

Evaluating the Effect of Catalyst Nuclearity in Ni-Catalyzed Alkyne Cyclotrimerizations

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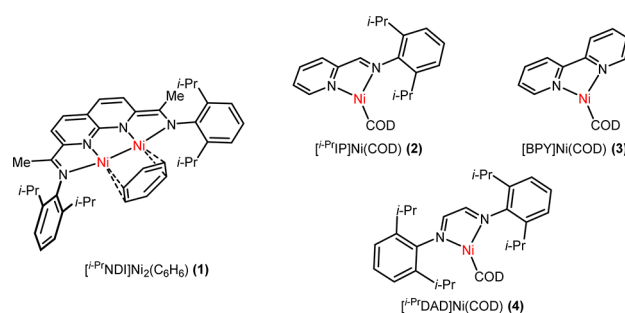
S Supporting Information

ABSTRACT: An evaluation of catalyst nuclearity effects in Ni-catalyzed alkyne oligomerization reactions is presented. A dinuclear complex, featuring a Ni–Ni bond supported by a naphthyridine–diimine (NDI) ligand, promotes rapid and selective cyclotrimerization to form 1,2,4-substituted arene products. Mononuclear congeners bearing related N-donor chelates (2-iminopyridines, 2,2'-bipyridines, or 1,4-diazadienes) are significantly less active and yield complex product mixtures. Stoichiometric reactions of the dinickel catalyst with hindered silyl acetylenes enable characterization of the alkyne complex and the metallacycle that are implicated as catalytic intermediates. Based on these experiments and supporting DFT calculations, the role of the dinuclear active site in promoting regioselective alkyne coupling is discussed. Together, these results demonstrate the utility of exploring nuclearity as a parameter for catalyst optimization.

Transition-metal catalysts containing polynuclear active sites are underdeveloped alternatives to mononuclear catalysts for organic transformations.¹ Polynuclear complexes have the potential to exhibit unique catalytic properties by binding substrates and delocalizing redox activity across multiple metals. Platforms featuring direct metal–metal bonds are particularly well-suited to capitalize on these cooperative processes due to the enforced proximity of the metals and the strong electronic coupling between them. Consequently, ligands that support reactive metal–metal bonds have emerged as synthetic targets. The resulting complexes have been demonstrated to engage organic and small inorganic molecules in well-defined stoichiometric reactions.² Despite these advances, the cooperativity effects attributed to metal–metal bonds have rarely been evaluated in a catalytic process.³ Such studies would complement those characterizing dinuclear effects in catalyst systems where direct metal–metal interactions either are not relevant⁴ or are formed transiently.⁵

Dinuclear complexes of naphthyridine–diimine (NDI) ligands are versatile platforms to study stoichiometric and catalytic redox processes at discrete metal–metal bonds.⁶ The $[\text{i-Pr}^{\text{NDI}}\text{Ni}_2(\text{C}_6\text{H}_6)]$ complex (**1**) is an analog of known mononuclear complexes bearing N-donor chelates (e.g., 2-iminopyridines, 2,2'-bipyridines, and 1,4-diazadienes), providing an opportunity to probe nuclearity effects within a family of related catalysts (Scheme 1). Here, we report a comparative study of mono- and dinickel catalysts in the oligomerization of terminal alkynes. Whereas mononuclear $[\text{N},\text{N}]\text{Ni}$ catalysts 2–4

Scheme 1. Mononuclear and Dinuclear Ni Complexes of Chelating N-Donor Ligands



uniformly yield complex product mixtures, the dinuclear catalyst **1** promotes rapid and selective cyclotrimerizations to form 1,2,4-trisubstituted arenes (Figure 1). Stoichiometric reactivity studies, combined with DFT calculations, provide insight into this nuclearity effect.

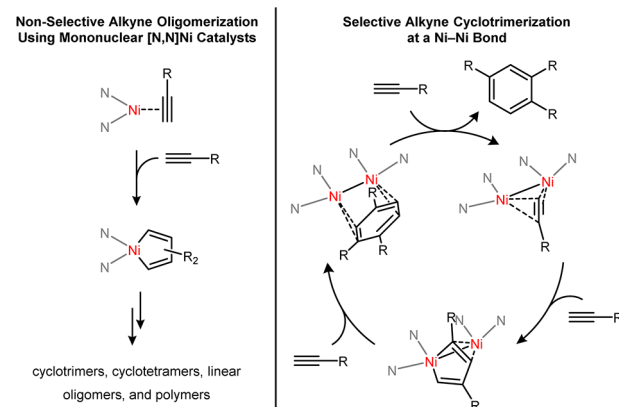


Figure 1. Mononuclear and dinuclear pathways for alkyne oligomerizations using Ni catalysts.

