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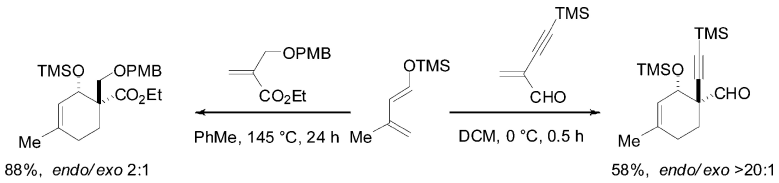

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Creating Quaternary Centers with High Exo Stereoselectivity Using Activated α-Alkynyl Dienophiles

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The stereoselective creation of quaternary centers in complex organic molecules is a daunting challenge. Approaches based on C−C bond formation with hindered centers continue to be reported.[1] We have found that electronic activation and small steric demand by the ethynyl group provide a facile method for stereospecific creation of quaternary centers and provide a theoretical explanation of these phenomena.

The general discovery began with the successful total synthesis of paecilomycine A (**1**),[2] a small molecule natural product reported to enhance neurite outgrowth at 10 nM concentrations.[3] The key step in this synthesis was the Diels-Alder (DA) reaction of activated butadiene **2**[4] with Danheiser's alkynylacrolein **3**[5] (Scheme 1). This strategy circumvented the use of α-alkyl-substituted acrylates that have been used in DA reactions to construct quaternary carbon centers of natural products[6] but which require elevated temperatures and give low selectivities.[7]

We showed that ethynyl substituents have a large effect on the rates of DA reactions of alkenes with electron-rich dienes,[8] an observation not previously reported in the literature. Table 1 summarizes new experimental results for the DA reactions of α,β-unsaturated carbonyl compounds α-substituted by alkyl and ethynyl groups with acyclic and cyclic dienes. In general, use of α-ethynyl substituted dienophiles (**3**, **8**) significantly lowered the temperatures required for DA reactions and provided major increases in the endo selectivity in comparison with the dienophiles involving α-alkyl substituted acrylates (**5**) or acroleins (**7**) (cf. entries 1−3 vs 4−9).

We next expanded these studies to the formation of *cis*-decalins containing a quaternary center, a frequent synthetic target. Notably, the cycloaddition of diene **2** or synergistically activated diene **9** with the α-ethynylcyclohexenone **13**[9] proceeds in high yield and provides greater than 20:1 endo selectivity (Scheme 2). This is remarkable given the lack of reactivity of 2-alkyl substituted cyclohexenones in Diels−Alder reactions without requisite Lewis acid activation.[10] Furthermore, the cycloadduct can be converted to the ester **16** via hydroboration/oxidation,[11] affording a synthetically useful carboxymethyl group.

Transition-state calculations help isolate the origin of these dramatic substituent effects. Reactants and transition structures were optimized with B3LYP/6-31G(d)[12,13] in the Gaussian 03 suite of computational programs.[14] Figure 1 shows transition structures (TSs) and activation enthalpies for cycloadditions of 1-siloxy-3-methyl-1,3-butadiene, a computational model for **2**, with various dienophiles.

Whereas the vinyl substituent slightly (1.3 kcal/mol) lowers the activation barrier, the ethynyl and ethynylsilyl substituents provide 4−6 kcal/mol lowering of activation barriers (10^3−10^4 acceleration at 25 °C). The combination of formyl and ethynylsilane activation provides a 16 kcal/mol reduction (10^{10} acceleration) in the barrier of the reaction. The ethynyl group better stabilizes the charge transfer from diene to dienophile. This is reflected in the charge separation computed for the transition states (0.04*e* for butadiene vs 0.07*e* for butenyne). An ethynyl group stabilizes a negative charge more than a vinyl group, reflecting the greater electronegativity of the ethynyl group.[15]

Scheme 1. The Synthesis of Paecilomycine A

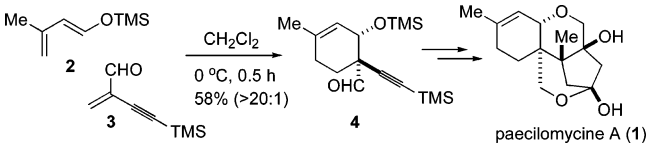
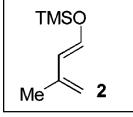
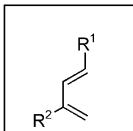
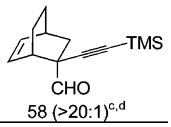


Table 1. DA Reactions of α-Substituted-α,β-Unsaturated Carbonyl Compounds with Various Dienes

Diene	Dienophile			Conditions (solvent, °C,h)	Product %yield (*endo/exo*)
					
		R^1	R^2		
1[a] **2**	**5**	(CH_2OPMB,	OEt)	Tol, 145, 24	88 (2:1)[b]
2 **2**	**6**	(H,	OMe)	PhH, 80, 16	96 conversion (2:1)
3[a] **2**	**7**	(CH_2OPMB,	H)	PhH, 80, 22	87 (6:1)
4[a] **2**	**8**	(≡—TMS,	OMe)	DCM, 25, 2.5	86 (>10:1)
					
		R^1	R^2		
5[a] **2**	(OTMS,	Me)	**3**	DCM, 0, 0.5	58 (>20:1)[c,d]
6 **9**	(OMe,	OTMS)	**3**	DCM, 0, 0.5	67 (13:1)[c,d]
7 **10**	(Me,	H)	**3**	DCM, 23,15	48 (13:1)[c,d]
8 **11**	(H,	Me)	**3**	DCM, 23, 8	46[c,d,e]
9 **12**			**3**	DCM, 23, 20	 58 (>20:1)[c,d]

[a] Reference 2. [b] The yield and the ratio were obtained after removal of TMS group by TBAF. [c] The yield was calculated from 2-methylene-4-(trimethylsilyl)but-3-yn-1-ol. [d] As originally identified in ref 5, small amounts of dimerized **3** were produced in some cases (see Supporting Information for details). [e] 4:1 regioselectivity.

