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Nickel-Catalyzed Facile [2+2+2] Cyclotrimerization of Unactivated Internal Alkynes to Polysubstituted Benzenes

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Abstract: Catalytic [2+2+2] cyclotrimerization of unactivated internal alkynes giving cyclotrimerization products in excellent yields with high regioselectivity is accomplished through the use of simple and common catalytic mixture comprising $Ni(acac)_2$, imidazolium salt and Grignard reagent at r.t. or 60 °C for 20 min or 1 h.

Introduction

Transition metal-catalyzed [2+2+2] cyclotrimerization of alkynes is an effective tool for constructing polysubstituted benzenes which are useful building blocks for synthesis of new materials and biologically active compounds.[1] In spite of the progress, cyclotrimerization of unactivated internal alkynes is still challenging in terms of catalytic efficiency and regioselectivity. In many known protocols of internal alkynes cyclotrimerization,[2] high catalyst loading, high reaction temperature and/or prolonged reaction time are generally required, and the internal alkyne substrates have been often restricted to those bearing small or activated substituents such as ethyl phenylpropiolate. Since Reppe's pioneering cyclotrimerization of alkyne using a Ni based catalyst,[3] many Ni(0/II) compounds supported by different ligands have been found to be efficient in catalyzing inter- and intramolecular cyclotrimerization of alkynes and the related reactions.[1,2a,2j,4] Nickel NHC (N-heterocyclic carbene) complexes are catalytically active for many organic transformations.[5] The combination of $Ni(cod)_2$/NHC could catalyze the cyclotrimerization of unsymmetrical internal alkynes with ester substituent,[2j] the cyclotrimerization of diynes with nitriles, isocynates or CO_2,[4m] and the [2+2+2] cycloaddition of 1,n-enyne to form substituted 1,3-cyclohexadiene.[4n] As part of our ongoing investigations in Grignard-assisted Ni catalyzed C-C bond formation reactions,[6] we herein report a combinative use of $Ni(acac)_2$/imidazolium salt/Grignard reagent in an effective catalysis of [2+2+2] cyclotrimerization of unactivated internal alkynes under mild conditions. The easily accessible NHC precursors, in form of imidazolium salts, IMes·HX (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride or bromide), IBz·HX (1,3-dibenzylimidazolium chloride or bromide), IPr·HCl (1,3-bis-(2,6-diisopropylphenyl)I)imidazolium chloride chloride) and IPr*·HCl (1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazolium chloride) were used in this study.

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Results and Discussion

[2+2+2] Cyclotrimerization of 1-phenyl-1-propyne catalyzed by $Ni(acac)_2$/NHC·HX/^{n}BuMgCl

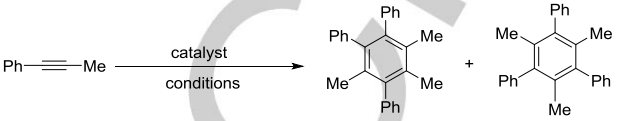
Preliminary screenings of reaction conditions were carried out on the [2+2+2] cyclotrimerization of unsymmetrical internal alkyne, *viz.* 1-phenyl-1-propyne (**1a**) by using the catalyst system containing $Ni(acac)_2$ (1 mol%), imidazolium salt and ^{n}BuMgCl in a ratio of 1:3:20. The results are summarized in Table 1. Among the imidazolium salts used, the system containing IMes·HX showed the highest catalytic activity, yielding the cyclotrimerization products, 1,2,4-isomer **2a** and 1,3,5-isomer **2a'** in quantitative yield (**2a**: **2a'** = 80: 20) after 20 min at r.t. in the mixed-solvent of THF/toluene (entry 1). In all THF solvent, the system showed similarly high catalytic activity. However, no reaction occurred when toluene was replaced with CH_2Cl_2 or CH_3CN. In the absence of either IMes·HX or Grignard reagent, no reaction took place (entries 2, 3). Use of IPr*·HCl could give a high total yield of **2a** and **2a'**, however, with poor regioselectivity (entry 4). The use of IPr·HCl led to both low total yield and poor selectivity (entry 5). The combination of $Ni(acac)_2$/IBz·HX/^{n}BuMgCl gave the highest regioselectivity (**2a**: **2a'** ≥ 99: 1) and a quantitative yield of **2a** could be obtained at 60 °C after 1 h (entries 6, 7). This catalyst system is therefore more efficient than Hilt's cobalt diimine catalyst ($CoBr_2$(Cy-diimine) (5 mol%)/Zn/ZnI_2) which produced **2a** and **2a'** in 98% of yield (**2a**: **2a'** = 96: 4) at 80 °C for 15 h.[2d] Other alkyl or aryl Grignard reagents combined with $Ni(acac)_2$ and IMes·HX could catalyze the reaction as efficiently as ^{n}BuMgCl, whilst alkenyl Grignard reagent was much less active and alkynyl Grignard reagent was inactive (Table S1 in the Supporting Information). The influence of the basicity of Grignard reagent on the catalytic activity is thus evident.

