Org Lett. Author manuscript; available in PMC 2011 May 7.

Published in final edited form as:
Org Lett. 2010 May 7; 12(9): 2084–2087. doi:10.1021/ol100574y.

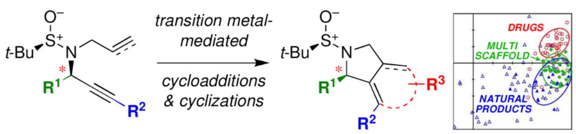
The *t*-Butylsulfinamide Lynchpin in Transition Metal-Mediated Multiscaffold Library Synthesis

Renato A. Bauer[†], **Christine M. DiBlasi**[‡], and **Derek S. Tan**[*,†,‡]

[†]Tri-Institutional Training Program in Chemical Biology, Tri-Institutional Research Program, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065

[‡]Molecular Pharmacology and Chemistry Program, Tri-Institutional Research Program, Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065

Abstract



A unified synthetic approach to diverse polycyclic scaffolds has been developed using transition metal-mediated cycloaddition and cyclization reactions of enynes and diynes. The *t*-butylsulfinamide group has been identified as a particularly versatile lynchpin in these reactions, with a reactivity profile uniquely suited for efficient, stereoselective substrate synthesis and downstream transformations. This approach provides ten distinct, functionalized scaffold classes related to common core structures in alkaloid and terpenoid natural products.

Polycyclic alkaloid and terpenoid natural products exhibit a tremendous array of chemical scaffolds and biological activities.[1,2] Accordingly, these structures are attractive targets for the synthesis of natural product-based libraries.[3] Ideally, a concise, unified synthetic route would provide an array of distinct, polycyclic scaffolds for use in discovery screening against a wide range of targets. The synthesis of such multiscaffold libraries remains a major challenge in diversity-oriented synthesis.[4,5] We envisioned that the modern arsenal of transition-metal mediated cycloaddition and cyclization reactions[6,7] would provide a powerful means to generate such libraries from simple tethered enyne and diyne substrates. We report herein the development of a unified synthetic approach leading to ten classes of polycyclic scaffolds, and the emergence of the *t*-butylsulfinamide moiety[8] as a versatile lynchpin for these reactions, affording uniquely suited reactivity and a novel motif for biological evaluation.

To identify transition metal-mediated cycloaddition and cyclization reactions suitable for diversity-oriented synthesis, we set out to evaluate candidate reactions systematically across a panel of substrates having electronically and sterically distinct groups at sites expected to influence reactivity. This would also provide broad insights into the scope and efficiency of these reactions.

To assemble the requisite enyne and diyne substrates, we initially investigated ether, carbamate (*N*-Boc), and sulfonamide (*N*-Ts, *N*-Ns) tethers. After extensive experimentation, the *t*-

tand@mskcc.org.

Supporting Information Available: Detailed experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

butylsulfinamide[8] emerged as a uniquely suited lynchpin. This group provides asymmetric induction during substrate assembly, can be readily deprotonated and *N*-alkylated, does not exhibit rotamers on the NMR timescale, and can be deprotected or oxidized under mild conditions. The *t*-butylsulfinamide is also a novel motif for biological evaluation, related to sulfonamides in synthetic drugs and natural products. Notably, although a picture of compatibility of the *t*-butylsulfinamide with metal catalysts is beginning to emerge,[9] its stability and reactivity in transition metal-mediated cycloadditions and cyclizations has not yet been explored in detail.

Thus, synthesis of enynes **4** and diynes **5** began with condensation of aldehyde **1** and (*R*)-*t*-butylsulfinamide (Scheme 1). The R^1 sidechain was designed with a TPDPS-protected alcohol as a potential handle for later functionalization and as a mimic of our reported TBDAS linker for future solid phase syntheses.[10] Diastereoselective addition of terminal alkynes afforded sulfinamides **3a–c**.[11] *N*-Alkylation with allyl and propargyl bromide was achieved efficiently using *n*-BuLi/ HMPA to afford enynes **4a–c** and diynes **5a–c**.[12] *C*-desilylation of TMS-alkynes **4c** and **5c** then provided terminal alkynes **4d** and **5d**. Additional functionalized alkenes and alkynes can be envisioned to provide an even broader assessment of reactivity trends in the future.

With gram quantities of enynes **4** and diynes **5** in hand, we evaluated their reactivities in various transition metal-mediated reactions. Initial experiments with Au and Ag π-acids (Group 11) commonly used in such reactions[13] resulted in decomposition, possibly initiated by sulfinamide cleavage. In contrast, these substrates were compatible with a variety of Ru, Co, Rh, and Ni catalysts (Groups 8–10), and, after investigation of over 25 different reactions, eight were identified as having suitable selectivity and efficiency for use in library synthesis (Scheme 2).

The venerable Pauson–Khand reaction[12b,14] was effective for all four enynes **4a–d**, providing [5,5]-bicyclic cyclopentapyrrolidinone scaffolds **6a–d** (Table 1). Krische's Rh-catalyzed reductive enyne cyclization[15] provided excellent yields of *exo*-pyrroline scaffolds **7a,b,d**, with reagent-controlled diastereoselectivity for the internal alkynes **4a,b**, while the TMS-alkyne **4c** was unreactive under these conditions. Evans' Rh-catalyzed butadiene [4+2+2] cycloaddition also proved useful;[16] while enynes **4** underwent AgOTf-induced sulfinamide cleavage under the reaction conditions, consistent with our earlier findings, the reaction proceeded effectively after oxidation to the corresponding *t*-butylsulfonamides, affording [5,8]-bicyclic cyclooctapyrrolidine scaffolds **8a–d** in moderate yields but complete diastereoselectivity. Enyne metathesis of **4** with Grubbs' 2nd generation catalyst[17] led to vinylpyrrolines **9a,b,d**; the TMS-alkyne **4c** was again unreactive. Interestingly, the diene products **9** proved recalcitrant to subsequent Diels–Alder reactions with numerous dienophiles.[18,19] However, these reactions could be achieved after oxidation to the corresponding *t*-butylsulfonamides; subtle conformational effects may account for this reactivity difference. Thus, reactions with *N*-phenylmaleimide provided [5,6,5]-tricyclic benzodipyrrolidine scaffolds **10a,b,d**.[1] Reactions with dimethylacetylene dicarboxylate (DMAD) afforded diastereomeric mixtures that converged conveniently to [5,6]-bicyclic isoindoline dicarboxylate scaffolds **11a,b,d** upon oxidation with DDQ.[1]

