A stereoselective intramolecular cyclopropanation *via* a *de novo* class of push–pull carbenes derived from DMDO-epoxidations of chiral ynamides†

Hongyan Li, Jennifer E. Antoline, Jin-Haek Yang, Ziyad F. Al-Rashid* and Richard P. Hsung*

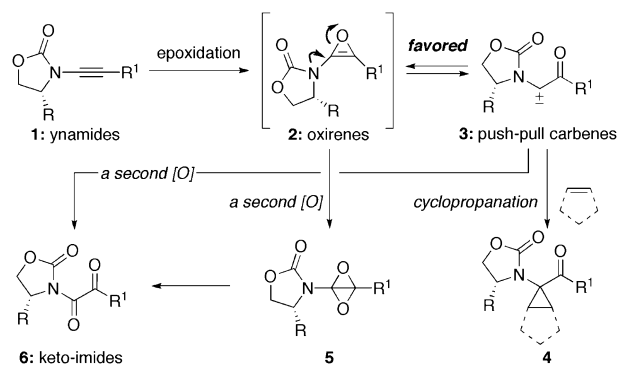
Received (in Montpellier, France) 26th January 2010, Accepted 18th March 2010
First published as an Advance Article on the web 26th April 2010
DOI: 10.1039/c0nj00063a

This work describes the first examples of diastereoselective intramolecular cyclopropanations of a *de novo* class of push–pull carbenes derived from DMDO-epoxidations of chiral ynamides. This reaction sequence essentially constitutes a tandem epoxidation–cyclopropanation that effectively gives rise to a series of structurally unique amido-cyclopropanes. A plausible mechanistic model is proposed revealing insights into this novel cyclopropanation process.

Introduction

Epoxidations of alkynes have long been shown to give rise to oxocarbene formation *via* rearrangement of initial oxirene intermediates.[1] In the last three decades, a plethora of subsequent transformations of these oxocarbenes have been documented including Wolff rearrangement and further reaction of the resultant ketene, C–H insertion, hydrogen or alkyl migration, secondary oxidation, and formation of stable metalla-keto carbene complexes.[2] However, despite a diverse array of possible reactivities, efforts in exploring the vast synthetic potential through this simple π-bond oxidation has been rather underwhelming.[1] Our interest in chemistry of ynamides,[3–5] a new class of electron rich and electronically biased alkynes, has provided us with a unique opportunity for the tuning and unleashing of such reactivity.

Specifically, as shown in Scheme 1, the postulated oxirenes **2** derived from epoxidation of ynamides **1**[6] could rearrange to a *de novo* class of push–pull carbenes **3**, which possesses dual stabilization.[7] While both intermediates **2** and **3** could undergo a second oxidation to afford keto-imides **6**[8] with the former proceeding through bis-epoxides **5**, push–pull carbenes **3** represent a novel species that is intriguing both in reactivity and synthetic potential.[9] Were such a carbene to arise, one may expect promiscuity with respect to the reactive partners it may choose [electron rich *versus* deficient] in transformations such as cyclopropanations.[7b,10] While we[11,12] had communicated the possibility of succeeding in such cyclopropanation reaction manifold, we wish to report here details of these tandem ynamide-epoxidation–intramolecular cyclopropanation reactions *via* this novel class of chiral push–pull carbenes.

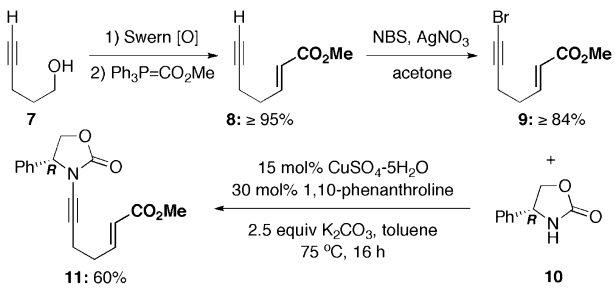


Scheme 1 *De novo* carbenes from epoxidations of ynamides.

Results and discussions

Chiral ynamides to be employed in this study could be readily constructed using the standard synthetic sequence illustrated in Scheme 2 for ynamide **11**. Ynamide **11** could be prepared through a copper(I)-catalyzed amidative cross-coupling of acetylenic bromide **9** with amide **10** using conditions that were developed in our lab.[13–15] Acetylenic bromides such as **9** could be accessed in a few steps using well established chemistry from respective alkynols such as **7**.

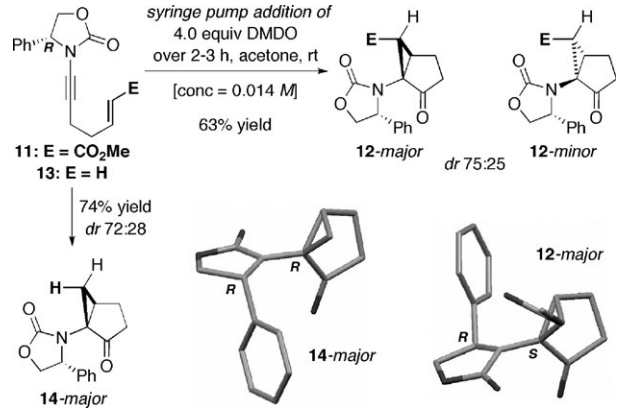
Epoxidation of ynamide **11** was accomplished employing 4.0 equiv. of dimethyldioxirane[16] [DMDO] [Scheme 3]. Although the optimized conditions called for the addition of DMDO solution through a syringe pump over 2–3 h, the oxidation process was highly selective for the ynamido-motif



Scheme 2 Synthesis of ynamide **11**.

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, WI 53705-2222, USA. E-mail: rhsung@wisc.edu, zalrashid@alchemicalresearch.com

† CCDC reference numbers 680316, 680317, 763759–763761. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c0nj00063a



Scheme 3 Epoxidation and cyclopropanation of ynamides **11** and **13**.

over the acrylic moiety, leading to the desired cyclopropanation product **12** in 63% yield as a 75 : 25 isomeric mixture. We were able to also demonstrate that the intramolecular cyclopropanation was equally effective when using ynamide **13** containing a simple olefin, and that the epoxidation remained selective for the ynamido-motif over the electron-rich olefin. The success in isolating cyclopropanation product **14** suggests that these novel push–pull oxocarbenes are electronically ambiphilic in nature.

While the stereoselectivity is modest, the ynamide-epoxidation took place very effectively and is relatively faster than reported alkyne epoxidations.[17] This reaction sequence constitutes a tandem ynamide-epoxidation–cyclopropanation, leading to a series of structurally unique if not unprecedented amido-cyclopropanes. The cyclopropanation process would most likely proceed through the push–pull oxocarbene derived *via* rearrangement of oxirene as proposed in Scheme 1, or alternatively, an electrophilic attack of the ynamide on the oxidant would give arise initially to an oxy-ketene-iminium ion intermediate **A** [see Fig. 1].

Single crystal X-ray structures of **12**-*major*‡ and **14**-*major*§ were attained to unambiguously assign the relative configuration of the major isomer [Scheme 3], thereby revealing the same sense of stereoselectivity for both cyclopropanation reactions [we note here that five X-ray determinations provided in this paper only established the relative stereochemistries]. Based on stereochemical assignments, a mechanistic model could be proposed as shown in Scheme 4.

Two possible conformational approaches could account for the stereochemical outcome of the intramolecular cyclopropanation: **15** and **16** or "*endo*" and "*exo*", leading respectively to **12**- or **14**-*major* and **12**- or **14**-*minor*. Hartree–Fock 3-21G* calculations using Spartan™ program reveal that the oxocarbene motif itself would orient in a conformational manner where (a) the empty carbene p-orbital is aligned with the nitrogen lone-pair, allowing an n-to-p overlap; (b) the carbene lone pair is co-planar with the adjacent carbonyl group for a perfect n-to-π* delocalization; and lastly, (c) the carbene lone pair would prefer to point away from the oxazolidinone carbonyl to minimize electrostatic interactions. Such conformational preference further underscores the distinctiveness of these novel push–pull oxocarbenes.

