

Novel Chemoselectivity and Stereochemical Aspects of Nickel-Catalyzed [2 + 2 + 2] Cycloadditions

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Metal-catalyzed cyclotrimerizations are well-precedented with a range of substrate classes and with a variety of metal catalysts.^{1,2} Features that are shared by nearly all variants include a high propensity for the incorporation of alkynes over alkenes and a high degree of stereospecificity in cases in which alkenes are incorporated. While investigating the role of organozinc structure in determining selectivities between reductive and alkylative pathways in nickel-catalyzed cyclizations of alkynyl enones,^{3,4} we found that an unexpected dimerization involving a formal [2 + 2 + 2] cycloaddition process was observed as a side reaction in some instances. A control experiment demonstrated that the organozinc component was not required for the [2 + 2 + 2] cycloaddition to occur, and that nearly quantitative yields of the [2 + 2 + 2] product were obtained upon exposure of alkynyl enones to Ni(COD)₂ and PPh₃ (Table 1).

In addition to the inherent interest in a reaction that assembles two rings and four contiguous stereocenters in a completely stereoselective fashion from an acyclic, achiral substrate, several additional features were perhaps even more intriguing. First, the reaction chemoselectivity was quite unusual. The formal dimerization by a [2 + 2 + 2] reaction of an alkynyl enone requires that three unsaturated groups are incorporated while one is left unchanged, and an alkyne is the one functional group that does not participate in the cyclization. This chemoselectivity was confirmed to be quite general since treatment of alkynyl enone (**E**)-**1** with Ni(COD)₂ in the presence of 5 equiv of a variety of internal and terminal alkynes all led to efficient formation of dimer **4** without incorporation of the simple alkyne. For the alkyne unit to remain unaffected during this process goes against all expectations based on earlier investigations of related processes.⁵ This general trend was particularly well demonstrated in the early cobalt-catalyzed cyclotrimerizations of Vollhardt,² and numerous related observations have been reported.^{6–10} The structurally distinct case of the nickel-catalyzed homo-Diels–Alder reaction of norbornadienes largely explored by Lautens is a rare example in which multiple alkene units are selectively incorporated in a metal-catalyzed [2 + 2 + 2] cycloaddition process.¹¹

A second intriguing feature is that the initial trans stereochemistry of the starting enone (**E**)-**1** was cleanly inverted in product **4** at the position adjacent to the ring juncture. This unexpected stereochemistry was confirmed by single-crystal X-ray analysis.¹² Metal-catalyzed cycloadditions typically display high stereospecificity

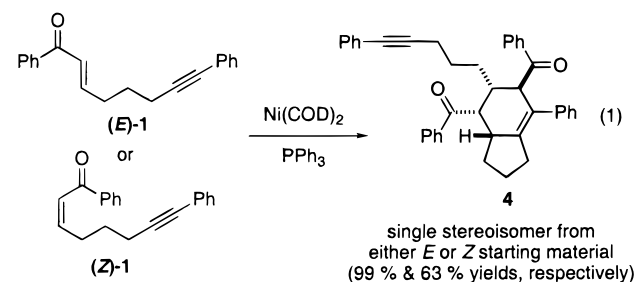
[§] To whom correspondence regarding X-ray structure determinations should be addressed.

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Table 1

additive	yield of 2	yield of 3	yield of 4
<i>n</i> -BuLi / ZnCl ₂	19	47	trace
<i>sec</i> -BuLi / ZnCl ₂	9	36	34
<i>t</i> -BuLi / ZnCl ₂	0	10	71
none	0	0	99

with alkene stereochemistry being maintained during the process. This issue has been well demonstrated in several related contexts.^{13–15} In a study of palladium-catalyzed [2 + 2 + 2] cycloadditions involving enyne additions to alkynes, Trost demonstrated that *Z* enynes underwent completely stereospecific couplings, whereas *E* enynes displayed moderate stereospecificity.¹³ In a study of nickel-catalyzed [4 + 2] cycloadditions, Wender demonstrated that both *E,E*-dienes and *E,Z*-dienes added to alkynes in a completely stereospecific fashion.¹⁴ However, we observed that treatment of enone (**Z**)-**1** to the dimerization conditions led to the same single stereoisomer as that seen in the dimerization of enone (**E**)-**1** (eq 1). Recovered starting material



from reactions carried out to partial conversion was unchanged with both *E* and *Z* alkynyl enones.

