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Cyclotrimerization of alkynes catalyzed by a self-supported cyclic tri-nuclear nickel(0) complex with α -diimine ligands

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A cyclic tri-nuclear α -diimine nickel(0) complex $[\{\text{Ni}(\mu\text{-L}^{\text{Me-2,4}})\}_3]$ (**2**) was synthesized from a “pre-organized”, trimerized trigonal LNiBr₂-type precursor $[\text{Ni}_3(\mu^2\text{-Br})_3(\mu^3\text{-Br})_2(\mu\text{-L}^{\text{Me-2,4}})_3]\text{-Br}$ (**1**; $\text{L}^{\text{Me-2,4}} = [(2,4\text{-Me}_2\text{C}_6\text{H}_3)\text{NC}(\text{Me})_2]$). In complex **2**, the α -diimine ligands not only exhibit the normal *N,N'*-chelating mode, but they also act as bridges between the Ni atoms through an unusual π -coordination of a C=N bond to Ni. Complex **2** is able to catalyze the cyclotrimerization of alkynes to form substituted benzenes in good yield and regio-selectivity for the 1,3,5-isomers, which is found to vary with the nature of the alkyne employed. This complex represents a convenient self-supported nickel(0) catalyst with no need for additional ligands and reducing agent.

Introduction

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes is one of the most efficient synthetic methods for the construction of benzene derivatives because of the high atom-efficiency and variety of substrates that can be used. Since Reppe reported the nickel-catalyzed [2 + 2 + 2] cycloaddition of alkynes in 1948,¹ a plethora of metal (Ni, Rh, Pd, Co, Ti, Ru, Nb, In, U, Ir, Fe, Cr, Ge, Ta) systems have been developed to catalyze the intermolecular cycloaddition of three individual alkyne molecules.² In general, the cyclotrimerization of asymmetric alkynes ($\text{R}^1\text{C}\equiv\text{CR}^2$) produces two regio-isomers, namely the 1,3,5- and 1,2,4-isomers, in which the same substituents (R^1 or R^2) are positioned differently on the resulting benzene ring. Although a mixture of these two isomers is often observed with a slight excess of one over the other,^{2e,2f,3-5} higher regio-selectivity has also been achieved. However, in the majority of the examples, the less symmetric 1,2,4-isomers are favored,^{2j,6,7} while selective formation of the 1,3,5-products is rare.^{2g,2h,2k} Nonetheless, *C*₃-symmetrical molecules such as benzene-1,3,5-tricarboxamide (BTA) and derivatives are useful building blocks for a variety of applications including in supramolecular assembly, nanotechnology, liquid crystals, gels, polymer and biomedical science.⁸⁻¹⁰

In the nickel catalysts for alkyne cyclotrimerization, e.g. Reppe's nickel-carbonyl-phosphine complexes¹ and Dieck's α -diimine-nickel(0) catalysts,¹¹ the active Ni(0) center is normally stabilized by unsaturated molecules (e.g. COD,^{11,12} CO,^{1,13} nitriles¹⁴ etc.) which are π -bonded to the [LNi] fragment. Alternatively, the Ni(0) center can also be in-site generated by using extra reducing agent such as zinc, Mg, BuLi, DIBALH (diisobutylaluminum hydride) and Grignard reagents to reduce nickel salts^{6,15} or Ni^{II} precursors.¹⁶ Nevertheless, these additives may require more polar organic solvents such as THF, CH₃CN, toluene, DMF etc.

We have been interested in the redox non-innocent α -diimine ligands and have synthesized a series of dinuclear metal-metal-bonded compounds with (reduced) α -diimines. These complexes displayed excellent reactivity towards unsaturated organic species, such as azobenzenes, alkynes, and alkenes.^{17,18} In the current work, we designed an α -diimine ligand $\text{L}^{\text{Me-2,4}}$ ($\text{L}^{\text{Me-2,4}} = [(2,4\text{-Me}_2\text{C}_6\text{H}_3)\text{NC}(\text{Me})_2]$), which bears methyl groups at the 2,4-positions of the *N*-aryl ring instead of the commonly employed ‘symmetric’ ligands $\text{L}^{\text{R-2,6}}$ (with 2,6-substituents).¹⁹ The LNiBr₂-type complex of this ligand shows an unusual trimerized structure with bromide bridges, $[\{\text{LNiBr}_2\}_3]$, and thus it was expected to give a Ni₃ cluster upon reductive elimination of the bromide ions. Indeed, a tri-nuclear complex $[\{\text{Ni}(\mu\text{-L}^{\text{Me-2,4}})\}_3]$ (**2**, Scheme 1) was obtained, which features nickel(0) centers and neutral α -diimine ligands serving as both *N,N*-donor ligands and bridges to link the metals. Very promisingly, complex **2** can catalyze the cyclotrimerization of both terminal and internal alkynes. The synthesis, structure, and catalytic properties of this nickel(0) trimer are reported herein.

