Published in final edited form as:

Tetrahedron. 2011 July 8; 67(27-28): 5046–5053. doi:10.1016/j.tet.2011.03.115.

Heterocycles via intramolecular platinum-catalyzed propargylic substitution

Qiren Liang^a and Jef K. De Brabander^{a,*}

^aDepartment of Biochemistry and Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, 75390-9038

Abstract

We report a Pt(II)-catalyzed cyclization of nucleophile-tethered propargylic acetates yielding substituted heterocycles containing multiple heteroatoms including morpholines, dioxanes and sulfamates with high *cis*-selectivity.

Keywords

propargylic substitution; tetrahydropyrans; morpholines; dioxanes; sulfamates; Platinum catalysis

1. Introduction

Heterocyclic compounds continue to dominate the curiosity of biologists and chemist alike.¹ With a seemingly limitless range of structures and substitution patterns, all of which possess inherent value in medicinal chemistry and as synthetic building blocks, the need for improved and increasingly creative methods for their preparation persists. Tetrahydropyrans in particular are important substructures found in many polyketide-derived natural products which bear the 1,3-dioxygenation pattern. Recently, we reported a novel platinum-catalyzed propargylic substitution of ω -hydroxy propargylic esters.² This cyclization yielded 2,6-*cis*-disubstituted tetrahydropyrans and tetrahydrofurans by way of a Pt(II)-templated activation of the ester and subsequent intramolecular S_N2' substitution (Figure 1). Given the importance of heterocyclic compounds in chemistry and biology, we wondered if it would be feasible to access heterocycles with multiple heteroatoms using this methodology. In the context of biologically important tetrahydropyran-containing natural products, this strategy would allow access to heterocyclic analogs with potential improved potency.³ Herein, we describe that this can be achieved by incorporation of heteroatoms within the tether linking the propargylic acetate and the cyclizing nucleophile (see box in Fig. 1). We also demonstrate that in addition to alcohols, sulfonamides and sulfamates are equally competent nucleophiles in this chemistry.

© 2011 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +1-214-648-7808; fax: +1-214-648-0320; jef.debrabander@utsouthwestern.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary Material

Additional experimental details, spectroscopic data and copies of ¹H and ¹³C NMR spectra for new compounds are available on the Internet at <http://www.sciencedirect.com>.

2. Results and discussion

First, we explored the possibility of implementing the intramolecular propargylic substitution for the construction of non-symmetrical 2,6-disubstituted morpholines. The 1,4-morpholine unit is prevalent in nature and is featured in compounds with a range of functions including antidepressant,⁴ antiparasitic,⁵ anti-tumor,⁶ antioxidant,⁷ and anti-inflammatory⁸ activities.⁹ Over 100 compounds listed in the world drug index contain a morpholine subunit. Additionally, morpholines have enjoyed use as tools in chemical synthesis.¹⁰ Given the ubiquity of morpholines it is unsurprising that many preparatory methods have been developed.^{11,12} Despite these notable advances, to the best of our knowledge there are few examples of selective formation of non-*C*₂-symmetrical *cis*-2,6-disubstituted morpholines.^{11e,f,l,o}

As alluded to earlier, our approach towards 2,6-disubstituted morpholines hinges on the cyclization of ω -hydroxy propargylic acetates containing a Boc-protected nitrogen atom in the tether, materials that were readily prepared on scale and in high yield.¹³ As shown in Table 1, treatment of propargylic acetates **1a–i** with a catalytic amount of Zeise's dimer ($[(CH_2CH_2)Cl_2Pt]_2$, 2.5 mol%) in tetrahydrofuran at room temperature provided morpholines **2a–i** in excellent yields. When diastereomeric mixtures of secondary alcohols **1b–d**, **1f**, or **1h** were used as starting materials, only *cis*-products were obtained in high diastereomeric excess (>10:1 ratio). This dynamic kinetic resolution, *via* epimerization at the propargylic position,¹⁴ was also observed in our previous study for the synthesis of alkyne-substituted tetrahydropyrans.^{2a,15} As shown in equation 1, we had previously postulated that the propargylic substitution occurs from a metal-templated allenyl acetate (**B**) via SN_2' substitution.

The allenylester arises from a 1,3-acetate or double 1,2-acetate shift of propargylic acetate **A**.¹⁶ Both the stepwise rearrangement and a hapto-2 to hapto-1 isomerization (**B** to **C**) would permit epimerization at the propargylic carbon.

With these results in hand, it was of interest to assess whether the nucleophilic residue could be switched to nitrogen and the tether residue to oxygen as an entry to alternatively substituted morpholines. As shown in Table 2, cyclization of oxygen-tethered sulfonamides **3a–d**, readily prepared from simple starting materials,¹³ under the standard conditions provided 3-substituted morpholines **4a–d** in good yield (65–76%).¹⁷

We next pursued 2,6-disubstituted-1,4-dioxanes, which have previously been prepared by a number of methods including epoxide opening,¹⁸ cyclodimerization of epoxides,¹⁹ selenylation²⁰ and by use of iron-promoted intramolecular cyclizations of allylic ethers.²¹ As their utility in a number of applications continues to be investigated, for example, in use as photoreceptors,²² in perfumes,²³ and as anti-tumoral²⁴ and anti-viral agents,²⁵ there remains a pressing need for additional methods for their preparation. A simple derivation of the original substrates by inclusion of an oxygen atom in the tether was envisaged to allow access to 1,4-dioxanes of varying substitution patterns. Satisfyingly, stirring oxygen-tethered ω -hydroxy propargylic acetates **5a–h**, materials which were readily prepared on gram

scale,¹³ with a catalytic amount of Zeise's dimer in THF at room temperature, afforded the *cis*-2,6-disubstituted-1,4-dioxanes **6a–h** in excellent yields (85–90%) and diastereoselectivity (**6e–h**, 14:1 to 19:1) as illustrated in Table 3. There are few preparations in the literature for *cis*-2,6-disubstituted-1,4-dioxanes where the substituents are non-identical.²⁶ Therefore, this methodology represents a valuable route to these synthetically useful synthons without the need for desymmetrization before further elaboration.

Cyclic sulfamates, while only rarely occurring in nature,²⁷ have enjoyed use as building blocks in synthetic chemistry. Du Bois *et al.* elegantly demonstrated their use in cross-coupling reactions²⁸ and subsequently as intermediates in the synthesis of the *bis*-guanidinium toxin (+)-saxitoxin.²⁹ Despite a promising future for their continued use as intermediates towards amino alcohols and polyamines, preparations of cyclic sulfamates have been relatively limited; including, for example, rhodium-catalyzed C-H insertions²⁸ and reduction of the corresponding sulfamidates.³⁰

We envisaged a route towards these increasingly important heterocycles by incorporation of a terminal, unsubstituted sulfamate as the nucleophilic residue for propargylic substitution. The substrates **7a–g** were prepared from commercially available materials in good yield.¹³ Armed with the knowledge from the morpholine preparation that sulfonamides were effective nucleophiles in these propargylic substitutions (Table 2), we were pleased to confirm that unsubstituted sulfamates were equally competent in this chemistry, as illustrated in Table 4. Gratifyingly, the transformations to cyclic sulfamates proceeded in high yields (81–88%), and *syn:anti* mixtures of starting materials **7c–g** (1:1) converged to single *cis*-disubstituted products **8** with excellent diastereoselectivity (20:1 to 25:1).¹⁵

3. Conclusion

In conclusion, we have demonstrated the usefulness of the intramolecular propargylic substitution of nucleophile tethered propargylic acetates. Particularly noteworthy is the incorporation of a range of functionality to produce a range of mono- and disubstituted heterocycles containing multiple heteroatoms such as morpholines, dioxanes and cyclic sulfamates. The methodology described herein provides these heterocycles from readily available starting materials under operationally mild conditions, and with high diastereoselectivity. Further extension of this work to gain entry to other classes of heterocycles is currently underway.

4. Experimental section

4.1. General experimental

Unless otherwise stated, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Solvents used for moisture-sensitive operations were dried over molecular sieves (4 Å, Aldrich). Pyridine was dried over solid KOH; anhydrous *N,N*-dimethylformamide and CH₃CN were purchased from commercial sources. Reactions were performed under an atmosphere of nitrogen with magnetic stirring unless noted otherwise. Flash chromatography was performed using *E. Merck* silica gel 60 (240–400 mesh) according to the protocol of Still *et al.*³⁰ TLC was performed using pre-coated plates purchased from *E. Merck* (silica gel 60 PF254, 0.25 mm) and were visualized using a KMnO₄ or Ce (IV) stain. NMR spectra were recorded with an internal deuterium lock and referenced to the residual solvent peak³¹ on the following instruments: 500 MHz: Varian Inova-500; 400 MHz: Varian Inova-400; 300 MHz Mercury-300 spectrometers. ¹H NMR data are presented as follows: chemical shift (in ppm), integration, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad, *app.*= apparent) and coupling constants (H / Hz). ¹H-¹H coupling constants were taken from the spectra. Infrared

spectra were recorded on a *Perkin-Elmer* 1000 series FTIR, with wavenumbers expressed in cm^{-1} , using samples prepared as thin films between NaCl plates. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS. Procedures for the preparation of all substrate materials **1a–i**, **3a–d**, **5a–h**, and **7a–g** can be found in the Supplementary Information.

4.2. Propargylic acetates **1a–i**

4.2.1. 1-((*tert*-Butoxycarbonyl) (2-hydroxyethyl)-amino)-6-phenylhex-3-yn-2-yl acetate (1a**)**— δ_H (400 MHz, CDCl_3) 7.28–7.24 (2H, m), 7.20–7.15 (3H, m), 5.53 (1H, m), 3.67 (2H, m), 3.58–3.14 (4H, m), 2.78 (2H, t, $J = 7.6$ Hz), 2.46 (2H, t, $J = 7.6$ Hz), 2.04 (3H, s), 1.44 (9H, s); δ_C (75 MHz, CDCl_3) 169.6, 156.6, 140.1, 128.3, 128.2, 126.3, 86.6, 80.8, 76.2, 62.7, 62.0, 52.4, 51.5, 34.5, 28.2, 20.9, 20.8; ν_{max} (liquid film) 3436, 2959, 1728, 1638, 1463, 1274, 1123, 1072, 742 cm^{-1} ; MS (ESI): MNa^+ , found 398.1. $\text{C}_{21}\text{H}_{29}\text{NO}_5$ requires 398.1.