The "endo" and "exo" approaches are informally defined as the following. They are associated with the position of the vinyl strand with respect to the carbene lone pair. The "endo" approach is such that the vinyl strand points toward the lone pair, while "exo" being the vinyl strand pointing away the lone pair. Assumptions were made to ignore the possibility of olefin approaching from the sterically congested bottom face. Although TS-calculations were not conclusive [revealing a negligible ΔE value], based on aforementioned conformational preferences, simple molecular modelling suggests that the "endo" pathway seems to be better oriented conformationally than "exo" for a synchronous or concerted cyclopropanation transition state.

When pursuing other epoxidation–cyclopropanation examples, we appear to have reached the maximum in the diastereoselectivity as evident with cyclopropanation products **17–20**,¶‖ although yields of for these tandem epoxidation–cyclopropanations are quite high [Scheme 5]. While additional examples using ynamides **21** and **22** led to better diastereomeric ratios [Scheme 6], these reactions were not as effective giving either a lower yielding [see **23**] and/or a greater amount of keto-imide [see **24** and **26**].

On the other hand, epoxidation–cyclopropanations using ynamides **27** and **28** were quite selective, leading to six-membered ring formation in cyclopropanation products **30** and **31** [Scheme 7]. In these reactions, although yields were lower, keto-imide formation was not a major concern. More importantly, stereochemical assignment of **30**-*major*** through its single crystal X-ray structure is consistent with the proposed mechanistic model. From the molecular modeling, with an additional atom linkage [see **X** = CH_2 and NTs for ynamides **27** and **28**, respectively], the "endo" approach of the olefin during the cyclopropanation [see **33**] appears to be even

‡ **Crystallographic data for 12-major**: $C_{17}H_{17}NO_5$, M = 315.32, orthorhombic, $P2_12_12_1$, a = 9.419(2), b = 12.174(3), c = 13.334(3) Å, α = 90, β = 90, γ = 90°, V = 1529.0(5) Å^3, T = 173(2) K, Z = 4, μ = 0.102 mm^{-1}, 1562(R_{int} = 0.0271), final R indices [$I > 2\sigma(I)$], R_1 = 0.0300, wR_2 = 0.0699, R indices (all data) R_1 = 0.0332, wR_2 = 0.0718.

§ **Crystallographic data for 14-major**: $C_{15}H_{15}NO_3$, M = 257.28, monoclinic, $P2_1$, a = 8.293(2), b = 6.0494(10), c = 12.923(3) Å, α = 90, β = 98.616(17), γ = 90°, V = 641.0(2) Å^3, T = 173(2) K, Z = 2, μ = 0.093 mm^{-1}, 1573(R_{int} = 0.0258), final R indices [$I > 2\sigma(I)$], R_1 = 0.0307, wR_2 = 0.0697, R indices (all data) R_1 = 0.0360, wR_2 = 0.0720.

¶ **Crystallographic data for 17-major [there are three independent molecules in the asymmetric unit all with the same relative C3-R, C4-R stereochemistry]**: $C_{16}H_{17}NO_3$, M = 271.31, monoclinic, $P2_1$, a = 11.821(3), b = 5.9677(17), c = 29.515(8) Å, α = 90, β = 94.257(4), γ = 90°, V = 2076.4(10) Å^3, T = 173(2) K, Z = 6, μ = 0.090 mm^{-1}, 7331(R_{int} = 0.0474), final R indices [$I > 2\sigma(I)$], R_1 = 0.0432, wR_2 = 0.0940, R indices (all data) R_1 = 0.0682, wR_2 = 0.1056.

‖ **Crystallographic data for 20-major**: $C_{21}H_{19}NO_3$, M = 333.37, monoclinic, $P2_1$, a = 10.959(2), b = 6.0746(12), c = 12.943(3) Å, α = 90, β = 102.432(3), γ = 90°, V = 841.4(3) Å^3, T = 100(2) K, Z = 2, μ = 0.009 mm^{-1}, 1715(R_{int} = 0.0707), final R indices [$I > 2\sigma(I)$], R_1 = 0.0388, wR_2 = 0.0834, R indices (all data) R_1 = 0.0587, wR_2 = 0.0926.

** **Crystallographic data for 30-major**: $C_{16}H_{17}NO_3$, M = 271.31, orthorhombic, $P2_12_12_1$, a = 10.2183(9), b = 10.4772(9), c = 12.5802(11) Å, α = 90, β = 90, γ = 90°, V = 1346.8(2) Å^3, T = 123(2) K, Z = 4, μ = 0.093 mm^{-1}, 1771(R_{int} = 0.0298), final R indices [$I > 2\sigma(I)$], R_1 = 0.029 = 6, wR_2 = 0.0772, R indices (all data) R_1 = 0.0323, wR_2 = 0.0799.

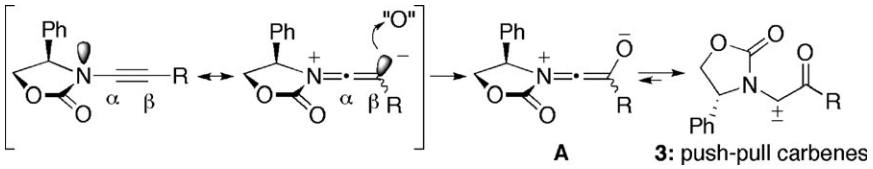
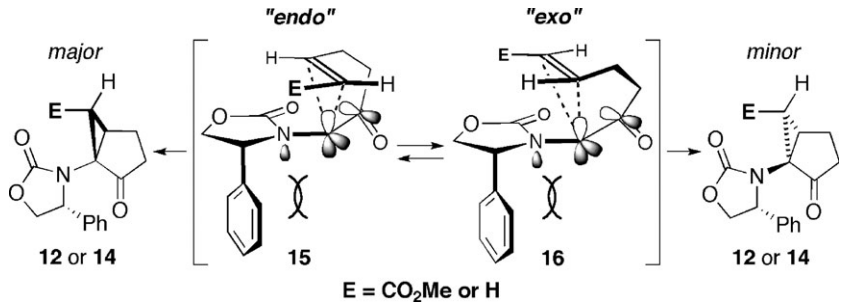
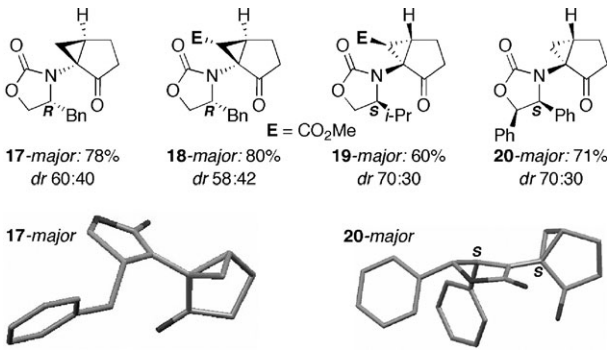


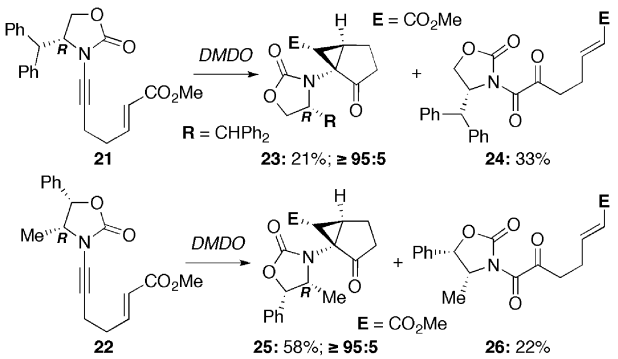
Fig. 1 A proposed mechanistic model.