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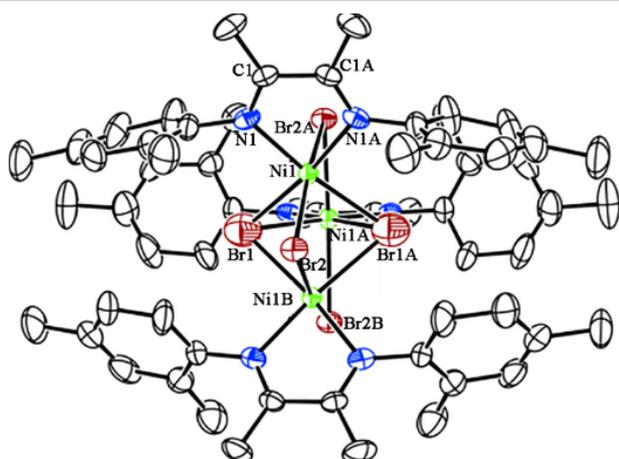


Fig. 1 Molecular structure of **1** (thermal ellipsoids are set at the 30% probability level; hydrogen atoms and the free Br⁻ anion are omitted for clarity). Selected bond lengths (Å): Ni1–C1, 1.286(10); C1–C1A, 1.503(18); Ni1–N1, 2.030(6); Ni1–Br1, 2.529(2); Ni1–Br2, 2.6061(15). Symmetry code: A, 1–y, x–y, z; B, 1–x+y, 1–x, z.

Results and discussion

Synthesis and structure of [Ni₃(μ₂-Br)₃(μ₃-Br)₂(μ-L^{Me-2,4})₃]-Br (1**).** The bromo-nickel(II) precursor **1** was synthesized from [(DME)NiBr₂] and the ligand L^{Me-2,4} as a highly symmetric (space group *P6₃m*) trimer, in which the three Ni atoms are arranged in a triangle (Fig. 1). Each Ni atom is chelated by a ligand, while each two adjacent Ni atoms are bridged by a μ₂-Br atom, and the three Ni atoms are further bridged by two μ₃-Br atoms, thus resulting in six-coordinate Ni centers adopting distorted octahedral geometries. The last bromide (Br3) acts as a counter-anion in the crystal lattice. This tri-nuclear structure is different from most of the mono- or di-nuclear [LNiBr₂]-type complexes with α-diimine ligands but is similar to the complex [Ni₃(μ-Br)₅(L^{Me,Cl-2,4})₃]-Br (L^{Me,Cl-2,4} = [(2-Me-4-Cl-C₆H₃)NC(Me)]₂) that was reported as a catalyst for the polymerization of ethylene.^{19b} We speculated that substitution at the 2,4-positions on the N-phenyl of the α-diimine may “pre-organize” the triangular structure, which prompted us to employ the ligand L^{Me-2,4} in this work.

Synthesis and structure of [Ni₃(μ-L^{Me-2,4})₃] (2**).** The bromo-complex **1** was then reduced by sodium metal (6 equiv.) in order to yield Ni₃ clusters through salt elimination. Unexpectedly, the tri-nuclear complex **2** was isolated (as deep purple crystals). In the molecular structure of **2**, the three Ni atoms, each chelated by a ligand through the N,N' donors, form a triangle as in precursor **1** (Fig. 2a). Upon reduction by Na metal, all of the bromide ions in **1** have been eliminated, giving the cyclic [Ni₃L₃] complex self-bridged by the coordination of Ni to a C=N bond of another ligand. Neither the expected Ni₃ cluster nor the Ni–Ni-bonded complex [Ni₂L₂], the latter of which was resulted when reducing the dibromo species [L^{IPr-2,6}NiBr₂],²⁰ was obtained. These results further suggest that 2,4-substitution might be essential to “pre-organize” the tri-nuclear structure of **2**.