4.2.2. 1-((*tert*-Butoxycarbonyl) (2-hydroxybutyl)amino)-6-phenylhex-3-yn-2-yl acetate (1b**)**— δ_H (300 MHz, CDCl_3) 7.31–7.26 (2H, m), 7.23–7.17 (3H, m), 5.57 (1H, m), 3.68 (1H, m), 3.55–3.18 (4H, m), 2.81 (2H, *app.* t, $J = 7.5$ Hz), 2.48 (2H, *app.* t, $J = 6.6$ Hz), 2.05 (3H, s), 1.46 (11H, s), 0.96 (3H, t, $J = 7.8$ Hz); δ_C (75 MHz, CDCl_3) 169.8, 157.2, 140.5, 128.6, 128.5, 126.6, 86.9, 81.2, 76.5, 73.1, 62.9, 55.3, 53.2, 52.7, 34.8, 28.3, 21.2, 21.1, 10.0; ν_{max} (liquid film) 3474, 2974, 1746, 1694, 1455, 1411, 1368, 1230, 1157, 1025, 749, 700 cm^{-1} ; MS (ESI): MNa^+ , found 426.2. $\text{C}_{23}\text{H}_{33}\text{NO}_5$ requires 426.2.

4.2.3. 1-((*tert*-Butoxycarbonyl) (2-hydroxy-3-methyl-butyl)amino)-6-phenylhex-3-yn-2-yl acetate (1c**)**— δ_H (500 MHz, CDCl_3) 7.31–7.27 (2H, m), 7.23–7.19 (3H, m), 5.64 (1H, m), 3.55 (2H, m), 3.50 (1H, m), 3.32 (2H, m), 2.83 (2H, t, $J = 7.0$ Hz), 2.51 (2H, *app.* td, $J = 8.0, 2.0$ Hz), 2.07 (3H, s), 1.61–1.69 (1H, m), 1.48 (9H, s), 0.96 (3H, m), 0.95 (3H, m); δ_C (75 MHz, CDCl_3) 169.9, 157.3, 140.5, 128.6, 128.5, 126.6, 86.9, 81.2, 76.6, 76.1, 62.7, 53.6, 52.9, 34.9, 32.5, 28.5, 21.2, 21.1, 18.9, 17.4; ν_{max} (liquid film) 3477, 2962, 1745, 1692, 1454, 1411, 1367, 1229, 1166, 1022, 889, 748, 699 cm^{-1} ; MS (ESI): MNa^+ , found 440.2. $\text{C}_{24}\text{H}_{35}\text{NO}_5$ requires 440.2.

4.2.4. 1-((*tert*-Butoxycarbonyl) (2-hydroxy-2-phenyl-ethyl)amino)-6-phenylhex-3-yn-2-yl acetate (1d**)**— δ_H (500 MHz, CDCl_3) 7.40–7.25 (10H, m), 5.61 (1H, m), 4.94 (1H, m), 3.54 (2H, m), 3.48 (1H, d, $J = 3.0$ Hz), 3.45 (1H, d, $J = 3.0$ Hz), 2.81 (2H, t, $J = 7.5$ Hz), 2.48 (2H, td, $J = 7.5, 2.0$ Hz), 2.04 (3H, s), 1.51 (9H, s); δ_C (75 MHz, CDCl_3) 169.8, 157.6, 142.4, 140.5, 128.7, 128.6, 127.8, 126.6, 126.0, 87.1, 81.6, 76.5, 74.2, 62.8, 57.6, 52.8, 34.8, 28.5, 21.2, 21.1; ν_{max} (liquid film) 3452, 2929, 1744, 1693, 1454, 1409, 1367, 1229, 1164, 1024, 750, 700 cm^{-1} ; MS (ESI): MNa^+ , found 464.4. $\text{C}_{27}\text{H}_{33}\text{NO}_5$ requires 474.2.

4.2.5. 1-((*tert*-Butoxycarbonyl) (2-hydroxyethyl)-amino)-4-phenylbut-3-yn-2-yl acetate (1e**)**— δ_H (400 MHz, CDCl_3) 7.43–7.41 (2H, m), 7.32–7.25 (3H, m), 5.85 (1H, m), 3.77 (2H, m), 3.65 (2H, m), 3.53 (2H, m), 2.64 (1H, *br.* s), 2.10 (3H, s), 1.46 (9H, s); δ_C (75 MHz, CDCl_3) 169.9, 157.0, 132.1, 129.1, 128.5, 121.9, 86.7, 84.4, 81.4, 63.1, 62.6, 52.6, 52.1, 28.5, 21.2; ν_{max} (liquid film) 3446, 2976, 1747, 1695, 1478, 1410, 1368, 1225, 1166, 1032, 758, 691 cm^{-1} ; MS (ESI): MNa^+ , found 370.1. $\text{C}_{19}\text{H}_{25}\text{NO}_5$ requires 370.1.

4.2.6. 1-((*tert*-Butoxycarbonyl) (2-hydroxy-2-phenyl-ethyl)amino)-4-phenylbut-3-yn-2-yl acetate (1f**)**— δ_H (400 MHz, CDCl_3) 7.41–7.25 (10H, m), 5.86 (1H, m), 4.97 (1H, m), 3.46 (4H, m), 2.68 (1H, *br.* s), 2.09 (3H, s), 1.49 (9H, s); δ_C (75 MHz, CDCl_3) 169.9, 157.4, 142.3, 132.1, 129.1, 128.7, 128.5, 128.4, 127.8, 125.5, 84.4, 81.6,

74.1, 63.0, 57.8, 53.2, 28.5, 28.4, 21.3; $\nu_{\max}$ (liquid film) 2360, 1747, 1692, 1408, 1367, 1223, 1164, 1026, 757 cm^{-1} ; MS (ESI): MNa^+ , found 446.3. $\text{C}_{25}\text{H}_{29}\text{NO}_5$ requires 446.2.

4.2.7. 1-((*tert*-Butoxycarbonyl) (2-hydroxyethyl)-amino)dec-3-yn-2-yl acetate (1g)— δ_{H} (400 MHz, CDCl_3) 5.60 (1H, m), 3.74 (2H, m), 3.51 (2H, m), 3.48 (2H, m), 2.18 (2H, td, $J = 7.2, 2.0$ Hz), 2.06 (3H, s), 1.52–1.46 (2H, m), 1.46 (9H, s), 1.38–1.24 (6H, m), 0.88 (3H, t, $J = 7.2$ Hz); δ_{C} (75 MHz, CDCl_3) 169.9, 157.1, 88.0, 81.3, 75.5, 63.1, 62.4, 52.8, 51.9, 31.4, 28.6, 28.4, 22.7, 21.2, 18.8, 14.2; $\nu_{\max}$ (liquid film) 3463, 2933, 1748, 1697, 1466, 1409, 1367, 1226, 1158, 1023, 775 cm^{-1} ; MS (ESI): MNa^+ , found 378.1. $\text{C}_{19}\text{H}_{33}\text{NO}_5$ requires 378.2.

4.2.8. 1-((*tert*-Butoxycarbonyl) (2-hydroxy-3-methyl-butyl)amino)dec-3-yn-2-yl acetate (1H)— δ_{H} (400 MHz, CDCl_3) 5.61 (1H, m), 3.71 (1H, m), 3.54 (2H, m), 3.29 (2H, m), 2.18 (2H, *app.* t, $J = 7.2$ Hz), 2.05 (3H, s), 1.52–1.41 (4H, m), 1.46 (9H, s), 1.38–1.26 (6H, m), 0.96 (3H, t, $J = 7.6$ Hz), 0.88 (3H, t, $J = 7.2$ Hz); δ_{C} (75 MHz, CDCl_3) 169.8, 157.2, 88.0, 81.1, 75.6, 73.1, 63.1, 55.3, 54.8, 52.8, 31.4, 28.7, 28.5, 28.3, 22.7, 21.2, 18.8, 14.2, 10.0; $\nu_{\max}$ (liquid film) 2932, 2360, 1747, 1693, 1467, 1410, 1367, 1228, 1156, 1023, 766 cm^{-1} ; MS (ESI): MNa^+ , found 405.9. $\text{C}_{21}\text{H}_{37}\text{NO}_5$ requires 406.2.

4.2.9. 1-((*tert*-Butoxycarbonyl)(2-hydroxyethyl)-amino)oct-3-yn-2-yl acetate (1i)— δ_{H} (400 MHz, CDCl_3) 5.59 (1H, m), 3.73 (2H, *app.* t, $J = 2.8$ Hz), 3.49–3.43 (4H, m), 2.18 (2H, td, $J = 6.8, 2.0$ Hz), 2.05 (3H, s), 1.50–1.43 (2H, m), 1.47 (9H, s), 1.41–1.29 (2H, m), 0.88 (3H, t, $J = 7.2$ Hz); δ_{C} (75 MHz, CDCl_3) 169.9, 157.1, 87.9, 81.3, 75.5, 63.1, 62.4, 52.8, 51.9, 30.5, 28.5, 22.1, 21.2, 18.5, 13.7; $\nu_{\max}$ (liquid film) 3455, 2935, 1747, 1697, 1466, 1409, 1367, 1227, 1160, 1023, 878, 775 cm^{-1} ; MS (ESI): MNa^+ , found 350.0. $\text{C}_{17}\text{H}_{29}\text{NO}_5$ requires 350.1.

4.3. General procedure for the preparation of 2,6-substituted morpholines 2a–i

To a 0.1 M solution of propargylic ester **1a–i**¹³ in THF at RT was added $[\text{Cl}_2\text{Pt}(\text{CH}_2\text{CH}_2)]_2$ (2.5 mol%). The resulting yellow solution was stirred for 0.5–2.0 h¹³ before being quenched by the addition of NEt_3 (0.5 mL/mmol substrate). The solution was concentrated *in vacuo* and the crude material was filtered through a plug of silica gel to give the title compound **2a–i** as a colorless oil.

4.3.1. *tert*-Butyl 2-(4-phenylbut -1-yn-1-yl)-morpholine-4-carboxylate (2a)— δ_{H} (500 MHz, CDCl_3) 7.31–7.27 (2H, m), 7.22–7.19 (3H, m), 4.18 (1H, m), 3.88 (1H, dt, $J = 12.5, 4.0$ Hz), 3.78 (1H, *br.* d, $J = 12.5$ Hz), 3.60 (1H, *app.* dt, $J = 13.5, 3.0$ Hz), 3.49 (1H, ddd, $J = 13.5, 9.0, 3.0$ Hz), 3.22–3.14 (2H, m), 2.84 (2H, t, $J = 7.5$ Hz), 2.52 (2H, td, $J = 8.0, 2.0$ Hz), 1.49 (9H, s); δ_{C} (125 MHz, CDCl_3) 154.6, 140.7, 128.6, 128.4, 126.5, 86.5, 80.2, 77.4, 66.2, 65.1, 49.1, 43.6, 35.1, 28.6, 20.9; $\nu_{\max}$ (liquid film) 2975, 1698, 1454, 1417, 1250, 1171, 1099, 1016, 868, 748, 699 cm^{-1} ; MS (ESI): MNa^+ , found 338.1. $\text{C}_{19}\text{H}_{25}\text{NO}_3$ requires 338.1.