Several effective transition metal-mediated cycloaddition reactions were also identified for diynes **5a–d**. While [2+2+2]-cyclotrimerization with various alkynes using reported Rh(I), Ni(0), or Ir(I) catalysts[20] suffered from poor regioselectivity and competing dimerization, treatment of **5a–d** with Grubbs' 1st generation catalyst[21] and propargyl alcohol yielded [5,6]-bicyclic isoindoline scaffolds **12a–d** efficiently (Table 2). The reactions were regioselective, except in the case of the pseudosymmetric substrate **5d**, and regioisomers were readily separated in all cases. Diynes **5a–d** also cyclotrimerized with benzyl isocyanate under the agency of Yamamoto's Ru(II) catalyst[22] to provide [5,6]-bicyclic pyrrolopyridone scaffolds

13a–d, and regioisomeric products were again readily separated. No other transition metals were found to catalyze this reaction. Cyclotrimerizations of **5a–d** with ethyl cyanoformate proceeded effectively using Tanaka's Rh(I) catalyst[23] to afford [5,6]-bicyclic pyrrolopyridine carboxylate scaffolds **14a,b,d**. Notably, the reaction was regioselective even for the pseudosymmetric substrate **5d**, while the TMS-alkyne **5c** was unreactive. In contrast, reactions with aryl or alkyl nitriles proceeded with low to moderate regioselectivity, while the use of alternative Ni(0), Co(I), or Ru(II) catalysts24 gave no reaction or poor regioselectivity. Saito's Ni(0)-catalyzed [3+2+2]-cyclotrimerization 25 with ethyl cyclopropylideneacetate provided larger [5,7]-bicyclic cycloheptapyrrolidine scaffolds **15a–c** as single regioisomers and inseparable *E:Z* mixtures. While the *E:Z* ratios could not be improved using alternative cyclopropylidenes, solvents, or phosphine ligands, conversion to the corresponding Weinreb amides[26] **16a–c** allowed convenient separation of the isomers.

To probe the potential influence of the remote sulfinamide stereogenic center on the diastereoselectivity of the enyne cycloaddition reactions, we also carried out Pauson–Khand reactions with *anti*-enyne substrates **17a–d** having the opposite stereochemistry relative to *syn*-enynes **4a–d** (Scheme 3).[1] Increased diastereoselectivities were observed for **18a,b** versus **6a,b**, suggesting a matched/mismatched scenario.[12b,27] While these effects have not yet been studied in other reactions, access to both *syn*- and *anti*- diastereomers would also provide increased stereochemical diversity in resulting libraries.

Overall, we identified 27 reaction/substrate combinations suitable for use in multiscaffold library synthesis (≥84:16 dr or isolable as single regioisomer), leading to a total of 32 different scaffolds related to alkaloid and terpenoid natural products (after *in silico* desilylation; includes six additional Diels–Alder products).[1] To assess the structural diversity of the multiscaffold library accessible using our synthetic strategy, and its relationship in chemical space to synthetic drugs, natural products, and drug-like libraries, we evaluated these compounds for 20 structural and physicochemical properties in the context of our reported principal component analysis. (Figure 1).[1,3b,28] As expected, our scaffolds sample a distinct region of chemical space compared to drugs and drug-like libraries, and overlap with alkaloids and terpenoids. Analysis of parameter loadings indicates that aromatic ring content and stereochemical complexity are two major factors that distinguish the natural products and the multiscaffold library from drugs and drug-like libraries.[1]

In conclusion, we have used a systematic approach to analyze the effectiveness of transition-metal catalyzed cycloaddition and cyclization reactions across a range of enyne and diynes, resulting in the identification of eight reactions suitable for use in multiscaffold library synthesis. More broadly, our results provide valuable insights into the effective scope of such reactions across a panel of differentially substituted substrates and into the reactivity of the *t*-butylsulfinamide lynchpin. Synthesis of discovery libraries using this approach is ongoing and will set the stage for quantitative comparison of the abilities of drug-like and natural product-like libraries to address distinct regions of biological space through screening against a broad range of biological targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

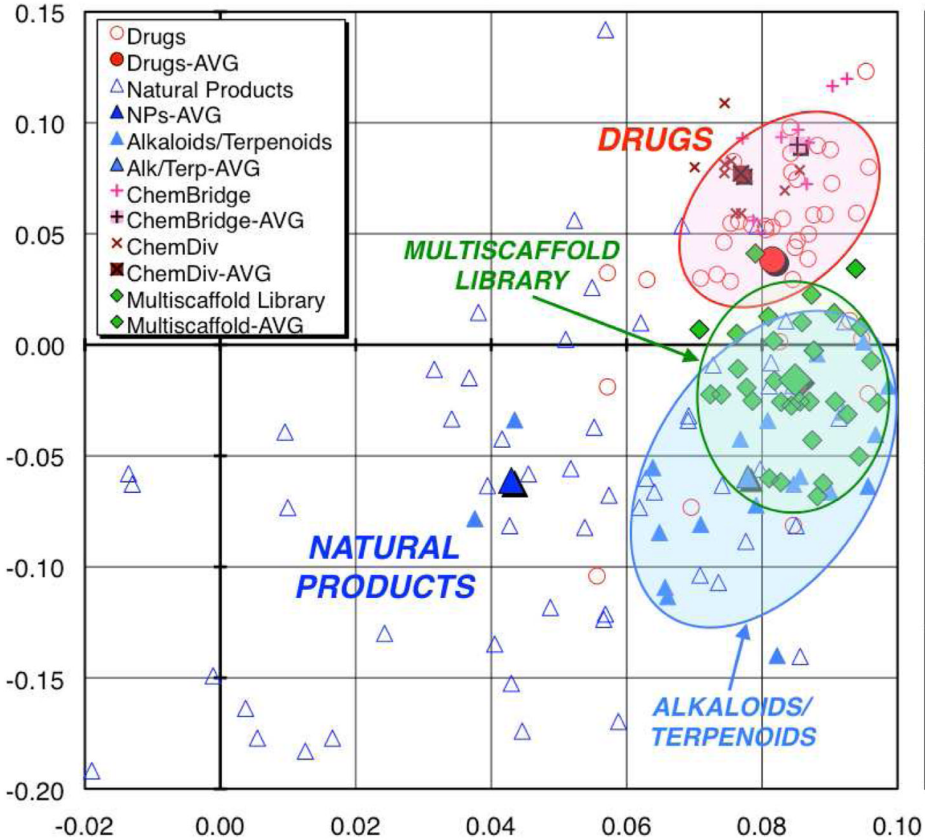
We thank Dr. George Sukenick, Dr. Hui Liu, Hui Fang, Dr. Sylvi Rusli, and Anna Dudkina for expert mass spectral analyses. D.S.T. is an Alfred P. Sloan Research Fellow. Financial support from the NIH (R21 GM104685, P41 GM076267, T32 CA062948-Gudas), NYSTAR Watson Investigator Program, William H. and Alice P. Goodwin and the Commonweath Foundation for Cancer Research, and MSKCC Experimental Therapeutics Center is gratefully acknowledged.

