Skeletal Diversity in Small-Molecule Synthesis Using Ligand-Controlled Catalysis

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Two Pd-catalyzed reductive transformations of diynes tethered through a silyl ether linkage were developed, where the reaction outcomes were controlled solely by selection of phosphine ligand. We screened Pd precatalysts, ligands, and additives to optimize conditions selective either for reductive cyclization or hydrogenation of this substrate class. Sixteen silyl ether-tethered diynes were prepared and subjected to the best catalyst/ligand combinations for each pathway. Silacyclic dienes and silyl-tethered enyne products of these reactions were elaborated to densely substituted, stereochemically- and appendage-rich, bicyclic and tricyclic small molecules in 1–3 synthetic steps. These studies illustrate how small modifications to a transition-metal catalyst can be used to access a diverse set of small molecules, in a fashion analogous to biosynthetic pathways such as terpene biosynthesis, where minor changes to enzyme structure direct skeletal differentiation.

Introduction

In biosynthetic pathways, for example in terpene biosynthesis,[1] it is common to find a single biosynthetic intermediate converted to numerous small molecules having distinct skeletons. Here, minor differences in enzyme structure direct branching of common, polyunsaturated precursors to distinct skeletons (Figure 1, path a).[2] Analogous pathways in diversity-oriented synthesis (DOS)[3] would use minimal perturbations to a catalyst,[4] rather than wholesale modification of reagent sets,[5] to influence reaction outcome. Along these lines, we hypothesized that polyunsaturated compounds (**II**) might undergo different reductive transformations controlled by minor modifications of a transition-metal catalyst.

Whereas metal-mediated transformations of alkyl-, ether-, and ester-tethered diynes have been used frequently in organic synthesis,[6] similar reactions involving alkynes tethered through silyl ethers have been less well studied.[7] For example, to date no reductive cyclization to produce silylcyclic dienes of type **IV** has been described. Herein, we report a catalyst-controlled branching pathway from diynes **II** that, coupled to complexity-generating steps, allows the rapid assembly of bicyclic (**VII**, **VIII**, and **X**) and tricyclic small molecules (**IX**), which are both suited for high-throughput, small-molecule screening[8] (Figure 1, path b) and poised for post-screening optimization.[5]

Results and Discussion

Synthesis of a Collection of Silyl Ether-Tethered Diynes. Silyl ether-tethered diynes **II** contain four discrete appending sites for incorporation of building-block diversity, and are constructed efficiently in three steps,[9] rendering them well suited as branching intermediates for DOS pathways. The synthesis of a collection of diynes commenced with alkynylsilane formation using alkynes **1**–**6** and either diisopropylchlorosilane **7** or diphenylchlorosilane **8** (Table 1). Treatment with *N*-bromosuccinimide resulted in the synthesis of the corresponding silyl bromides, which were converted to ethers of chiral propargyl alcohols **9**–**12** by reaction with triethylamine and catalytic DMAP. Terminal acetylenes bearing linear (entries 1–5 and 18–20), branched alkyl (entries 13–16), and aromatic groups (entries 6–12) were suitable substrates. Silyl etherification of chiral secondary alcohols bearing alkyl (entries 2, 3, 5, 8, 10, 11, 14, 15, 19), aryl (entries 1, 6, 13, 18), and mixed aryl ethers (entries 4, 9, 12, 16) also worked well.

Development of a Ligand-Controlled Differentiation Process. In initial studies, it was found that treatment of **16** with Pd_2dba_3-$CHCl_3$ adduct **33** (2.5 mol %), tri-*o*-tolylphosphine **38** (10 mol %), acetic acid, and excess triethylsilane in toluene at 23 °C[10] gave an inseparable mixture of products **50** (via reductive cyclization) and **51** (via reduction of the terminal alkyne), along with cyclodimerization adduct **52** (>95% conv, 2.4:1 **50**:**51**, 38% **52**).[11] Reduction of the reaction temperature during formation of the catalyst increased the combined conversion and yield of **50** and **51** (10 °C: >95% conv, 1.9:1 **50**:**51**, 8% **52**; –20 °C: >95% conv, 2.7:1 **50**:**51**, 9% **52**). Conversely, the temperature at which substrate was introduced to the preformed catalyst was determined to have little effect on reaction efficacy (e.g., 23 °C: >95% conv, 2.7:1 **50**:**51**, 9% **52**; 10 °C: >95% conv, 2.2:1 **50**:**51**, 8% **52**; –20 °C: >95% conv, 1.6:1 **50**:**51**, 8% **52**, when catalyst was formed at −20 °C). However, failure to increase the temperature to 23 °C *after* substrate addition resulted in incomplete reactions, despite improved ratios of diene to enyne (e.g., 0 °C: 14% conv, 3.2:1 **50**:**51**; −2 0 °C: 11% conv, 3.6:1 **50**:**51**; −7 8 °C: 18% conv, 3.0:1 **50**:**51**). Adopting a standard set of conditions from this early set of

