

Nickel-Catalyzed Cyclizations and
Couplings with Vinylzirconium Reagents

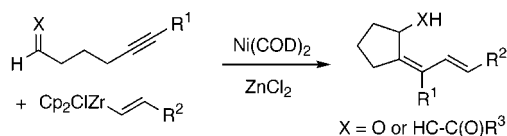
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ABSTRACT



1,3-Dienes were prepared by a variety of nickel-catalyzed couplings and cyclization processes. Intermolecular or partially intramolecular couplings of alkynes, vinylzirconium reagents, and either aldehydes or enones efficiently proceeded to generate a broad range of functionalized dienes.

Many classes of multicomponent couplings involving nickel catalysis have been developed in recent years.¹ One widely studied group of reactions is the three-component addition of two π -participants with one main group organometallic or metal hydride.² The combinations of π -systems that have been incorporated include aldehydes with dienes,³ aldehydes with alkynes,⁴ alkenes with alkynes,⁵ alkenes with dienes,^{5c} alkenes with allenes,^{5d} allyl halides with alkynes,⁶ two enones,⁷ and two alkynes.⁸ The main group organometallics

that have participated in these processes include organozincs, organostannanes, organoaluminums, organoboranes, and organosilanes.^{3–8} Given the broad utility of this general strategy for transition metal-catalyzed multicomponent couplings, we envisioned that the generation of a reactive vinyl organometallic from an alkyne precursor could significantly expand the scope and utility of many of the above-mentioned processes. Therefore, we have explored the participation of alkyne-derived vinylzirconium reagents⁹ in intra- and intermolecular versions of aldehyde–alkyne and enone–alkyne couplings. These new coupling processes provide a novel entry into several classes of highly substituted 1,3-dienes¹⁰ that can serve as versatile intermediates in numerous applications.

Our studies began with the cyclization of alkynyl enones with Schwartz reagent-derived vinylzirconium reagents in the presence of 10 mol % $Ni(COD)_2$ (Table 1). Numerous minor variations in the coupling procedure were unsuccessful until we observed that catalytic $ZnCl_2$ (20 mol %) was an essential additive in promoting the desired couplings. Negishi first reported that $ZnCl_2$ was an important additive in other classes of organozirconium cross couplings,¹¹ and Wipf has recently made extensive use of reagents derived from

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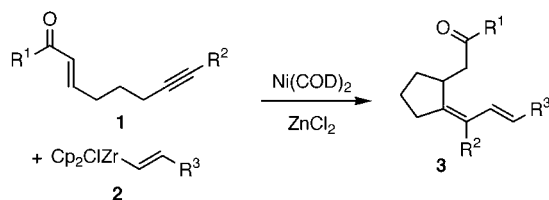
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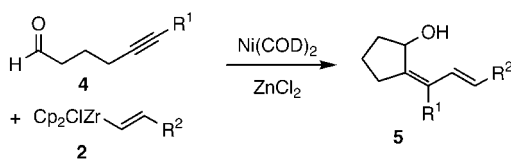
Table 1. Cyclizations of Alkynyl Enones with Vinylzirconiums

entry	R ₁	R ₂	R ₃	yield, %
1	Me	Ph	C ₆ H ₁₃	74
2	Ph	H	C ₆ H ₁₃	80
3	Ph	Me	C ₆ H ₁₃	77
4	Ph	Me	(CH ₂) ₄ OTBS	75
5	Ph	Ph	C ₆ H ₁₃	76

vinylzirconiums and dimethylzinc.¹² Optimized conditions for the couplings involved 1 equiv of alkynyl enone **1** (0.1 M in THF), 2.5 equiv of vinyl zirconium **2**, 20 mol % ZnCl₂, and 10 mol % Ni(COD)₂. The alkynyl enone may possess an aryl or alkyl enone and an aryl, alkyl, or terminal alkyne moiety, and vinylzirconium reagents that possess functionalized or unfunctionalized alkyl substituents were examined. The exocyclic dienes **3** were obtained as single isomers.