Ni(0) species is known to be an active catalyst in the commonly accepted mechanism of cyclotrimerization of alkynes and other related reactions.[1] As expected, no reaction took place when ^{t}BuOK, commonly used to form free NHC ligand *in situ* in the synthesis of metal NHC complexes, replaced Grignard reagent (entry 8), while the system containing ^{n}BuLi was found to be active with 82% yield of **2a** and **2a'** (entry 9). Neither $Ni(acac)_2$/IPr or $Ni(cod)_2$/IPr·HCl could catalyze the reaction

(entries 10, 11), while the catalytic activity of $Ni(cod)_2$/IPr was similar to that of $Ni(acac)_2$/IPr·HCl/^{n}BuMgCl (entry 12 *cf.* entry 5). The Grignard reagent used herein thus serves both as a base and reducing agent and the catalytically active Ni(0)-NHC species is generated *in situ*. This is further supported by the observation that simple nickel salts, $NiCl_2·6H_2O$ and $Ni(OAc)_2·4H_2O$ could catalyze the reaction as efficiently as $Ni(acac)_2$ when mixing with IMes·HCl and ^{n}BuMgCl (entries 13, 14). Although the definitive explanations are not forthcoming, the results above also suggest some general trends of the effect of NHC ligand on the catalytic performance. The catalytic activity increases when the donor ability of the NHC ligand[7a-c] decreases. On the other hand, when the steric bulk of the NHC ligand[7d] decreases (IPr>IMes>IBz), the regioselectivity of the 1,2,4-isomer (**2a**) increases. The similar steric effect of NHC was also indicated in the $Ni(cod)_2$/NHC catalyzed cyclotrimerization of ethyl but-2-ynoate where the less bulky SIMes (1,3-bis-(2,4,6-trimethylphenyl)imidazolidin-2-ylidene) ligand gave higher regioselectivity to 1,2,4-isomer than SIPr (1,3-bis-(2,6-diisopropylphenyl)imidazolidin-2-ylidene) ligand.[2j] It was, thus expected that the most bulky IPr* ligand could give the highest selectivity of the 1,3,5-isomer (**2a'**). However its regioselectivity was found to be comparable to that of IPr ligand. It might be attributed to the ability of IPr* to adjust its steric surrounding.[7e] Under the conditions applied in this work, no reaction took place when using phosphine ligands such as PPh_3, dppe or dppb or $CoCl_2$ as metal source (entries 15, 16).

The synthesis of nickel(II) NHC complexes, $Ni(acac)_2(NHC)$[8] and $NiCl_2(NHC)_2$[9] (NHC = IPr, IMes) have been reported previously. The presence of Ni(II) precursor, Grignard reagent and imidazolium salt in the catalyst system implies that a Ni(II)-NHC complex formed *in situ* could be a precatalyst. Using the mixture of $Ni(acac)_2(IPr)$/^{n}BuMgCl as catalyst in which $Ni(acac)_2(IPr)$ was obtained from the reaction of $Ni(acac)_2$ with free IPr ligand, the [2+2+2] cyclotrimerization products of **1a** could be obtained in 41% of yield (**2a**:**2a'**= 59:41) under similar conditions given in Table 1. It suggests that $Ni(acac)_2(NHC)$ could be responsible for the catalytic activity of $Ni(acac)_2$/IPr·HCl/^{n}BuMgCl (*cf.* entry 5). However, attempt to isolate $Ni(acac)_2(NHC)$ from the reaction between $Ni(acac)_2$ and IMes.HCl or IPr.HCl treated by ^{n}BuMgCl (1.1 equiv) was futile. In contrast, $NiCl_2(IMes)_2$ could be isolated by treating anhydrous $NiCl_2$ (1 equiv.) and IMes·HCl (2 equiv.) with ^{n}BuMgCl (2 equiv.) in THF at r. t. (see the Supporting Information). However the mixture of $NiCl_2(IMes)_2$/^{n}BuMgCl could not catalyze the [2+2+2] cyclotrimerization of **1a**. When $NiCl_2(IMes)_2$ (1 equiv.) was treated with ^{n}BuMgCl (2 equiv.) in THF at r.t., no color change of the reaction solution was observed even after 12 h. Interestingly, from the reaction mixture of IMes·HCl (3 equiv.), $NiCl_2$ (1 equiv.), diphenylacetylene (2 equiv.) and ^{n}BuMgCl (10 equiv.) at r.t. $NiCl_2(IMes)_2$ was isolated and identified by single-crystal X-ray diffraction analysis. The structural features of $NiCl_2(IMes)_2$ (see the Supporting Information), which have not been reported in the literature, are similar to those of the bis(carbene) Ni(II) complexes, such as $NiCl_2(IPr)_2$[9] and $NiCl_2(SIMes)_2$[10]. On the basis of these observations, the lack of the catalytic activity of $NiCl_2(IMes)_2$/^{n}BuMgCl could be attributed to the failure of Grignard reagent to activate $NiCl_2(IMes)_2$ under the catalytic reaction conditions. In the catalytic reaction mixture the active Ni(0)-NHC complex could be also formed through the direct reaction between the in *situ* formed NHC ligand and Ni(0) species obtained from the reduction of Ni(II) precursor by Grignard reagent.