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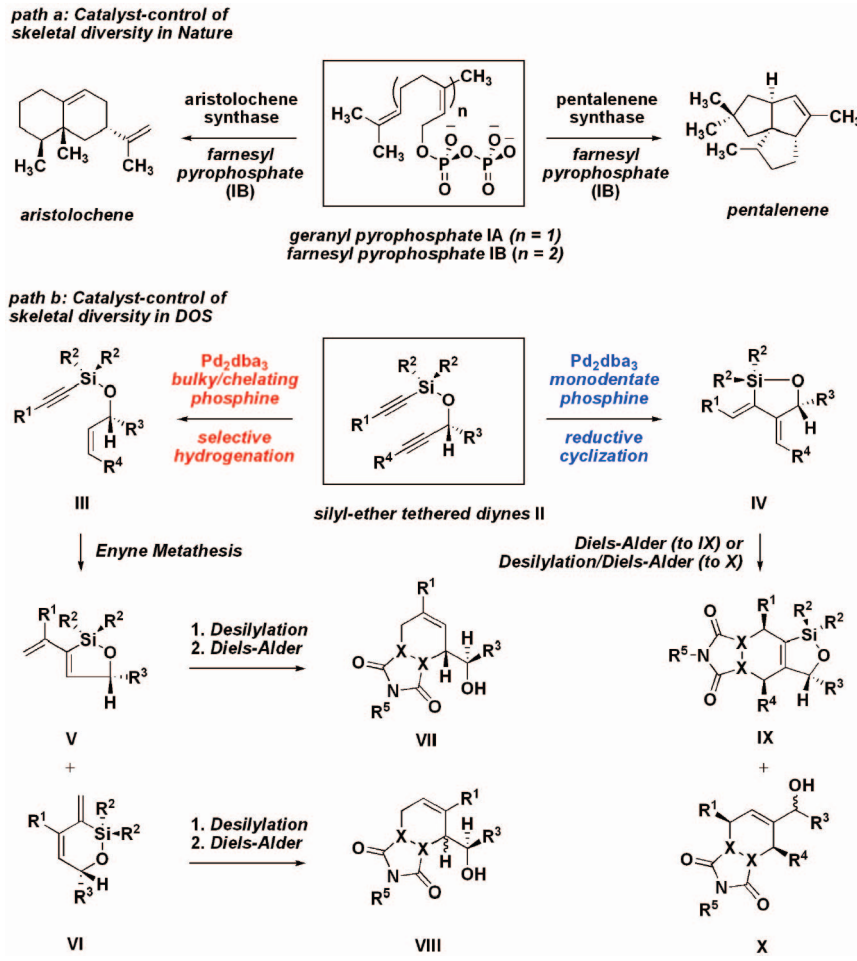


Figure 1. Examples of catalyst-based control of skeletal formation in cells and in the laboratory. (a) Terpene diversity generated by the actions of different enzyme cyclases on farnesyl pyrophosphate. (b) Small-molecule diversity initiated by different Pd/ligand combinations.

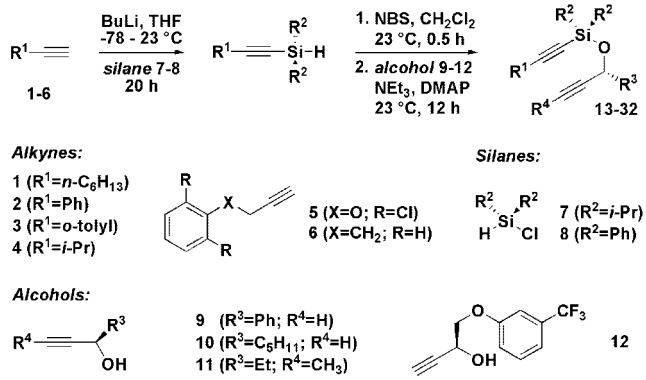
data (see Supporting Information for full details), a systematic variation of Pd(0) and Pd(II) precatalysts, ligands, and hydride sources was undertaken in an effort to discover active catalysts selective for either reductive cyclization or enyne formation (Table 2).[12]

Several notable observations emerged from these screens. Both Pd(0) and Pd(II) complexes constitute competent precatalysts for this reaction; however, a change in metal precatalyst was not sufficient to induce a crossover in product selectivity to **51** (entries 1–5: 1.6:1–2.7:1 **50**:**51**).[13] On the contrary, selection of the *ligand* was found to play a predominant role in tuning the reaction pathway,[14] with tri-*o*-tolylphosphine **38** best for reductive cyclization (entry 2, 2.7:1 **50**:**51**), and monovalent, bulky biaryl phosphines such as X-PHOS **41**, Cy_2P-biphen **46**, and *t*-Bu_2P-biphen **48** were found best for selective hydrogenation (entries 10, 15, and 17, 1:3.7–1:6.8 **50**:**51**). Additionally, use of the polymeric PMHS as reductant resulted in very high selectivity for the enyne product (entry 6, 1:11.2 **50**:**51**); however, this additive proved difficult to separate from the product chromatographically and thus was not further pursued. (*R*)-MeO-MOP **42**, a monodentate ligand bearing a phosphine and methoxy group, was also shown to be selective for **51** (entry 11).[15] However, bisphosphines such as dppe **43** and dppb **44** abrogated catalytic activity (entries 12–13).[16]

Scope and Limitations of Pd_2dba_3-Catalyzed Reductive Transformations with Silyl Ether-Tethered Diynes. The generality of this ligand-controlled process was assayed next across a range of silyl ether-tethered diyne substrates (Table 3). The catalyst system preformed from Pd_2dba_3 **34** and tri-*o*-tolylphosphine **38** and identified as the optimal system for reductive cyclization of **16** displayed good generality (10 of 16 cases tested). Sterics at the silylated alkyne proved important, with product ratios highest for compounds containing *i*-Pr (entries 11–14, 1.6–8.3:1 **IV**:**III**) and $Ph(CH_2)_2$ (entries 15–16; 4.5–7.1:1 **IV**:**III**). *n*-Hexyl substituted diynes underwent selective cycloreduction in four of five cases (entries 1, 2, 4, 5, 1.8–3.2:1 **IV**:**III**). The nature of substitution at silicon did not affect selectivity (compare entries 1 and 5; 1.8:1 vs. 1.9:1 **IV**:**III**). Similiarly, the effect of the secondary alcohol building block on selectivity was usually not strong enough to override catalyst preference (e.g., entries 11–14; 1.6–8.3:1 **IV**:**III**). Aromatic-substituted diynes, on the contrary, were not routinely diene selective, usually yielding enyne as the major adduct and often at incomplete conversions (entries 6–10; 1:1.5–4.4 **IV**:**III**).[17] Additionally, with **15**, discrimination between the two internal acetylenes was not achieved.