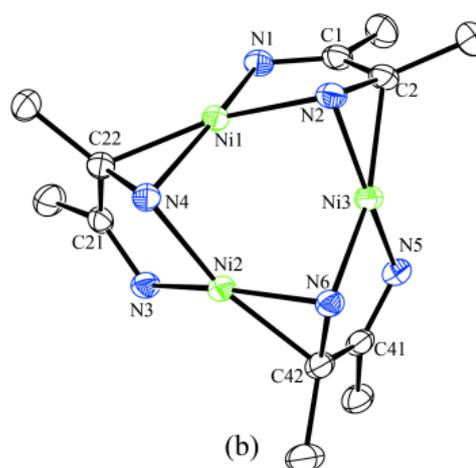
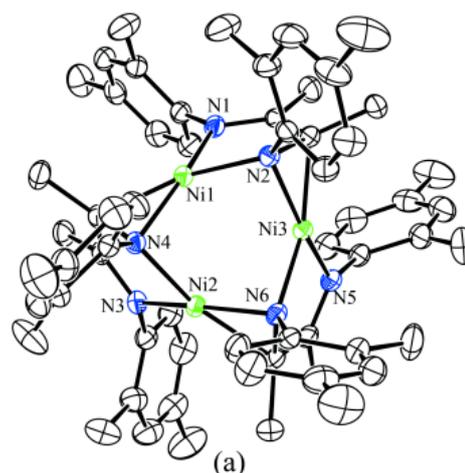
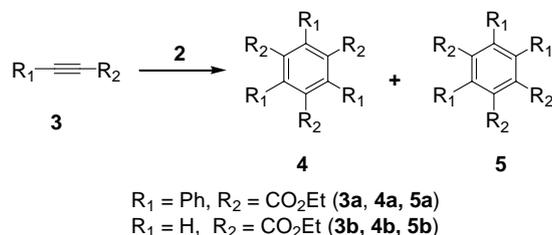


Fig. 2 a) Molecular structure of **2**; b) simplified coordination environment of Ni atoms. Selected bond lengths (Å): Ni⋯Ni, 2.718–2.735; N1–C1, 1.305(4); C1–C2, 1.452(5); C2–N2, 1.423(4); N3–C21, 1.316(3); C21–C22, 1.446(4); C22–N4, 1.435(4); N5–C41, 1.319(4); C41–C42, 1.452(5); C42–N6, 1.425(4); Ni1–N1, 1.908(3); Ni1–N2, 1.996(3); Ni2–N3, 1.908(3); Ni2–N4, 1.997(3); Ni3–N5, 1.920(3); Ni3–N6, 1.990(3); Ni1–C22, 1.983(3); Ni2–C42, 1.984(3); Ni3–C2, 1.987(3).

The C–N bonds that coordinate to nickel are stretched to 1.423(4)–1.435(4) Å, which are significantly longer than those in the neutral ligand. The other, free C–N (av. 1.313 Å) and the C–C (av. 1.449 Å) bond lengths are close to those in the neutral ligand (C–N: 1.29 Å, C–C: 1.47 Å).²¹ Thus, the ligands can best be described as the neutral form in **2**, while the Ni centers show a formal oxidation state of zero. Each Ni atom is three-coordinate (with two N atoms and a C=N bond) and resides in a trigonal geometry. The Ni⋯Ni distances (2.72 to 2.74 Å) are significantly longer than the Ni–Ni bond lengths among α-diimine Ni–Ni-bonded complexes (up to 2.4649(8) Å) and the sum of the covalent radii of Ni (2.492 Å),²² indicating the lack of Ni–Ni bonding.