Scheme 4 A proposed mechanistic model.



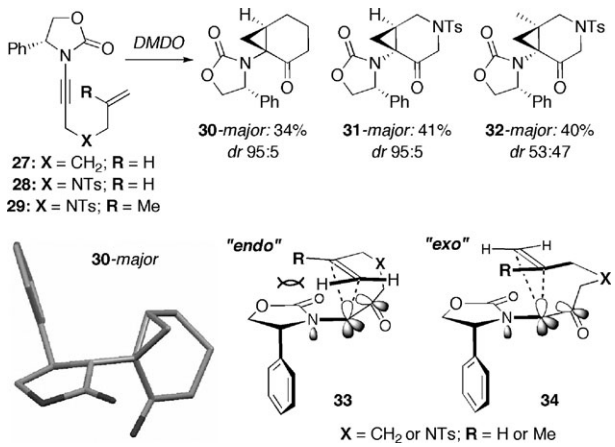
Scheme 5 Ynamide-epoxidation–cyclopropanation examples.



Scheme 6 Attempts of improving the diastereoselectivity.

better oriented conformationally than in the "exo" case [see **34**] for a synchronized transition state.

In addition, most revealingly, when using ynamide **29** [**X** = NTs, **R** = Me], the diastereomeric ratio of cyclopropane **32** dropped significantly relative to that of **31** [**X** = NTs, **R** = H]. This dramatic change suggests that the "endo" pathway as shown in **33** is being destabilized due to the enhanced steric interaction [**R** = Me *vs.* H].



Scheme 7 Epoxidation–cyclopropanations of ynamides **27–29**.

Conclusion

We have described here the first examples of diastereoselective intramolecular cyclopropanations of a *de novo* class of push–pull carbenes derived from DMDO-epoxidations of chiral ynamides. This reaction sequence essentially constitutes a tandem epoxidation–cyclopropanation that effectively gives rise to a series of structurally unique if not unprecedented amido-cyclopropanes. A plausible mechanistic model is also proposed here to reveal insights into this novel cyclopropanation process.

Experimental

General information

All reactions were performed in flame-dried glassware under a nitrogen or argon atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Fluka), except where noted. Chromatographic separations were performed

using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ as solvent. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected or calibrated. Infrared spectra were collected on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or were performed at University of Wisconsin Mass Spectrometry Laboratories. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported. X-Ray analyses were performed at the X-ray facility in University of Minnesota.

General procedures for preparation of ynamides *via* Cu(I)-catalyzed cross-coupling

To a flame-dried 100 mL RB-flask were added a respective amide (2.07 g, 9.80 mmol), $CuSO_4{\cdot}5H_2O$ (368.0 mg, 1.47 mmol), 1,10-phenanthroline (529.0 mg, 2.94 mmol) and K_2CO_3 (3.38 g, 24.5 mmol), followed by anhydrous toluene (15 mL) and the respective acetylenic bromide (3.20 g, 12.3 mmol). The flask was filled with argon by three vacuum-flush cycles and the solution was heated in a 75 °C oil bath overnight. When complete, the crude reaction mixture was cooled to rt, filtered through Celite™, and concentrated *in vacuo*. Purification of the crude residue using silica gel flash column chromatography (gradient eluent) gave the pure ynamide.

General procedures for intramolecular cyclopropanations through DMDO-epoxidations of ynamides

A respective ynamide (50.0 mg, 0.167 mmol) in acetone (12 mL) was stirred at rt. A solution of DMDO (6.0 mL, 0.11 M in acetone, 4.0 equiv.) was added by syringe pump over 2 h (maintaining DMDO/acetone over dry ice). The reaction mixture was stirred for another 30 min before being filtered and concentrated *in vacuo*. The resulting mixture was purified by silica gel flash column chromatography (gradient elution: EtOAc in hexanes) to provide the desired amido cyclopropane as a pure product, or as an isomeric mixture. In most cases of an isomeric mixture, when employing MPLC, the major isomer could be purified from the minor isomer with high *dr*, allowing unambiguous characterizations of the major isomer. Concise characterizations of the minor isomer are reported here whenever it could be sufficiently purified.

Ynamide 11. R_f 0.45 [EtOAc]; $[\alpha]_D^{25} = -155$ (*c* 0.365, CH_2Cl_2); white solid: mp = 93–94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (m, 2H), 2.36 (m, 2H), 3.73 (s, 3H), 4.23 (dd, 1H, J = 8.8, 7.2 Hz), 4.71 (dd, 1H, J = 8.8, 8.8 Hz), 5.00 (dd, 1H, J = 8.8, 7.2 Hz), 5.73 (ddd, 1H, J = 15.6, 1.6, 1.6 Hz), 6.80 (ddd, 1H, J = 15.6, 6.8, 6.8 Hz), 7.32–7.34 (m, 2H), and 7.39–7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 31.5, 51.7, 62.2, 70.3, 70.8, 71.3, 122.2, 127.0, 129.5, 129.6, 136.4, 146.9, 156.4, and 166.9; IR (film) cm^{-1} 3030w, 2952w, 2918w, 2850w, 1759s, 1722m, 1408m, 1222m, 1069m, 949m, and 855w; mass spectrum (APCI): *m*/*z* (% relative intensity) 300 (100) $(M + H)^+$, and 268 (95); HRMS (MALDI) *m*/*z* calcd for $C_{17}H_{17}NO_4Na^+$ $(M + Na^+)$ 322.1055, found 322.1050.

Cyclopropane 12-*major*. R_f 0.31 [EtOAc]; $[\alpha]_D^{25} = -125$ (*c* 0.600, CH_2Cl_2); white solid: mp = 147–148 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (dddd, 1H, J = 13.5, 9.5, 9.5, 5.0 Hz), 1.85 (ddd, 1H, J = 13.0, 8.0, 2.0 Hz), 2.03 (dd, 1H, J = 4.5, 4.0 Hz), 2.04 (ddd, 1H, J = 19.0, 9.5, 8.0 Hz), 2.10 (ddd, 1H, J = 19.0, 9.5, 2.0 Hz), 2.53 (d, 1H, J = 4.5 Hz), 3.76 (s, 3H), 4.20 (dd, 1H, J = 9.5, 8.5 Hz), 4.67 (dd, 1H, J = 9.0, 9.0 Hz), 4.91 (dd, 1H, J = 9.5, 9.0 Hz), 7.40–7.44 (m, 3H), and 7.45–7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 30.37, 30.40, 31.2, 52.5, 52.8, 61.1, 70.3, 128.5, 129.2, 129.7, 136.6, 158.4, 168.1, and 206.7; IR (film) cm^{-1} 3063w, 2952w, 1759s, 1728s, 1402m, 1216m, 1092m, 1028m, and 933w; mass spectrum (APCI): *m*/*z* (% relative intensity) 316 (100) $(M + H)^+$, and 284 (40); HRMS (MALDI) *m*/*z* calcd for $C_{17}H_{17}NO_5Na^+$ $(M + Na^+)$ 338.1004, found 338.1001. **12-*Minor***: pale yellow oil; R_f 0.22 [EtOAc]; $[\alpha]_D^{25} = -65.8$ (*c* 0.480, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (dddd, 1H, J = 13.0, 9.5, 9.5, 5.0 Hz), 1.81 (dd, 1H, J = 18.5, 9.5 Hz), 1.87 (dd, 1H, J = 13.0, 9.0 Hz), 1.96 (ddd, 1H, J = 18.5, 9.5, 9.0 Hz), 2.54 (d, 1H, J = 4.5 Hz), 2.60 (dd, 1H, J = 4.5, 4.5 Hz), 3.74 (s, 3H), 4.23 (dd, 1H, J = 9.5, 9.0 Hz), 4.64 (dd, 1H, J = 8.5, 8.5 Hz), 4.88 (dd, 1H, J = 9.5, 8.5 Hz), and 7.33–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 30.5, 32.0, 32.9, 51.6, 52.9, 62.3, 70.8, 128.3, 129.4, 129.5, 136.4, 158.1, 169.3, and 206.0; IR (neat) cm^{-1} 3062w, 2952w, 2907w, 1759s, 1742s, 1724s, 1439m, 1400m, 1243m, 1171m, 1089m, 1032m, and 902w; mass spectrum (APCI): *m*/*z* (% relative intensity) 316 (100) $(M + H)^+$, and 284 (10); HRMS (MALDI) *m*/*z* calcd for $C_{17}H_{17}NO_5Na^+$ $(M + Na^+)$ 338.1004, found 338.1005.