4.3.2. *tert*-Butyl 2-ethyl-6-(4-phenylbut-1-yn-1-yl)-morpholine-4-carboxylate (2b)— δ_{H} (500 MHz, CDCl_3) 7.31–7.27 (2H, m), 7.22–7.20 (3H, m), 4.12 (1H, m), 4.02 (1H, *br.* d, $J = 12.5$ Hz), 3.93 (1H, *br.* d, $J = 12.5$ Hz), 3.31–3.25 (1H, m), 2.85 (2H, t, $J = 7.5$ Hz), 2.79 (1H, *app.* t, $J = 12.5$ Hz), 2.53 (2H, *app.* td, $J = 7.5, 1.5$ Hz), 2.49 (1H, m), 1.64–1.57 (1H, m), 1.53–1.47 (1H, m), 1.49 (9H, s), 0.98 (3H, t, $J = 7.5$ Hz); δ_{C} (125 MHz, CDCl_3) 154.5, 140.7, 128.6, 128.5, 126.5, 86.1, 80.3, 77.7, 77.5, 67.0, 49.0, 47.8, 35.1, 28.6, 26.3, 21.1, 9.6; $\nu_{\max}$ (liquid film) 3449, 2923, 2107, 1703, 1654, 1453, 1419, 1365, 1232, 1171, 1084, 880, 699 cm^{-1} ; MS (ESI): MNa^+ , found 366.0. $\text{C}_{21}\text{H}_{29}\text{NO}_3$ requires 366.1.

4.3.3. tert-Butyl 2-isopropyl-6-(4-phenylbut-1-yn-1-yl)morpholine-4-carboxylate (2c)— δ_H (500 MHz, $CDCl_3$) 7.31-7.27 (2H, m), 7.23-7.20 (3H, m), 4.10 (1H, *br. d*, $J = 10.5$ Hz), 3.98 (2H, m), 3.06 (1H, t, $J = 7.5$ Hz), 2.85 (2H, t, $J = 7.5$ Hz), 2.77 (1H, t, $J = 12.5$ Hz), 2.55 (3H, m), 1.76 (1H, m), 1.49 (9H, s), 1.01 (3H, d, $J = 7.0$ Hz), 0.94 (3H, d, $J = 7.0$ Hz); δ_C (125 MHz, $CDCl_3$) 154.7, 140.7, 128.6, 128.5, 126.5, 85.9, 81.1, 80.3, 77.8, 77.4, 67.1, 35.1, 31.3, 28.6, 21.1, 18.8, 18.3; ν_{max} (liquid film) 3432, 2964, 2929, 1699, 1454, 1366, 1250, 1150, 1082, 886, 699 cm^{-1} ; MS (ESI): MNa^+ , found 380.1. $C_{22}H_{31}NO_3$ requires 380.2.

4.3.4. tert-Butyl 2-phenyl-6-(4-phenylbut-1-yn-1-yl)morpholine-4-carboxylate (2d)— δ_H (400 MHz, $CDCl_3$) 7.39-7.18 (10H, m), 4.42 (1H, dd, $J = 10.8, 2.4$ Hz), 4.30 (1H, m), 4.10 (2H, m), 2.90 (1H, dd, $J = 12.8, 11.2$ Hz), 2.84 (2H, t, $J = 7.6$ Hz), 2.78 (1H, m), 2.52 (2H, td, $J = 7.6, 1.2$ Hz), 1.49 (9H, s); δ_C (125 MHz, $CDCl_3$) 154.4, 140.6, 138.7, 128.6, 128.5, 128.4, 126.6, 126.5, 86.5, 80.6, 78.2, 67.3, 60.6, 49.0, 34.9, 28.6, 21.2, 14.4; ν_{max} (liquid film) 3419, 2976, 2929, 2859, 2243, 1694, 1454, 1416, 1366, 1305, 1251, 1168, 1120, 1074, 1029, 886, 750, 699 cm^{-1} ; MS (ESI): MNa^+ , found 414.2. $C_{25}H_{29}NO_3$ requires 414.2.

4.3.5. tert-Butyl 2-(phenylethynyl)morpholine-4-carboxylate (2e)— δ_H (400 MHz, $CDCl_3$) 7.44-7.42 (2H, m), 7.33-7.25 (3H, m), 4.43 (1H, dd, $J = 8.0, 2.8$ Hz), 3.98 (1H, *app. d*, $J = 11.2$ Hz), 3.89 (1H, *br. d*, $J = 8.0$ Hz), 3.65-3.55 (2H, m), 3.36-3.24 (2H, m), 1.46 (9H, s); δ_C (125 MHz, $CDCl_3$) 154.6, 132.1, 128.8, 128.4, 122.5, 86.5, 85.4, 80.4, 66.4, 65.2, 48.8, 43.7, 28.6; ν_{max} (liquid film) 2975, 1698, 1490, 1454, 1417, 1366, 1250, 1168, 1127, 1085, 757, 691 cm^{-1} ; MS (ESI): MNa^+ , found 310.1. $C_{17}H_{21}NO_3$ requires 310.1.

4.3.6. tert-Butyl 2-phenyl-6-(phenylethynyl)-morpholine-4-carboxylate (2f)— δ_H (500 MHz, $CDCl_3$) 7.49-7.27 (10H, m), 4.59 (1H, dd, $J = 3.0, 11.0$ Hz), 4.53 (1H, dd, $J = 11.0, 2.5$ Hz), 4.29 (1H, *br. d*, $J = 11.5$ Hz), 4.18 (1H, *br. d*, $J = 9.0$ Hz), 3.11 (1H, *app. t*, $J = 12.0$ Hz), 2.88 (1H, *app. t*, $J = 12.0$ Hz), 1.49 (9H, s); δ_C (125 MHz, $CDCl_3$) 154.5, 138.8, 132.1, 128.8, 128.6, 128.4, 128.3, 126.6, 122.5, 86.2, 85.4, 80.7, 78.3, 67.7, 49.7, 48.6, 28.6; ν_{max} (liquid film) 2360, 1694, 1413, 1249, 1165, 1125, 1071, 756 cm^{-1} ; MS (ESI): MNa^+ , found 386.1. $C_{23}H_{25}NO_3$ requires 386.1.

4.3.7. tert-Butyl 2-(oct-1-yn-1-yl)morpholine-4-carboxylate (2g)— δ_H (500 MHz, $CDCl_3$) 4.17 (1H, m), 3.89 (1H, *app. dt*, $J = 12.0, 4.0$ Hz), 3.80 (1H, *br. d*, $J = 12.0$ Hz), 3.61 (1H, dt, $J = 12.0, 3.5$ Hz), 3.49 (1H, ddd, $J = 14.5, 11.5, 3.5$ Hz), 3.19-3.10 (2H, m), 2.20 (2H, td, $J = 7.0, 2.0$ Hz), 1.53-1.48 (2H, m), 1.46 (9H, s), 1.44-1.24 (6H, m), 0.88 (3H, t, $J = 7.0$ Hz); δ_C (125 MHz, $CDCl_3$) 154.6, 87.4, 80.2, 76.5, 66.3, 65.2, 49.1, 43.1, 31.4, 28.6, 28.5, 22.6, 18.8, 14.0; ν_{max} (liquid film) 3445, 2931, 2859, 2360, 1702, 1455, 1417, 1250, 1172, 1100, 1015, 869, 767 cm^{-1} ; MS (ESI): MNa^+ , found 318.2. $C_{17}H_{29}NO_3$ requires 318.2.

4.3.8. tert-Butyl 2-ethyl-6-(oct-1-yn-1-yl)-morpholine-4-carboxylate (2h)— δ_H (500 MHz, $CDCl_3$) 4.12 (1H, m), 4.03 (1H, *br. d*, $J = 11.0$ Hz), 3.91 (1H, *br. d*, $J = 11.0$ Hz), 3.27 (1H, m), 2.80 (1H, t, $J = 12.0$ Hz), 2.50 (1H, t, $J = 12.0$ Hz), 2.21 (2H, td, $J = 7.0, 2.0$ Hz), 1.64-1.55 (1H, m), 1.54-1.43 (3H, m), 1.47 (9H, s), 1.24-1.41 (6H, m), 0.97 (3H, t, $J = 7.5$ Hz), 0.89 (3H, t, $J = 7.0$ Hz); δ_C (125 MHz, $CDCl_3$) 154.5, 86.9, 80.3, 77.5, 76.8, 67.1, 49.1, 47.7, 31.4, 28.7, 28.6, 28.5, 26.3, 22.6, 18.9, 14.1, 9.7; ν_{max} (liquid film) 2931, 2858, 1703, 1415, 1318, 1235, 1173, 1147, 1083, 882 cm^{-1} ; MS (ESI): M^+ , found 323.1. $C_{19}H_{33}NO_3$ requires 323.2.

4.4. Propargylic acetates 3a–d

4.4.1. 1-(2-(4-Methylphenylsulfonamido)ethoxy)-4-phenylbut-3-yn-2-yl acetate (3a)— δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, $J = 8.4$ Hz), 7.45–7.42 (2H, m), 7.36–7.27 (5H, m), 5.73 (1H, dd, $J = 7.2, 4.0$ Hz), 5.05 (1H, m), 3.73–3.63 (2H, m), 3.61–3.53 (2H, m), 3.12 (2H, br. dd, $J = 10.0, 5.6$ Hz), 2.41 (3H, s), 2.13 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.2, 143.6, 137.0, 132.1, 129.9, 129.8, 129.1, 128.5, 127.2, 126.5, 121.8, 86.6, 83.3, 72.5, 69.8, 63.3, 42.9, 21.6, 21.2; ν_{max} (liquid film) 3278, 1744, 1492, 1371, 1329, 1228, 1161, 1093, 815 cm^{-1} ; MS (ESI): MNa^+ , found 424.5. $C_{21}H_{23}NSO_5$ found 424.2.

4.4.2. 1-(2-(4-Methylphenylsulfonamido)ethoxy)-6-phenylhex-3-yn-2-yl acetate (3b)— δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, $J = 8.4$ Hz), 7.27 (4H, app. t, $J = 8.0$ Hz), 7.21–7.17 (3H, m), 5.45 (1H, m), 4.90 (1H, br. t, $J = 5.6$ Hz), 3.56–3.44 (4H, m), 3.08 (2H, dd, $J = 10.8, 6.0$ Hz), 2.80 (2H, t, $J = 7.2$ Hz), 2.49 (2H, td, $J = 7.6, 2.0$ Hz), 2.40 (3H, s), 2.07 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.2, 143.6, 140.4, 137.0, 129.9, 128.6, 128.5, 127.2, 126.5, 87.0, 75.5, 72.6, 69.7, 63.2, 42.9, 34.8, 21.7, 21.2, 21.0; ν_{max} (liquid film) (cm^{-1}) 2360, 1741, 1371, 1329, 1231, 1161, 1092, 1037, 815, 667; MS (ESI): MNa^+ , found 452.1. $C_{23}H_{27}NSO_5$ requires 452.1.