The NMR spectrum of complex **2** implies a diamagnetic species, and the HR ESI-MS spectrum shows the molecular ion of [Ni₃(L^{Me-2,4})₃]⁺ (appearing at *m/z* 1052.4467, calc. 1052.3846; Fig. 3). Moreover, optimization of complex **2** by DFT computations reproduced the X-ray crystal structure. Natural bonding orbital (NBO) analysis gave a natural charge of about

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Table 1. Optimization of the reaction conditions.^a

Entry	Substrate	Solvent	Time (h)	Temp. (°C)	Yield of 4+5 (%) ^b	4:5 ^c
1	3a	<i>n</i> -hexane	5	100 ^d	96	69:31
2	3a	benzene	5	100	93	64:36
3	3a	toluene	5	100	87	66:34
4	3a	DMF	5	100	15	21:79
5	3a	acetonitrile	5	100	45	26:74
6	3a	dioxane	5	100	68	56:44
7	3a	DME	5	100	55	44:45
8	3a	THF	5	100 ^d	54	55:45
9	3a	<i>n</i> -hexane	5	r.t.	5	n.d.
10	3a	<i>n</i> -hexane	5	60	58	58:42
11	3a	<i>n</i> -hexane	5	80	94	69:31
12	3a	<i>n</i> -hexane	5	100 ^d	96	69:31
13	3b	<i>n</i> -hexane	0.5	r.t.	78	71:29
14	3b	toluene	0.5	r.t.	42	55:45
15	3b	diethyl ether	0.5	r.t.	80	34:66
16	3b	acetonitrile	0.5	r.t.	73	38:62

^a Reactions were performed in a sealed pressure tube under an argon atmosphere using 2.5×10^{-1} mmol of the alkyne in 0.5 mL *n*-hexane and 7.5×10^{-3} mmol of complex **2** (9 mol % of Ni). ^b Yield determined by ¹H NMR spectroscopy using CH₂I₂ as an internal standard. ^c Ratio determined by ¹H NMR. ^d At this temperature the solution in the sealed pressure tube started to boil.

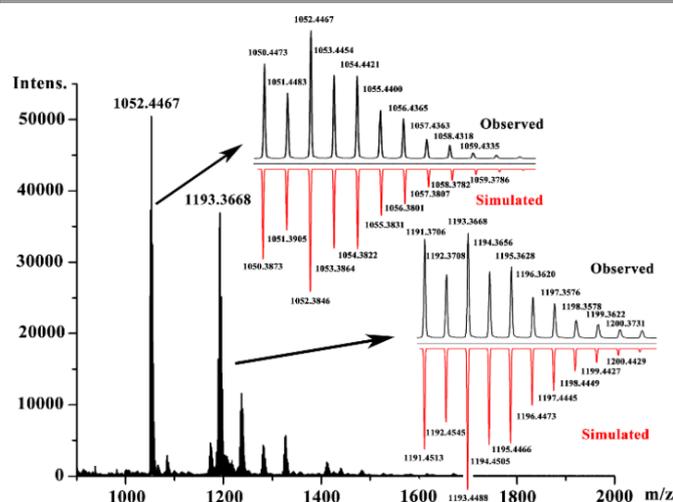


Fig. 3 HR ESI-MS spectrum of complex **2**. The *m/z* peaks at 1052.4467 and 1193.3668 correspond to $[\text{Ni}_3(\text{L}^{\text{Me}-2,4})_3]^+$ and $[\text{Ni}_3(\text{L}^{\text{Me}-2,4})_3 \cdot 2\text{MeCN} \cdot 2\text{H}_2\text{O} \cdot \text{Na}]^+$. Inset: experimental and simulated isotopic splitting pattern of the two peaks.

0.56 for each nickel center (and -0.56 for each ligand), which is similar to previously reported nickel(0) complexes with dienes (0.555).²³ This partial positive charge may indicate the π -back bonding of nickel(0) to ligand L in **2**.

As a continuing exploration of the reactivity of metal–metal-bonded (and related) compounds towards small molecules, reactions of the tri-nuclear complex **2** with alkynes were carried out. Surprisingly, treatment of **2** with an excess of ethyl phenylpropiolate in hexane did not yield the anticipated metal-alkyne adducts as in the cases of other complexes bearing related diimine ligands.²⁴ Instead, benzene derivatives were isolated, indicating possible cyclotrimerization of the alkyne molecules.

Catalytic studies. To confirm (and better understand) the catalytic effect of **2** on the cyclotrimerization of alkynes, we studied the reactions of **2** with alkynes in more detail. The identification of optimal conditions was carried out by using

ethyl phenylpropiolate and ethyl propiolate as the substrates, and the results are summarized in Table 1. Notably, among the solvents tested, the non-polar, less toxic solvent *n*-hexane was found to be a much better medium for the 1,3,5-product than more polar solvents both for ethyl phenylpropiolate and ethyl propiolate. This is different from previous literature reports where the catalytic reaction was mostly found to proceed better in toluene or benzene for which the 1,2,4-isomers were the main product.