References

1. See Supporting Information for full details.
2. (a) Messer R, Fuhrer CA, Häner R. Curr. Opin. Chem. Biol 2005;9:259–265. [PubMed: 15939327] (b) Koch MA, Schuffenhauer A, Scheck M, Wetzel S, Casaulta M, Odermatt A, Ertl P, Waldmann H. Proc. Natl. Acad. Sci. U.S.A 2005;102:17272–17277. [PubMed: 16301544]
3. (a) Tan DS. Nat. Chem. Biol 2005;1:74–84. [PubMed: 16408003] (b) Bauer RA, Wurst JM, Tan DS. Curr. Opin. Chem. Biol 2010;14 in press; doi:10.1016/j.cbpa.2010.02.001.
4. For reviews, see: (a) Burke MD, Schreiber SL. Angew. Chem., Int. Ed 2004;43:46–58. (b) Nielsen TE, Schreiber SL. Angew. Chem., Int. Ed 2008;47:48–56.
5. For selected key examples, see: (a) Burke MD, Schreiber SL. Science 2003;302:613–618. [PubMed: 14576427] (b) Taylor SJ, Taylor AM, Schreiber SL. Angew. Chem., Int. Ed 2004;43:1681–1685. (c) Oguri H, Schreiber SL. Org. Lett 2005;7:47–50. [PubMed: 15624974] (d) Spiegel DA, Schroeder FC, Duvall JR, Schreiber SL. J. Am. Chem. Soc 2006;128:14766–14767. [PubMed: 17105261] (e) Wyatt EE, Fergus S, Galloway WRJD, Bender A, Fox DJ, Plowright AT, Jessiman AS, Welch M, Spring DR. Chem. Commun 2006:3296–3298.
6. Nakamura I, Yamamoto Y. Chem. Rev 2004;104:2127–2198. [PubMed: 15137788]
7. Several such reactions have been used recently in diversity-oriented synthesis: (a) Brummond KM, Mitasev B. Org. Lett 2004;6:2245–2248. [PubMed: 15200331] (b) Zhou Y, Porco JA Jr, Snyder JK. Org. Lett 2007;9:393–396. [PubMed: 17249770] (c) Kumagai N, Muncipinto G, Schreiber SL. Angew. Chem., Int. Ed 2006;45:3635–3638. (d) Gray BL, Wang X, Brown WC, Kuai L, Schreiber SL. Org. Lett 2008;10:2621–2624. [PubMed: 18510333]
8. For reviews, see: (a) Ferreirra F, Botuha C, Chemla F, Perez-Luna A. Chem. Soc. Rev 2009;38:1162–1186. [PubMed: 19421587] (b) Morton D, Stockman RA. Tetrahedron 2006;62:8869–8905. (c) Zhou P, Chen B-C, Davis FA. Tetrahedron 2004;60:8003–8030. (d) Ellman JA. Pure Appl. Chem 2003;75:39–46.
9. (a) Dai H, Lu X. Org. Lett 2007;9:3077–3080. [PubMed: 17608432] (b) Grigg R, McCaffrey S, Sridharan V, Fishwick CWG, Kilner C, Korn S, Bailey K, Blacker J. Tetrahedron 2006;62:12159–12171. (c) Beenen MA, Weix DJ, Ellman JA. J. Am. Chem. Soc 2006;128:6304–6305. [PubMed: 16683780] (d) McMahon JP, Ellman JA. Org. Lett 2005;7:5393–5396. [PubMed: 16288514] (e) Kong J-R, Cho C-W, Krische MJ. J. Am. Chem. Soc 2005;127:11269–11276. [PubMed: 16089454] (f) Schenkel LB, Ellman JA. J. Org. Chem 2004;69:1800–1802. [PubMed: 15058921] (g) Schenkel LB, Ellman JA. Org. Lett 2003;5:545–548. [PubMed: 12583765] (h) Souers AJ, Owens TD, Oliver AG, Hollander FJ, Ellman JA. Inorg. Chem 2001;40:5299–5301. [PubMed: 11559098]
10. DiBlasi CM, Macks DE, Tan DS. Org. Lett 2005;7:1777–1780. [PubMed: 15844904]
11. Ding C-H, Chen D-D, Luo Z-B, Dai L-X, Hou X-L. Synlett 2006;8:1272–1274.
12. (a) Kuduk SD, Marco CND, Pitzenberger SM, Tsou N. Tetrahedron Lett 2006;47:2377–2381. (b) Hiroi K, Watanabe T. Heterocycles 2001;54:73–76.
13. Michelet V, Toullec PY, Genet J-P. Angew. Chem. Int. Ed 2008;47:4268–4315.
14. Schore NE. Org. React 1991;40:1–90.
15. Jang H-Y, Hughes FW, Gong H, Zhang J, Brodbelt JS, Krische MJ. J. Am. Chem. Soc 2005;127:6174–6175. [PubMed: 15853314]
16. Robinson JE, Baum EW, Fazal AN, Evans PA. J. Am. Chem. Soc 2002;124:8782–8783. [PubMed: 12137516]
17. Diver ST, Giessert AJ. Chem. Rev 2004;104:1317–1382. [PubMed: 15008625]
18. For examples of RCM/Diels–Alder strategies, see: (a) Schurer SC, Blechert S. Chem. Commun 1999:1203–1204. (b) Bentz D, Laschat S. Synthesis 2000:1766–1773. (c) Micalizio GC, Schreiber SL. Angew. Chem., Int. Ed 2002;41:152–154. (d) Ref. [7c] (e) Ref. 5d
19. An exception was *N*-phenyltriazolinedione, which reacted with **9a,b,d** at −78 °C.
20. Saito S, Yamamoto Y. Chem. Rev 2000;100:2901–2915. [PubMed: 11749309]
21. Witulski B, Stengel T, Fernandez-Hernandez JM. Chem. Commun 2000:1965–1966.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