In contrast to the above results, subjection to the complex derived from Pd_2dba_3 **34** and X-PHOS **41** resulted in an enyne-selective reaction in 12 of 16 cases. Many of the trends

Table 1. Synthesis of Silyl Ether-Tethered Diyne Substrates **13–32**



entry	alkyne[a]	silane[b]	yield (%)[c]	alcohol[d]	yield (%)[e]	product
1	**1**(R^1=C_6H_{13})	**7**(R^2=*i*-Pr)	97	**9**(R^3=Ph; R^4=H)	63	**13**
2	**1**(R^1=C_6H_{13})	**7**(R^2=*i*-Pr)	97	**10**(R^3=C_5H_{11}; R^4=H)	91	**14**
3	**1**(R^1=C_6H_{13})	**7**(R^2=*i*-Pr)	97	**11**(R^3=C_2H_5; R^4=CH_3)	71	**15**
4	**1**(R^1=C_6H_{13})	**7**(R^2=*i*-Pr)	97	**12**(R^4=H)	66	**16**
5	**1**(R^1=C_6H_{13})	**8**(R^2=Ph)	94	**10**(R^3=C_5H_{11}; R^4=H)	74	**17**
6	**2**(R^1=Ph)	**7**(R^2=*i*-Pr)	97	**9**(R^3=Ph; R^4=H)	88	**18**
7	**2**(R^1=Ph)	**7**(R^2=*i*-Pr)	97	**10**(R^3=C_5H_{11}; R^4=H)	<5	**19**
8	**2**(R^1=Ph)	**7**(R^2=*i*-Pr)	97	**11**(R^3=C_2H_5; R^4=CH_3)	80	**20**
9	**2**(R^1=Ph)	**7**(R^2=*i*-Pr)	97	**12**(R^4=H)	54	**21**
10	**2**(R^1=Ph)	**8**(R^2=Ph)	87	**10**(R^3=C_5H_{11}; R^4=H)	80	**22**
11	**3**(R^1=*o*-tol)	**7**(R^2=*i*-Pr)	93	**10**(R^3=C_5H_{11}; R^4=H)	90	**23**
12	**3**(R^1=*o*-tol)	**7**(R^2=*i*-Pr)	93	**12**(R^4=H)	55	**24**
13	**4**(R^1=*i*-Pr)	**7**(R^2=*i*-Pr)	85	**9**(R^3=Ph; R^4=H)	59	**25**
14	**4**(R^1=*i*-Pr)	**7**(R^2=*i*-Pr)	85	**10**(R^3=C_5H_{11}; R^4=H)	73	**26**
15	**4**(R^1=*i*-Pr)	**7**(R^2=*i*-Pr)	85	**11**(R^3=C_2H_5; R^4=CH_3)	77	**27**
16	**4**(R^1=*i*-Pr)	**7**(R^2=*i*-Pr)	85	**12**(R^4=H)	66	**28**
17	**5**	**7**(R^2=*i*-Pr)	86	**10**(R^3=C_5H_{11}; R^4=H)	<5	**29**
18	**6**(R^1=PhC_2H_4)	**7**(R^2=*i*-Pr)	86	**9**(R^3=Ph; R^4=H)	58	**30**
19	**6**(R^1=PhC_2H_4)	**7**(R^2=*i*-Pr)	86	**10**(R^3=C_5H_{11}; R^4=H)	74	**31**
20	**6**(R^1=PhC_2H_4)	**8**(R^2=Ph)	83	**10**(R^3=C_5H_{11}; R^4=H)	<5	**32**

[a] Acetylenes. **1**: $\mathbf{R^1}$ = *n*-C_6H_{13}; **2**: $\mathbf{R^1}$ = Ph; **3**: $\mathbf{R^1}$ = *o*-tolyl; **4**: $\mathbf{R^1}$ = *i*-Pr; **5**: $\mathbf{R^1}$ = 2,6-$Cl_2C_6H_3OCH_2$-; **6**: $\mathbf{R^1}$ = $Ph(CH_2)_2$. [b] Silanes. **7**: $\mathbf{R^2}$ = *i*-Pr; **8**: $\mathbf{R^2}$ = Ph. [c] Yield of alkynyl silane adduct. [d] Alcohols. **9**: $\mathbf{R^3}$ = Ph, $\mathbf{R^4}$ = H; **10**: $\mathbf{R^3}$ = C_5H_{11}, $\mathbf{R^4}$ = H; **11**: $\mathbf{R^3}$ = C_2H_5, $\mathbf{R^4}$ = CH_3; **12**: $\mathbf{R^3}$ = $CH_2OC_7H_4F_3$, $\mathbf{R^4}$ = H. [e] Yield of silyl ether from alkynyl silane species.

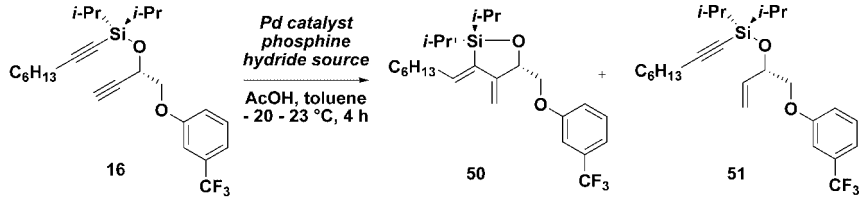
evident in the earlier Pd_2dba_3/P-(*o*-tolyl)$_3$ system are also evident here; for example, aromatic-substituted diynes display the highest selectivities for **III** with **41** as ligand (entries 6–10; 1:2.6–20 **IV**:**III**) and substitution at silicon again displayed little effect (compare entries 1 and 5; 1:1.9 vs. 1:1.9 **IV**:**III**). Despite the broad generality of this catalyst, however, four substrates still overrode ligand bias and gave mixtures enriched in diene. Importantly, in three of these cases, the ratio of diene to enyne was less than in the reaction with tri-*o*-tolylphosphine **38** (entry 2: 3.2:1 vs. 1.4:1 **IV**:**III**; entry 12: 8.3:1 vs. 2.4:1 **IV**:**III**; entry 16: 7.1:1 vs. 1.4:1 **IV**:**III**). The sole compound for which this move towards a more enyne-selective reaction was not found was **15**, again not unsurprising given the steric similarity between the two alkynes. Gratifyingly, subjection of the same substrate set to the catalyst preformed from Pd_2dba_3 and *t*-Bu_2P-biphen **48** resulted in enyne-selective reactions in all but a single case (entry 1: 1.4:1 **IV**:**III**), generally with high selectivity. Even substrates displaying inherent bias towards reductive cyclization with **38** and **41** were transformed efficiently into enyne (entry 2: 1:3.0 **IV**:**III**; entry 12: 1:7.0 **IV**:**III**; entry 16: 1:6.2 **IV**:**III**).