Table 1. [2+2+2] Cyclotrimerization of 1-phenyl-1-propyne[a]



1a **2a** **2a'**

Entry	Metal salt or complex	NHC·HX or other ligand	RMgX or other additive	Yield[b] of **2a**+**2a'** (%)	Ratio[c] of **2a** : **2a'**
1	$Ni(acac)_2$	IMes·HCl/ IMes·HBr	^{n}BuMgCl	98/99	80:20/ 79:21
2	$Ni(acac)_2$	-	^{n}BuMgCl	NR[d]	-
3	$Ni(acac)_2$	IMes·HCl	-	NR	-
4	$Ni(acac)_2$	IPr*·HCl	^{n}BuMgCl	93	57 : 43
5	$Ni(acac)_2$	IPr·HCl	^{n}BuMgCl	40	52 : 48
6	$Ni(acac)_2$	IBz·HCl/ IBz·HBr	^{n}BuMgCl	29/34	99 : 1
7[e]	$Ni(acac)_2$	IBz·HCl/ IBz·HBr	^{n}BuMgCl	98/99	99 : 1
8	$Ni(acac)_2$	IMes·HCl	^{t}BuOK	NR	-
9	$Ni(acac)_2$	IMes·HCl	^{n}BuLi	82	80 : 20
10	$Ni(acac)_2$	IPr	-	NR	-
11	$Ni(cod)_2$	IPr·HCl	-	NR	-
12	$Ni(cod)_2$	IPr	-	42	60 : 40
13	$NiCl_2·6H_2O$	IMes·HCl	^{n}BuMgCl	90	75 : 25
14	$Ni(OAc)_2·4H_2O$	IMes·HCl	^{n}BuMgCl	99	80 : 20
15	$Ni(acac)_2$	dppe/dppb /PPh_3	^{n}BuMgCl	NR	-
16	$CoCl_2·6H_2O$	IMes·HCl	^{n}BuMgCl	<1	-

[a] Conditions: to a mixture of **1a** (0.50 mmol), metal salt or complex (0.005 mmol, 1 mol%) and NHC·HX (0.015 mmol, 3 mol%) in toluene (1.0 mL) was added RMgX (0.1 M in THF, 1.0 mL, 0.10 mmol) dropwise within 30 sec. The resulted mixture was stirred under N_2 at r.t. for 20 min. [b] Isolated yield. [c] Determined by GC-MS and ^{1}H NMR analyses. [d] NR = no reaction. [e] At 60 °C, for 1h.

Herrmann *et al.* reported that a mixture of $Ni(acac)_2$/IPr·HX (1:1) or $Ni(acac)_2$/IMes·HX (1:1) was an efficient catalyst system for the cross-coupling of aryl Grignard reagents with aryl chlorides.[11] The catalyst systems $Ni(cod)_2$/SIPr and $Ni(cod)_2$/SIMes in 1:1 ratio could catalyze the cyclotrimerization of unsymmetrical internal alkynes with ester substituent.[2j] These results prompted us to examine the catalytic activity of the

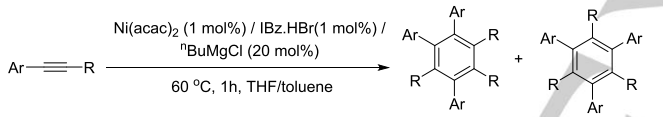
mixture of $Ni(acac)_2$ and NHC·HX in 1:1 ratio in the presence of ^{n}BuMgCl. The results are very similar to those obtained in the mixtures of $Ni(acac)_2$ and NHC·HX in 1:3 ratio (see Table S2 in the Supporting Information). The ratio of 1:1 has therefore been used in the subsequent study.

