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

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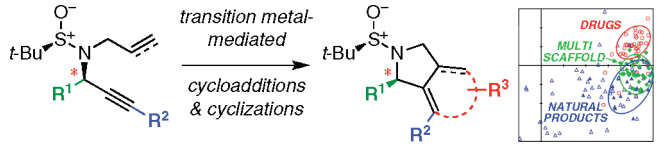
ABSTRACT



A unified synthetic approach to diverse polycyclic scaffolds has been developed using transition-metal-mediated cycloaddition and cyclization reactions of enynes and diynes. The *tert*-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 10 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 10 classes of polycyclic scaffolds and the emergence of the *tert*-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

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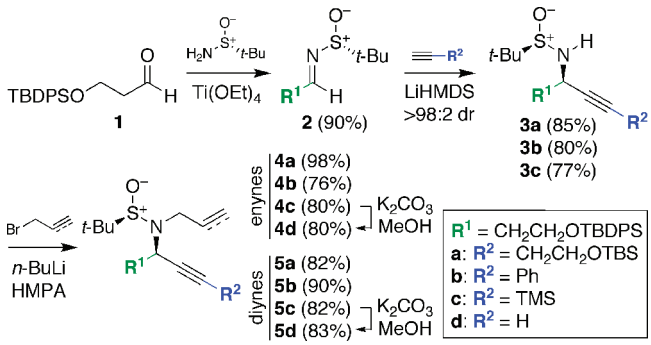
Scheme 1. Stereoselective Synthesis of Enynes and Diynes Using a *tert*-Butylsulfinimide Tether[a]



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

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 *tert*-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 time scale, and can be deprotected or oxidized under mild conditions. The *tert*-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 *tert*-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*)-*tert*-butylsulfinamide (Scheme 1). The R^1 side chain 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 various Ru, Co, Rh, and Ni catalysts (groups 8−10), and after investigation of over 25 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 *tert*-butylsulfonamides, affording [5,8]-bicyclic cyclooctapyrrolidine scaffolds **8a**−**d** in moderate yields but complete diastereoselectivity. Enyne metathesis of **4** with Grubbs' second-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 *tert*-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 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' first-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

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(19) An exception was *N*-phenyltriazolinedione, which reacted with **9a**,**b**,**d** at −78 °C.

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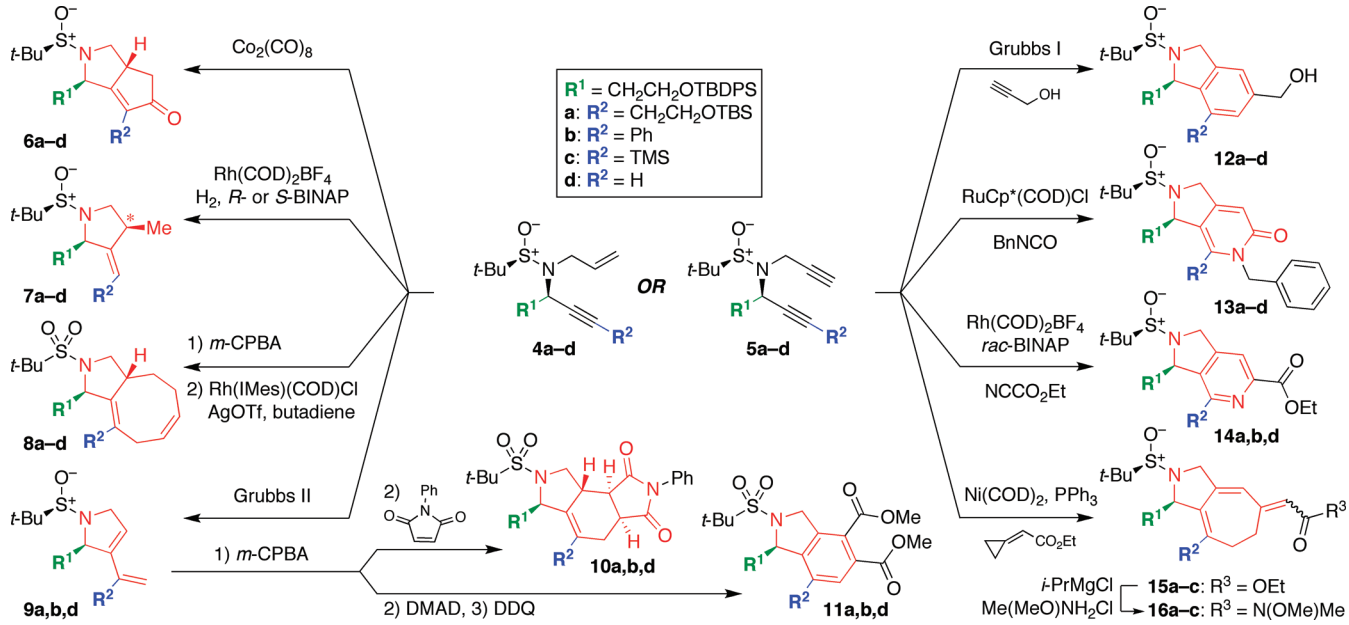
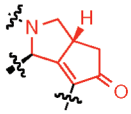
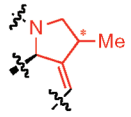
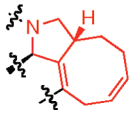
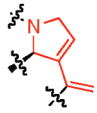
Scheme 2. Transition-Metal-Mediated Cycloadditions and Cyclizations of *tert*-Butylsulfinamide-Tethered Enynes **4a−d** and Diynes **5a−d**[a−c]