Catalyst Comparison Studies. Transition-metal-catalyzed cycloadditions are direct and efficient routes to cyclic organic molecules;⁷ however, complex selectivity considerations must be addressed in order to obtain high yields of a single product. Among the catalysts that have been surveyed in alkyne oligomerization reactions, the low-valent Ni catalysts initially reported by Reppe are unusual in the breadth of accessible

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products.⁸ Simple Ni(0) sources such as Ni(COD)₂,⁹ activated Ni metal,¹⁰ and combinations of divalent Ni halide salts and reductants¹¹ convert terminal alkynes to mixtures of cyclic (arene and cyclooctatetraene regioisomers) and acyclic (oligomers and polymers) products. Supporting ligands have been effectively utilized to improve the selectivity of these reactions.¹² For example, phosphine-ligated complexes generally yield benzene derivatives,^{12a–g} whereas 1,4-diazadiene complexes favor cyclooctatetraenes.^{12h–j}

In order to assess the viability of using catalyst nuclearity to control selectivity in these reactions, terminal alkyne substrates with diverse electronic properties were selected for comparison studies (Figure 2). For ethyl propiolate, all examined

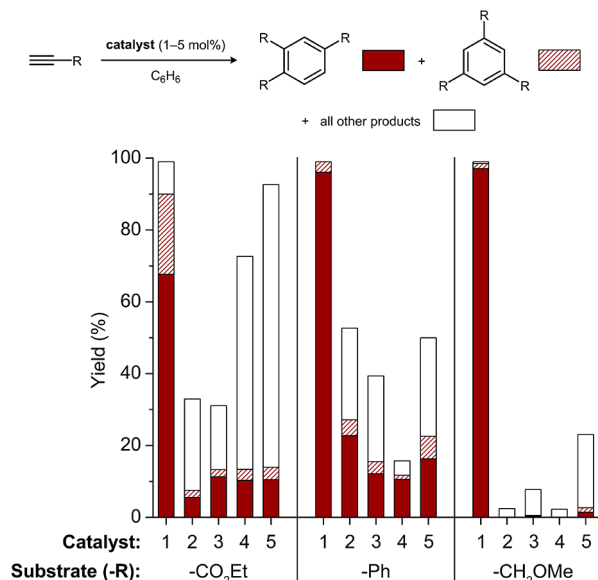


Figure 2. A comparison of catalytic activity for the cyclotrimerization of ethyl propiolate, phenylacetylene, and methyl propargyl ether. Data for catalysts 1–4 and Ni(COD)₂ (5) are shown. Reaction conditions for ethyl propiolate and methyl propargyl ether: 22 °C, 11 min, 1 mol % catalyst. Reaction conditions for phenylacetylene: 60 °C, 40 min, 5 mol % catalyst. Yields and conversions were averaged over two runs and determined by GC-FID analysis. The total heights of the bars are the total conversion of starting material. The product fraction corresponding to the 1,2,4-isomer (solid red), 1,3,5-isomer (dashed red), and all other products (white) are plotted.

mononuclear and dinuclear catalysts (Scheme 1) were active, with **1** affording the highest conversion of substrate under a standardized set of conditions. Consistent with previous reports,^{12j} [*i*-PrIP]Ni(COD) (**2**), [BPY]Ni(COD) (**3**), [*i*-PrDAD]Ni(COD) (**4**), and Ni(COD)₂ (**5**) yielded significant amounts of both cyclotrimerized and cyclotetramerized products. Among these four mononickel catalysts, no greater than 14% combined yield of aromatic products was observed, with cyclooctatetraenes being formed in 11–71% yield. By comparison, **1** was selective for cyclotrimerization, affording a 90% combined yield of the 1,2,4- and 1,3,5-regioisomer. No cyclooctatetraene products were detected using **1**.