Since simple proton exchange could lead to the unusual epimerization, incorporation of a quaternary center was attempted to measure the inherent reaction stereospecificity. None of the dimer analogous to **4** was obtained upon exposure of α -methyl enone (**E**)-**5** to Ni(COD)₂/PPh₃.^{16,17} However, treatment of (**E**)-**5** to the identical reaction conditions in the presence of 5 equiv of

(12) The author has deposited atomic coordinates for **4** and **6** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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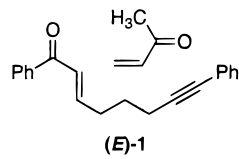
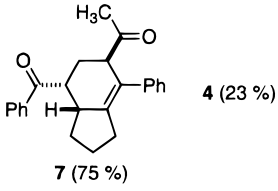
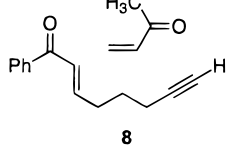
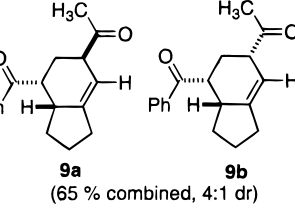
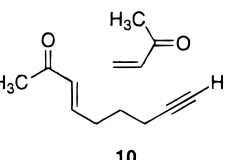
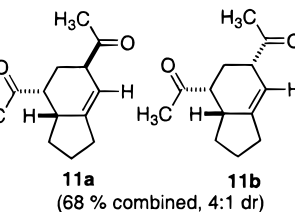
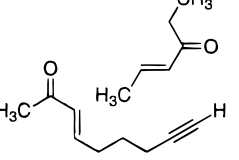
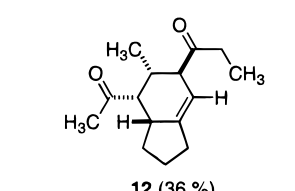
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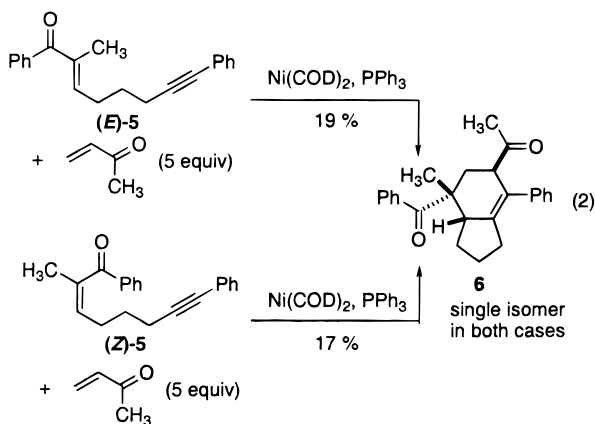
(16) Treatment of α -methyl enone (**E**)-**5** to the dimerization reaction conditions led to two major and three minor inseparable regioisomers of a different [2 + 2 + 2] cycloaddition product in which one enone and two alkynes were incorporated.

(17) A mixed [2 + 2 + 2] cycloaddition reaction between the parent alkynyl enone (**E**)-**1** and 2-methyl-1-phenylprop-2-en-1-one was attempted. However, a 90% isolated yield of the alkynyl enone dimer with no incorporation of the α -methyl enone was obtained.