4.4.3. 1-(2-(4-Methylphenylsulfonamido)ethoxy)dec-3-yn-2-yl acetate (3c)— δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, $J = 8.4$ Hz), 7.27 (2H, app. t, $J = 8.4$ Hz), 5.46 (1H, m), 4.96 (1H, br. t, $J = 6.0$ Hz), 3.57–3.45 (4H, m), 3.07 (2H, m), 2.39 (3H, s), 2.17 (2H, td, $J = 7.2, 1.6$ Hz), 2.06 (3H, s), 1.49–1.42 (2H, m), 1.36–1.21 (6H, m), 0.86 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 143.6, 137.1, 129.9, 127.2, 88.0, 74.5, 72.8, 69.7, 63.3, 43.0, 31.4, 28.6, 28.4, 22.7, 21.7, 21.2, 18.8, 14.2; ν_{max} (thin film) 3288, 2930, 1738, 1599, 1428, 1372, 1329, 130, 1160, 1092, 945, 814, 661 cm^{-1} ; MS (ESI): MNa^+ , found 432.2. $C_{21}H_{31}NSO_5$ requires 432.1.

4.4.4. 1-(2-(4-Methylphenylsulfonamido)ethoxy)oct-3-yn-2-yl acetate (3d)— δ_H (400 MHz, $CDCl_3$) 7.75–7.71 (2H, m), 7.31–7.25 (2H, m), 5.47 (1H, m), 4.93 (1H, br. t, $J = 6.0$ Hz), 3.59–3.46 (4H, m), 3.13–3.05 (2H, m), 2.40 (3H, s), 2.18 (2H, td, $J = 7.2, 2.0$ Hz), 2.07 (3H, s), 1.49–1.42 (2H, m), 1.40–1.31 (2H, m), 0.88 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 143.6, 137.1, 129.9, 127.3, 88.0, 74.5, 72.8, 69.7, 63.3, 43.0, 30.5, 22.1, 21.7, 21.2, 18.5, 13.7; ν_{max} (liquid film) 3284, 2933, 2873, 1743, 1431, 1372, 1330, 1231, 1161, 1093, 1037, 944, 815 cm^{-1} ; MS (ESI): MNa^+ , found 404.2. $C_{19}H_{27}NSO_5$ requires 404.1.

4.5. General procedure for the preparation of 3-substituted morpholines 4a–d

To a 0.1 M solution of propargylic ester **3a–d** in THF at RT was added $[Cl_2Pt(CH_2CH_2)]_2$ (2.5 mol%). The resulting yellow solution was stirred for 3–4h¹³ before being quenched by the addition of NEt_3 (0.5 mL/mmol substrate). The solution was concentrated *in vacuo* and the crude material was filtered through a plug of silica gel.

4.5.1. 3-(Phenylethynyl)-4-tosylmorpholine (4a)— δ_H (500 MHz, $CDCl_3$) 7.73 (2H, d, $J = 8.5$ Hz), 7.29–7.20 (5H, m), 6.99 (2H, dd, $J = 8.5, 1.0$ Hz), 4.79 (1H, m), 3.99 (2H, m), 3.83 (1H, dd, $J = 11.0, 3.0$ Hz), 3.70 (1H, td, $J = 11.0, 3.0$ Hz), 3.58 (1H, m), 3.18 (1H, td, $J = 12.0, 3.0$ Hz), 2.27 (3H, s); δ_C (75 MHz, $CDCl_3$) 144.0, 134.4, 131.8, 129.6, 128.6, 128.4, 128.2, 122.2, 86.9, 82.8, 71.4, 66.9, 47.2, 42.3, 21.6; ν_{max} (liquid film) 2933, 1597, 1491, 1443, 1346, 1260, 1165, 1111, 936 cm^{-1} ; MS (ESI): MNa^+ , found 364.3. $C_{19}H_{19}NSO_3$ requires 364.1.

4.5.2. 3-(4-Phenylbut-1-yn-1-yl)-4-tosylmorpholine (4b)— δ_H (400 MHz, $CDCl_3$) 7.65 (2H, d, $J = 8.0$ Hz), 7.27–7.17 (5H, m), 7.08 (2H, m), 4.55 (1H, m), 3.88–3.80 (2H, m), 3.68 (1H, dd, $J = 11.2, 2.8$ Hz), 3.60 (1H, td, $J = 11.2, 2.8$ Hz), 3.41 (1H, m), 2.98 (1H, td, $J = 11.2, 2.8$ Hz).

= 12.0, 3.2 Hz), 2.51 (2H, m), 2.38 (3H, s), 2.11 (2H, m); δ_C (75 MHz, $CDCl_3$) 143.7, 140.5, 134.7, 129.3, 128.6, 128.5, 126.5, 86.6, 82.6, 74.3, 71.5, 66.8, 46.7, 41.9, 34.7, 21.8, 20.8; ν_{max} (liquid film) 2921, 2858, 1598, 1494, 1453, 1346, 1261, 1166, 1110, 936 cm^{-1} ; MS (ESI): MNa^+ , found 392.2. $C_{21}H_{23}NSO_3$ requires 392.1.

4.5.3. 3-(Oct-1-yn-1-yl)-4-tosylmorpholine (4c)— δ_H (400 MHz, $CDCl_3$) 7.71-7.68 (2H, m), 7.30-7.25 (2H, m), 4.55 (1H, m), 3.88 (1H, dd, $J = 11.2, 3.2$ Hz), 3.83 (1H, m), 3.69 (1H, dd, $J = 11.2, 3.2$ Hz), 3.65-3.62 (1H, td, $J = 11.6, 2.8$ Hz), 3.47-3.41 (1H, m), 3.05 (1H, td, $J = 11.2, 3.2$ Hz), 2.41 (3H, s), 1.79 (2H, d, $J = 1.6$ Hz), 1.26-1.21 (2H, m), 1.17-1.16 (6H, m), 0.87 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 143.6, 134.7, 129.4, 128.5, 73.5, 71.6, 68.4, 66.8, 46.7, 41.9, 31.5, 28.7, 28.4, 22.7, 21.7, 18.7, 14.2; ν_{max} (liquid film) 2929, 2858, 1348, 1261, 1167, 1113, 937 cm^{-1} ; MS (ESI): MNa^+ , found 372.0. $C_{19}H_{27}NSO_3$ requires 372.1.

4.5.4. 3-(Hex-1-yn-1-yl)-4-tosylmorpholine (4d)— δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, $J = 8.4$ Hz), 7.27 (2H, d, $J = 8.4$ Hz), 4.55 (1H, m), 3.88 (1H, dd, $J = 11.6, 2.8$ Hz), 3.82 (1H, *app.* d, $J = 10.8$ Hz), 3.70 (1H, dd, $J = 11.2, 2.8$ Hz), 3.61 (1H, td, $J = 11.6, 2.8$ Hz), 3.46 (1H, m), 3.05 (1H, td, $J = 11.6, 3.2$ Hz), 2.41 (3H, s), 1.80 (2H, t, $J = 6.8$ Hz), 1.24-1.14 (4H, m), 0.81 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 143.6, 134.7, 129.4, 128.5, 87.5, 73.4, 71.6, 66.9, 46.7, 41.9, 30.5, 22.1, 21.7, 18.4, 13.7; ν_{max} (liquid film) 2929, 2859, 2360, 1598, 1444, 1346, 1261, 1167, 1111, 936 cm^{-1} ; MS (ESI): MNa^+ , found 344.3. $C_{17}H_{23}NSO_3$ requires 344.2.

4.6. Propargylic acetates 5a–h

4.6.1. 1-(2-Hydroxyethoxy)-6-phenylhex-3-yn-2-yl acetate (5a)— δ_H (400 MHz, $CDCl_3$) 7.30-7.25 (2H, m), 7.22-7.17 (3H, m), 5.54 (1H, m), 3.71-3.55 (6H, m), 2.80 (2H, td, $J = 7.6, 2.4$ Hz), 2.51-2.46 (2H, m), 2.09 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.3, 140.5, 128.6, 128.5, 126.5, 86.8, 75.6, 72.8, 72.7, 63.4, 61.8, 34.8, 21.2, 21.1; ν_{max} (liquid film) 3455, 2931, 2239, 1741, 1495, 1454, 1371, 1231, 1131, 1037, 946, 748 cm^{-1} ; MS (ESI): MNa^+ , found 299.1. $C_{16}H_{20}O_4$ requires 299.1.

4.6.2. 1-(2-Hydroxyethoxy)-4-phenylbut-3-yn-2-yl acetate (5b)— δ_H (400 MHz, $CDCl_3$) 7.46-7.43 (2H, m), 7.36-7.26 (3H, m), 5.84 (1H, dd, $J = 4.0, 6.8$ Hz), 3.88-3.73 (2H, m), 3.73-3.64 (4H, m), 2.10 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.3, 132.1, 129.1, 128.5, 121.9, 86.6, 83.6, 72.9, 72.7, 63.5, 61.9, 21.2; ν_{max} (liquid film) 3432, 2935, 2229, 1742, 1644, 1491, 1443, 1372, 1226, 1131, 1039, 844, 758, 692 cm^{-1} ; MS (ESI): MNa^+ , found 271.1. $C_{14}H_{16}O_4$ requires 271.1.

4.6.3. 1-(2-Hydroxyethoxy)dec-3-yn-2-yl acetate (5c)— δ_H (400 MHz, $CDCl_3$) 5.55-5.53 (1H, m), 3.69-3.54 (6H, m), 2.31 (1H, *br.* s), 2.15 (2H, td, $J = 7.2, 2.0$ Hz), 2.06 (3H, s), 1.48-1.41 (2H, m), 1.34-1.20 (6H, m), 0.84 (3H, t, $J = 6.0$ Hz); δ_C (75 MHz, $CDCl_3$) 170.2, 87.6, 74.6, 72.8, 72.7, 63.3, 61.6, 31.3, 28.5, 28.3, 22.5, 21.0, 18.7, 14.0; ν_{max} (liquid film) 3440, 2931, 2240, 1745, 1454, 1371, 1230, 1132, 1036 cm^{-1} ; MS (ESI): MNa^+ , found 279.1. $C_{14}H_{24}O_4$ requires 279.1.