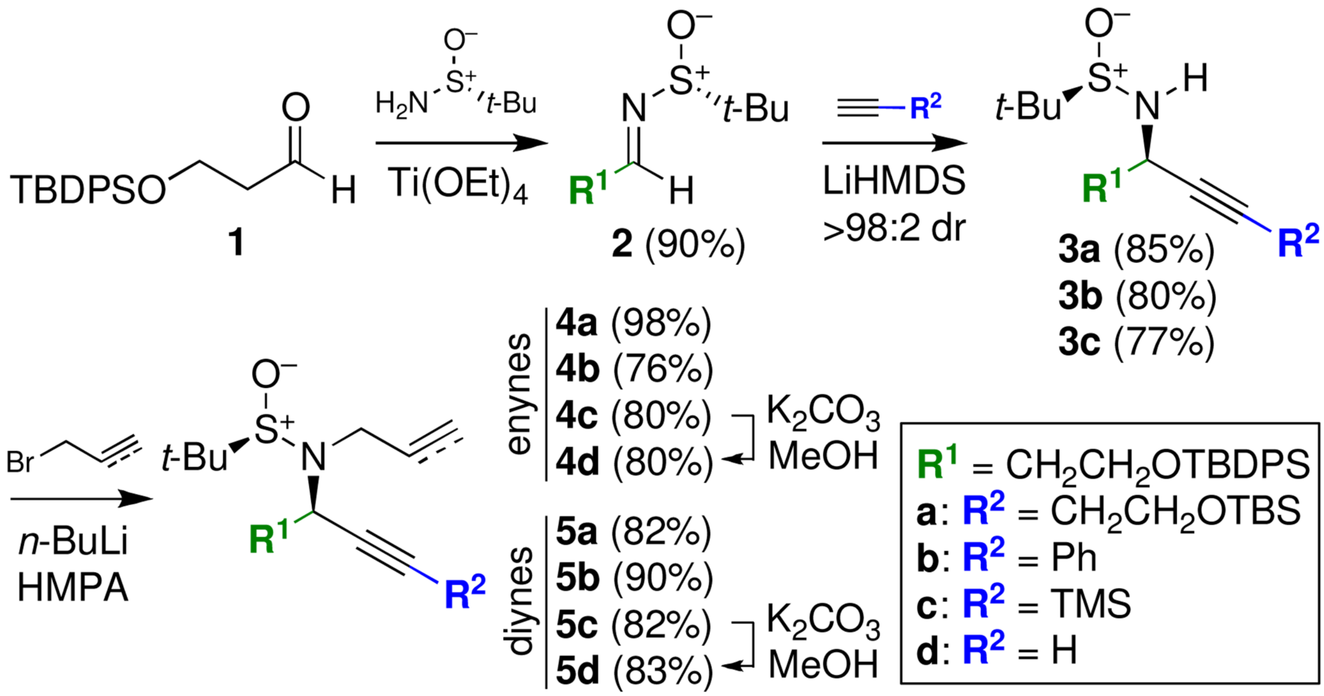
22. Yamamoto Y, Kinpara K, Saigoku T, Takagishi H, Okuda S, Nishiyama H, Itoh K. J. Am. Chem. Soc 2005;127:605–613. [PubMed: 15643884]
23. Tanaka K, Suzuki N, Nishida G. Eur. J. Org. Chem 2006:3917–3922.
24. For a review, see: Chopade PR, Louie J. Adv. Synth. Catal 2006;348:2307–2327.
25. Maeda K, Saito S. Tetrahedron Lett 2007;48:3173–3176.
26. Williams JM, Jobson RB, Yasuda N, Marchesini G, Dolling U-H, Grabowski EJJ. Tetrahedron Lett 1995;36:5461–5464.
27. (a) Mukai C, Kim JS, Uchiyama M, Sakamoto S, Hanaoka M. J. Chem. Soc., Perkin Trans 1998;1:2903–2916. (b) Clive DLJ, Cole DC, Tao Y. J. Org. Chem 1994;59:1396–1406.
28. (a) Haggarty SJ. Curr. Opin. Chem. Biol 2005;9:296–303. [PubMed: 15939332] (b) Shelat AA, Guy RK. Curr. Opin. Chem. Biol 2007;11:244–251. [PubMed: 17524728]



AVGs	Drugs	Nat Prod	Alk/Terp	ChemBr	ChemDiv	Multi
MW	361	629	267	381	446	369
N	2.2	2.6	0.6	4.3	4.7	1.4
O	2.9	9.7	3.3	3.1	3.4	3.9
XLogP	2.7	1.5	1.6	2.9	1.8	0.8
HBD	1.5	4.9	1.9	1.1	1.9	1.5
HBA	5.4	10.8	3.8	5.9	7.7	5.0
RotB	6.3	9.7	2.2	5.3	6.1	6.4
tPSA	69	183	63	103	94	74
ALOGPs	2.8	2.1	1.8	3.3	2.7	1.7
ALOGpS	-3.9	-3.8	-2.6	-4.0	-3.8	-2.4
nStereo	1.4	9.1	3.6	0.0	1.0	2.3
R	0.6	4.1	1.3	0.0	0.5	2.1
S	0.8	5.0	2.3	0.0	0.5	0.2
nStMW†	3.7	13.9	12.7	0.0	2.2	6.4
RSdelta	-0.2	-0.9	-1.0	0.0	0.0	2.0
Rings	2.9	3.8	2.7	3.2	4.2	2.4
RngAr	2.1	1.0	0.5	2.9	2.9	0.8
RngSys	2.1	2.0	1.3	3.1	3.1	1.5
RngLg	8.4	15.8	10.2	6.3	9.4	8.7
RRSys	1.4	2.3	2.3	1.0	1.4	1.6

Figure 1.