Table 2

entry	starting materials	product (yield)
1		 7 (75 %)
2		 9a and 9b (65 % combined, 4:1 dr)
3		 11a and 11b (68 % combined, 4:1 dr)
4		 12 (36 %)

methyl vinyl ketone did afford the desired [2 + 2 + 2] cycloaddition product in low yield (eq 2).¹⁸ Both (*E*)-5 and (*Z*)-5

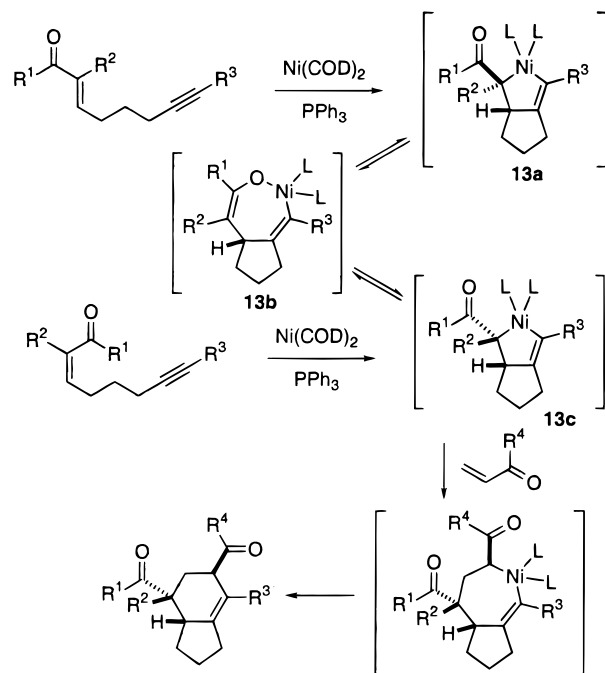


led to the same single stereoisomer of the [2 + 2 + 2] product.

Related crossed reactions without quaternary center incorporation were more efficient than the above example. For instance, substrate (*E*)-1 and methyl vinyl ketone produced **7** as a single diastereomer in 75% yield, and substrate **8** and methyl vinyl ketone produced **9a** and **9b** in 52% and 13% yield, respectively (Table 2, entries 1–2). A methyl ketone in the alkyne enone partner was tolerated in the [2 + 2 + 2] cycloaddition in yields and selectivities comparable to the phenyl-substituted enones (Table 2, entry 3). β -Substitution in the simple enone partner was also tolerated, albeit in modest yield (Table 2, entry 4). In every

(18) In addition to the products shown in eq 2, several isomers of the [2 + 2 + 2] product between 2 equiv of methyl vinyl ketone and the alkyne of (*E*)-5 were isolated.

Scheme 1



instance, the initial alkene stereochemistry of the (*E*)-alkynyl enone partner was completely inverted during the reaction.

To further probe the mechanistic basis for the absence of reaction stereospecificity, we chose an example that was not highly stereoselective, the addition of alkyne enone **8** with methyl vinyl ketone, and rigorously documented that product epimerization did not occur on the time scale of catalytic reactions (typically several hours at 0–25 °C). Accordingly, isomer **9a** was added to a catalytic reaction involving the conversion of (*E*)-1 to dimer **4**. No detectable isomerization of **9a** to **9b** was observed. The identical experiment, replacing **9a** with **9b**, was carried out, and no isomerization of **9b** to **9a** was observed. Therefore, we speculate that the lack of reaction stereospecificity may be attributed to the involvement of a preequilibrium between nickel metallacycles **13a–c** (Scheme 1).¹⁹ A kinetic preference for the addition of **13b** or **13c** to the simple enone could explain the unusual stereochemical observations.

In summary, a novel method for effecting a nickel-catalyzed [2 + 2 + 2] cycloaddition between an alkyne enone and an electron-deficient alkene has been developed. The potential for introducing four contiguous chiral centers via two alkene components is a distinguishing feature of the reaction. This method provides a cycloaddition protocol for the preparation of highly functionalized cyclohexenes that is complementary to the Diels-Alder reaction. Further mechanistic studies and synthetic applications of the procedure are in progress.

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Supporting Information Available: Experimental procedures and spectral data including NOE data for **6**, **7**, **9a**, **9b**, and **12**, copies of ¹H NMR spectra of all compounds, and X-ray structural information on **4** and **6** (33 pages, PDF). See any current masthead page for Web access instructions.

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