Synthesis of Diverse, Bicyclic and Tricyclic Small Molecules. The utility of dienes **IV** and enynes **III** as substrates for complexity-generating transformations was explored next. Diels–Alder cycloaddition between silacycle **53** and either *N*-ethylmaleimide or *N*-methylmaleimide proceeded to completion after 2 h at 80 °C, yielding **54** and **55**, respectively, as single diastereoisomers.[18] The stereochemistry of these cycloadducts was determined through one-dimensional nOe experiments (Figure 2 for key enhancements; see Supporting Information for full details). In contrast to cycloaddition of **53**, when the diene was first desilylated and then treated with 4-methyl-4-*H*-1,2,4-triazole-3,5-dione, a statistical mixture of cycloadducts **57** and **58** was generated in 62% combined yield. Interestingly, the high level of diastereocontrol with the cyclic diene **53** (>20:1 dr) was not carried over to its desilylated counterpart **56** (1:1 dr). At the present time, we have no explanation for this phenomenon.

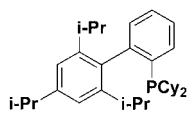
A different set of skeletons could be accessed starting from tethered enynes. Similar to the systems studied by Lee et al., metathesis of **59** with Grubbs II catalyst proceeded at 140 °C to a 4.1:1 mixture of the *exo*-silacycle **60** and six-membered *endo*-silacycle **61** (Figure 3).[19] Desilylation after chromatographic separation allowed access to the corresponding acyclic isomeric dienes **62** and **63** in 97% and 74% yields, respectively.

Although cycloaddition of **60** proved difficult due both to the hindered nature of the diene and instability of the various corresponding cycloadducts,[20] **63** was cleanly converted under thermal conditions to cycloadducts **64** and **65**, and **62** was subjected to various dienophiles to provide bicyclic compounds **66–73** (Table 4). Facial selectivity in these systems was variable; however, when maleimides were used,

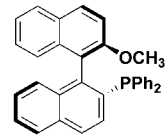
Table 2. Catalyst, Ligand, and Additive Screening



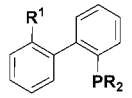
Selected phosphines:



X-PHOS 41

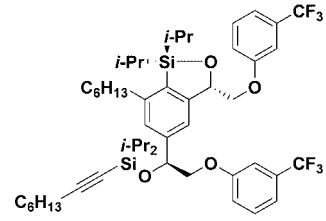


(R)-MOP 42



Cy_2P-Biphen 46 (R=Cy; R^1=H)
Ph_2P-Biphen-NMe_2 47 (R=Ph; R^1=NMe_2)
t-Bu_2P-Biphen 48 (R=*t*-Bu; R^1=H)
Cy_2P-Biphen-NMe_2 49 (R=Cy; R^1=NMe_2)

Cyclodimerization adduct:



52

entry[a]	subst	Pd[b]	ligand	hydride source[c]	ratio **50**:**51**[d]	conv (%)[e]	**52** (%)[e]
1	**16**	**33**	P(*o*-tolyl)$_3$ **38**	Et_3SiH	1.6:1	>95	8
2	**16**	**34**	P(*o*-tolyl)$_3$ **38**	Et_3SiH	2.7:1	>95	9
3	**16**	**35**	P(*o*-tolyl)$_3$ **38**	Et_3SiH	2.1:1	>95	12
4	**16**	**36**	P(*o*-tolyl)$_3$ **38**	Et_3SiH		<5	<2
5	**16**	**37**	P(*o*-tolyl)$_3$ **38**	Et_3SiH	2.0:1	>95	12
6	**16**	**33**	P(*o*-tolyl)$_3$ **38**	PMHS	1:11.2	>95	<2
7	**16**	**33**	P(*o*-tolyl)$_3$ **38**	Bu_3SnH		<5	<2
8	**16**	**33**	PPh_3 **39**	Et_3SiH	1.4:1	>95	13
9	**16**	**33**	PCy_3 **40**	Et_3SiH	1:1.3	>95	7
10	**16**	**33**	X-PHOS **41**	Et_3SiH	1:6.0	70	<2
11	**16**	**33**	(*R*)-MOP **42**	Et_3SiH	1:3.1	>95	4
12	**16**	**34**	dppe **43**	Et_3SiH		<5	<2
13	**16**	**34**	dppb **44**	Et_3SiH		<5	<2
14	**16**	**34**	Ctc-Q-PHOS **45**	Et_3SiH	1:1.4	>95	9
15	**16**	**34**	Cy_2P-biphen **46**	Et_3SiH	1:3.7	>95	<2
16	**16**	**34**	Ph_2P-biphen-NMe_2 **47**	Et_3SiH	1.7:1	>95	4
17	**16**	**34**	*t*-Bu_2P-biphen **48**	Et_3SiH	1:6.8	54	<2
18	**16**	**34**	Cy_2P-biphen-NMe_2 **49**	Et_3SiH	1:1.4	>95	<2

[a] See Supporting Information for experimental procedure. [b] Pd precatalysts: **33** = Pd_2dba_3-$CHCl_3$; **34** = Pd_2dba_3; **35** = $Pd(dba)_2$; **36** = $Pd(PPh_3)_4$; **37** = $Pd(OAc)_2$. [c] 10 μg/mmol PMHS/**16** (polymethylhydrosiloxane) was used in entry 6. [d] Product ratios determined by ^{1}H NMR spectroscopy; see Supporting Information for details. [e] Conversions determined by ^{1}H NMR spectroscopy; see Supporting Information for details.

complete *endo*-selectivity was observed. Stereochemical assignments were made on the basis of nOe enhancement studies of cycloadducts and derivatives thereof (see Supporting Information).