4.6.4. 1-(2-Hydroxyethoxy)oct-3-yn-2-yl acetate (5d)— δ_H (400 MHz, $CDCl_3$) 5.55-5.52 (1H, m), 3.69-3.54 (6H, m), 2.34 (1H, *br.* s), 2.18-2.13 (2H, m), 2.06 (3H, s), 1.47-1.39 (2H, m), 1.38-1.29 (2H, m), 0.88-0.83 (3H, m); δ_C (75 MHz, $CDCl_3$) 170.3, 87.7, 74.7, 72.9, 72.8, 63.4, 61.7, 30.5, 22.0, 21.2, 18.5, 13.7; ν_{max} (liquid film) 3448, 2934, 2360, 1743, 1371, 1228, 1131, 1035 cm^{-1} ; MS (ESI): MNa^+ , found 251.1. $C_{12}H_{20}O_4$ requires 251.1.

4.6.5. 1-(2-Hydroxy-2-phenylethoxy)-4-phenylbut-3-yn-2-yl acetate (5e)— δ_H (400 MHz, $CDCl_3$) 7.45–7.25 (10H, m), 5.84 (1H, m), 4.91 (1H, m), 3.86–3.83 (2H, m), 3.75 (1H, m), 3.62–3.51 (1H, m), 2.93 (1H, m), 2.14 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.2, 139.9, 132.1, 129.1, 128.6, 128.5, 128.1, 126.3, 121.9, 86.7, 83.6, 77.6, 72.8, 72.7, 63.5, 21.2; ν_{max} (liquid film) 2913, 1745, 1491, 1443, 1371, 1226, 1129, 1028, 757, 700 cm^{-1} ; MS (ESI): MNa^+ , found 347.1. $C_{20}H_{20}O_4$ requires 347.1.

4.6.6. 1-(2-Hydroxy-2-phenylethoxy)dec-3-yn-2-yl acetate (5f)— δ_H (400 MHz, $CDCl_3$) 7.37–7.25 (5H, m), 5.58 (1H, m), 4.86 (1H, m), 3.73–3.69 (2H, m), 3.66 (1H, dd, $J = 10.0, 3.2$ Hz), 3.49 (1H, m), 2.95 (1H, dd, $J = 6.4, 2.0$ Hz), 2.18 (2H, m), 2.08 (3H, s), 1.48 (2H, m), 1.37–1.22 (6H, m), 0.87 (3H, t, $J = 6.8$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 140.0, 128.6, 128.1, 126.3, 88.0, 74.7, 73.0, 72.8, 72.7, 63.4, 31.4, 28.7, 28.5, 22.7, 21.2, 18.9, 14.2; ν_{max} (liquid film) 2930, 2858, 1743, 1453, 1371, 1230, 1128, 1028, 757, 700 cm^{-1} ; MS (ESI): MH^+ , found 333.2. $C_{20}H_{28}O_4$ requires 333.2.

4.6.7. 1-(2-Hydroxybutoxy)dec-3-yn-2-yl acetate (5g)— δ_H (400 MHz, $CDCl_3$) 5.54 (1H, m), 3.72–3.60 (3H, m), 3.54 (1H, m), 3.32 (1H, m), 2.42 (1H, d, $J = 2.8$ Hz), 2.17 (2H, m), 2.08 (3H, s), 1.48–1.40 (4H, m), 1.36–1.23 (6H, m), 0.93 (3H, t, $J = 6.4$ Hz), 0.86 (3H, t, $J = 6.4$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 87.9, 75.7, 74.8, 73.0, 71.7, 63.4, 31.4, 28.6, 28.4, 26.1, 22.6, 21.2, 18.8, 14.2, 10.0; ν_{max} (liquid film) 2931, 2858, 1744, 1635, 1457, 1371, 1231, 1118, 1039 cm^{-1} ; MS (ESI): M^+ , found 284.2. $C_{16}H_{28}O_4$ requires 284.2.

4.6.8. 1-(2-Hydroxybutoxy)oct-3-yn-2-yl acetate (5h)— δ_H (400 MHz, $CDCl_3$) 5.56–5.53 (1H, m), 3.72–3.59 (3H, m), 3.54 (1H, m), 3.2 (1H, m), 2.42 (1H, *br. s*), 2.18 (2H, m), 2.08 (3H, s), 1.51–1.28 (6H, m), 0.93 (3H, t, $J = 7.2$ Hz), 0.87 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 87.9, 75.7, 73.0, 72.9, 71.7, 63.5, 30.5, 26.1, 22.0, 21.2, 18.5, 13.7, 10.0; ν_{max} (liquid film) 2933, 1747, 1464, 1372, 1231, 1119, 1039 cm^{-1} ; MS (ESI): MNa^+ , found 279.1. $C_{14}H_{24}O_4$ requires 279.1.

4.7. General procedure for the preparation of 3,5-substituted 1,4-dioxanes 6a–h

To a 0.1 M solution of propargylic ester **5a–h** in THF at RT was added $[Cl_2Pt(CH_2CH_2)]_2$ (2.5 mol%). The resulting yellow solution was stirred for 0.5–1.0 h¹³ before being quenched by the addition of NEt_3 (0.5 mL/mmol substrate). The solution was concentrated *in vacuo* and the crude material was filtered through a plug of silica gel.

4.7.1. 2-(4-Phenylbut-1-yn-1-yl)-1,4-dioxane (6a)— δ_H (400 MHz, $CDCl_3$) 7.30–7.27 (2H, m), 7.26–7.18 (3H, m), 4.31–4.28 (1H, m), 3.87–3.76 (2H, m), 3.70–3.55 (3H, m), 3.54–3.49 (1H, m), 2.86–2.81 (2H, m), 2.54–2.48 (2H, m); δ_C (75 MHz, $CDCl_3$) 140.6, 128.6, 128.5, 126.6, 87.0, 76.5, 70.8, 66.6, 66.4, 65.9, 35.1, 21.1; ν_{max} (liquid film) 2962, 2854, 1603, 1453, 1338, 1260, 1119, 1091, 876, 699 cm^{-1} ; MS (ESI): MNa^+ , found 239.0. $C_{14}H_{16}O_2$ requires 239.1.

4.7.2. 2-(Phenylethynyl)-1,4-dioxane (6b)— δ_H (400 MHz, $CDCl_3$) 7.45–7.44 (2H, m), 7.32–7.25 (3H, m), 4.56 (1H, dd, $J = 8.8, 3.2$ Hz), 3.95–3.89 (2H, m), 3.77–3.65 (4H, m); δ_C (75 MHz, $CDCl_3$) 132.0, 128.9, 128.5, 122.2, 86.7, 84.5, 70.6, 66.6, 66.5, 66.0; ν_{max} (liquid film) 2853, 1491, 1443, 1337, 1263, 1119, 1092, 903, 874, 756, 691 cm^{-1} ; MS (ESI): M^+ , found 187.9. $C_{12}H_{12}O_2$ requires 188.0.

4.7.3. 2-(Oct-1-yn-1-yl)-1,4-dioxane (6c)— δ_H (400 MHz, $CDCl_3$) 4.28 (1H, ddd, $J = 8.8, 4.8, 2.4$ Hz), 3.80 (2H, m), 3.68–3.61 (3H, m), 3.50 (1H, dd, $J = 11.2, 8.8$ Hz), 2.18 (2H, td, $J = 7.2, 2.0$ Hz), 1.47 (2H, td, $J = 15.2, 7.2$ Hz), 1.37–1.20 (6H, m), 0.85 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) 87.8, 75.5, 70.9, 66.5, 66.0, 31.4, 28.7, 28.6, 22.7, 18.8, 14.2;

$\nu_{\max}$ (liquid film) 2958, 2885, 2245, 1452, 1337, 1259, 1120, 912, 877 cm^{-1} ; MS (ESI): MH^+ , found 197.1. $\text{C}_{12}\text{H}_{21}\text{O}_2$ requires 197.1.

4.7.4. 2-(Hex-1-yn-1-yl)-1,4-dioxane (6d)— δ_{H} (400 MHz, CDCl_3) 4.28 (1H, ddd, $J = 8.8, 4.8, 2.4$ Hz), 3.86–3.76 (2H, m), 3.69–3.58 (3H, m), 3.50 (1H, dd, $J = 11.2, 8.8$ Hz), 2.19 (2H, td, $J = 7.2, 2.0$ Hz), 1.50–1.45 (2H, m), 1.44–1.34 (2H, m), 0.87 (3H, t, $J = 7.2$ Hz); δ_{C} (75 MHz, CDCl_3) 87.8, 75.5, 70.9, 66.5, 66.0, 30.6, 22.1, 18.5, 13.7; $\nu_{\max}$ (liquid film) 2959, 2856, 2359, 1451, 1336, 1259, 1119, 1092, 915, 874 cm^{-1} ; MS (ESI): MH^+ , found 169.0. $\text{C}_{10}\text{H}_{16}\text{O}_2$ requires 169.1.

4.7.5. 2-Phenyl-6-(phenylethynyl)-1,4-dioxane (6e)— δ_{H} (400 MHz, CDCl_3) 7.49–7.26 (10H, m), 4.80 (1H, dd, $J = 10.4, 2.8$ Hz), 4.72 (1H, dd, $J = 10.4, 2.6$ Hz), 4.03 (1H, dd, $J = 11.5, 2.8$ Hz), 3.87 (1H, dd, $J = 11.7, 2.7$ Hz), 3.70 (1H, *app.* t, $J = 10.8$ Hz), 3.50 (1H, dd, $J = 11.6, 10.8$ Hz); δ_{C} (75 MHz, CDCl_3) 137.4, 132.1, 128.9, 128.6, 128.5, 128.4, 126.7, 122.2, 86.8, 84.1, 78.3, 71.8, 70.0, 67.5; $\nu_{\max}$ (liquid film) 2962, 2852, 1490, 1450, 1311, 1116, 1075, 909, 756, 698 cm^{-1} ; MS (ESI): MH^+ , found 265.0. $\text{C}_{18}\text{H}_{16}\text{O}_2$ requires 265.1.

4.7.6. 2-(Oct-1-yn-1-yl)-6-phenyl-1,4-dioxane (6f)— δ_{H} (400 MHz, CDCl_3) 7.42–7.20 (5H, m), 4.64 (1H, dd, $J = 10.4, 2.8$ Hz), 4.54 (1H, ddd, $J = 10.4, 4.4, 2.0$ Hz), 3.89 (1H, dd, $J = 11.6, 2.8$ Hz), 3.82 (1H, dd, $J = 11.6, 2.8$ Hz), 3.55 (1H, *app.* t, $J = 10.8$ Hz), 3.43 (1H, dd, $J = 10.8, 10.4$ Hz), 2.21 (2H, td, $J = 7.2, 2.0$ Hz), 1.58–1.45 (2H, m), 1.44–1.21 (6H, m), 0.88 (3H, t, $J = 6.8$ Hz); δ_{C} (75 MHz, CDCl_3) 137.6, 128.6, 128.4, 126.7, 88.0, 78.2, 75.3, 71.7, 70.4, 67.4, 31.4, 28.7, 28.5, 22.7, 18.9, 14.2; $\nu_{\max}$ (liquid film) 2957, 2929, 1452, 1305, 1227, 1116, 1075, 911, 754, 698 cm^{-1} ; MS (ESI): MH^+ , found 296.1. $\text{C}_{18}\text{H}_{24}\text{O}_2$ requires 295.1.