Ynamide 13. Yellow oil; R_f 0.37 [33% EtOAc/hexanes]; $[\alpha]_D^{25} = -136$ (*c* 1.87, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (m, 2H), 2.26 (dd, 2H, J = 7.2, 7.2 Hz), 4.22 (dd, 1H, J = 8.8, 7.2 Hz), 4.71 (dd, 1H, J = 8.8, 8.8 Hz), 4.89 (m, 2H), 5.00 (dd, 1H, J = 8.4, 7.2 Hz), 5.63 (dddd, 1H, J = 16.8, 10.4, 6.4, 6.4 Hz), 7.34 (m, 2H), and 7.40–7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 33.0, 62.3, 69.7, 70.8, 72.3, 115.8, 127.1, 129.4, 129.5, 136.6, 136.8, and 156.5; IR (neat) cm^{-1} 3068w, 3035w, 2979w, 2918w, 2848w, 2267w, 1765s, 1641w, 1495w, 1477w, 1457w, 1404m, 1328w, 1186m, 1106m, 1081m, 1036m, and 1001m; mass spectrum (APCI): *m*/*z* (% relative intensity) 242 (100) $(M + H)^+$, and 198 (10); HRMS (MALDI) *m*/*z* calcd for $C_{15}H_{15}NO_2{-}Na^+$ $(M + Na^+)$ 264.0995, found 264.0999.

Cyclopropane 14-*Major*. R_f 0.52 [EtOAc]; $[\alpha]_D^{25} = -215$ (*c* 0.887, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.49 (dd, 1H, J = 5.5, 5.5 Hz), 1.53 (m, 1H), 1.77 (m, 3H), 2.05 (m, 2H), 4.19 (dd, 1H, J = 9.0, 9.0 Hz), 4.66 (dd, 1H, J = 9.0, 9.0 Hz), 4.92 (dd, 1H, J = 9.0, 9.0 Hz), 7.32–7.34 (m, 2H), and 7.38–7.41 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 21.1, 27.5, 30.5, 47.7, 60.7, 69.8, 127.9, 129.3, 129.6, 137.8, 158.4, and 208.8; IR (film) cm^{-1} 3061w, 3036w, 3008w, 2947w, 2916w, 2882w, 1758s, 1726s, 1459m, 1413m, 1264m, 1216m,

1170m, 1080m, 1029m, 944w, and 923w; mass spectrum (APCI): *m*/*z* (% relative intensity) 258 (100) $(M + 1)^+$, and 214 (7); HRMS (MALDI) *m*/*z* calcd for $C_{15}H_{15}NO_3{\_}Na^+$ $(M + Na^+)$ 280.0944, found 280.0946. **14-*Minor***: R_f 0.52 [EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (m, 2H), 1.86 (ddd, 1H, J = 12.5, 7.5, 2.5 Hz), 2.05 (m, 2H), 2.23 (m, 1H), 2.36 (ddd, 1H, J = 8.0, 5.5, 5.5 Hz), 4.19 (dd, 1H, J = 9.0, 8.0 Hz), 4.71 (dd, 1H, J = 9.0, 9.0 Hz), 5.23 (dd, 1H, J = 8.5, 8.5 Hz), 7.31–7.33 (m, 2H), and 7.38–7.40 (m, 3H); mass spectrum (APCI): *m*/*z* (% relative intensity) 258 (100) $(M + H)^+$, and 214 (5); HRMS (MALDI) *m*/*z* calcd for $C_{15}H_{15}NO_3{\_}Na^+$ $(M + Na^+)$ 280.0944, found 280.0945.

Cyclopropane 17-*Major*. white waxy solid; R_f 0.15 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = −78.9 (*c* 1.27, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (dd, 1H, J = 5.5, 5.5 Hz), 1.63 (dd, 1H, J = 8.5, 6.0 Hz), 1.96 (m, 1H), 2.09–2.27 (m, 3H), 2.33 (ddd, 1H, J = 8.5, 5.0, 5.0 Hz), 2.90 (dd, 1H, J = 14.0, 9.5 Hz), 3.15 (dd, 1H, J = 14.0, 5.0 Hz), 4.01 (dddd, 1H, J = 9.5, 8.0, 6.0, 5.0 Hz), 4.05 (dd, 1H, J = 8.5, 6.0 Hz), 4.19 (dd, 1H, J = 8.0, 8.0 Hz), 7.16 (m, 2H), 7.25 (m, 1H), and 7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 21.0, 30.2, 30.9, 39.8, 47.2, 57.4, 67.5, 127.3, 129.1, 136.2, 157.8, and 209.1 (one carbon signal missing due to overlap at 129.1; IR (film) cm^{-1} 3061w, 3029w, 3003w, 2947w, 2918w, 2883w, 1750s, 1727s, 1603w, 1497w, 1454w, 1422m, 1263m, 1226m, 1173m, 1077m, 1031m, 1021m, 988w, 947w, and 922w; mass spectrum (APCI): *m*/*z* (% relative intensity) 272 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{16}H_{17}NO_3{\_}Na^+$ $(M + Na^+)$ 294.1101, found 294.1104. **17-*Minor***: yellow oil; R_f 0.12 [50% EtOAc/hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J = 5.5, 5.5 Hz), 1.62 (dd, 1H, J = 8.5, 5.5 Hz), 1.92 (m, 1H), 2.02 (m, 1H), 2.13 (m, 2H), 2.44 (ddd, 1H, J = 8.5, 5.0, 5.0 Hz), 2.65 (dd, 1H, J = 13.5, 9.0 Hz), 3.19 (dd, 1H, J = 13.5, 5.5 Hz), 3.97 (dd, 1H, J = 9.0, 7.5 Hz), 4.22 (dd, 1H, J = 8.5, 8.5 Hz), 4.45 (m, 1H), 7.15 (m, 2H), 7.26 (m, 1H), and 7.32 (m, 2H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.8, 27.5, 31.3, 39.8, 46.9, 57.6, 67.9, 127.4, 129.07, 129.13, 135.8, 158.3, and 210.7; IR (neat) cm^{-1} 3087w, 3060w, 3029w, 3004w, 2947w, 2918w, 1754s, 1727s, 1604w, 1513w, 1497w, 1478w, 1467w, 1425m, 1365w, 1289m, 1264m, 1228m, 1181m, 1161m, 1073m, 1027m, 943w, and 921w; mass spectrum (APCI): *m*/*z* (% relative intensity) 272 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{16}H_{17}NO_3{\_}Na^+$ $(M + Na^+)$ 294.1101, found 294.1105.