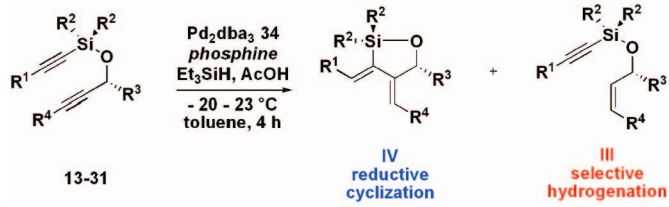
Conclusions

In summary, we describe two reductive transformations of silyl ether-tethered diynes, including the first reductive cyclization of this substrate class. The key feature of this method relies on ligand selection to control product outcome. Densely substituted, stereochemically and appendage-rich bicyclic and tricyclic small molecules were accessed that are especially suited to explore the role of positional isomerism on biological activity. Towards this end, molecules described herein have been submitted to multidimensional, small-molecule screening to elucidate the roles of skeletons, stereochemistry, and appendages on bioactivity.[21]

Experimental Section

General Techniques. Except as otherwise noted, reactions were carried out under nitrogen with dry, freshly purified solvents. Solvents were purified by passage through a column of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). NMR spectra were recorded at 600, 500, 400, or 300 MHz for all compounds using Varian I-600, Varian I-500, Varian M-400, Varian M-300, and Bruker Biospin 300 instruments. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR data were recorded at 125, 100, or 75 MHz for all compounds using Varian I-500, Varian M-400, or Bruker Biospin 300 MHz instruments, respectively. ^{13}C NMR chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded using a Perkin-Elmer FT–IR spectrometer (thin film or neat, as indicated). Mass spectra were obtained with JEOL AX 505, JEOL SX-102, and Micromass ESI-LCT spectrometers. *N*-bromosuccinimide was purchased from Aldrich and dried *in vacuo* prior to use. Pd_2dba_3, Pd_2dba_3-chloroform adduct, $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $Pd(dba)_2$ were purchased from Strem, stored, and weighed in a dry box under inert atmosphere. Tri-*o*-tolylphosphine, tricyclohexylphosphine, 2-(dicyclohexylphosphino)-2′,4′,6′-tri-*i*-propyl-1,1′-biphenyl, and (*R*)-(+)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl were purchased from Strem, stored, and weighed in a dry box under inert atmosphere. Diphenylphosphinobutane (dppb)

Table 3. Substrate Scope under Different Catalyst Systems



						34/P(*o*-tolyl)$_3$		**34**/X-PHOS		**34**/*t*-Bu$_2$P **48**	
entry[a]	subst	R^1	R^2	R^3	R^4	ratio[b] **IV**:**III**	conv (%)[c]	ratio[b] **IV**:**III**	conv (%)[c]	ratio[b] **IV**:**III**	conv (%)[c]
1	**13**	C_6H_{13}	*i*-Pr	Ph	H	1.8:1	>95	1:1.9	32	1.4:1	>95
2	**14**	C_6H_{13}	*i*-Pr	C_5H_{11}	H	3.2:1	>95	1.4:1	>95	1:3.0	>95
3	**15**	C_6H_{13}	*i*-Pr	C_2H_5	CH_3	1:1.8	67	2.5:1	30	1:3.4	27
4	**16**	C_6H_{13}	*i*-Pr	**12**	H	2.7:1	>95	1:6.0	70	1:6.8	54
5	**17**	C_6H_{13}	Ph	Ph	H	1.9:1	53	1:1.9	>95	1:6.7	>95
6	**18**	Ph	*i*-Pr	Ph	H	1:1.5	60	<1:20	22	<1:20	47
7	**20**	Ph	*i*-Pr	C_2H_5	CH_3	1:4.1	71	<1:20	7	<1:20	>95
8	**21**	Ph	*i*-Pr	**12**	H	1:1.9	72	<1:20	>95	<1:20	>95
9	**23**	*o*-tol	*i*-Pr	C_5H_{11}	H	1:4.4	>95	1:2.6	43	1:8.5	28
10	**24**	*o*-tol	*i*-Pr	**12**	H	1:2.5	>95	1:8.9	56	<1:20	34
11	**25**	*i*-Pr	*i*-Pr	Ph	H	3.3:1	>95	1:2.0	39	1:7.1	39
12	**26**	*i*-Pr	*i*-Pr	C_5H_{11}	H	8.3:1	>95	2.4:1	>95	1:7.0	68
13	**27**	*i*-Pr	*i*-Pr	C_2H_5	CH_3	1.6:1	>95	1:1.1	>95	<1:20	54
14	**28**	*i*-Pr	*i*-Pr	**12**	H	2.8:1	>95	1:2.7	>95	<1:20	>95
15	**30**	$Ph(CH_2)_2$	*i*-Pr	Ph	H	4.5:1	>95	1:4.5	34	<1:20	>95
16	**31**	$Ph(CH_2)_2$	*i*-Pr	C_5H_{11}	H	7.1:1	>95	1.4:1	>95	1:6.2	47%

[a] See Supporting Information for experimental procedure. [b] Product ratios determined by ^{1}H NMR spectroscopy; see Supporting Information for details. [c] Conversions determined by ^{1}H NMR spectroscopy; see Supporting Information.

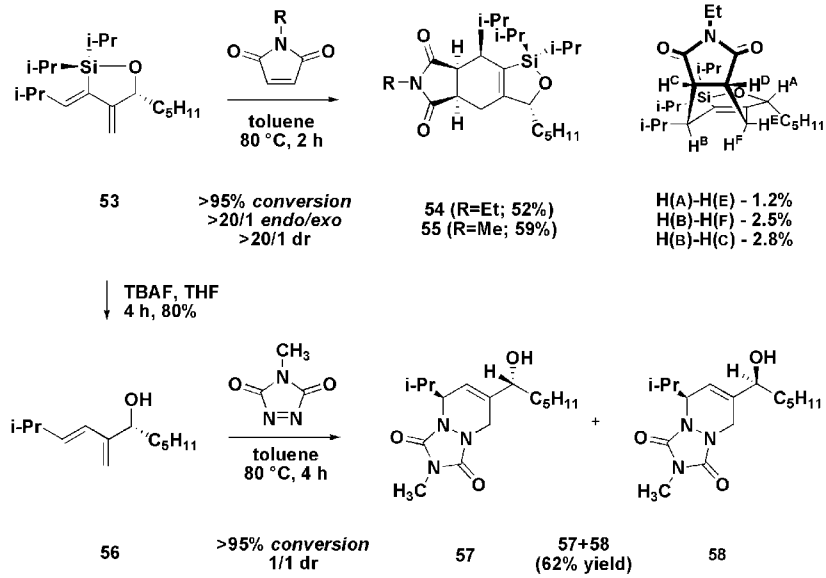


Figure 2. Utility of reductive cyclization products in complexity-generating transformations. Tricyclic, silicon-containing, and fused bicyclic structures were obtained by cycloaddition and desilylation/cycloaddition sequences, respectively. Stereochemical assignments of **54–55** were made on the basis of one-dimensional nOe experiments.