[2+2+2] Cyclotrimerization of alkyl(aryl)acetylenes catalyzed by $Ni(acac)_2$/IBz·HBr/^{n}BuMgCl

The catalytic [2+2+2] cyclotrimerization of other unsymmertrical alkyl(aryl)acetylenes was examined using the mixture of $Ni(acac)_2$/IBz·HBr/^{n}BuMgCl (1:1:20) as catalyst (at 60 °C, 1 h). The results are summarized in Table 2. The catalytic system applied well to 1-aryl-1-propyne with either electron donating or withdrawing group in either *para*- or *meta*-position of the phenyl ring (entries 1-9). However, when 1-(hex-1-yn-1-yl)-2-methylbenzene was used, no cyclotrimerization product was formed.

High yield and high regioselectivity could be also obtained when the methyl group of **1a** was replaced with n-butyl group or ethyl group (entries 10-11). When (cyclohexylethynyl)benzene or methyl phenylpropiolate was used as substrate, no cyclotrimerization product was observed. The present catalyst system is not active for the cyclotrimerization of dialkylalkynes.

Table 2. [2+2+2] Cyclotrimerization of alkyl(aryl)acetylenes[a]



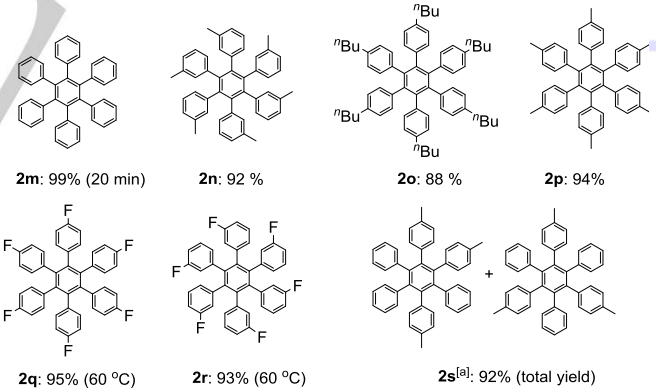
1 **2** **2'**

Entry	Ar	R	Yield of 2 (%)[b]	Ratio of 2 :2'
1	4-MeC_6H_4	Me	99 (**2b**)	98 : 2
2	4-$MeOC_6H_4$	Me	86 (**2c**)	98 : 2
3	4-^{t}BuC_6H_4	Me	92 (**2d**)	98 : 2
4	4-FC_6H_4	Me	96 (**2e**)	98 : 2
5	3-$MeOC_6H_4$	Me	90 (**2f**)	97 : 3
6	3-MeC_6H_4	Me	95 (**2g**)	97 : 3
7	3-FC_6H_4	Me	98 (**2h**)	99 : 1
8[c]	4-$PhOC_6H_4$	Me	95 (**2i**)	98 : 2
9[c]	6-MeONaphthyl	Me	92 (**2j**)	98 : 2
10	Ph	^{n}Bu	98 (**2k**)	98 : 2
11	Ph	Et	92 (**2l**)	97 : 3

[a] Conditions: ^{n}BuMgCl (0.1 M in THF, 1.0 mL, 0.10 mmol) was added dropwise to a mixture of alkyne (0.50 mmol), $Ni(acac)_2$ (0.005 mmol, 1 mol%) and IBz.HBr (0.005 mmol, 1 mol%) in toluene (1.0 mL) within 30 seconds. The resulted mixture was stirred under N_2 at 60 °C for 1h. [b] Isolated yield. [c] ^{n}BuMgCl (0.1 M in THF, 2.0 mL, 0.20 mmol) was added.

[2+2+2] Cyclotrimerization of diarylacetylenes catalyzed by $Ni(acac)_2$/IMes·HCl/^{n}BuMgCl

The cyclotrimerization of an array of diarylacetylenes could be catalyzed efficiently when $Ni(acac)_2$/IMes·HCl/^{n}BuMgCl (1:1:20) was used as catalyst (Scheme 1). At r. t. hexaphenylbenzene **2m** was obtained in nearly quantitative yield after 20 min. Using cobalt diimine ($CoBr_2$(Cy-diimine)/Zn/ZnI_2)[2d] or $Ni(cod)_2$/PPh_3[2j] as catalyst, **2m** could be obtained in good yields (76% and 83%, respectively), however, longer reaction time (15 and 24 h, respectively) and higher temperature (80°C) were required. For the substrates with phenyl ring containing electron donating substituent at the *para*- or *meta*-position, a longer reaction time of 1 h gave **2n**-**2p** in high yields. Cyclotrimerization of diarylacetylenes with electron withdrawing group on the phenyl ring needed to be conducted at elevated temperature (60 °C) to produce **2q** and **2r** in high yield. The preparation of **2n** has been reported previously using well-known cobalt catalyst, $Co_2(CO)_8$ under reflux condition in dioxane for 3 h.[12]. Hexakis(4-fluorophenyl)benzene (**2q**), a precursor to hexa-fluoro-hexa-peri-hexabenzocoronene used for n-type organic field-effect transistors, could not be obtained from $Co_2(CO)_8$ catalyzed cyclotrimerization of 4,4'-difluorodiphenylacetylene.[13] It was hence prepared from a multi-step synthesis with harsh conditions such as at 260 °C and long reaction time of 9 h, and even so with low total yields.[13] When unsymmetrical diarylacetylene was used, the cyclotrimerization products with the same high yield could be obtained. The method developed in this work, thus, provides a convenient synthetic route to various π-conjugated systems.