It should be mentioned that the reaction of the terminal ethyl propiolate at room temperature was quite fast (0.5 h) and there was about 20% of the tetra-substituted cyclooctatetraene as determined by ¹H NMR spectroscopy. In contrast, in the case of ethyl phenylpropiolate, when the reaction was carried out at room temperature, the yield for the trimerized benzene products was very low. However, when the temperature was increased to 100 °C (at which point the solution started boiling), the total yield of benzene products increased dramatically from 5% up to 96%, and the selectivity for the 1,3,5-substituted product was also improved to about 3:2 (Table 1, entries 9–14). On the other hand, for ethyl propiolate, change of the temperature above ambient temperature had no effect on the reaction/reaction products.

The optimized conditions were then applied to explore the scope of the reaction with a variety of alkynes. The cyclotrimerization was found to be catalyzed by 3/100 equiv. of complex **2** in moderate to excellent yields (Table 2). The results demonstrated that different functionalities such as ester (substrates **3a–3d**), ketone (**3e**), and alkyl (**3g** and **3h**) groups were well tolerated, establishing the generality of this catalytic [2 + 2 + 2] cyclization process. The reaction rate was found to be dependent on the electronic properties of the monomer. Alkynes **3b–3e** containing electron-withdrawing substituents were readily cyclotrimerized at room temperature within 0.5 h in good to excellent yields (78–89%), while the aryl- (**3h**) and alkyl-substituted (**3a** and **3f**) alkyne substrates required heating to 100 °C (for 0.5 h) to give benzene derivatives in satisfactory yields (38–93%). Moreover, for the diphenylacetylene **3i**, no cyclized product was detected, which might be caused by the steric hindrance of the substrate.

As mentioned above, cyclotrimerization of asymmetric alkynes may generate both the 1,3,5- and 1,2,4-isomers. In our experiments, good regio-selectivity for the 1,3,5-isomer was observed in three cases (entries 1, 2, 5), which appears to arise from both the electronic properties and the poor solubility of the 1,3,5- products in *n*-hexane. This latter factor can promote both the reaction to proceed and the separation of products. As shown in Table 2, alkynes **3b** and **3e** that contain the EWG ester or ketone (entries 2 and 5) gave mostly the head-to-tail cyclotrimerized 1,3,5-isomer, with a regio-selectivity of **4/5** = 71:29 and 75:25, respectively. In contrast, alkynes **3g** and **3h** with electron-donating substituents gave predominantly the 1,2,4-product (ratio of **4/5** = 9:91 and 33:67, respectively).

Table 2. Cyclotrimerization of alkynes catalyzed by **2**.^a

Entry	R ₁	R ₂	Substrate	Time (h)	Temp. (°C)	Yield of 4+5 (%) ^e	4:5 ^c
1	Ph	CO ₂ Et	3a	5	100	93	69:31
2	H	CO ₂ Et	3b	0.5	r.t	78	71:29
3	Me	CO ₂ Et	3c	5	100	86	9:91
4	CO ₂ Me	CO ₂ Me	3d	0.5	r.t	89	-
5	H	(CO)CH ₃	3e	0.5	r.t	79	75:25
6	H	Ph	3f	5	100	83	50:50
7	H	TMS	3g	5	100	52	8:92
8	H	<i>n</i> -Bu	3h	5	100	38	33:67
9	Ph	Ph	3i	5	100	n.d.	n.d.

^a Reactions were performed under Ar using 2.5×10⁻¹ mmol of the alkyne in 0.5 mL hexane and 7.5×10⁻³ mmol of **2** (9 mol % of Ni) for 5 h. ^c Ratio determined by ¹H NMR. ^e Isolated yield.