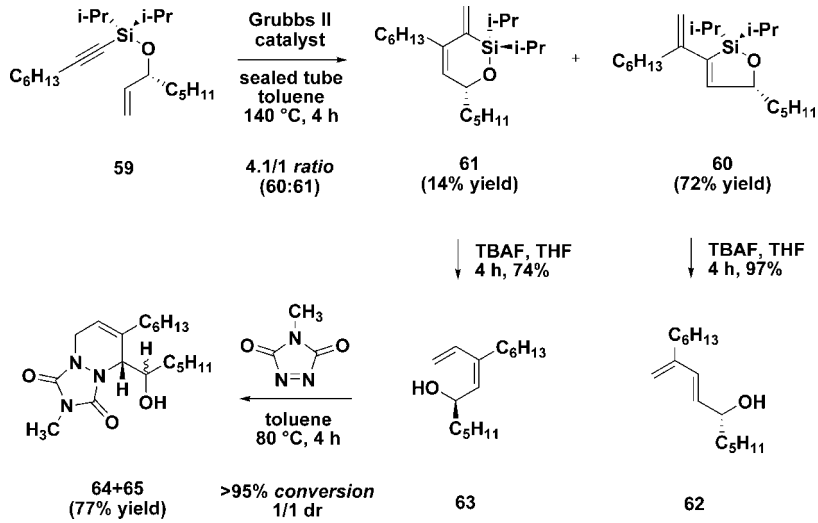
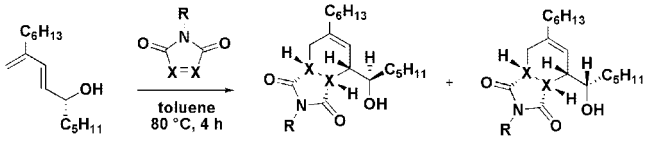


Figure 3. Silyl ether-tethered enynes were used as substrates for complexity-generating transformations. Fused bicyclic structures were obtained by a three-step sequence involving metathesis, desilylation, and cycloaddition.

Table 4. Cycloaddition Reactions Initiated from Diene **62**



entry	R	X	prod[a]	conv (%)[b]	dr	endo (%)	yields
1	Bn	C	**66**; **67**	>95	1.4/1	>20/1	52; 38
2	Me	C	**68**; **69**	>95	1.2/1	>20/1	45; 34
3	Me	N	**70**; **71**	71	2.0/1		(59)
4	Ph	N	**72**; **73**	72	2.0/1		(64)

[a] Product ratios determined by ^{1}H NMR spectroscopy; see Supporting Information for details. [b] Conversions determined by ^{1}H NMR spectroscopy; see Supporting Information. [c] Yields in parentheses for cases in which product diastereomers were chromatographically inseparable and were recovered together.

and diphenylphosphinoethane (dppe) were purchased from Aldrich, stored, and weighed in a dry box under inert atmosphere. Triphenylphosphine was recrystallized prior to use, stored, and weighed in a dry box under inert atmosphere. All other reagents were purchased commercially and used as received.

Representative Procedure for Silyl Ether Formation. Reaction Sequence Used for the Generation of 16. 1-Octyne (1.00 g, 9.07 mmol) was weighed into a flame-dried round-bottom flask equipped with magnetic stirrer and dissolved in THF (9.0 mL). The solution was cooled to −78 °C and a 2.5 M *n*-BuLi solution in hexanes (3.62 mL, 9.07 mmol) was introduced dropwise. After 45 min, chlorodiisopropylsilane (1.55 mL, 9.07 mmol) was added dropwise, and the mixture warmed to ambient temperature. After 20 h, the solution was diluted with Et_2O (9.0 mL) and quenched with a saturated solution of NH_4Cl (18.0 mL). Extraction was carried out using Et_2O, and combined organics were washed using saturated aqueous NaCl and H_2O. Drying over $MgSO_4$ and concentration afforded diisopropyl(oct-1-ynyl)silane (1.97 g, 8.78 mmol, 97%) which was used without further purification. Diisopropyl(oct-1-ynyl)silane (250 mg, 1.11 mmol) was moved to a tapered flask equipped with a magnetic stirrer and dissolved in CH_2Cl_2 (2.5 mL). *N*-bromosuccinimide (198 mg, 1.11 mmol) was slowly introduced in 10–15 mg portions to the rapidly stirring solution, giving a pale yellow solution that was maintained under argon for 30 min and then added to a stirring solution of 1-(3-(trifluoromethyl)phenoxy)but-3-yn-2-ol (230 mg, 1.00 mmol), triethylamine (155 μL, 1.10 mmol), and 4-dimethylaminopyridine (13 mg, 0.10 mmol, 10 mol %) in CH_2Cl_2 (2.0 mL). After 12 h, the solution was concentrated and the crude mixture was purified by silica chromatography using an Isco Combiflash 40 g column with 20:1 hexanes/EtOAc as eluant to give diisopropyl(oct-1-ynyl)(1-(3-(trifluoromethyl)phenoxy)but-3-yn-2-yloxy)silane **16** (332 mg, 0.73 mmol, 66%) as a clear oil.

Diisopropyl(oct-1-ynyl)(1-(3-(trifluoromethyl)phenoxy) but-3-yn-2-yloxy)silane 16. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (t, J = 7.91, 1 H); 7.21 (d, J = 7.91, 1 H); 7.10 (dd, J = 8.35, 2.34, 1 H); 5.00–4.98 (m, 1 H); 4.15–4.11 (m, 2 H); 2.48 (d, J = 2.05, 1 H); 2.24 (t, J = 7.03, 2 H); 1.54–1.49 (m, 2 H); 1.43–1.38 (m, 2 H); 1.32–1.23 (m, 4 H); 1.09–1.08 (m, 6 H); 1.03–1.02 (m, 6 H); 1.05–0.98 (m, 2 H); 0.87 (t, J = 6.74, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 129.9, 118.1, 117.7, 117.6, 111.7, 111.1, 82.1, 77.8, 73.5, 71.8, 62.8, 31.2, 28.4, 28.4, 22.5, 19.7, 17.1, 17.0, 16.9, 16.9, 14.0, 13.3, 12.9. IR (film): 3322, 2930, 2860, 2168, 1602, 1442, 1330, 1246, 1183, 1120, 1050, 959, 882, 784, 694, 659 cm^{-1}.