Scheme 1. [2+2+2] cyclotrimerization of diarylacetylenes. (Conditions: ^{n}BuMgCl (0.1 M in THF, 1.0 mL, 0.10 mmol) was added dropwise to a mixture of alkyne (0.50 mmol), $Ni(acac)_2$ (0.005 mmol, 1 mol%) and IMes.HCl (0.005 mmol, 1 mol%) in toluene (1.0 mL) within 30 seconds. The resulted mixture was stirred under N_2 at r.t. for 1h, Isolated yield. [a] Unsymmetrical substrate was used and the ratio of the 1,2,4 isomer to the 1,3,5 isomer was not determined.)

Conclusions

We have developed a facile and effective catalyst system comprising simple nickel complex, easily accessible imidazolium salt and common Grignard reagent for the [2+2+2] cyclotrimerization of simple unactivated alkyl(aryl)acetylenes and diarylacetylenes under mild conditions. This methodology provides a new and operationally simple synthetic method of polysubstituted benzenes. This work also offers an opportunity to tune the activity and regioselectivity of the catalyst system by using different NHC ligands.

Experimental Section

General Methods

All preparations and manipulations were performed using standard Schlenk techniques under a nitrogen atmosphere. NMR spectra were measured at 25 °C (unless stated otherwise) using a Bruker ACF 500 MHz NMR spectrometer. GC-MS analyses were recorded on Agilent 6890N/5973N system. HRMS was conducted on Bruker MicrOTOF-QII spectrometer. Solvents were dried according to standard procedures. All Grignard reagents were obtained from Sigma-Aldrich. All Grignard reagents were diluted to 0.1M by THF before use. The imidazolium salts, IMes·HX[14a-c], IPr·HCl[14a,c], and IPr*·HCl[14d] IBz·HX[14e] and the alkynes[15] were prepared according to the literature methods.

Representative procedure of [2+2+2] cyclotrimerization of alkyne (Entry 7, Table 1)

After standard cycles of evacuation and refill with pure N_2, $Ni(acac)_2$ (1.3 mg, 0.005 mmol), 1-phenyl-1-propyne (58 mg, 0.50 mmol), IBz.HBr (4.9 mg, 0.015 mmol) and toluene (1.0 mL) were introduced into a 25 mL-Schlenk tube equipped with a magnetic stir bar. Butylmagnesium chloride solution (0.1 M in THF) (1.0 mL, 0.10 mmol) was then added to the mixture dropwise within 30 seceonds. The reaction mixture was stirred at 60 °C. After 1 h, the reaction was diluted with hexane (20 mL). The mixture was passed through a pad of silica gel with hexane as eluent. The resulting solution was concentrated under vacuum and then subjected to a column chromatography (silica gel) with hexane as eluent to give 1,2,4-trimethyl-3,5,6-triphenylbenzene (**2a:** 57.5 mg, 99%).

*1,2,4-Trimethyl-3,5,6-triphenylbenzene (**2a**)*[2d]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.37-7.34 (m, 1H), 7.27-7.25 (m, 2H), 7.15-6.97 (m, 10H), 2.055, 2.051 (s, total 6H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 141.63, 141.60, 141.4, 140.6, 139.2, 133.9, 131.9, 131.2, 130.30, 129.4, 128.4, 127.30. 127.28, 126.5, 125.7, 125.6, 19.4, 18.3, 18.1; HRMS (EI) m/z calcd for $C_{27}H_{24}$ 348.1873, found: 348.1876.

*1,3,5-Trimethyl-2,4,6-triphenylbenzene (**2a'**)*[2d]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.41 (m, 6H), 7.34-7.31 (m, 3H), 7.24-7.23 (m, 6H), 1.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 139.8, 133.2, 129.4, 128.4, 126.4, 19.4.