4.7.7. 2-Ethyl-6-(oct-1-yn-1-yl)-1,4-dioxane (6g)— δ_{H} (400 MHz, CDCl_3) 4.32 (1H, ddd, $J = 10.4, 4.4, 2.0$ Hz), 3.78 (1H, dd, $J = 11.4, 2.8$ Hz), 3.72–3.64 (1H, m), 3.51–3.43 (1H, m), 3.39 (1H, *app.* t, $J = 10.8$ Hz), 3.20 (1H, *app.* t, $J = 10.8$ Hz), 2.19 (2H, td, $J = 7.2, 2.0$ Hz), 1.56–1.18 (10H, m), 0.93 (3H, t, $J = 7.6$ Hz), 0.87 (3H, t, $J = 6.8$ Hz); δ_{C} (75 MHz, CDCl_3) 87.7, 77.1, 75.4, 70.6, 70.5, 67.0, 31.4, 28.7, 28.5, 24.8, 22.7, 18.9, 14.2, 9.8; $\nu_{\max}$ (liquid film) 2960, 2931, 2853, 1456, 1320, 1101, 1077, 904 cm^{-1} ; MS (ESI): MH^+ , found 247.1. $\text{C}_{14}\text{H}_{24}\text{O}_2$ requires 247.1.

4.7.8. 2-Ethyl-6-(hex-1-yn-1-yl)-1,4-dioxane (6h)— δ_{H} (400 MHz, CDCl_3) 4.32 (1H, d, $J = 10.4$ Hz), 3.78 (1H, dd, $J = 11.2, 2.8$ Hz), 3.69 (1H, m), 3.50–3.40 (1H, m), 3.39 (1H, *app.* t, $J = 10.8$ Hz), 3.20 (1H, t, $J = 10.8$ Hz), 2.20 (2H, t, $J = 7.2$ Hz), 1.55–1.23 (6H, m), 0.93 (3H, t, $J = 7.5$ Hz), 0.88 (3H, t, $J = 7.3$ Hz); δ_{C} (75 MHz, CDCl_3) 87.7, 77.1, 75.5, 70.6, 70.5, 67.0, 30.7, 24.8, 22.2, 18.7, 13.8, 9.9; $\nu_{\max}$ (liquid film) 2961, 2933, 2853, 1464, 1320, 1101, 1077, 909 cm^{-1} ; MS (ESI): MH^+ , found 197.0. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires 197.1.

4.8. Propargylic acetates 7a–g

4.8.1. 7-Phenyl-1-(sulfamoyloxy)hept-4-yn-3-yl acetate (7a)— δ_{H} (500 MHz, CDCl_3) 7.33–7.27 (2H, m), 7.25–7.21 (3H, m), 5.49 (1H, t, $J = 7.0$ Hz), 5.04 (2H, s), 4.25 (2H, m), 2.83 (2H, t, $J = 7.0$ Hz), 2.52 (2H, td, $J = 7.5, 1.5$ Hz), 2.22–2.07 (2H, m), 2.09 (3H, s); δ_{C} (125 MHz, CDCl_3) 170.6, 140.6, 128.8, 128.7, 126.7, 105.0, 86.9, 67.1, 61.3, 34.8, 34.4, 21.3, 21.0; $\nu_{\max}$ (liquid film) 3335, 3281, 2933, 2246, 1728, 1559, 1372, 1241, 1183, 1020, 931, 751, 700 cm^{-1} ; MS (ESI): MNa^+ , found 348.0. $\text{C}_{15}\text{H}_{19}\text{NSO}_5$ requires 348.0.

4.8.2. 1-Phenyl-5-(sulfamoyloxy)pent-1-yn-3-yl acetate (7b)— δ_{H} (400 MHz, CDCl_3) 7.44–7.41 (2H, m), 7.33–7.25 (3H, m), 5.74 (1H, t, $J = 6.4$ Hz), 5.34 (2H, s), 4.36

(2H, m), 2.34-2.23 (2H, m), 2.10 (3H, s); δ_C (125 MHz, $CDCl_3$) 170.6, 132.0, 129.1, 128.5, 121.8, 86.4, 85.1, 66.9, 61.3, 34.2, 21.1; ν_{max} (liquid film) 3281, 2234, 1731, 1557, 1491, 1372, 1237, 1183, 1022, 932, 759 cm^{-1} ; MS (ESI): MNa^+ , found 319.9. $C_{13}H_{15}NSO_5$ requires 320.0.

4.8.3. 8-Phenyl-2-(sulfamoyloxy)oct-5-yn-4-yl acetate (7c)— δ_H (400 MHz, $CDCl_3$) 7.30-7.25 (2H, m), 7.21-7.18 (3H, m), 5.34-5.29 (1H, m), 5.06-4.98 (1H, m), 4.82 (2H, s), 2.82 (2H, t, $J = 7.6$ Hz), 2.49 (2H, td, $J = 8.0, 2.0$ Hz), 2.10 (1H, ddd, $J = 10.6, 8.8, 6.4$ Hz), 2.02 (3H, s), 1.81 (1H, ddd, $J = 10.6, 8.8, 6.4$ Hz), 1.25 (3H, d, $J = 6.0$ Hz); δ_C (75 MHz, $CDCl_3$) 170.7, 140.6, 128.6, 128.5, 126.5, 86.5, 77.7, 68.1, 62.8, 41.2, 34.9, 21.5, 21.1, 20.3; ν_{max} (liquid film) 2360, 1722, 1371, 1243, 1043, 668 cm^{-1} ; MS (ESI): MNa^+ , found 361.9. $C_{16}H_{21}NSO_5$ requires 362.1.

4.8.4. 1-Phenyl-5-(sulfamoyloxy)hex-1-yn-3-yl acetate (7d)— δ_H (400 MHz, $CDCl_3$) 7.45-7.40 (2H, m), 7.35-7.15 (3H, m), 5.73 (1H, dd, $J = 8.0, 6.0$ Hz), 5.12 (2H, s), 4.98-4.90 (1H, m), 2.38-2.27 (1H, m), 2.15-2.03 (1H, m), 2.08 (3H, s), 1.53 (3H, d, $J = 6.8$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 132.1, 129.2, 128.6, 121.7, 86.7, 85.4, 77.6, 61.8, 41.5, 21.3, 21.2; ν_{max} (liquid film) 3277, 2360, 1729, 1491, 1370, 1239, 1183, 1023, 918, 759, 692 cm^{-1} ; MS (ESI): MNa^+ , found 333.9. $C_{14}H_{17}NSO_5$ requires 334.1.

4.8.5. 2-(Sulfamoyloxy)dodec-5-yn-4-yl acetate (7e)— δ_H (400 MHz, $CDCl_3$) 5.50-5.45 (1H, m), 4.95 (2H, s), 4.90-4.82 (1H, m), 2.26-2.18 (3H, m), 2.07 (3H, s), 1.95 (1H, ddd, $J = 12.4, 8.8, 4.4$ Hz), 1.53-1.45 (2H, m), 1.48 (3H, d, $J = 6.4$ Hz), 1.38-1.24 (6H, m), 0.87 (3H, t, $J = 6.4$ Hz); δ_C (75 MHz, $CDCl_3$) 170.3, 88.2, 77.9, 76.8, 61.8, 41.8, 31.4, 28.7, 28.5, 22.7, 21.4, 21.3, 18.8, 14.2; ν_{max} (liquid film) 3374, 2927, 2360, 1729, 1457, 1370, 1239, 1182, 1023, 923, 668 cm^{-1} ; MS (ESI): MNa^+ , found 342.1. $C_{14}H_{25}NSO_5$ requires 342.1.

4.8.6. 1-((tert-Butyldiphenylsilyl)oxy)-2-(sulfamoyloxy)dodec-5-yn-4-yl acetate (7f)— δ_H (400 MHz, $CDCl_3$) 7.78-7.55 (m, 4H), 7.42 (6H, m), 5.48 (1H, m), 4.81 (3H, m), 3.87 (2H, d, $J = 4.4$ Hz), 2.32 – 2.08 (4H, m), 2.02 (3H, s), 1.56-1.40 (2H, m), 1.43-1.17 (6H, m), 1.06 (9H, s), 0.87 (3H, t, $J = 7.2$ Hz); δ_C (75 MHz, $CDCl_3$) δ 170.0, 135.8, 135.7, 133.0, 132.7, 130.25, 130.22, 128.1, 88.1, 80.9, 76.6, 65.4, 61.8, 36.8, 31.4, 28.7, 28.5, 27.0, 22.7, 21.2, 19.4, 18.8, 14.2; ν_{max} (liquid film) 3279, 2930, 2857, 1730, 1427, 1370, 1236, 1185, 1112, 933, 702 cm^{-1} ; MS (ESI): M^+ , found 573.2. $C_{30}H_{43}NO_6SSi$ requires 573.2.

4.8.7. 6-((tert-Butyldiphenylsilyl)oxy)-1-phenyl-5-(sulfamoyloxy)hex-1-yn-3-yl acetate (7g)— δ_H (400 MHz, $CDCl_3$) 7.78-7.57 (4H, m), 7.52-7.20 (11H, m), 5.89-5.62 (1H, dd, $J = 6.8, 6.0$ Hz), 4.91 (2H, s), 4.88 (1H, dd, $J = 7.6$ Hz, 4.8 Hz), 3.91 (2H, d, $J = 4.8$ Hz), 2.45 – 2.21 (2H, m), 2.05 (3H, s), 1.08 (9H, s); δ_C (75 MHz, $CDCl_3$) 170.0, 135.9, 135.7, 133.0, 132.7, 132.1, 130.26, 130.24, 129.1, 128.5, 128.1, 121.9, 86.7, 85.4, 80.6, 65.4, 61.8, 36.6, 27.0, 21.2, 19.4; ν_{max} (liquid film) 3389, 2931, 1731, 1428, 1371, 1233, 1186, 1113, 1022, 922, 758 cm^{-1} ; MS (ESI): MNa^+ , found 588.5. $C_{30}H_{35}NSiSO_6$ requires 588.2.