Cyclopropane 18-*Major*. White powder; R_f 0.50 [EtOAc]; $[\alpha]_D^{25}$ = −5.93 (*c* 0.840, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (dddd, 1H, J = 13.5, 9.5, 9.5, 5.0 Hz), 1.75 (dd, 1H, J = 13.0, 9.0 Hz), 1.86 (dd, 1H, J = 18.5, 9.5 Hz), 1.98 (ddd, 1H, J = 18.5, 9.0, 9.0 Hz), 2.48 (dd, 1H, J = 4.5, 4.5 Hz), 2.55 (d, 1H, J = 4.0 Hz), 2.89 (m, 2H), 3.68 (s, 3H), 4.08–4.17 (m, 2H), 4.46 (m, 1H), 7.17 (m, 2H), 7.25–7.28 (m, 1H), and 7.29–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 30.6, 33.36, 33.43, 41.4, 52.8, 57.8, 68.7, 69.9, 127.5, 129.1, 129.3, 136.3, 158.5, 169.1, and 206.6; IR (film) cm^{-1} 3062w, 3029w, 2952w, 2909w, 1754s, 1738s, 1726s, 1439m, 1283m, 1241m, 1199m, 1175m, 1093w, 1067w, and 1030w; mass spectrum (APCI): *m*/*z* (% relative intensity) 330 (100) $(M + H)^+$, and 228 (10); HRMS (MALDI) *m*/*z* calcd for $C_{18}H_{19}NO_5{\_}Na^+$ $(M + Na^+)$ 352.1155, found 352.1154.

Cyclopropane 19-*Major*. Yellow oil; R_f 0.25 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = 36.6 [*c* = 3.0, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 7.0 Hz), 1.05 (d, 3H, J = 7.0 Hz), 2.07 (m, 1H), 2.11–2.29 (m, 3H), 2.32 (br, 1H), 2.55 (d, 1H, J = 4.7 Hz), 2.89 (brt, 1H, J = 4.7 Hz), 3.66 (br, 1H), 3.74 (s, 3H), 4.08 (dd, 1H, J = 7.0, 7.0 Hz), 4.25 (t, 1H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 18.7, 21.2, 28.7, 30.7, 30.8, 52.9, 53.1, 61.2, 63.5, 159.0, 168.3, 207.0; IR (thin film) cm^{-1} 2956w, 2926w, 2878w, 1754s, 1727s; mass spectrum (APCI): *m*/*z* (% relative intensity) 282 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{14}H_{19}NO_5Na$ $(M + Na)^+$ 304.1155, found 304.1157. **19-*Minor***: R_f 0.13 [50% EtOAc/hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 7.0 Hz), 1.71–1.77 (m, 1H), 2.15–2.26 (m, 4H), 2.67 (d, 1H, J = 4.4 Hz), 2.77–2.78 (m, 1H), 3.64–3.68 (m, 1H), 3.71 (s, 3H), 4.13 (dd, 1H, J = 6.0, 8.4 Hz), 4.31 (dd, 1H, J = 8.4, 9.6 Hz); mass spectrum (APCI): *m*/*z* (% relative intensity) 282.1 (100) $(M + H)^+$.

Cyclopropane 20-*Major*. White powder; R_f 0.50 [EtOAc]; $[\alpha]_D^{25}$ = +174 (*c* 0.900, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J = 5.6, 5.6 Hz), 1.73–1.86 (m, 3H), 1.94 (dd, 1H, J = 8.4, 6.0 Hz), 2.09 (m, 2H), 5.13 (d, 1H, J = 8.8 Hz), 5.94 (d, 1H, J = 8.8 Hz), 6.85 (m, 2H), 6.95–6.98 (m, 2H), and 7.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.0, 27.5, 30.4, 48.4, 65.3, 79.7, 126.3, 128.1, 128.26, 128.30, 128.6, 134.9, 135.1, 158.4, and 209.0 (one carbon signal missing due to overlap (128.1)); IR (film) cm^{-1} 3091w, 3069w, 3038w, 2954w, 2937w, 2878w, 1741s, 1726s, 1500m, 1454m, 1420m, 1266m, 1235m, 1217m, 1201m, 1172m, 1106w, 1092w, 1078w, 1039w, 1023m, 998w, 969w, 949w, and 924m; mass spectrum (APCI): *m*/*z* (% relative intensity) 334 (100) $(M + H)^+$, and 290 (95); HRMS (MALDI) *m*/*z* calcd for $C_{21}H_{19}NO_3{\_}Na^+$ $(M + Na^+)$ 356.1257, found 356.1257. **20-*Minor***: R_f 0.47 [EtOAc]; ^{1}H NMR (500 MHz, $CDCl_3$) (two aliphatic proton signals missing, only resolved peaks presented due to ambiguity resulting from overlap) δ 1.02 (dd, 1H, J = 5.5, 5.5 Hz), 1.12 (dd, 1H, J = 8.5, 6.0 Hz), 2.15 (ddd, 1H, J = 18.5, 9.0, 1.5 Hz), 2.29 (dddd, 1H, J = 12.5, 9.5, 9.5, 5.0 Hz), 2.54 (ddd, 1H, J = 8.5, 5.0, 5.0 Hz), 5.35 (d, 1H, J = 8.5 Hz), 6.06 (d, 1H, J = 8.5 Hz), 6.83 (m, 2H), 6.96 (m, 2H), and 7.08 (m, 6H); mass spectrum (APCI): *m*/*z* (% relative intensity) 334 (100) $(M + H)^+$, and 290 (95); HRMS (MALDI) *m*/*z* calcd for $C_{21}H_{19}NO_3{\_}Na^+$ $(M + Na^+)$ 356.1257, found 356.1251.

Ynamide 21. Yellow oil; R_f 0.26 [33% EtOAc/hexanes]; $[\alpha]_D^{25}$ = −140 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21–2.29 (m, 4H), 3.70 (s, 3H), 4.16 (dd, 1H, J = 9.0, 5.5 Hz), 4.40 (d, 1H, J = 7.0 Hz), 4.46 (dd, 1H, J = 8.5, 8.5 Hz), 4.79 (ddd, 1H, J = 8.5, 7.0, 5.5 Hz), 5.84 (ddd, 1H, J = 15.5, 1.5, 1.5 Hz), 6.89 (ddd, 1H, J = 15.5, 7.0, 7.0 Hz), 7.18–7.20 (m, 2H), 7.24–7.27 (m, 4H), and 7.30–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 31.4, 51.7, 53.8, 60.0, 66.7, 70.7, 72.3, 122.2, 127.6, 127.9, 128.6, 128.7, 129.0, 129.3, 138.9, 139.9, 147.2, 156.4, and 167.0; IR (neat) cm^{-1} 3063w, 3031w, 2983w, 2952w, 2910w, 2272w, 1772s, 1722s, 1660m, 1415m, 1282m, 1201s, 1160m, 1121m, and 1035m; mass

spectrum (APC = *I*): *m*/*z* (% relative intensity) 390 (100) $(M + H)^+$, 358 (20), and 254 (10); HRMS (MALDI) *m*/*z* calcd for $C_{24}H_{23}NO_4{-}Na^+$ $(M + Na^+)$ 412.1519, found 412.1503.

Ynamide 22. Yellow oil; R_f 0.35 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = 15.3 [*c* = 4.0, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, *J* = 6.8 Hz), 2.41–2.49 (m, 2H), 2.49–2.54 (m, 2H), 3.72 (s, 3H), 4.30 (dq, 1H, *J* = 6.8, 13.6 Hz), 5.69 (d, 1H, *J* = 8.0 Hz), 5.89 (dt, 1H, *J* = 1.7, 15.6 Hz), 6.97 (dt, 1H, *J* = 6.4, 15.2 Hz), 7.25 (m, 1H), 7.34–7.44 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 17.8, 31.7, 51.8, 58.3, 70.5, 70.7, 79.8, 122.4, 126.2, 129.0, 129.2, 134.2, 147.1, 156.2, 167.0; IR (thin film) cm^{-1} 3034w, 2951w, 1750s, 1497m; mass spectrum (APCI): *m*/*z* (% relative intensity) 314 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{18}H_{19}NO_4Na$ $(M + Na)^+$ 336.1206, found 336.1204.