Similar effects were observed using more electron-rich alkyl- and aryl-substituted terminal alkynes. Phenylacetylene and methyl propargyl ether were poorly reactive using catalysts **2**–**5** and produced a mixture of coupled products. Catalyst **1** effected rapid cyclotrimerization, with nearly exclusive formation of the 1,2,4-regioisomer. Methyl propargyl ether is converted to

1,2,4-tris(methoxymethyl)benzene in 98% GC yield using 1 mol % of **1** in <15 min at room temperature. This rate and selectivity is noteworthy among those observed using the most efficient cyclotrimerization catalysts, including precious metal-based systems.¹³

Substrate Scope for Alkyne Cyclotrimerizations. The high selectivity for cyclotrimerization using **1** is general across a range of terminal alkynes (Figure 3). In all cases, the 1,2,4-

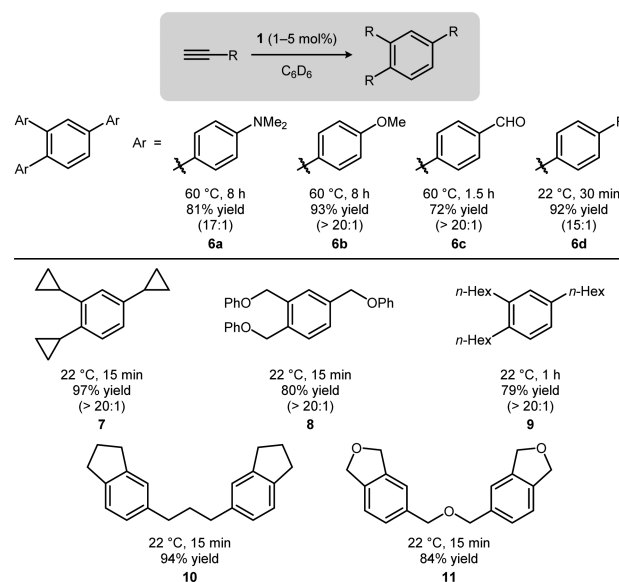


Figure 3. Substrate scope for alkyne cyclotrimerizations catalyzed by **1**. Conditions: 5 mol % catalyst loading for arylacetylenes and 1 mol % for all other substrates. Yields are of isolated products and are averaged over two runs. The ratio of the 1,2,4- to 1,3,5-regioisomer is shown in parentheses.

regioisomer is highly favored, and no competing formation of cyclooctatetraenes is observed.¹⁴ Alkylacetylenes reach full conversion within 1 h at room temperature using 1 mol % of **1** (products **7**–**11**). A higher catalyst loading of 5 mol % was used for arylacetylenes (products **6a**–**d**). To probe electronic effects, a series of para-substituted phenylacetylenes was studied. Substrates bearing electron-withdrawing substituents reacted at a faster rate than substrates bearing electron-donating substituents. Using cyclopropylacetylene, cyclotrimerization occurred without cyclopropane rearrangement through either a radical or organometallic mechanism. Finally, 1,6-heptadiyne and propargyl ether reacted to form the corresponding tethered diarene products (**10** and **11**).

Stoichiometric Alkyne Coupling Reactions. We investigated the origin of the observed dinuclear effect by pursuing the characterization of plausible intermediates. Terminal alkynes bearing bulky silyl substituents, such as $-\text{SiMe}_3$ and $-\text{SiMe}_2\text{Ph}$, react with **1** but do not generate the cyclized product (Scheme 2). The reaction between **1** and dimethylphenylsilylacetylene (2.0 equiv or greater) in C₆D₆ is complete in 3 h at room temperature, producing the head-to-tail coupled product **12**. In the ¹H NMR spectrum, two signals are observed at 6.20 and 4.79 ppm (doublets with ⁴J = 4.5 Hz), corresponding to the two nonequivalent C–H groups of the bound butadienyl fragment. No other isomeric complexes arising from head-to-head or tail-to-tail dimerization are detected under these conditions. The solid-state structure (Figure 4a) reveals that the metallacycle incorporates one Ni into a five-membered ring. The second Ni