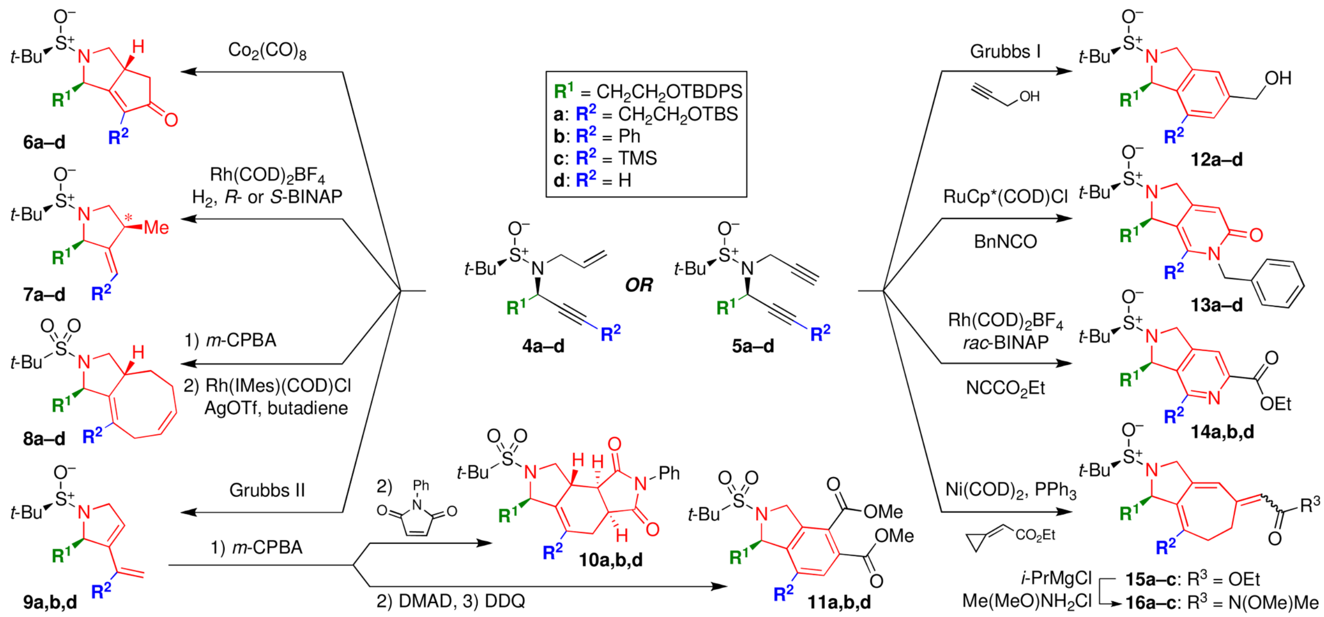
Principal component analysis of 20 structural and physicochemical descriptors of the 40 top-selling drugs, 60 diverse natural products, 20 polycyclic alkaloids and terpenoids, 20 ChemBridge and Chem Div library members, and 32 multiscaffold library members. Average values for each parameter are indicated by group.[1]



Scheme 1.

Stereoselective Synthesis of Enynes and Diynes Using a *t*-Butylsulfinimide Tether.a

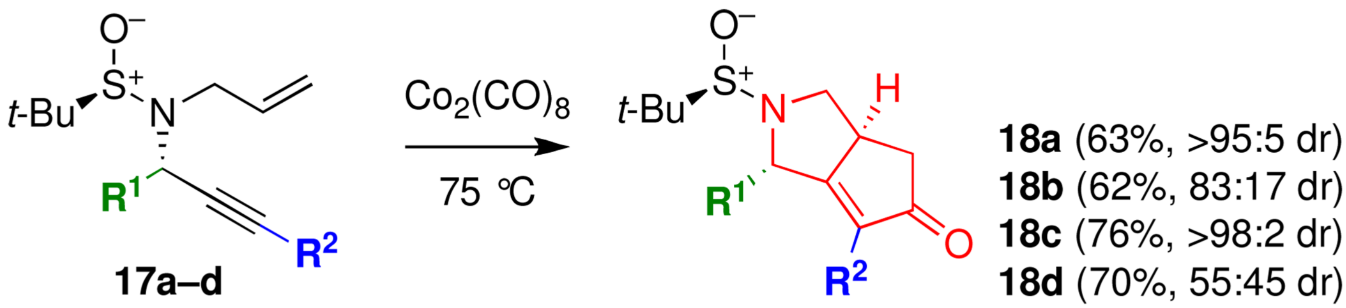
[a] HMPA = hexamethylphosphoramide; LiHMDS = lithium hexamethyldisilazide; TBDPS = *t*-butyldiphenylsilyl; TBS = *t*-butyldimethylsilyl; TMS = trimethylsilyl.



Scheme 2.

Transition Metal-Mediated Cycloadditions and Cyclizations of *t*-Butylsulfinamide-Tethered Enynes **4a–d** and Diynes **5a–d**a,b,c

[a] See Tables 1 and 2 for results. [b] Subsequent Diels–Alder reactions also shown (center). [c] BINAP = 2,2´-bis(diphenylphosphino)-1,1´-binaphthyl; COD = 1,4-cyclooctadiene; Cp* = pentamethylcyclopentadienyl; *m*-CPBA = *meta*-chloroperbenzoic acid; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAD = dimethylacetylene dicarboxylate; Grubbs I = benzylidene-bis(tricyclohexylphosphine)dichloro-ruthenium; Grubbs II = benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine) ruthenium; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazoly-2-ylidene; Tf = trifluoromethanesulfonate.