*1,2,4-Trimethyl-3,5,6-tri-(4-methylphenyl)benzene (**2b**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.25 (m, 2H), 7.14-7.12 (m, 2H), 6.96-6.84 (m, 8H), 2.42 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.04, 2.03 (s, total 6H), 1.71 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 140.6, 139.5, 139.2, 138.7, 135.8, 134.9, 134.8, 133.9, 132.0, 131.6, 130.11, 130.09, 129.3, 129.1, 128.03, 127.99, 21.2, 21.1, 19.5, 18.3, 18.1; HRMS (EI) m/z calcd for $C_{30}H_{30}$ 390.2342, found: 390.2353.

*1,2,4-Trimethyl-3,5,6-tri-(4-methoxyphenyl)benzene (**2c**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.70-6.66 (m, 4H), 3.87 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 2.04 (s, 6H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 157.4, 157.3, 140.9, 140.5, 139.1, 134.8, 134.22, 134.18, 132.24, 132.17, 131.24, 131.20, 130.4, 113.8, 112.80, 112.77, 55.2, 55.03, 55.00, 19.6, 18.3, 18.2; HRMS (EI) m/z calcd for $C_{30}H_{30}O_3$ 438.2190, found: 438.2204.

*1,2,4-Trimethyl-3,5,6-tri-(4-t-butylphenyl)benzene (**2d**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.09-7.05 (m, 4H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 2.11 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H), 1.39 (s, 9H), 1.21 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 148.1, 148.0, 141.2, 140.9, 139.6, 139.4, 138.6, 134.0, 131.7, 131.5, 130.01, 129.98, 129.95, 129.0, 125.1, 123.8, 123.8, 34.5, 34.23, 34.21, 31.5, 31.30, 31.28, 19.6, 18.4, 18.3; HRMS (EI) m/z calcd for $C_{39}H_{48}$ 516.3751, found: 516.3762.

*1,2,4-Trimethyl-3,5,6-tri-(4-fluorophenyl)benzene (**2e**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.13 (m, 4H), 6.94-6.80 (m, 8H), 2.02 (s, 6H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 (d, $J_{C\text{-}F}$ = 243.7 Hz), 161.10 (d, $J_{C\text{-}F}$ = 243.5 Hz), 161.06 (d, $J_{C\text{-}F}$ = 243.2 Hz), 140.6 140.0, 138.4, 138.0 (d, $J_{C\text{-}F}$ = 3.5 Hz), 137.32 (d, $J_{C\text{-}F}$ = 3.5 Hz), 137.26 (d $J_{C\text{-}F}$ = 3.5 Hz), 134.5, 132.3, 131.7, 131.6 (d, $J_{C\text{-}F}$ = 7.8 Hz), 130.8 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.4 (d, $J_{C\text{-}F}$ = 21.0 Hz), 114.5 (d, $J_{C\text{-}F}$ = 21.1 Hz), 114.4 (d, $J_{C\text{-}F}$ = 21.1 Hz), 19.4, 18.3, 18.1; HRMS (EI) m/z calcd for $C_{27}H_{21}F$ 402.1590, found: 402.1601.

*1,2,4-Trimethyl-3,5,6-tri-(3-methoxyphenyl)benzene (**2f**)*

^{1}H NMR (500 MHz, DMSO-d_6, 100 °C), δ 7.40-7.38 (m, 1H), 7.05-6.93 (m 3H), 6.77-6.50 (m, 8H), 3.81 (s, 3H), 3.63 (s, 6H), 2.01, 2.00 (s, total 6H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C), δ 159.2, 158.2, 142.8, 142.1, 142.0, 140.3, 139.4, 137.9, 132.4, 130.6, 129.5, 128.9, 127.6, 122.0, 120.9, 115.5, 115.4, 114.4, 111.9, 111.4, 54.7, 54.5, 18.1, 17.0, 16.9; HRMS (EI) m/z calcd for $C_{30}H_{30}O_3$ 438.2190, found: 438.2203.

*1,2,4-Trimethyl-3,5,6-tri-(3-methylphenyl)benzene (**2g**)*

^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.37-7.34 (m, 1H), 7.18-7.17 (m, 1H), 7.02-6.99 (m, 4H), 6.88-6.76 (m, 6H), 2.38 (s, 3H), 2.18, 2.16 (s, total 6H), 1.98, 1.97 (s, total 6H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 141.4, 140.7, 140.60, 140.3, 139.6, 138.2, 136.9, 135.4, 132.2, 130.4, 130.2, 130.15, 130.08, 129.4, 129.1, 127.6, 126.4, 126.3, 125.54, 125.48, 20.2, 20.04, 20.02, 18.3, 17.1, 16.9; HRMS (EI) m/z calcd for $C_{30}H_{30}$ 390.2342, found: 390.2357.