4.9. General procedure for the preparation of 2,6-substituted morpholines 8a–g

To a 0.1 M solution of sulfamate **7a–g** in THF at RT was added $[Cl_2Pt(CH_2CH_2)]_2$ (2.5 mol %). The resulting yellow solution was stirred for 0.5–5.0 h¹³ before being quenched by the addition of NEt_3 (0.5 mL/mmol substrate). The solution was concentrated *in vacuo* and the crude material was filtered through a plug of silica gel.

4.9.1. 4-(4-Phenylbut-1-yn-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (8a)— δ_H (400 MHz, CDCl_3) 7.32-7.24 (2H, m), 7.23-7.18 (3H, m), 4.67 (1H, td, $J = 12.0, 2.8$ Hz), 4.51-4.47 (2H, m), 4.10 (1H, d, $J = 10.4$ Hz), 2.80 (2H, t, $J = 7.2$ Hz), 2.49 (2H, *app.* td, $J = 7.2, 1.6$ Hz), 2.04-1.88 (2H, m); δ_C (75 MHz, CDCl_3) 140.3, 128.6, 128.5, 126.6, 86.4, 76.0, 71.4, 47.8, 34.6, 31.2, 20.8; ν_{max} (liquid film) 3268, 2360, 2089, 1651, 1417, 1368, 1188, 1061, 1012, 781 cm^{-1} ; MS (ESI): M-H^- , found 264.0. $\text{C}_{13}\text{H}_{15}\text{NSO}_3$ requires 264.0.

4.9.2. 4-(Phenylethynyl)-1,2,3-oxathiazinane 2,2-dioxide (8b)— δ_H (400 MHz, CDCl_3) 7.43-7.41 (2H, m), 7.38-7.30 (3H, m), 4.80-4.71 (2H, m), 4.56 (1H, ddd, $J = 12.0, 4.8, 2.0$ Hz), 4.49 (1H, d, $J = 9.2$ Hz), 2.25-2.14 (1H, m), 2.09-2.03 (1H, m); δ_C (75 MHz, CDCl_3) 132.0, 129.4, 128.6, 121.5, 86.1, 84.1, 71.5, 48.2, 30.9; ν_{max} (liquid film) 3263, 2360, 1491, 1420, 1373, 1189, 1064, 1002, 934, 874, 783, 758, 691 cm^{-1} ; MS (ESI): M-H^- , found 235.9. $\text{C}_{11}\text{H}_{11}\text{NSO}_3$ requires 236.0.

4.9.3. 6-Methyl-4-(4-phenylbut-1-yn-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (8c)— δ_H (400 MHz, CDCl_3) 7.32-7.28 (2H, m), 7.25-7.18 (3H, m), 4.84-4.76 (1H, m), 4.43 (1H, *app.* td, $J = 10.0, 2.0$ Hz), 4.02 (1H, d, $J = 10.4$ Hz), 2.80 (2H, t, $J = 7.2$ Hz), 2.48 (2H, td, $J = 7.2, 2.0$ Hz), 1.96 (1H, dt, $J = 17.5, 2.0$ Hz), 1.70-1.58 (1H, m), 1.40 (3H, d, $J = 6.4$ Hz); δ_C (75 MHz, CDCl_3) 140.3, 128.6, 126.7, 86.2, 80.2, 76.6, 47.2, 38.5, 34.7, 21.1, 20.8; ν_{max} (liquid film) 2388, 1414, 1360, 1189, 1069, 867, 700 cm^{-1} ; MS (ESI): MNa^+ , found 301.8. $\text{C}_{14}\text{H}_{17}\text{NSO}_3$ requires 302.0.

4.9.4. 6-Methyl-4-(phenylethynyl)-1,2,3-oxathiazinane 2,2-dioxide (8d)— δ_H (400 MHz, CDCl_3) 7.42-7.37 (2H, m), 7.36-7.25 (3H, m), 4.93-4.85 (1H, m), 4.73 (1H, *app.* t, $J = 10.0$ Hz), 4.22 (1H, d, $J = 10.0$ Hz), 2.14 (1H, m), 1.86 (1H, dt, $J = 14.4, 12.0$ Hz), 1.45 (3H, d, $J = 6.4$ Hz); δ_C (75 MHz, CDCl_3) 132.0, 129.4, 128.6, 121.5, 86.0, 84.1, 80.3, 47.6, 38.2, 21.2; ν_{max} (thin film) (cm^{-1}) 3254, 2360, 1422, 1365, 1189, 1076, 929, 865, 758; MS (ESI): M^+ , found 250.9. $\text{C}_{12}\text{H}_{13}\text{NSO}_3$ requires 251.0.

4.9.5. 6-Methyl-4-(oct-1-yn-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (8e)— δ_H (400 MHz, CDCl_3) 4.81 (1H, m), 4.45 (1H, m), 4.06 (1H, d, $J = 10.0$ Hz), 2.16 (2H, td, $J = 7.2, 2.0$ Hz), 2.01 (1H, dt, $J = 14.4, 2.4$ Hz), 1.69 (1H, dt, $J = 14.8, 12.0$ Hz), 1.50-1.45 (2H, m), 1.44 (3H, d, $J = 6.8$ Hz), 1.37-1.20 (6H, m), 0.88 (3H, t, $J = 6.8$ Hz); δ_C (75 MHz, CDCl_3) 87.1, 80.2, 75.6, 47.3, 38.6, 31.4, 28.6, 28.4, 22.7, 21.1, 18.7, 14.2; ν_{max} (liquid film) 2931, 2359, 1415, 1363, 1190, 1070, 869 cm^{-1} ; MS (ESI): M^+ , found 259.0. $\text{C}_{12}\text{H}_{21}\text{NSO}_3$ requires 259.1.

4.9.6. 6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-(oct-1-yn-1-yl)-1,2,3-oxathiazinane 2,2-dioxide (8f)— δ_H (500 MHz, CDCl_3) 7.82-7.59 (4H, m), 7.58-7.35 (6H, m), 4.77 (1H, m), 4.51 (1H, *app.* t, $J = 10.0$ Hz), 4.09 (1H, d, $J = 10.0$ Hz), 3.79 (2H, d, $J = 4.5$ Hz), 2.20 (2H, td, $J = 17.0, 8.5$ Hz), 2.04 (1H, dt, $J = 14.5, 2.5$ Hz), 1.92 (1H, dt, $J = 14.5, 12.0$ Hz), 1.56-1.47 (2H, m), 1.45-1.22 (6H, m), 1.08 (9H, s), 0.91 (3H, t, $J = 7.0$ Hz); δ_C (125 MHz, CDCl_3) 135.8, 135.7, 132.8, 132.7, 130.2, 128.1, 128.0, 87.3, 82.9, 75.8, 65.1, 47.2, 33.5, 31.4, 28.6, 28.4, 26.9, 22.7, 19.4, 18.7, 14.2; ν_{max} (liquid film) 2927, 2855, 1718, 1427, 1374, 1191, 1113, 1067, 823, 702 cm^{-1} ; MS (ESI): M^+ , found 513.1. $\text{C}_{28}\text{H}_{39}\text{NSSiO}_4$ requires 513.2.

4.9.7. 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-(phenylethynyl)-1,2,3-oxathiazinane 2,2-dioxide (8g)— δ_H (500 MHz, CDCl_3) 7.88-7.60 (4H, m), 7.55-7.32 (11H, m), 4.96-4.64 (2H, m), 4.24 (1H, d, $J = 10.5$ Hz), 3.81 (2H, *br.* d, $J = 4.5$ Hz), 2.24-2.12 (1H, m), 2.06 (1H, m), 1.10 (9H, s); δ_C (125 MHz, CDCl_3) 135.85, 135.81, 132.8, 132.7, 132.09, 132.07, 130.2, 129.4, 128.7, 128.14, 128.13, 121.5, 86.1, 84.2, 83.0, 65.2,

47.5, 33.2, 27.0, 19.5; ν_{max} (liquid film) 3272, 2931, 1427, 1377, 1192, 1113, 1072, 873, 824, 702 cm^{-1} ; MS (ESI): M^+ , found 505.0. $\text{C}_{28}\text{H}_{31}\text{NSSiO}_4$ requires 505.2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Justin Du Bois (Stanford University) for suggesting our propargylic substitutions as an entry towards cyclic sulfamates, and Mina Razzak (UTSW) for help with preparing this manuscript. Financial support was provided by the Robert A. Welch Foundation (Grant I-1422), Reata Pharmaceuticals, and the NIH (Grant CA90349).

References

- For selected reviews and examples see: (a) Kumar K, Waldmann H. *Angew. Chem. Int. Ed.* 2009; 48:3224–3242. (b) Nicolaou KC, Chen JS. *Pure Appl. Chem.* 2008; 80:727–742. (c) Elliot MC. *J. Chem. Soc., Perkin Trans. 1.* 2000:1291–1318. (d) Sromek AW, Kel'in AV, Gevorgyan V. *Angew. Chem. Int. Ed.* 2004; 43:2280–2282. (e) Zhang L. *J. Am. Chem. Soc.* 2005; 127:16804–16805. [PubMed: 16316224]
- (a) De Brabander JK, Liu B, Qian M. *Org. Lett.* 2008; 10:2533–2536. [PubMed: 18505261] For a cycloisomerization strategy towards spiroketals, tetrahydrofuran, and tetrahydropyran acetals from our laboratory, see: (b) Liu B, De Brabander JK. *Org. Lett.* 2006; 8:4907–4910. [PubMed: 17020333]
- In an important precedent, it was demonstrated that replacement of the tetrahydropyran B-ring of the bryostatins with a dioxane heterocycle not only significantly improved synthetic access, but also provided analogs with equal or superior biological activity, see: Wender PA, DeBrabander J, Harran PG, Jimenez J-M, Koehler MFT, Lippa B, Park C-M, Shiozaki M. *J. Am. Chem. Soc.* 1998; 120:4534–4535.
- (a) Fish PV, Deur G, Gan X, Greene K, Hoople D, Mackenny M, Para KS, Reeves K, Ryckmans T, Stiff C, Stobie A, Wakenhut F, Whitlock GA. *Bioorg. Med. Chem. Lett.* 2008; 18:2562–2566. [PubMed: 18387300] (b) Kelley JL, Musso DL, Boswell GE, Soroko FE, Cooper BR. *J. Med. Chem.* 1996; 39:347–349. [PubMed: 8558500]
- Kuettel S, Zamboni A, Kaiser M, Brun R, Scapozza L, Perozzo R. *J. Med. Chem.* 2007; 50:5833–5839. [PubMed: 17949068]
- (a) Allison BD, Phuong VK, McAtee LC, Rosen M, Morton M, Prendergast C, Barrett T, Lagaud G, Freedman J, Li L, Wu X, Venkatesan H, Pippel M, Woods C, Rizzolio MC, Hack M, Hoey K, Deng X, King C, Shankley NP, Rabinowitz MH. *J. Med. Chem.* 2006; 49:6371–6390. [PubMed: 17034143] (b) Kim DK, Ryu DH, Lee JY, Lee N, Kim YW, Kim JS, Chang K, Im GJ, Kim TK, Choi WS. *J. Med. Chem.* 2001; 44:1594–1602. [PubMed: 11334569] (c) Acton EM, Tong GL, Mosher CW, Wolgemuth RL. *J. Med. Chem.* 1984; 27:638–640. [PubMed: 6716401]
- Chrysselis MC, Rekka EA, Siskou IC, Kourounakis PN. *J. Med. Chem.* 2002; 45:5406–5409. [PubMed: 12431068]
- Hale JJ, Mills SG, MacCoss M, Shah SK, Qi H, Mathre DJ, Cascieri MA, Sadowski S, Strader CD, MacIntyre DE, Metzger JM. *J. Med. Chem.* 1996; 39:1760–1762. [PubMed: 8627597]
- Letnicer, D. *Organic Chemistry of Drug Synthesis*. Vol. vol. 7. New York: Wiley; 2008.
- (a) Pettigrew JD, Freeman RR, Wilson PD. *Can. J. Chem.* 2004; 82:1640–1648. (b) Dave R, Sasaki NA. *Tetrahedron: Asymmetry*. 2006; 17:388–401.
- For selected recent examples, see: (a) Bandini M, Monari M, Romaniello A, Tragni M. *Chem. Eur. J.* 2010; 16:14272–14277. (b) Leathen ML, Rosen BR, Wolfe JP. *J. Org. Chem.* 2009; 74:5107–5110. [PubMed: 19480462] (c) Nonnenmacher J, Grellepois F, Portella C. *Eur. J. Org. Chem.* 2009:3726–3731. (d) Yar M, McGarrigle EM, Aggarwal VK. *Org. Lett.* 2009; 11:257–260. [PubMed: 19072319] (e) Breuning M, Hein D, Steiner M, Gessner VH, Strohmman C. *Chem. Eur. J.* 2009; 15:12764–12769. (f) Penso M, Lupi V, Albanese D, Foschi F, Landini D, Tagliabue A.