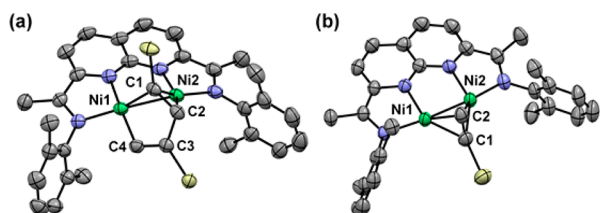
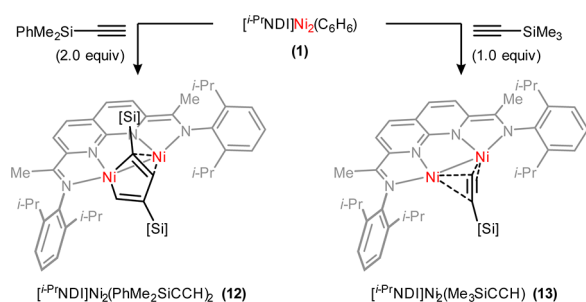
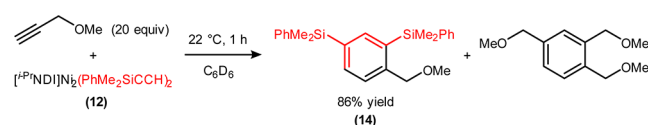
Scheme 2. Stoichiometric Reactions of **1** with Trialkylsilylacetylenes

Figure 4. Solid-state structures of (a) **12** and (b) **13** (ellipsoids at 50% probability). *i*-Pr groups on the NDI ligand and substituents on silicon are truncated for clarity. Selected bond distances for **12** (Å): Ni1–Ni2, 2.4814(6); Ni1–C1, 1.942(2); Ni1–C4, 1.868(2); Ni2–C1, 1.875(2); Ni2–C2, 2.042(2); C1–C2, 1.416(4); C2–C3, 1.482(3); C3–C4, 1.350(3). Selected bond distances for **13** (Å): Ni1–Ni2, 2.3140(6); Ni1–C1, 2.023(3); Ni1–C2, 1.911(3); Ni2–C1, 2.015(2); Ni2–C2, 1.904(2); C1–C2, 1.301(4).

provides additional stabilization through an η^2 -interaction with a double bond of the diene system. Related π -interactions have been invoked in alkyne cyclotrimerizations^{3c,15} and Pauson–Khand reactions^{3a,b} mediated by $\text{Co}_2(\text{CO})_8$. In support of the catalytic relevance of the structurally characterized complex **12**, a directly analogous metallacycle is observed with phenylacetylene under turnover conditions (¹H NMR: 6.70 and 4.52 ppm, ⁴J = 4.3 Hz).

The reversibility of the C–C coupling was examined to determine whether the regioisomer **12** is formed under thermodynamic or kinetic control. When **12** is exposed to trimethylsilylacetylene (10 equiv), no exchange of –SiMe₂Ph for –SiMe₃ in the metallacycle is observed even after heating at 70 °C for 48 h. The formation of **12** is therefore sufficiently thermodynamically favorable to preclude the reverse reaction from occurring at catalytically relevant temperatures. A plausible explanation for the high head-to-tail selectivity is the steric hindrance imposed by the flanking 2,6-diisopropylphenyl substituents of the catalyst. The solid-state structure of **12** suggests that substituents at C2 or C4 would be highly disfavored by interactions with a catalyst *i*-Pr group or arene respectively (Figure 4a).

The metallacycle **12** does not react with additional equivalents of dimethylphenylsilylacetylene; however, when a less hindered alkyne, methyl propargyl ether, is introduced, cyclotrimerization proceeds to form the heterocoupled product **14** (Scheme 3). This reaction is accompanied by catalytic homocyclotrimerization of methyl propargyl ether. The regioselectivity in this stoichiometric process is consistent with that observed under standard catalytic conditions. Collectively, these experiments support the competence of metallacycles analogous to **12** as intermediates in the formation of 1,2,4-substituted arene products.

Scheme 3. Stoichiometric Conversion of **12** to the Heterocoupled Product **14**

The presumed monoalkyne complex (**13**), en route to the metallacycle **12**, was characterized from the reaction of **1** with one equivalent of trimethylsilylacetylene. In the solid state, the alkyne exhibits μ - η^2 : η^2 coordination and is perpendicular to the Ni–Ni bond vector (Figure 4b). The C–C distance is significantly elongated from approximately 1.20 Å for free trimethylsilylacetylene¹⁶ to 1.301(4) Å in the complex. The alkyne complex **13** is sufficiently stable to permit structural characterization; however, over the course of 24 h at room temperature in C₆D₆, it disproportionates to form a mixture of the corresponding metallacycle and the benzene complex **1**.