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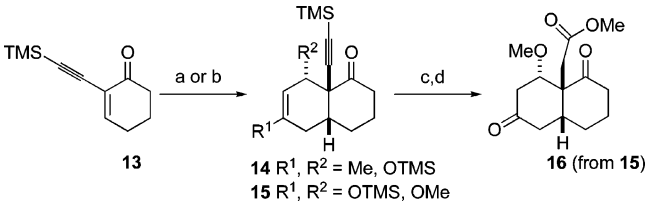
Scheme 2. The Synthesis of *cis*-Decalins with Quaternary Centers by Ethynyl Activation[a]



[a] Reagents and conditions: (a) **2**, PhH, 85−90 °C, 40 h, 96% (>20:1); (b) **9**, PhH, 85−90 °C 24 h, 95% (>60:1); (c) Cy_2BH, $NaHCO_3$ H_2O_2, AcOH, 44%; (d) $TMSCHN_2$ PhH/MeOH, 81%.

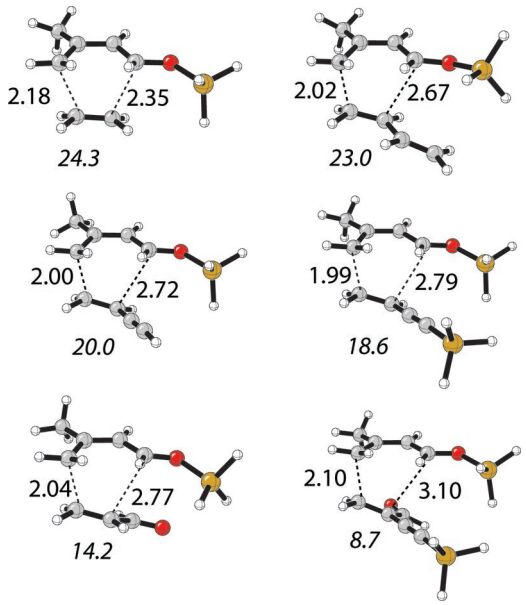


Figure 1. Transition structures and activation enthalpies, in italics, for cycloadditions of 1-siloxy-3-methyl-1,3-butadiene with ethylene, butadiene, butenyne, 1-silylbutenyne, acrolein, and α-silylethynyl acrolein.

Table 2. Activation Enthalpies, in kcal/mol, for the Formation of Endo and Exo Adducts in the Reactions of 1-siloxy-3-methyl-1,3-butadiene with Various Alkenes[a,b]

	$\Delta H^{\ddagger}_n$	$\Delta H^{\ddagger}_x$	$\Delta\Delta H^{\ddagger}_{n\text{-}x}$
−CHO	14.2	15.9	−1.7
$-CO_2Me$	16.9	17.1	−0.2
$-CH_3$	27.0	27.2	−0.2
$-CH{=}CH_2$	23.8	23.0	+0.8
$-OCH_3$	31.4	28.9	+2.5
−C≡C−H	21.1	18.6	+2.5
$-C{\equiv}C-SiH_3$	22.7	20.0	+2.7

[a] The subscripts "*n*" and "*x*" refer to the *endo* and *exo* cycloadditions. [b] Activation enthalpies for formation of the 1,2,4-trisubstituted adducts.

Turning to endo/exo selectivities, Table 2 shows computed activation enthalpies and enthalpic differences, $\Delta\Delta H_{n-x}$, for endo and exo cycloadditions. Reactions involving the electron-deficient alkenes, acrolein and methyl acrylate, are slightly endo selective ($\Delta\Delta H_{n-x} = -1.7$ and -0.2 kcal/mol, respectively). These are the result of stabilizing secondary orbital and Coulombic interactions in the TSs of the reactions.[16] By contrast, reactions involving conjugated or electron-rich alkenes, that is, those substituted with vinyl, methoxy, ethynyl, and ethynylsilane substituents, are exo selective with relative enthalpic barriers ranging from +1 to +3 kcal/mol. Notably, the small ethynyl groups show the largest exo selectivity. This is evidence for the role of closed-shell repulsion between the filled π-orbitals of the substituent and the diene in the endo TSs.[17,18] For methyl, the predicted selectivity is negligible ($\Delta\Delta H_{n-x} = -0.2$ kcal/mol). Notably, the combination of *endo*-formyl (1.7 kcal/mol) and *exo*-ethynylsilyl (2.7 kcal/mol) monosubstitution is predicted to be favored by a combined 4.4 kcal/mol, which overestimates the experimentally observed selectivity (~1.8 kcal/mol for 20:1 endo/exo product ratio).

The α-ethynyl-substituted alkenes readily participate in thermal Diels−Alder cycloadditions at room temperature. The experimentally observed high *exo*-ethynyl preference results from repulsive orbital interactions between the ethynylsilane substituent and the electron-rich diene in the disfavored endo TS, while the high selectivity results from charge stabilization in the highly asynchronous TS.

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Supporting Information Available: Complete ref 14, experimental details, B3LYP Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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