In the reaction of catalyst **2** with ethyl phenylpropiolate **3a**, excellent yields of trimerized products and high selectivity of the 1,3,5-isomer **4a** were observed (the substitution pattern was further confirmed by X-ray diffraction, Fig. S9). In this case, the preference for the C₃-symmetric 1,3,5-substituted product is possibly determined mainly by the poorer solubility of **4a** in *n*-hexane versus the 1,2,4-isomer **5a**. For ethyl propiolate **3b**, about 35% of the product precipitates from the reaction solution after standing overnight, which contains only the 1,3,5-substituted benzene. Another 14% of this isomer can be precipitated by concentrating the filtrate, while the remaining solution consists of about 6% of 1,3,5- and 23% of 1,2,4-substituted benzene and about 22% of tetrameric products, thus equating to a total of 55% of the 1,3,5-isomer. Such a difference in solubility is advantageous to the separation and purification of the 1,3,5-product as desired. Moreover, yields of 1,3,5-product from the cyclotrimerization of ethyl phenylpropiolate greater than 20% have not been reported^{11a,25} and the substrates are often restricted to alkynes bearing small or activated substituents.^{16a} Also, to our knowledge, for most transition metal systems, such cyclotrimerization reactions work inefficiently using hexane as the medium due to the poor solubility of the catalyst.³

According to previous reports by Dieck *et al.*, the nickel(0) compound with a similar α-diimine (^HL^{IPr-2,6}) behaves as a catalyst for cyclotetramerization of alkynes.^{11a} In other cases, for nickel complexes of L^{IPr-2,6}, only Ni-diimine-alkyne adducts were obtained from the reaction with alkynes, indicating poor catalytic activity of these complexes.²⁴ Thus the current ligand L^{Me-2,4} and the self-supporting for the nickel(0) species may be the key to the activity of **2** toward alkynes.

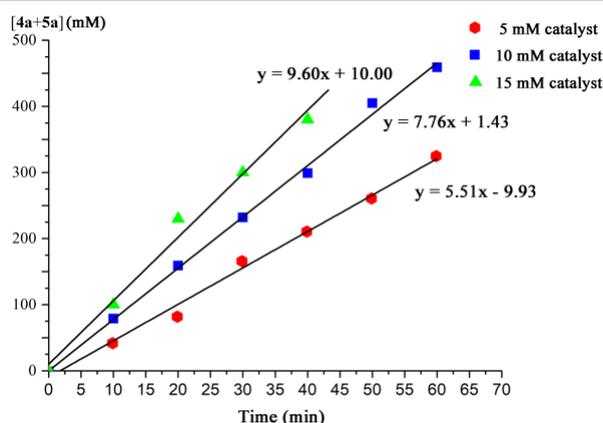


Fig. 4 Plots of [4a+5a] vs. time with variable catalyst concentrations. 1% equiv. (slope = 5.51, $R^2 = 0.98$), 2% equiv. (slope = 7.76, $R^2 = 0.99$), and 3% equiv. (slope = 9.60, $R^2 = 0.99$) of catalyst relative to the concentration of **3a**. Reaction conditions: 0.5 mL of *n*-hexane, 500 mM of **3a** (41 μ L, 0.25 mmol), 100 °C. Each point represents the average of two independent catalytic reactions and each is analyzed by ^1H NMR spectroscopy.

Kinetics study. The kinetics of the catalytic reaction was investigated using established procedures.²⁶ To study the dependence on catalyst concentration, we determined v_{obs} from plots of $\ln[\text{catalyst}]$ at varying catalyst concentrations of 5.0–15.0 mM (Fig. 4) at 100 °C. The plots gave a linear relationship with slope $n = 0.5$ of the catalyst, consistent with half-order dependence on [catalyst **2**] (Fig. S10), which implies that the catalyst resting state is not trimeric. Based on this, the mechanism of the catalytic reaction reported here may be proposed to be similar to that commonly accepted for the cyclotrimerization of alkynes by mononuclear complexes (Scheme S1).^{2a,27}

Conclusions

In summary, a cyclic tri-nickel(0) complex (**2**) bearing the *N*-2,4-dimethylphenyl substituted α -diimine ligand $\text{L}^{\text{Me-2,4}}$ displays high catalytic activity towards alkyne cyclotrimerization to form benzene derivatives. The aggregation of the Ni complex provides stabilization for the nickel(0) center. Moreover, the reactions can be performed in the less toxic, non-polar solvent *n*-hexane, which also facilitates the separation of the 1,3,5-products due to the different solubility of 1,3,5- versus 1,2,4-isomers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Experimental

Synthesis and characterization of complex $[\text{Ni}_3(\mu_2\text{-Br})_3(\mu_3\text{-Br})_2(\text{L}^{\text{Me-2,4}})_3]\cdot\text{Br}$ (**1**)