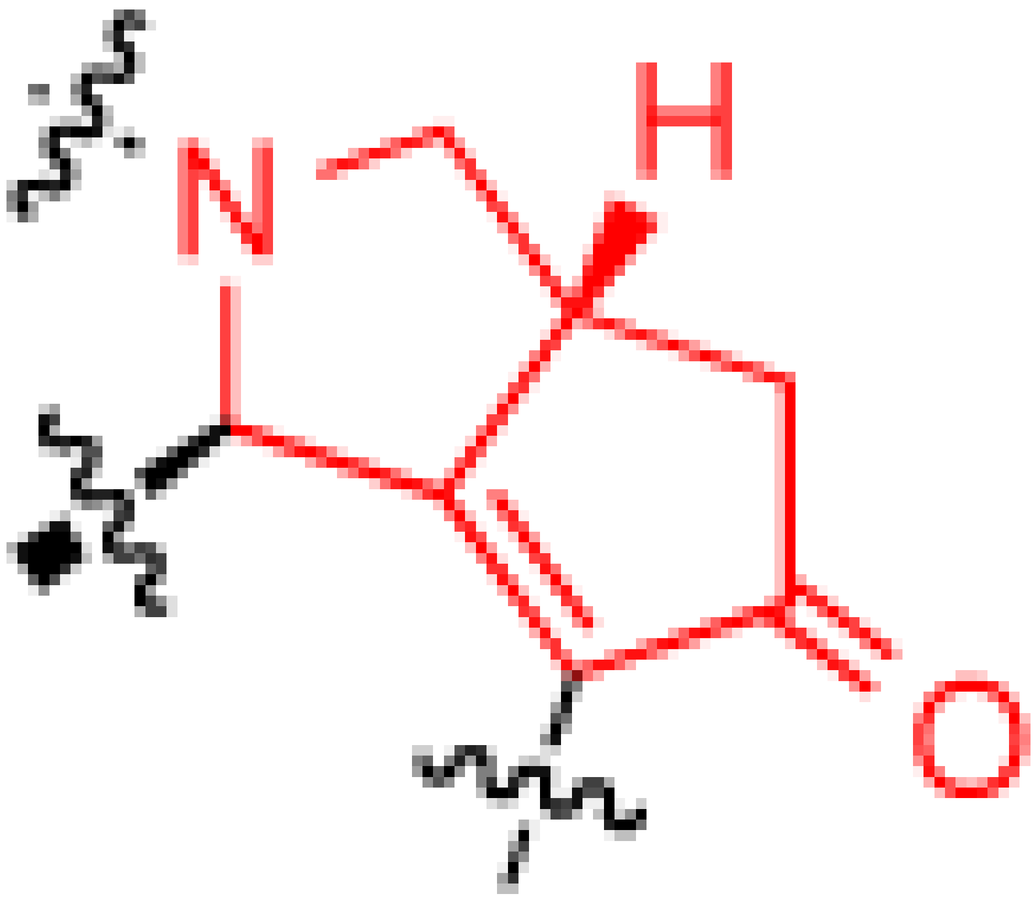


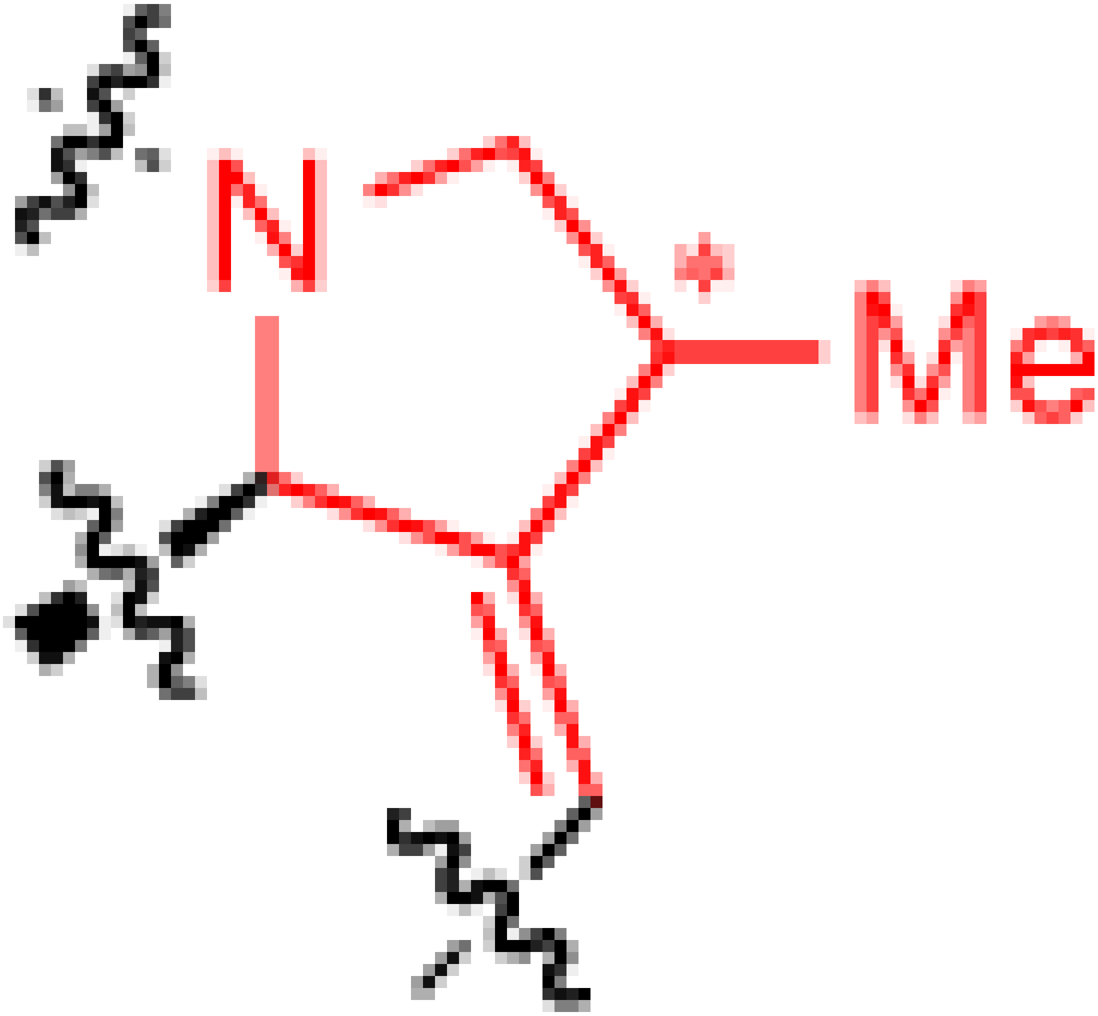
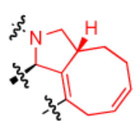
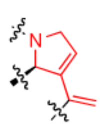
Scheme 3.
Pauson-Khand Reactions of *anti*-Enynes **17a–d**.[1]