- Synlett. 2008;2451–2454. (g) Leijondahl K, Boren L, Braun R, Bäckvall J-E. *Org. Lett.* 2008; 10:2027–2030. [PubMed: 18402460] (h) Wilkinson MC, Bell R, Landon R, Nikiforov PO, Walker AJ. *Synlett.* 2006;2151–2153. (i) D'hooghe MD, Vanlangendonck T, Törnroos KW, De Kimpe N. *J. Org. Chem.* 2006; 71:4678–4681. [PubMed: 16749806] (j) Lanman BA, Myers AG. *Org. Lett.* 2004; 6:1045–1047. [PubMed: 15012096] (k) Dave R, Sasaki NA. *Org. Lett.* 2004; 6:15–18. [PubMed: 14703339] (l) Grotenberg GM, Christina AE, Buizert AEM, van der Marel GA, Overkleeft HS, Overhead M. *J. Org. Chem.* 2004; 69:8331–8339. [PubMed: 15549804] (m) Tiecco M, Testaferri L, Marini F, Sternativo S, Santi C, Bagnoli L, Temperini A. *Tetrahedron: Asymmetry.* 2003; 14:2651–2657. (n) Takahata H, Takahashi S, Kouno S-i, Momose T. *J. Org. Chem.* 1998; 63:2224–2231. (o) Lai J-Y, Shi X-X, Gong Y-S, Dai L-X. *J. Org. Chem.* 1993; 58:4775–4777.
12. For a review see: Wijtmans R, Vink MKS, Schoemaker HE, van Delft FL, Blaauw RH, Rutjes FPJT. *Synthesis.* 2004:641–662.
13. See the Supplementary Information for details.
14. For a detailed study on propargylic ester/ allenyl ester epimerization, see: Schlossarczyk H, Sieber W, Hesse M, Hansen H-J, Schmid H. *Helv. Chim. Acta.* 1973; 56:875–944.
15. As for all propargylic substitutions reported herein, diastereomeric mixtures of starting materials (equimolar ratios) always converged to single diastereomeric products *via* a dynamic kinetic resolution. See equation 1 for a potential mechanism for epimerization at the propargylic center.
16. Correa A, Marion N, Fensterbank L, Malacria M, Nolan SP, Cavallo L. *Angew. Chem. Int. Ed.* 2008; 47:718–721.
17. *N*-Boc-protected amines were not effective substrates.
18. Aubè J, Mossman CJ, Dickey S. *Tetrahedron.* 1992; 48:9819–9826.
19. Concellón JM, Bernad PL, del Solar V, García-Grandam S, Díaz MR. *Adv. Synth. Catal.* 2008; 350:477–481.
20. Tiecco M, Testaferri L, Marini F, Sternativo S, Santi C, Bagnoli L, Temperini A. *Tetrahedron: Asymmetry.* 2003; 14:1095–1102.
21. Braun A, Toupet L, Lellouche J-P. *J. Org. Chem.* 1996; 61:1914–1915.
22. Takekawa, I.; Nukata, H.; Nakamura, H.; Miyamoto, M. Japanese Patent. 10,265,564. 1998. *Chem. Abstr.* **1998**, 129, 337617
23. Conrad, J.; Schaper, UA.; Bruns, K. German Patent. 2,629,000. 1978. *Chem. Abstr.* **1978**, 89, 80129
24. Lee JY, Park YK, Seo SH, Yang BS, Park H, Lee YS. *Arch. Pharm.* 2002; 335:487–494.
25. Kim HY, Kuhn RJ, Patkar C, Warriar R, Cushman M. *Bioorg. Med. Chem.* 2007; 15:2667–2679. [PubMed: 17287124]
26. (a) Piergentili A, Quaglia W, Giannella M, Del Bello F, Bruni B, Buccioni M, Carrieri A, Ciattini S. *Bioorg. Med. Chem.* 2007; 15:886–896. [PubMed: 17084634] (b) Tarselli MA, Zuccarello JL, Lee SJ, Gagné MR. *Org. Lett.* 2009; 11:3490–3492. [PubMed: 19588972] (c) Quaglia W, Piergentili A, Del Bello F, Farande Y, Giannella M, Pigni M, Rafaiani G, Carrieri A, Amantini C, Lucciarini R, Santoni G, Poggesi E, Leonardi A. *J. Med. Chem.* 2008; 51:6359–6370. [PubMed: 18817363]
27. Dauban P, Dodd RH. *Tetrahedron Lett.* 2001; 42:1037–1040.
28. Wehn PM, Du Bois J. *Org. Lett.* 2005; 7:4685–4688. [PubMed: 16209510]
29. Fleming JJ, McReynolds MD, Du Bois J. *J. Am. Chem. Soc.* 2007; 129:9964–9975. [PubMed: 17658800]
30. Wang Y-Q, Yu C-B, Wang D-W, Wang X-B, Zhou Y-G. *Org. Lett.* 2008; 10:2071–2074. [PubMed: 18426218]
31. Still WC, Kahn M, Mitra A. *J. Org. Chem.* 1978; 43:2923–2925.
32. Gottlieb HE, Kotlyar V, Nudelman A. *J. Org. Chem.* 1997; 62:7512–7515. [PubMed: 11671879]

Figure. 1.
Pt(II)-catalyzed propargylic substitution

Table 1

Formation of 2,6-disubstituted morpholines **2^a**

Entry	Substrate	R ¹	R ²	Yield ^b	cis:trans ^c
1	1a	PhCH ₂ CH ₂	H	85	-
2	1b	PhCH ₂ CH ₂	Et	82	13:1
3	1c	PhCH ₂ CH ₂	<i>i</i> -Pr	86	10:1
4	1d	PhCH ₂ CH ₂	Ph	88	14:1
5	1e	Ph	H	88	-
6	1f	Ph	Ph	85	20:1
7	1g	CH ₃ (CH ₂) ₅	H	84	-
8	1h	CH ₃ (CH ₂) ₅	Et	98	10:1
9	1i	CH ₃ (CH ₂) ₃	H	87	-

^a Reaction conditions: propargylic acetate (0.1 M in THF), 2.5 mol% [Cl₂Pt(CH₂H₂)₂]₂, RT.^b Isolated yield (%).^c Determined by ¹H NMR spectroscopy.

Table 2

Formation of 3-substituted morpholines **4**^a

Entry	Substrate	R ¹	Yield ^b
1	3a	Ph	65
2	3b	PhCH ₂ CH ₂	76
3	3c	CH ₃ (CH ₂) ₅	74
4	3d	CH ₃ (CH ₂) ₃	71

^a Reaction conditions: propargylic acetate (0.1 M in THF), 2.5 mol% $[\text{Cl}_2\text{Pt}(\text{CH}_2\text{CH}_2)_2]_2$, RT.^b Isolated yield (%).

Table 3

Formation of 2,6-disubstituted-1,4-dioxanes **6**^a

Entry	Substrate	R ¹	R ²	Yield ^b	cis:trans ^c
1	5a	PhCH ₂ CH ₂	H	86	-
2	5b	Ph	H	88	-
3	5c	CH ₃ (CH ₂) ₅	H	85	-
4	5d	CH ₃ (CH ₂) ₃	H	87	-
5	5e	Ph	Ph	89	14:1
6	5f	CH ₃ (CH ₂) ₅	Ph	90	19:1
7	5g	CH ₃ (CH ₂) ₅	Et	85	14:1
8	5h	CH ₃ (CH ₂) ₃	Et	85	14:1

^a Reaction conditions: propargylic acetate (0.1 M in THF), 2.5 mol% [Cp₂Pt(CH₂H₂)₂]₂, RT.

^b Isolated yield (%).

^c Determined by ¹H NMR spectroscopy.

Table 4

Formation of cyclic sulfamates **8**^a

Entry	R ¹	R ²	Yield ^b	cis:trans ^c
1	7a PhCH ₂ CH ₂	H	88	-
2	7b Ph	H	85	-
3	7c PhCH ₂ CH ₂	CH ₃	81	22:1
4	7d Ph	CH ₃	82	25:1
5	7e CH ₃ (CH ₂) ₅	CH ₃	82	20:1
6	7f CH ₃ (CH ₂) ₅	CH ₂ OTBDPS	84	25:1
7	7g Ph	CH ₂ OTBDPS	84	20:1

^a Reaction conditions: propargylic acetate (0.1 M in THF), 2.5 mol% [Cl₂Pt(CH₂H₂)₂]₂, RT.^b Isolated yield (%).^c Determined by ¹H NMR spectroscopy.