*1,2,4-Trimethyl-3,5,6-tri-(3-fluorophenyl)benzene (**2h**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.40 (m, 1H), 7.16-6.95 (m, 5H), 6.82-6.67 (m, 6H), 2.03 (s, 6H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 161.9 (d, $J_{C\text{-}F}$ = 243.6 Hz), 161.1 (d, $J_{C\text{-}F}$ = 242.2 Hz), 143.4 (d, $J_{C\text{-}F}$ = 6.8 Hz), 142.8 (d, $J_{C\text{-}F}$ = 7.2 Hz), 142.6 (d, $J_{C\text{-}F}$ = 7.5 Hz), 139.6, 138.6, 136.9, 133.1, 130.9, 129.9 (d, $J_{C\text{-}F}$ = 8.6 Hz), 129.6, 128.6 (d, $J_{C\text{-}F}$

= 8.5 Hz), 125.7, 124.7, 116.2 (d, J_{C-F} = 21.1 Hz), 115.4 (d, J_{C-F} = 21.5 Hz), 113.0 (d, J_{C-F} = 20.6 Hz), 112.22 (d, J_{C-F} = 20.2 Hz), 112.18 (d, J_{C-F} = 21.2 Hz), 18.0, 17.0, 16.8; HRMS (EI) m/z calcd for $C_{27}H_{21}F$ 402.1590, found: 402.1598.

*1,2,4-Trimethyl-3,5,6-tri-(4-phenoxyphenyl)benzene (**2i**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.32-7.28 (m, 4H), 7.21-7.19 (m, 2H), 7.15-7.04 (m, 7H), 6.97-6.89 (m, 8H), 6.85-6.81 (m, 4H), 2.11 (s, 3H), 2.09 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 157.2, 156.0, 154.92, 154.85, 140.9, 140.4, 138.9, 137.2, 137.0, 134.4, 132.1, 131.73, 131.69, 130.7, 129.8, 129.67, 129.65, 123.3, 122.85, 122.83, 119.1, 118.7, 118.34, 118.31, 19.6, 18.4, 18.2; HRMS (EI) m/z calcd for $C_{45}H_{36}O_3$ 624.2659, found: 624.2661.

*1,2,4-Trimethyl-3,5,6-tri-(6-methoxynaphthyl)benzene (**2j**)*

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H),7.71-7.46 (m, 7H), 7.39-7.36 (m, 2H), 7.22-6.97 (m, 7H), 3.90 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 157.0, 156.7, 156.6, 140.5, 139.9, 138.4, 136.6, 132.8, 132.6, 131.9, 131.8, 131.1, 130.3, 128.7,128.4, 128.34, 128.28, 127.6, 127.5, 126.8, 126.3, 124.9, 117.96, 117.54, 117.49, 106.1, 105.8, 54.9, 54.7, 54.6, 18.5, 17.3, 17.1; HRMS (EI) m/z calcd for $C_{42}H_{36}O_3$ 588.2659, found: 588.2670.

*1,2,4-Tri-(n-Butyl)-3,5,6-triphenylbenzene (**2k**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.34-7.30 (m, 3H), 7.11-6.97 (m, 10H), 2.41-2.35 (m, 4H), 2.05-2.02 (m, 2H), 1.44-1.33 (m, 4H), 1.16-1.03 (m, 6H), 0.73-0.66 (m, 8H), 0.38-0.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 141.5, 141.24, 141.18, 139.2, 138.3, 136.5, 136.2, 130.6, 130.5, 130.0, 127.6, 126.87, 126.83, 126.3, 125.51, 125.45, 33.4, 32.8, 31.1, 30.5, 30.2, 23.23, 23.16, 22.7, 13.51, 13.48, 13.1; HRMS (EI) m/z calcd for $C_{36}H_{42}$ 474.3281, found: 474.3294.

*1,2,4-Triethyl-3,5,6-triphenylbenzene (**2l**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.43(m, 2H), 7.39-7.36 (m, 3H), 7.14-7.02 (m, 10H), 2.54-2.46 (m, 4H), 2.16-2.12 (m, 2H), 1.04-0.98 (m, 6H), 0.66 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 141.4, 141.3, 141.2, 141.1, 139.4, 139.3, 137.7, 137.3, 130.6, 130.5, 130.0, 127.7, 126.94, 126.90, 126.4, 125.6, 125.5, 24.6, 23.6, 23.4, 15.6, 15.3; HRMS (EI) m/z calcd for $C_{30}H_{30}$ 375.2113, found: 375.2108.