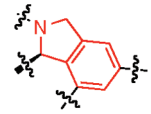
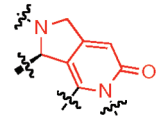
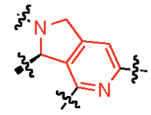
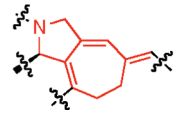
[a] See Tables 1 and 2 for results. [b] Subsequent Diels−Alder reactions also shown (center). [c] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; COD = 1,4-cyclooctadiene; Cp* = pentamethylcyclopentadienyl; *m*-CPBA = *m*-chloroperbenzoic acid; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAD = dimethylacetylene dicarboxylate; Grubbs I = benzylidene-bis(tricyclohexylphosphine)dichlororuthenium; 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.

Table 1. Yields and Diastereoselectivities of Tethered Cycloaddition and Cyclization Reactions of Enynes **4a−d**

scaffold	product	yield [%][a]	dr[b]
	**6a**	70	85:15
	6b	64	50:50
	6c	93	>98:2
	6d	67	58:42
	**β-7a** or **α-7a**[c]	87 / 78	92:8 / 16:84
	β-7b or **α-7b**[c]	80 / 78	84:16 / 9:91
	β-7c or **α-7c**[c]	0 / 0	n.a.
	β-7d or **α-7d**[c,d]	74 / 58	67:33 / 73:27
	**8a**	30	>98:2
	8b	64	>98:2
	8c	37	>98:2
	8d	52	>98:2
	**9a**	96	n.a.
	9b	86	n.a.
	9c	0	n.a.
	9d	100	n.a.

[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 $Rh(COD)_2BF_4$.

Table 2. Yields and Regioselectivities of Tethered Cycloaddition Reactions of Diynes **5a−d**

scaffold	product	yield [%][a]	r.r.[b]
	**12a**	90	>98:2
	12b	73	91:9
	12c	77	>98:2
	12d	33 / 33	50:50
	**13a**	74	>98:2
	13b	73	>98:2
	13c	92	94:6
	13d	40 / 40	50:50
	**14a**	74	96:4
	14b	99	>98:2
	14c	0	n.a.
	14d	80	80:20
	**15a**	70	>98:2[c]
	15b	70	>98:2[d]
	15c	55	>98:2[e]
	15d	0	n.a.

[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.

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

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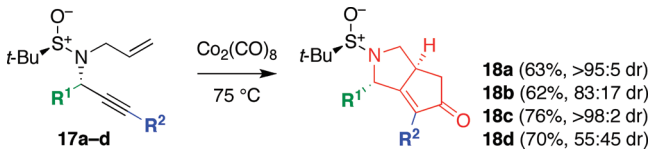
Scheme 3. Pauson−Khand Reactions of *anti*-Enynes **17a−d**[1]

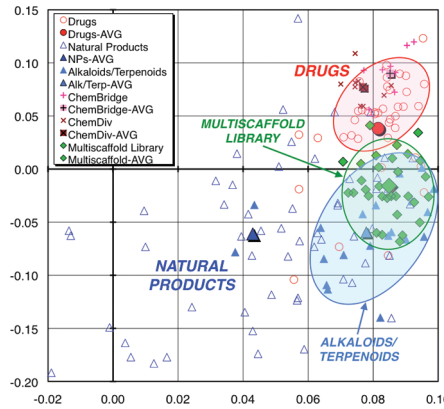


18a (63%, >95:5 dr)
18b (62%, 83:17 dr)
18c (76%, >98:2 dr)
18d (70%, 55:45 dr)

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) catalysts[24] 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 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 provide increased stereochemical diversity in 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 using 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 natural products and the multiscaffold library from drugs and drug-like libraries.[1]



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[1]	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]

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 *tert*-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.

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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.

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