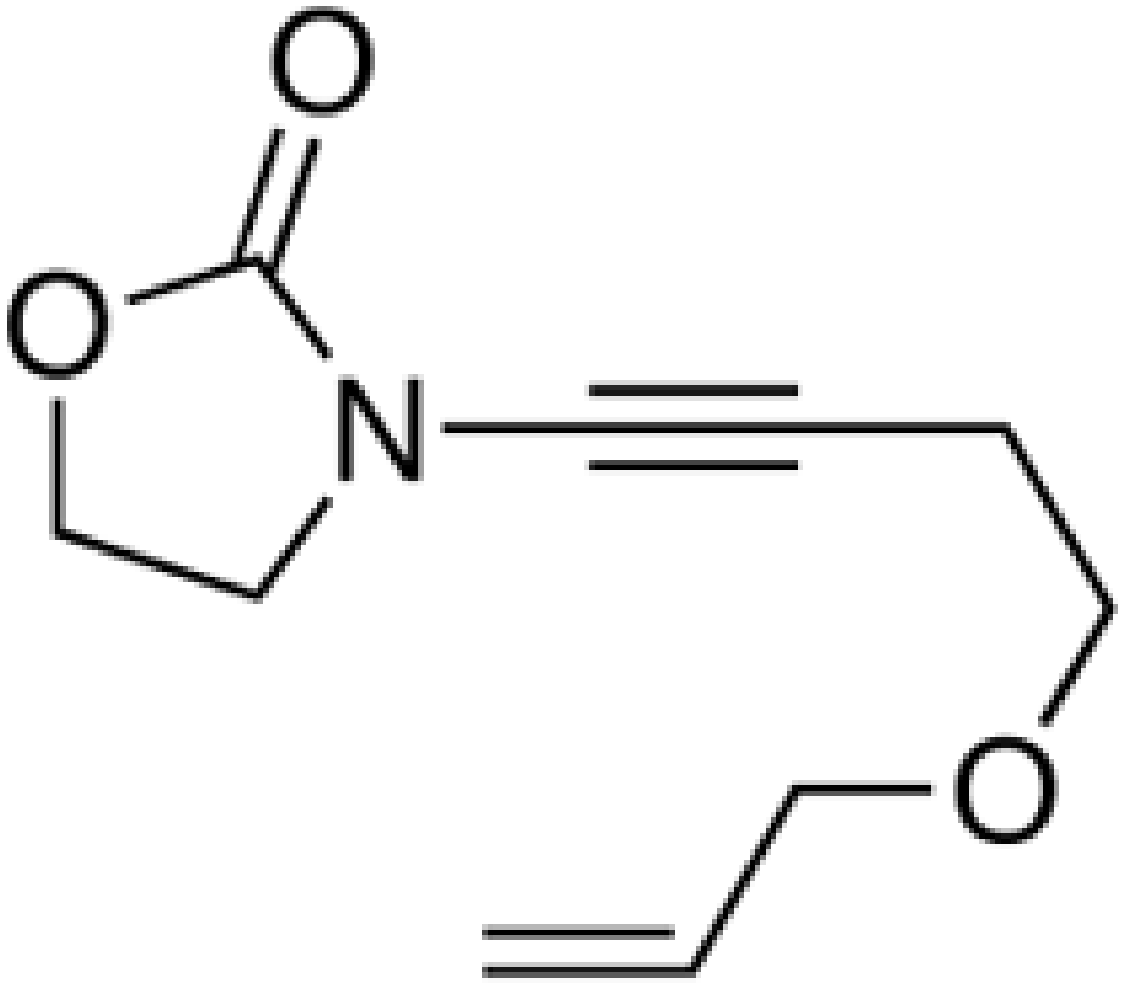
entry	ynamides
1	
	43

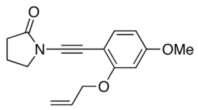
entry	ynamides
2	 **44**

entry	ynamides
3	 **45**
4	 **46**

entry	ynamides
5	

47

entry	ynamides
6	 **48**

entry	ynamides
7	 **49**

[a] 4 equiv DMDO, acetone, it, 2.5 h.

[b] Isolated yields.

[c] Also isolated~33% yield of the epoxidized α-keto-imide.