The corresponding intermolecular couplings of enones, alkynes, and vinylzirconiums were briefly examined, and our attempts to date have been largely unsuccessful. Rather than the desired three-component couplings, direct conjugate addition of the vinylzirconium reagent to the enone was observed. This is not surprising given that Schwartz previously reported that vinylzirconium conjugate additions to enones proceeded efficiently in the presence of Ni(acac)₂.¹³

We next examined cyclizations of ynals with vinyl zirconium reagents under identical conditions (Table 2). In

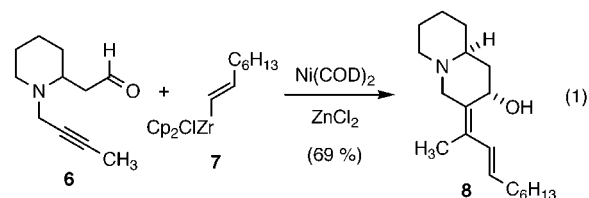
Table 2. Cyclizations of Ynals with Vinylzirconiums

entry	R ₁	R ₂	yield, %
1	H	C ₆ H ₁₃	56
2	Me	C ₆ H ₁₃	50
3	Ph	C ₆ H ₁₃	68
4	Me	Ph	66

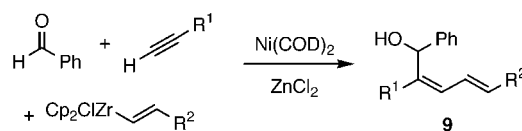
direct analogy to alkynyl enone cyclizations, we found that optimized conditions for the couplings involved 1 equiv of ynal **4** (0.1 M in THF), 2.5 equiv of vinylzirconium **2**, 20

mol % ZnCl₂, and 10 mol % Ni(COD)₂. Cyclizations to produce **5** were completely stereoselective and were efficient with aromatic, aliphatic, and terminal alkynes on the ynal substrate, and vinylzirconium reagents derived from aromatic and aliphatic alkynes were tolerated.

More highly functionalized ynals were also good substrates, as evidenced by the efficient cyclization of substrate **6** with the vinylzirconium reagent **7** derived from 1-octyne (eq 1). In this latter example, product **8** was obtained as a single diastereomer with formation of the (*Z,E*)-configuration of the exocyclic diene and the axial configuration of the hydroxyl within the quinolizidine core structure.



In contrast to the failure of intermolecular enone–alkyne–vinylzirconium couplings, the corresponding fully intermolecular aldehyde–alkyne–vinylzirconium couplings proceeded smoothly. Couplings of benzaldehyde with aromatic or aliphatic alkynes and functionalized or unfunctionalized vinylzirconium reagents afforded the desired hydroxy dienes **9a–c** in good yields with excellent stereocontrol. A particularly surprising feature of this coupling is that the regiochemistry of alkyne insertion is opposite that of aldehyde–organozinc–alkyne three-component couplings that were previously developed by our group.⁴ Irrespective of the mechanistic questions raised by these observations, the three-component nature of this coupling procedure stands to be particularly useful in various synthetic and combinatorial applications. Efforts to understand the mechanistic basis for the regiochemical reversal are in progress.

Table 3. Fully Intermolecular Couplings

entry	R ₁	R ₂	yield, %
1	Ph	(CH ₂) ₄ OTBS	63
2	Ph	C ₆ H ₁₃	56
3	C ₆ H ₁₃	C ₆ H ₁₃	71

The exact nature of the vinyl organometallic species that undergoes transmetalation to nickel has not been determined. It is worth noting that attempted three-component couplings of an aldehyde, alkyne, and vinylzinc derived from an

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alkenyllithium and ZnCl_2 failed to produce any of the desired products such as **9**. Instead, rapid 1,2-addition of the vinylzinc to the aldehyde was observed.^{4a}

In summary, vinylzirconium reagents are excellent participants in several classes of nickel-catalyzed cyclizations and multicomponent couplings. Their participation allows densely functionalized 1,3-dienes to be easily prepared in a convenient, efficient, and highly stereoselective fashion.

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Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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