Representative Procedure for Reductive Transformations. Palladium precatalyst **33**–**37** (0.4 μmol, 2.5 mol %) and phosphine ligand **38**–**49** (1.6 μmol, 10 mol %) were weighed into a flame-dried round-bottom flask under dry box conditions and sealed. After removal from the dry box, toluene (0.2 mL) was added under a N_2 atmosphere. The resultant burgundy solution was stirred for 3–5 min at temperature $\mathbf{T_I}$, at which time a solution of glacial acetic acid (1.92 mg, 32.0 μmol) in toluene (0.2 mL) was added by syringe. After an additional 3–5 min, a solution of triethylsilane (18.4 mg, 160 μmol) in toluene (0.2 mL) was introduced. The flask was then incubated for 5 min, at which time a solution of diyne **13**–**31** (16.0 μmol) in toluene (0.2 mL) was added. After stirring for 5 min at temperature $\mathbf{T_{II}}$, the flask was brought to the final reaction temperature $\mathbf{T_{III}}$

and incubated for 4 h. After cooling of the clear solution (Pd black was observed on the vessel walls), the reaction was concentrated *in vacuo* and taken up into $CDCl_3$ for analysis by ^1H NMR spectroscopy. For reactions involving substrate **16** (Table 2), conversions were determined by ^1H NMR spectroscopy, using integration of the alkenyl proton H(A) in **50** (6.7 ppm), the alkenyl proton H(B) in **51** (5.9 ppm), and the methine proton H(C) in **16** (5.0 ppm). Product ratios were determined by ^1H NMR spectroscopy, using integration of the alkenyl proton H(A) in **50** (6.7 ppm) and the alkenyl proton H(B) in **51** (5.9 ppm).

Results in Tables 2 and 3 given for $\mathbf{T}_{I} = -20$ °C, $\mathbf{T}_{II} = -20$ °C, and $\mathbf{T}_{III} = 23$ °C. See Supporting Information for full details of temperature optimization studies.

(*Z*)-2,2-Diisopropyl-4-methylene-3-(2-methylpropylidene)-5-phenyl-1,2-oxasilolane. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.27 (m, 5 H); 6.45 (d, $J = 10.25$, 1 H); 5.47 (t, $J = 1.83$, 1 H); 5.29 (d, $J = 2.20$, 1 H); 4.34 (d, $J = 2.20$, 1 H); 2.29–2.21 (m, 1 H); 1.21–1.04 (m, 20 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.2, 128.2, 127.8, 126.5, 116.6, 84.5, 76.9, 73.5, 65.7, 22.9, 21.4, 17.1, 17.0, 17.0, 13.4, 12.9. IR (film): 3308, 2944, 2860, 2168, 1470, 1309, 1190, 1043, 1001, 959, 882, 833, 736, 694, 652, 610, 575, 526 cm^{-1}. HRMS calcd for $C_{20}H_{30}OSi$ ($M^+ + H$), 315.2144; found, 315.2155.

Representative Procedure for Enyne Metathesis. Reaction Sequence Used for the Generation of 60 and 61. Diisopropyl(oct-1-en-3-yloxy)(oct-1-ynyl)silane **59** (436 mg, 1.24 mmol) was weighed into a sealed tube equipped with a magnetic stirrer and dissolved in toluene (14 mL). Grubbs' second-generation catalyst (262 mg, 0.31 mmol, 25 mol %) was introduced as a solid, and the tube was sealed and heated to 140 °C for 4 h. After cooling and evaporation of the solvent *in vacuo*, the crude reaction mixture was purified by silica chromatography using an Isco Combiflash 40 g column with 20:1 hexanes/EtOAc to 1:1 hexanes/EtOAc (as a gradient) to give 2,2-diisopropyl-3-(oct-1-en-2-yl)-5-pentyl-2,5-dihydro-1,2-oxasilole **60** (313 mg, 0.89 mmol, 72%) and 4-hexyl-2,2-diisopropyl-3-methylene-6-pentyl-3,6-dihydro-2H-1,2-oxasiline **61** (60.9 mg, 0.17 mmol, 14%), separately, as clear oils.

2,2-Diisopropyl-3-(oct-1-en-2-yl)-5-pentyl-2,5-dihydro-1,2-oxasilole (60). ^1H NMR (500 MHz, $CDCl_3$) δ: 6.62 (d, $J = 1.72$, 1 H); 4.96 (s, 1 H); 4.80 (s, 1 H); 4.66 (t, $J = 4.48$, 1 H); 2.27 (t, $J = 7.21$, 2 H); 1.52–1.42 (m, 6 H); 1.31–1.29 (m, 9 H); 1.08–0.91 (m, 15 H); 0.89 (t, $J = 5.40$, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.8, 145.6, 115.0, 82.2, 37.9, 34.2, 32.0, 31.7, 29.2, 28.3, 25.4, 22.6, 17.7, 17.4, 17.3, 17.1, 14.1, 14.0, 13.7, 12.9. IR (film): 2958, 2924, 2860, 1721, 1609, 1448, 1379, 1085, 1050, 931, 882, 791, 687 cm^{-1}.

4-Hexyl-2,2-diisopropyl-3-methylene-6-pentyl-3,6-dihydro-2*H*-1,2-oxasiline (61). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.79 (s, 1 H); 5.43 (br s, 1 H); 5.23 (s, 1 H); 4.52; (br s, 1 H); 2.30–2.20 (m, 2 H); 1.59–1.37 (m, 6 H); 1.29 (m, 9 H); 1.09–0.94 (m, 15 H); 0.89 (t, $J = 6.8$ Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.6, 139.1, 131.4, 128.4, 120.4, 73.3, 39.2, 35.7, 33.1, 31.8, 29.3, 28.9, 24.9, 22.6, 17.9, 17.6, 17.4, 17.3, 17.1, 14.0, 13.5, 12.2. IR (film): 2958, 2924, 2868, 1742, 1707, 1470, 1379, 1253, 1176, 1106, 1057, 910, 875, 680 cm^{-1}.