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Yields and diastereoselectivities of tethered cycloaddition and cyclization reactions of enynes **4a–d**.

scaffold	product	yield [
	**6a**	70
	6b	64
	6c	93
	6d	67

scaffold	product	yield [
	**β-7a** or **α-7a**[c]	87 /
	β-7b or **α-7b**[c]	80 /
	β-7c or **α-7c**[c]	0 /
	β-7d or **α-7d**[c,d]	74 /
	**8a**	30
	8b	64
	8c	37
	8d	52
	**9a**	96
	9b	86
	9c	0
	9d	100

[a]Combined yield of inseparable diastereomers.

[b]Determined by ^{1}H-NMR.

[c]β-isomer obtained using (*S*)-BINAP; α-isomer obtained using (*R*)-BINAP.

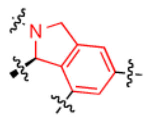
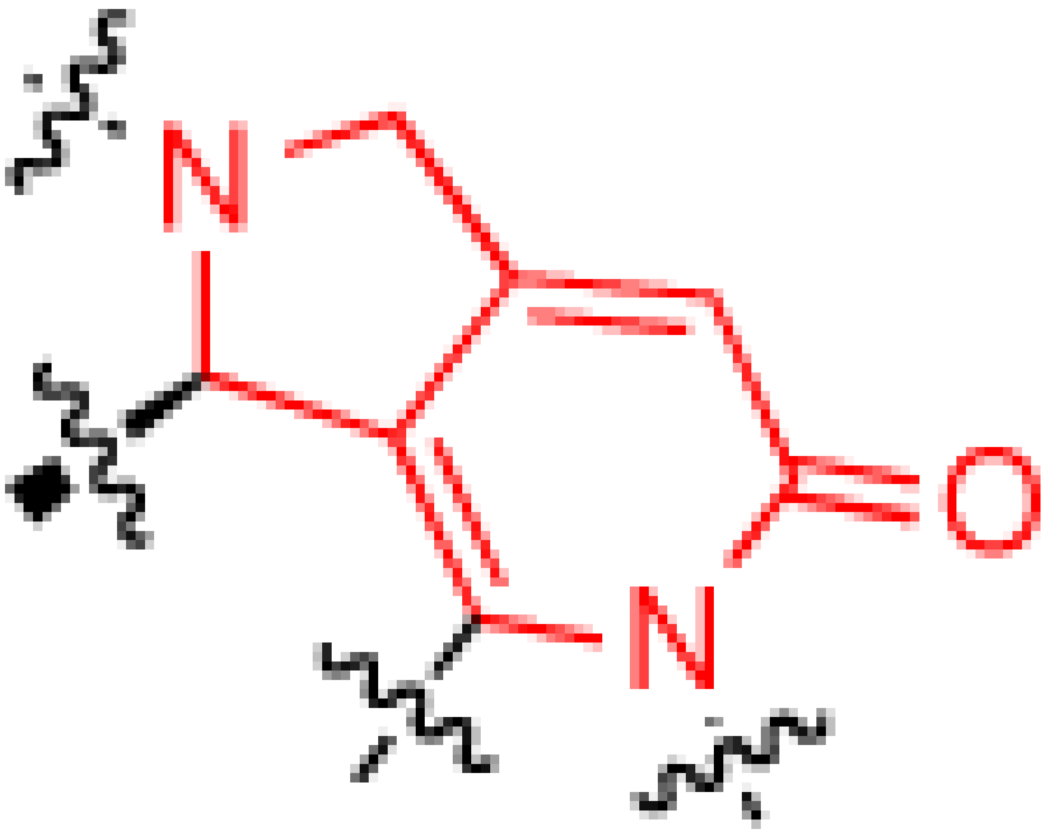
[d]With $Rh(COD)_2OTf$ instead of $Rh(COD)_2BF_4$.