*Hexakis(phenyl)benzene (**2m**)*[2d]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 140.3, 131.40, 126.6, 125.2; HRMS (EI) m/z calcd for $C_{42}H_{30}$ 534.2342, found: 534.2342.

*Hexakis(3-methylphenyl)benzene (**2n**)*[12]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73-6.60 (m, 24H), 1.99 (pseudo-triple, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 140.1, 135.53, 135.46, 135.39, 132.40, 128.36, 128.33, 126.15, 126.10, 126.04, 125.5, 21.0; ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ 6.73-6.60 (m, 24H), 2.00 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C) δ 140.8, 140.3, 135.5, 132.6, 128.6, 126.17, 125.6, 20.9; HRMS (EI) m/z calcd for $C_{48}H_{42}$ 618.3281, found: 618.3287.

*Hexakis(4-n-butylphenyl)benzene (**2o**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.1 Hz, 12H), 6.62 (d, *J* = 8.1 Hz, 12H), 2.35 (t, *J* = 7.4 Hz, 12H), 1.42-1.36 (m, 12H), 1.17-1.10 (m, 12H), 0.83 (t, *J* = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 139.0, 138.3, 131.3, 126.5, 35.0, 33.4, 21.8, 13.9; HRMS (EI) m/z calcd for $C_{66}H_{78}$ 870.6098, found: 870.6104.

*Hexakis(4-methylphenyl)benzene (**2p**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67-6.63 (m, 24H), 2.09 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 138.0, 134.0, 131.3, 127.2, 21.0; HRMS (EI) m/z calcd for $C_{48}H_{42}$ 618.3281, found: 618.3286.

*Hexakis(4-fluorophenyl)benzene (**2q**)*[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74-6.70 (m, 12H), 6.63-6.59 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (d, J_{C-F} = 244.3 Hz), 139.9, 135.9 (d, J_{C-F} = 3.5 Hz), 132.5 (d, J_{C-F} = 7.9 Hz), 114.1 (d, J_{C-F} = 21.2 Hz); HRMS (EI) m/z calcd for $C_{42}H_{24}F_6$ 642.1777, found: 642.1781.

*Hexakis(3-fluorophenyl)benzene (**2r**)*

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90-6.88 (m, 6H), 6.63-6.55 (m, 18H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 160.5 (d, J_{C-F} = 242.4 Hz), 140.9 (d J_{C-F} = 8.1 Hz), 138.4, 127.9 (d, J_{C-F} = 8.5 Hz), 126.4 (d, J_{C-F} = 2.4 Hz), 117.0 (d, J_{C-F} = 21.6 Hz), 112.1 (d, J_{C-F} = 20.7 Hz); HRMS (EI) m/z calcd for $C_{42}H_{24}F_6$ 642.1777, found: 642.1780.

1,2,4-Triphenyl-3,5,6-tri-(4-methylphenyl)benzene (**2s**) and 1,3,5-Triphenyl-2,4,6-tri-(4-methylphenyl)benzene (**2s'**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86-6.82 (m, 15H), 6.70-6.63 (m, 12H), 2.09 (s) and 2.08 (s) (total 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.02, 141.00, 140.97, 140.5, 140.4, 140.36, 140.23, 140.20, 140.08, 137.70, 137.68, 134.31, 134.26, 131.5, 131.3, 127.2, 126.5, 124.94, 124.88, 21.02, 20.98; HRMS (EI) m/z calcd for $C_{45}H_{36}$ 576.2817, found: 576.2808.

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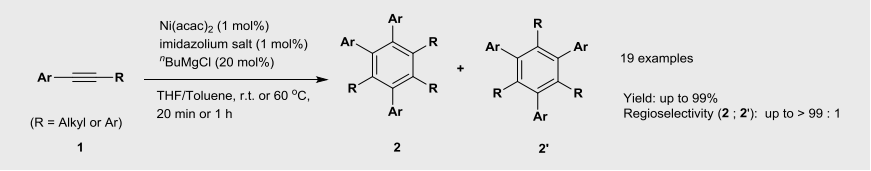

Fei Xue, Ying Kai Loh, Xiaolu Song, Wei Jie Teo, J. Y. Darrence Chua, Jin Zhao, and T. S. Andy Hor**

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Nickel-Catalyzed Facile [2+2+2] Cyclotrimerization of Unactivated Internal Alkynes to Polysubstituted Benzenes

Catalytic [2+2+2] cyclotrimerization of unactivated internal alkynes giving cyclotrimerization products in excellent yields with high regioselectivity is accomplished through the use of simple and common catalytic mixture comprising $Ni(acac)_2$, imidazolium salt and Grignard reagent at r.t. or 60 °C for 20 min or 1 h.