Cyclopropane 23-*Major*. Pale yellow oil; R_f 0.15 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = + 4.19 (*c* 0.535, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46 (dddd, 1H, *J* = 13.5, 10.0, 10.0, 5.0 Hz), 1.50 (m, 2H), 1.80 (ddd, 1H, *J* = 18.5, 9.0, 9.0 Hz), 2.42 (dd, 1H, *J* = 4.5, 4.5 Hz), 2.45 (d, 1H, *J* = 4.5 Hz), 3.68 (s, 3H), 3.96 (dd, 1H, *J* = 9.0, 5.5 Hz), 4.12 (d, 1H, *J* = 10.5 Hz), 4.37 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.66 (ddd, 1H, *J* = 10.5, 9.0, 5.5 Hz), 7.18–7.23 (m, 4H), 7.27–7.31 (m, 4H), and 7.33–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 30.4, 34.3, 34.7, 52.8, 53.7, 57.7, 59.9, 67.8, 127.5, 127.6, 127.7, 128.8, 129.3, 129.5, 141.3, 141.5, 159.0, 169.5, and 206.5; IR (neat) cm^{-1} 3060w, 3029w, 2952w, 2911w, 1757s, 1741s, 1722s, 1494w, 1438m, 1407m, 1383m, 1281m, 1237s, 1199m, 1175s, 1096m, 1068m, and 1031m; mass spectrum (APCI): *m*/*z* (% relative intensity) 406 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{24}H_{23}NO_5Na^+$ $(M + Na^+)$ 428.1468, found 428.1484.

Keto-imide 24. Pale yellow oil; R_f 0.48 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = −71.9 (*c* 0.795, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (m, 2H), 2.62 (ddd, 1H, *J* = 18.0, 8.0, 6.0 Hz), 2.69 (ddd, 1H, *J* = 18.0, 8.0, 7.0 Hz), 3.74 (s, 3H), 4.53 (dd, 1H, *J* = 9.5, 3.0 Hz), 4.59 (dd, 1H, *J* = 9.5, 8.0 Hz), 4.76 (d, 1H, *J* = 6.5 Hz), 5.25 (ddd, 1H, *J* = 8.0, 6.5, 3.0 Hz), 5.86 (ddd, 1H, *J* = 15.5, 1.5, 1.5 Hz), 6.93 (ddd, 1H, *J* = 15.5, 6.5, 6.5 Hz), 7.14 (d, 2H, *J* = 7.5 Hz), 7.21 (m, 2H), 7.28 (m, 1H), and 7.32–7.40 (m, 5H); ^{13}C NMR (125 MHz, = $CDCl_3$) δ 24.9, 37.5, 51.2, 51.7, 55.6, 67.5, 122.3, 127.7, 128.5, 128.6, 129.1, 129.40, 129.41, 137.5, 139.0, 146.5, 153.7, 166.6, 166.9, and 195.6; IR (neat) cm^{-1} 3061w, 3029w, 2982w, 2951w, 2903w, 1786s, 1720s, 1658m, 1496w, 1450w, 1436w, 1393m, 1342m, 1275m, 1204s, 1128m, 1072m, and 1031m; mass spectrum (APCI): *m*/*z* (% relative intensity) 422 (55) $(M + H)^+$, 390 (50), and 254 (100); HRMS (MALDI) *m*/*z* calcd for $C_{24}H_{23}NO_6Na^+$ $(M + Na^+)$ 444.1323, found 444.4323.

Cyclopropane 25-*major*. R_f 0.25 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = 7.60 [*c* 2.0, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 3H, *J* = 6.5 Hz), 2.93 (m, 2H), 2.26 (m, 2H), 2.37 (br, 1H), 2.55 (d, 1H, *J* = 4.7 Hz), 2.92 (brt, 1H, *J* = 4.0 Hz), 4.04 (br, 1H), 5.56 (d, 1H, *J* = 8.5 Hz), 7.27–7.31 (m, 2H), 7.32–7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 21.1, 30.4, 30.9, 52.5, 53.0, 56.1, 79.9, 127.0, 128.7, 135.1, 158.0, 168.2, 206.8; IR (thin film) cm^{-1} 3038w, 2925w, 2854w, 1758s, 1733s; mass spectrum (APCI): *m*/*z* (% relative intensity) 330 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{18}H_{19}NO_5Na$ $(M + Na)^+$ 352.1161, found 352.1160.

Keto-imide 26. R_f 0.10 [50% EtOAc–hexane]; $[\alpha]_D^{25}$ = 6.00 [*c* 1.80, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, 3H, *J* = 6.8 Hz), 2.66 (dq, 2H, *J* = 1.1, 6.5 Hz), 2.93 (t, 2H, *J* = 7.6 Hz), 3.74 (s, 3H), 4.72 (p, 1H, *J* = 6.8 Hz), 5.85 (d, 1H, *J* = 7.6 Hz), 5.92 (dt, 1H, *J* = 1.4, 15.6 Hz), 7.00 (dt, 1 H, *J* = 6.8, 13.6 Hz), 7.28–7.48 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.8, 25.1, 37.4, 51.8, 54.2, 81.5, 122.4, 126.0, 128.8, 129.1, 129.5, 132.7, 153.4, 167.0, 195.7, IR (thin film) cm^{-1} 3388bs, 2957s, 1695s, 1443s, 1250s; mass spectrum (APCI): *m*/*z* (% relative intensity) 346 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{18}H_{19}NO_6Na$ $(M + Na)^+$ 368.1110, found 368.1105.

Ynamide 27. Yellow oil; R_f 0.35 [50% EtOAc/hexanes]; $[\alpha]_D^{25}$ = −123 (*c* 1.31, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (m, 2H), 1.91 (ddddd, 2H, *J* = 8.5, 7.0, 7.0, 1.5, 1.5 Hz), 2.17 (m, 2H), 4.22 (dd, 1H, *J* = 9.0, 7.0 Hz), 4.71 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.87 (dddd, 1H, *J* = 17.0, 2.0, 1.5, 1.5 Hz), 4.89 (dddd, 1H, *J* = 10.5, 2.0, 1.0, 1.0 Hz), 5.00 (dd, 1H, *J* = 9.0, 7.0 Hz), 5.65 (dddd, 1H, *J* = 17.0, 10.5, 6.5, 6.5 Hz), 7.33–7.35 (m, 2H), and 7.39–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 27.8, 32.5, 62.3, 69.5, 70.8, 72.6, 115.2, 127.0, 129.4, 129.5, 136.5, 137.9, and 156.5; IR (neat) cm^{-1} 3068w, 3035w, 2930w, 2861w, 1765s, 1405m, 1186m, 1107m, 1001m, and 914w; mass spectrum (APCI): *m*/*z* (% relative intensity) 256 (100) $(M + H)^+$, and 164 (15); HRMS (MALDI) *m*/*z* calcd for $C_{16}H_{17}NO_2Na$ $(M + Na)^+$ 278.1157, found 278.1155.

Ynamide 28. Pale yellow oil; R_f 0.31 [100% EtOAc/hexanes]; $[\alpha]_D^{25}$ = −119 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.24 (br dd, 1H, *J* = 14.2, 7.2 Hz), 3.59 (ddddd, 1H, *J* = 14.2, 6.0, 1.2, 1.2, 1.2 Hz), 4.00 (d, 1H, *J* = 18.4 Hz), 4.15 (dd, 1H, *J* = 8.8, 7.2 Hz), 4.23 (dd, 1H, *J* = 18.4, 0.8 Hz), 4.66 (dd, 1H, *J* = 8.8, 8.8 Hz), 4.80 (m, 1H), 4.82 (dddd, 1H, *J* = 16.8, 1.2, 1.2, 1.2 Hz), 5.03 (dddd, 1H, *J* = 10.0, 1.2, 1.2, 1.2 Hz), 5.53 (dddd, 1H, *J* = 17.2, 10.0, 7.2, 6.0 Hz), 7.10–7.12 (m, 2H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.36–7.40 (m, 3H), and 7.70 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 36.3, 48.9, 61.9, 66.2, 70.9, 74.6, 120.1, 126.9, 128.1, 129.5, 129.75, 129.84, 131.9, 136.0, 136.2, 143.6, and 155.5; IR (neat) cm^{-1} 3067w, 3035w, 2985w, 2914w, 1776s, 1405m, 1342m, 1159s, 1105m, 1091m, 993w, and 893w; mass spectrum (APCI): *m*/*z* (% relative intensity) 411 (100) $(M + H)^+$, and 232 (20); HRMS (MALDI) *m*/*z* calcd for $C_{22}H_{22}N_2O_4SNa$ $(M + Na)^+$ 433.1198, found 433.1194.