(DME)NiBr₂ (1.55 g, 5.00 mmol) and $\text{L}^{\text{Me-2,4}}$ (1.46 g, 5.00 mmol) were added to 50 mL of CH_2Cl_2 in a Schlenk flask. The colour changed from orange to brown immediately, and the mixture was stirred for 18 h at room temperature. The mixture was concentrated and the precipitate was filtered and washed with ether to yield complex **1** (2.19 g, 86%). Brown crystals were grown from CH_2Cl_2 . M.p.: 291–293 °C. IR (KBr, v/cm^{-1}): 2951(m), 2918(m), 2864(m), 1638(m), 1595(m), 1493(s), 1377(s), 1229(s), 1165(m), 849(s), 735(m). $\text{C}_{60}\text{H}_{72}\text{N}_6\text{Ni}_3\text{Br}_6$ (1531.89): Calcd. (found): C, 47.02 (46.88); H, 4.73 (4.71); N 5.48 (5.49) %.

Synthesis and characterization of complex $[\{\text{Ni}(\mu\text{-L}^{\text{Me-2,4}})\}_3]$ (**2**)

Under strictly anhydrous and anaerobic conditions, the bromo complex **1** (0.766 g, 0.50 mmol) and sodium metal (0.069 g, 3.00 mmol) were added to 30 mL of Et_2O at room temperature. The mixture was stirred for 8 h whereupon the colour changed to dark purple. The mixture was filtered and the filtrate was concentrated to about 6 mL and stored at room temperature for several days to yield complex **2** as purple crystals (0.342 g, 65%). M.p.: 173–174 °C. ^1H NMR (400 MHz, C_6D_6 , 298 K): $\delta = 0.69$ (s, 9H, N-CCH₃), 0.76 (s, 9H, N-CCH₃), 2.18 (s, 18H, Ar-CH₃), 2.60 (s, 9H, Ar-CH₃), 2.73 (s, 9H, Ar-CH₃), 6.44–7.89 ppm (18H, Ar-H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, C_6D_6 , 298 K): $\delta = 16.7$ (N-CCH₃), 18.4 (Ar-*o*-CH₃), 19.6 (Ar-*o*-CH₃), 20.4 (Ar-*p*-CH₃), 20.5 (Ar-*p*-CH₃), 62.9 (N-CCH₃), 180.4 (N-CCH₃), 123.6–150.3 (aryl-C) ppm. IR (Nujol, v/cm^{-1}): 2968(m), 2920(s), 2859(m), 1641(m), 1606(m), 1490(s), 1448(m), 1367(w), 1185(m), 1124(m), 1031(m), 829(m), 719(w). $\text{C}_{60}\text{H}_{72}\text{N}_6\text{Ni}_3$ (1053.37): Calcd. (found): C 68.42 (68.54), H 6.89 (6.87), N 7.98 (7.95) %.

Procedures for catalytic [2+2+2] cyclotrimerization of ethyl propiolate and ethyl phenylpropiolate (optimization of the reaction conditions)

Under an argon atmosphere, complex **2** (7.9 mg, 7.5×10^{-3} mmol) and ethyl propiolate or ethyl phenylpropiolate were mixed in 0.5 mL of solvent (see Table 1 for details) at 25 °C (ethyl propiolate) or 100 °C (ethyl phenylpropiolate). The resulting mixture was stirred at the temperature for 0.5 h (ethyl propiolate) or 5 h (ethyl phenylpropiolate). The reaction was complete and the yield and isomeric ratio were determined by analyzing the ^1H NMR spectra.

General procedures for the separation and characterization of the cyclotrimerization products

In a 15 mL sealed pressure tube were added the alkyne (2.5 mmol) and catalyst **2** with 5 mL of *n*-hexane. The mixture was stirred at 100 °C for 5 h or at room temperature for 0.5 h (depending on the alkyne substrate) under Ar. After cooling down to room temperature, the volatiles were removed under reduced pressure and the pure 1,3,5- and 1,2,4-isomers were obtained by flash chromatography on silica gel (gradient ethyl acetate/petroleum ether = 1/20 (v/v) or petroleum ether). For

details of each individual reaction and characterization data of the trimerized products please see ESI).

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