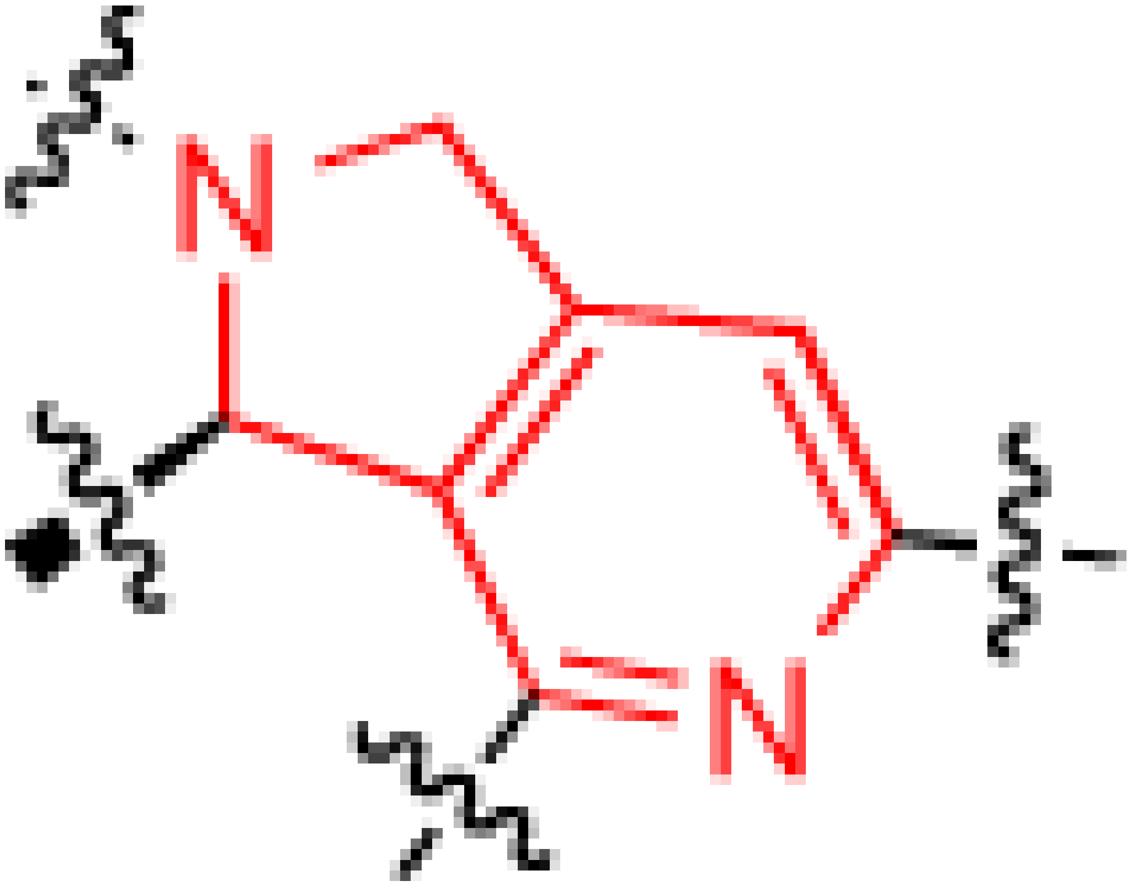
NIH-PA Author Manuscript

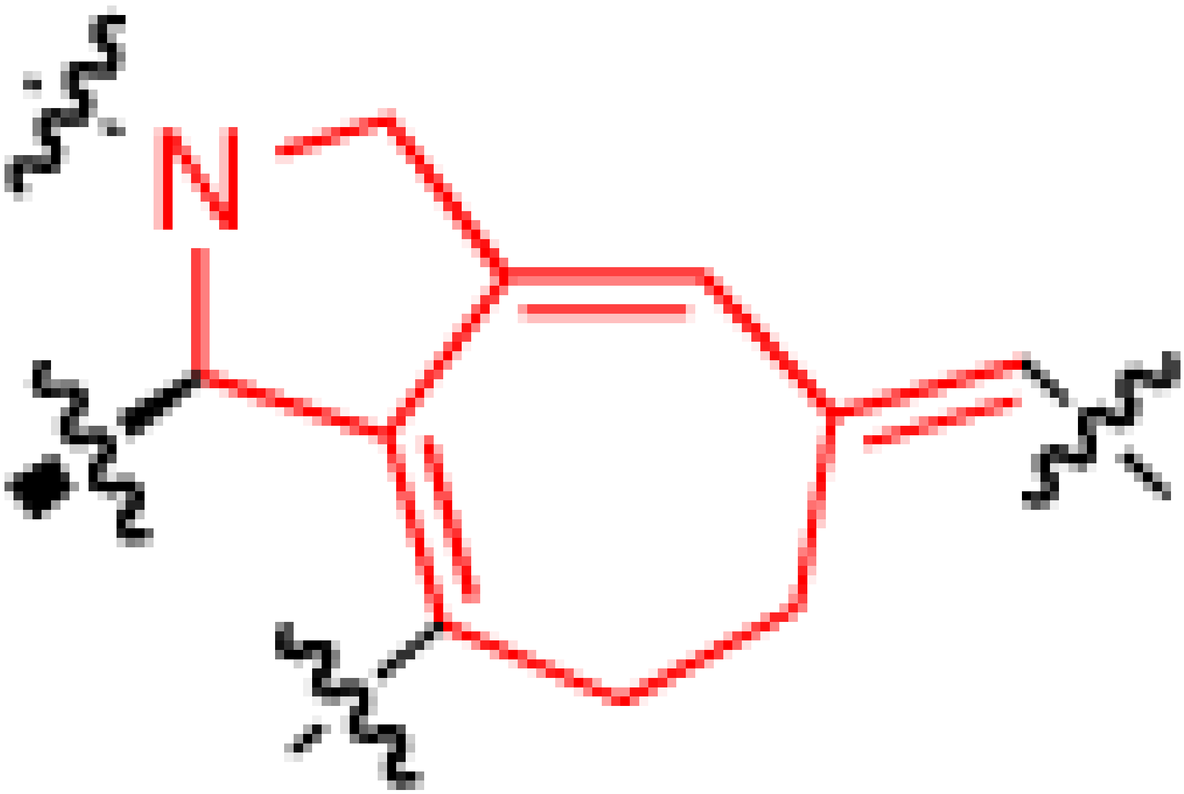
NIH-PA Author Manuscript

Table 2

Yields and regioselectivities of tethered cycloaddition reactions of diynes **5a–d**.

scaffold	product	yield [
	**12a**	90
	12b	73
	12c	77
	12d	33 /
	**13a**	74
	13b	73
	13c	92
	13d	40 /

scaffold	product	yield [
	**14a**	74
	14b	99
	14c	0
	14d	80

scaffold	product	yield [
	**15a**	70
	15b	70
	15c	55
	15d	0

[a]Yield of isolated major regioisomer or of each isolated regioisomer.

[b]Determined by ^{1}H-NMR.

[c]*E*/*Z* = 74:26.

[d]*E*/*Z* = 68:32.

[e]*E*/*Z* = 87:13.