Ynamide 29. Yellow oil; R_f 0.70 [50% EtOAc–hexane]; $[\alpha]_D^{25}$ = −113.8 [*c* = 1.28, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.42 (s, 3H), 3.10 (d, 1H, *J* = 14.0 Hz), 3.46 (d, 1H, *J* = 13.6 Hz), 3.92 (d, 1H, *J* = 18.4 Hz), 4.12 (dd, 1H, *J* = 7.2, 9.2 Hz), 4.21 (dd, 1H, *J* = 0.8, 18.4 Hz), 4.43 (s, 1H), 4.66 (dd, 1H, *J* = 8.8, 8.8 Hz), 4.75–4.79 (m, 2H), 7.05–7.07 (m, 2H), 7.32–7.38 (m, 5H), 7.70–7.72 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.8, 36.0, 52.2, 61.9,

66.1, 71.0, 74.8, 115.7, 126.9, 128.2, 129.5, 129.7, 129.8, 136.0, 136.2, 139.0, 143.6, 155.5; IR (Thin film) cm^{-1} 3548m, 3066brs, 2980s, 2914s, 2360m, 2262s, 1775s, 1158s; mass spectrum (APCI): *m*/*z* (% relative intensity) 425.1 (100) $(M + H)^+$, 262.1 (40); HRMS (MALDI) *m*/*z* calcd for $C_{23}H_{24}N_2O_4SNa$ $(M + Na)^+$ 447.1355, found 447.1360.

Cyclopropane 30-*major*. R_f 0.19 [100% EtOAc/hexanes]; $[\alpha]_D^{25} = -195$ (*c* 0.770, CH_2Cl_2); white solid; mp = 138–140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 1H), 1.37 (dddd, 1H, J = 13.2, 8.0, 8.0, 3.6 Hz), 1.58 (m, 2H), 1.66 (m, 1H), 1.74 (m, 2H), 2.11 (ddd, 1H, J = 18.4, 8.8, 8.8 Hz), 2.36 (ddd, 1H, J = 18.8, 5.2, 5.2 Hz), 4.19 (dd, 1H, J = 8.8, 8.8 Hz), 4.65 (dd, 1H, J = 8.8, 8.8 Hz), 4.87 (dd, 1H, J = 8.8, 8.8 Hz), 7.30–7.34 (m, 2H), and 7.37–7.42 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 18.8, 21.8, 26.4, 36.3, 46.3, 60.8, 69.5, 128.2, 129.3, 129.5, 138.0, 159.3, and 204.4; IR (film) cm^{-1} 3033w, 2918w, 2863w, 1759s, 1687m, 1402m, 1217m, 1038m, 915w, and 878w; mass spectrum (APCI): *m*/*z* (% relative intensity) 272 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{16}H_{17}NO_3Na$ $(M + Na)^+$ 294.1106, found 294.1104.

Cyclopropane 31-*major*. Pale yellow oil; R_f 0.19 [EtOAc]; $[\alpha]_D^{25} = -116$ (*c* 0.720, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.51 (br m, 1H), 1.75 (dd, 1H, J = 8.5, 6.5 Hz), 2.18 (ddd, 1H, J = 6.5, 6.5, 1.0 Hz), 2.45 (t, 3H, J = 0.5 Hz), 2.52 (br d, 1H, J = 12.0 Hz), 3.02 (d, 1H, J = 18.5 Hz), 3.89 (ddd, 1H, J = 12.5, 2.0, 1.0 Hz), 4.10 (dd, 1H, J = 18.5, 1.5 Hz), 4.21 (dd, 1H, J = 8.5, 8.5 Hz), 4.63 (dd, 1H, J = 9.0, 9.0 Hz), 4.75 (dd, 1H, J = 9.0, 9.0 Hz), 7.30–7.32 (m, 2H), 7.33 (dq, 2H, J = 8.5, 0.5 Hz), 7.36–7.38 (m, 3H), and 7.57 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 21.8, 25.8, 43.1, 45.2, 53.1, 60.4, 69.9, 127.7, 128.1, 129.4, 129.8, 130.3, 133.0, 137.3, 144.7, 158.5, and 197.2; IR (neat) cm^{-1} 3063w, 3035w, 2986w, 2912w, 2855w, 1756s, 1707m, 1597w, 1403m, 1348m, 1163s, 1037m, and 937m; mass spectrum (APCI): *m*/*z* (% relative intensity) 427 (100) $(M + H)^+$; HRMS (MALDI) *m*/*z* calcd for $C_{22}H_{22}N_2O_5SNa$ $(M + Na)^+$ 449.1147, found 449.1140.

Cyclopropane 32-*major*. Yellow oil; R_f 0.50 [5% MeOH–CH_2Cl_2]; $[\alpha]_D^{25} = +29.7$ [c 0.32, CH_2Cl_2]: ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 1H, J = 6.5 Hz), 1.30 (s, 3H), 2.16 (d, 1H, J = 6.5 Hz), 2.45 (s, 3H), 2.77 (d, 1H, J = 12.0 Hz), 2.97 (d, 1H, J = 18.0 H = *z*), 3.96 (d, 1H, J = 12.0 Hz), 4.0 (d, 1H, J = 18.0 Hz), 4.33 (dd, 1H, J = 6.0, 6.0 Hz), 4.66 (m, 2H), 7.33–7.39 (m, 5H), 7.49–7.50 (m, 2H), 7.57 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 21.8, 22.1, 31.8, 48.7, 48.9, 53.4, 61.5, 71.2, 127.7, 128.3, 129.2, 129.6, 130.3, 132.1, 136.8, 144.9, 157.6, 195.1; IR (Thin film) cm^{-1} 3064brs, 2981s, 2924s, 2852s, 2360s, 2341s, 1752s, 1709s, 1164s; mass spectrum (APCI): *m*/*z* (% relative intensity) 441.1 (100) $(M + H)^+$, 285.1 (54), 255.1 (23); HRMS (MALDI) *m*/*z* calcd for $C_{23}H_{24}N_2O_5SNa$ $(M + Na)^+$ 463.1304, found 463.1300.

Acknowledgements

Authors thank NIH-NIGMS [GM066055] for funding. We thank Mr Benjiman E. Kucera and Dr Vic Young of University of Minnesota for providing X-ray analysis. We thank Professor Ken N. Houk and Dr Elizabeth Krenske of UCLA for invaluable discussions.

References

1 For reviews on oxirenes, see: (*a*) K. P. Zeller, *Science of Synthesis*, 2002, **9**, 19; (*b*) E. G. Lewars, *Chem. Rev.*, 1983, **83**, 519; (*c*) M. Torre, E. M. Lown, H. E. Gunning and O. P. Strauzz, *Pure Appl. Chem.*, 1980, **52**, 1623.

2 For an example of metal keto-carbenoid formation by DMDO oxidation of alkynes see: S. Sun, J. O. Edwards, D. A. Sweigart, L. D'Accolti and R. Curci, *Organometallics*, 1995, **14**, 1545.

3 For reviews, see: (*a*) A. R. Katritzky, R. Jiang and S. K. Singh, *Heterocycles*, 2004, **63**, 1455; (*b*) J. A. Mulder, K. C. M. Kurtz and R. P. Hsung, *Synlett*, 2003, 1379; (*c*) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar and L.-L. Wei, *Tetrahedron*, 2001, **57**, 7575.