Origin of the Dinuclear Effect. The observed ratio of 1,2,4- to 1,3,5-substituted products in the alkyne cyclotrimerization arises from regioselectivity considerations in two sequential steps: the dimerization to form the metallacyclic intermediate and the subsequent incorporation of the third alkyne to yield the arene product. The stoichiometric reactivity studies described above provide insight into the selectivity of the first C–C coupling; however, less information is readily apparent regarding the product formation step.

DFT calculations (M06/6-31G(d,p) level of theory) were performed on a model catalyst system (*i*-Pr groups on the aryl substituent were truncated to Me groups) to assess potential pathways for the conversion of this intermediate into the final product. Using propyne as a substrate, a concerted transition state was optimized, corresponding to a [4 + 2]-cycloaddition of a Ni-coordinated alkyne to the butadienyl system (Figure 5a).¹⁷

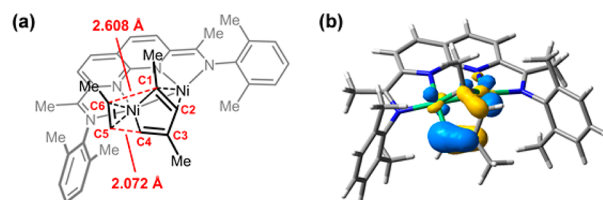


Figure 5. DFT calculations (M06/6-31G(d,p) level of theory) addressing the selectivity of alkyne addition to the bound butadienyl ligand. Propyne was used as a model substrate and *i*-Pr substituents on the catalyst were truncated to Me substituents. (a) The lowest-energy transition structure corresponding to the [4 + 2]-cycloaddition of the bound alkyne and butadienyl ligands. Distances for the two forming C–C bonds are shown in red. (b) The HOMO–1 for the metallacycle intermediate.

Stationary points associated with alternative stepwise pathways could not be located. Consistent with the fast rates observed experimentally for cyclotrimerizations with alkylacetylenes, the activation energy for this step was calculated to be only 9.3 kcal/mol. The competing transition state leading to the minor 1,3,5-substituted product was 2.0 kcal/mol higher in energy.

The calculated cycloaddition transition state (Figure 5a) is highly asynchronous with bond formation between C4 and C5 (2.07 Å) being significantly more advanced than that between C1 and C6 (2.61 Å). This asymmetry arises from stabilization of one of the double bonds through η^2 coordination to the second Ni

center. The calculated HOMO–1, which primarily corresponds to the delocalized π -orbital of the diene system, shows significantly greater density at the uncoordinated double bond (Figure 5b). This electronic structure is manifested in the solid-state geometry of **6** as an elongated C1–C2 (1.416(4) Å) distance relative to the C3–C4 distance (1.350(3) Å). A hypothesis that emerges from these calculations is that this electronic asymmetry, induced by the presence of the second Ni center in the catalyst, results in a steric preference for the substituent of the approaching alkyne to be positioned at the carbon where the forming C–C distance is longer in the transition state.

In summary, the dinuclear [NDI]Ni₂ platform provides access to an efficient cyclotrimerization pathway that is not available to its mononuclear counterparts. The catalyst nuclearity effect is particularly significant for alkyl-substituted alkynes: reactions are complete within 1 h at room temperature using 1 mol % loading of **1** with nearly exclusive formation of 1,2,4-substituted arene products. Stoichiometric reactivity studies provide structural insight into the metallacyclopentadiene intermediate that is implicated in the catalytic mechanism. Combined with DFT calculations, these experiments suggest several distinct features of the bimetallic system. First, binding across two metals constrains the geometry of the metallacycle, disfavoring the formation of other possible regioisomers. Second, the [4 + 2]-cycloaddition of the butadienyl ligand and the approaching alkyne is facilitated by metal coordination to both partners. Third, the selectivity of the cycloaddition is controlled by an electronic bias in the diene π -system, caused by a secondary η^2 interaction. Exploring the implications of these dinuclear effects for other catalytic cycloadditions is ongoing in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental methods, computational methods, characterization data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04990.

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Notes

The authors declare no competing financial interest.

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