Representative Procedure for Desilylation Reactions. Reaction Sequence Used for the Generation of 62. 2,2-Diisopropyl-3-(oct-1-en-2-yl)-5-pentyl-2,5-dihydro-1,2-oxasilole **60** (379 mg, 1.08 mmol) was weighed into a flame-dried round-bottom flask equipped with a magnetic stirrer and dissolved in THF (11 mL). *Tetra*butylammonium fluoride (2.16 mL, 2.16 mmol, 1 M solution) was introduced dropwise by syringe, yielding an orange solution that was maintained for 4 h. After addition of a saturated ammonium chloride solution to the reaction, the mixture was extracted with three portions of ethyl acetate (20 mL), and combined organics were washed twice with saturated sodium chloride solution (40 mL). After drying over magnesium sulfate and concentration *in vacuo*, the crude product was purified by silica chromatography using an Isco Combiflash 40 g column with 20:1 hexanes/EtOAc to 4:1 EtOAc/hexanes (as a gradient) to give (*E*)-9-methylenepentadec-7-en-6-ol **62** (250 mg, 97%) as a clear oil.

(*E*)-9-Methylenepentadec-7-en-6-ol (62). ^1H NMR (500 MHz, $CDCl_3$) δ: 6.22 (d, $J = 15.62$, 1 H); 5.70 (dd, $J = 15.62$, 6.83, 1 H); 4.99 (s, 1 H); 4.96 (s, 1 H); 4.15 (dd, $J = 12.93$, 6.83, 1 H); 2.19 (t, $J = 7.81$, 2 H); 1.60–1.26 (m, 16 H); 0.89 (app t, $J = 6.83$, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.8, 132.6, 131.8, 115.3, 73.2, 37.4, 32.1, 31.8, 31.7, 29.2, 28.2, 25.1, 22.6, 22.6, 14.1, 14.0. IR (film): 3343, 2972, 2930, 2860, 1616, 1470, 1379, 1148, 1015, 959, 882, 722 cm^{-1}. HRMS calcd for $C_{16}H_{30}O$ ($M^+ + H$), 239.2375; found, 239.2372.

Representative Optimized Procedure for Diels–Alder Cycloadditions. Reaction Sequence Used for the Generation of 68 and 69. (*E*)-9-methylenepentadec-7-en-6-ol **62** (9.3 mg, 0.04 mmol) was weighed into a sealed tube, and toluene (200 μL) was added by microsyringe. A separate solution of *N*-methylmaleimide (4.4 mg, 0.04 mmol, 1.0 equiv) in toluene (200 μL) was added dropwise to the resultant solution. The vessel was sealed and heated to 80 °C for 4 h, then cooled to ambient temperature. Solvent was removed under reduced pressure, and the crude material was then taken up in chloroform and purified using a 4 g Isco Combiflash silica column with hexanes/EtOAc as eluant (10:1 to 1:1 gradient). After removal of solvent *in vacuo*, (3a,7a)-2-benzyl-6-hexyl-4-(1-hydroxyhexyl)-3a,4,7,7a-tetrahydro-2H-isoindole-1,3-dione **68** (6.3 mg, 0.018 mmol, 45%) and (3a,7a)-2-benzyl-6-hexyl-4-(1-hydroxyhexyl)-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione **69** (4.7 mg, 0.014 mmol, 34%) was obtained.

(3a,7a)-6-Hexyl-4-(1-hydroxyhexyl)-2-methyl-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (68). ^1H NMR (500 MHz, $CDCl_3$) δ: 5.75 (s, 1 H); 4.12 (d, $J = 3.09$, 1 H); 3.64 (d, $J = 2.93$, 1 H); 3.19–3.13 (m, 2 H); 2.92 (s, 3 H); 2.58 (d, $J = 15.13$, 1 H); 2.20 (m, 1 H); 2.17–2.15 (m, 1 H); 1.99–1.96 (m, 2 H); 1.64 (dd, $J = 18.06$, 8.30, 2 H); 1.53–1.46 (m, 2 H); 1.38–1.28 (m, 6 H); 1.27–1.17 (m, 6 H); 0.90 (t, $J = 6.34$, 3 H); 0.86 (t, $J = 6.83$, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.2, 179.8, 141.3, 122.5, 71.8, 43.2, 41.2, 40.4, 36.9, 35.6, 31.9, 31.6, 28.8, 28.3, 27.1, 25.8,

24.9, 22.7, 22.6, 14.0. IR (film): 3504, 2958, 2930, 2854, 1770, 1679, 1448, 1386, 1337, 1281, 1141, 1106, 1057, 1008 cm^{-1}. HRMS calcd for $C_{21}H_{35}NO_3$ ($M^+ + H$), 350.2695; found, 350.2708.

(3a,7a)-6-Hexyl-4-(1-hydroxyhexyl)-2-methyl-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (69). ^1H NMR (500 MHz, $CDCl_3$) δ: 5.22 (s, 1 H); 3.76 (m, 1 H); 3.72 (d, J = 5.37, 1 H); 3.46 (app t, J = 8.30, 1 H); 3.15 (app t, J = 7.32, 1 H); 2.92 (s, 3 H); 2.62 (d, J = 15.13, 1 H); 2.24–2.23 (m, 1 H); 2.13 (dd, J = 14.89, 6.83, 1 H); 1.96 (t, J = 6.83, 2 H); 1.62–1.57 (m, 2 H); 1.55–1.40 (m, 2 H); 1.36–1.15 (m, 12 H); 0.90 (t, J = 6.83, 3 H); 0.87 (t, J = 6.83, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.8, 140.7, 121.1, 71.3, 45.2, 42.0, 40.6, 36.9, 36.4, 31.8, 28.8, 28.6, 27.3, 25.8, 24.9, 22.6, 22.6, 17.2, 14.0. IR (film): 3448, 2951, 2916, 2854, 1763, 1679, 1428, 1386, 1288, 1148, 1120, 1057, 1001 cm^{-1}. HRMS calcd for $C_{21}H_{35}NO_3$ ($M^+ + H$), 350.2695; found, 350.2683.

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Supporting Information Available. Experimental procedures, NMR, characterization data, and stereochemical assignments for cycloadducts. This information is available free of charge via the Internet at http://pubs.acs.org.

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