4 For efforts in 2009 alone, see: (*a*) B. Yao, Z. Liang, T. Niu and Y. Zhang, *J. Org. Chem.*, 2009, **74**, 4630; (*b*) A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2009, **48**, 4381; (*c*) A. Coste, F. Couty and G. Evano, *Org. Lett.*, 2009, **11**, 4454; (*d*) C. Laroche and M. S. Kerwin, *Tetrahedron Lett.*, 2009, **50**, 5194; (*e*) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208; (*f*) J. P. Das, H. Chechik and I. Marek, *Nat. Chem.*, 2009, **1**, 128; (*g*) D. C. Koester and D. B. Werz, *Angew. Chem., Int. Ed.*, 2009, **48**, 7971; (*h*) B. Gourdet and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 3802; (*i*) B. Gourdet, M. E. Rudkin, C. A. Watts and H. W. Lam, *J. Org. Chem.*, 2009, **74**, 7849; (*j*) A. Sato, H. Yorimitsu and K. Oshima, *Synlett*, 2009, 28; (*k*) N. Cockburn, E. Karimi and W. Tam, *J. Org. Chem.*, 2009, **74**, 5762; (*l*) N. Riddell, K. Villeneuve and W. Tam, *Org. Lett.*, 2005, **7**, 3681; (*m*) N. Shindoh, Y. Takemoto and K. Takasu, *Chem.–Eur. J.*, 2009, **15**, 7026; (*n*) A. Buzas, F. Istrate, X. F. Le Goff, Y. Odabachiam and F. Gagosz, *J. Organomet. Chem.*, 2009, **694**, 515; (*o*) P. Garcia, S. Moulin, Y. Miclo, D. Leboeuf, V. Gandon, C. Aubert and M. Malacria, *Chem.–Eur. J.*, 2009, **15**, 2129; (*p*) R. K. Friedman and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 10775; (*q*) A. K. Buzas, F. M. Istrate and F. Gagosz, *Tetrahedron*, 2009, **65**, 1889; (*r*) K. Dooleweerdt, T. Ruhland and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 221; (*s*) S. Couty, C. Meyer and J. Cossy, *Tetrahedron*, 2009, **65**, 1809; (*t*) C. Alayrac, D. Schollmeyer and B. Witulski, *Chem. Commun.*, 2009, 1464.

5 For our own recent efforts in 2009, see: (*a*) H. Li and R. P. Hsung, *Org. Lett.*, 2009, **11**, 4462; (*b*) J. Oppenheimer, W. L. Johnson, R. Figueroa, R. Hayashi and R. P. Hsung, *Tetrahedron*, 2009, **65**, 5001; (*c*) Y. Zhang, K. A. DeKorver, A. G. Lohse, Y.-S. Zhang, J. Huang and R. P. Hsung, *Org. Lett.*, 2009, **11**, 899.

6 For oxidations of ynamines employing ozone and oxygen, see: (*a*) C. S. Foote and J. W.-P. Lin, *Tetrahedron Lett.*, 1968, **9**, 3267; (*b*) K. Schank, H. Beck and G. Himbert, *Synthesis*, 1998, 1718.

7 For push–pull carbene stability and reactivity, see: (*a*) C. Buron, H. Gornitzka, V. Romanenko and G. Bertrand, *Science*, 2000, **288**, 834; (*b*) R. A. Moss, T. Zdrojewski and G.-J. Ho, *J. Chem. Soc., Chem. Commun.*, 1991, 946. For elegant work on donor–acceptor metal carbenoids, see: (*c*) S. J. Hedley, D. L. Ventura, P. M. Dominiak, C. L. Nygren and H. M. L. Davis, *J. Org. Chem.*, 2006, **71**, 5349; (*d*) H. M. L. Davis and S. Hedley, *Chem. Soc. Rev.*, 2007, **36**, 1109.

8 Z. F. Al-Rashid, W. L. Johnson, R. P. Hsung, Y. Wei, P.-Y. Yao, R. Liu and K. Zhao, *J. Org. Chem.*, 2008, **73**, 8780.

9 For some examples of related α-aza-carbenoids, see: (*a*) U. Schöllkopf, M. Hauptreif, J. Dippel, M. Nieger and E. Egert, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 192; (*b*) J. H. Rigby, A. Cavezza and M. Heeg, *Tetrahedron Lett.*, 1999, **40**, 2473; (*c*) R. P. Wurz and A. B. Charette, *J. Org. Chem.*, 2004, **69**, 1262; (*d*) G. Bégis, T. D. Sheppard, D. E. Cladingboel, W. B. Motherwell and D. A. Tocher, *Synthesis*, 2005, 3186. For elegant examples of α-aza-metallo-carbenoids, see: (*e*) L. S. Hegedus, *Tetrahedron*, 1997, **53**, 4105; (*f*) L. S. Hegedus, E. Lastra, Y. Narukawa and D. C. Snustad, *J. Am. Chem. Soc.*, 1992, **114**, 2991; (*g*) T. S. Powers, W. D. Wulff, J. Quinn, Y. Shi, W. Q. Jiang, R. P. Hsung, M. Parisi, A. Rahm, X. W. Jiang,

G. A. Yap and A. L. Rheingold, *J. Organomet. Chem.*, 2001, **617–618**, 182.
10 For leading reviews, see: (*a*) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*b*) F. Gnad and O. Reiser, *Chem. Rev.*, 2003, **103**, 1603.
11 (*a*) Z. F. Al-Rashid and R. P. Hsung, *Org. Lett.*, 2008, **10**, 661; (*b*) For our preliminary disclosure of this work, see: Z. F. Al-Rashid, R. P. Hsung, J. E. Antoline, C. Ko, Y. Wei and J. Yang, Abstract No. A-11, 40th ACS National Organic Symposium, Durham, NC, June 3, 2007.
12 Also see: S. Couty, C. Meyer and J. Cossy, *Synlett*, 2007, **18**, 2819.
13 For a review on synthesis of ynamides, see: M. R. Tracey, R. P. Hsung, J. A. Antoline, K. C. M. Kurtz, L. Shen, B. W. Slafer and Y. Zhang, in *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*, ed. Steve M. Weinreb, Georg Thieme Verlag KG, Stuttgart, Germany, 2005, ch. 21.4.
14 (*a*) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova and M. R. Tracey, *J. Org. Chem.*, 2006, **71**, 4170; (*b*) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2004, **6**, 1151; (*c*) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. J. Huang, K. C. M. Kurtz, L. Shen and C. J. Douglas, *J. Am. Chem. Soc.*, 2003, **125**, 2368; (*d*) I. K. Sagamanova, K. C. M. Kurtz and R. P. Hsung, *Org. Synth.*, 2007, **84**, 359.
15 Also see: (*a*) J. R. Dunetz and R. L. Danheiser, *Org. Lett.*, 2003, **5**, 4011; (*b*) A. L. Kohnen, J. R. Dunetz and R. L. Danheiser, *Org. Synth.*, 2007, **84**, 88; (*c*) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833.
16 DMDO/acetone solutions were prepared following the procedure reported in: (*a*) H. Xiong, R. P. Hsung, C. R. Berry and C. Rameshkumar, *J. Am. Chem. Soc.*, 2001, **123**, 7174. Aslo see: (*b*) R. W. Murray, M. Singh, T. G. Marron, L. A. Pfeifer and W. R. Roush, *Org. Synth.*, 1997, **74**, 91.
17 For DMDO-oxidation of alkynes, see: (*a*) K.-P. Zeller, M. Kowallik and P. Haiss, *Org. Biomol. Chem.*, 2005, **3**, 2310; (*b*) R. W. Murray and M. Singh, *J. Org. Chem.*, 1993, **58**, 5076; (*c*) R. Curci, M. Fiorentino, C. Fusco, R. Mello, F. P. Ballistreri, S. Failla and G. A. Tommaselli, *Tetrahedron Lett.*, 1992, **33**, 7929.

