Cycloadditions

How to cite: Angew. Chem. Int. Ed. **2021**, 60, 9627–9634
International Edition: doi.org/10.1002/anie.202017220
German Edition: doi.org/10.1002/ange.202017220

Robust Cobalt Catalyst for Nitrile/Alkyne [2+2+2] Cycloaddition: Synthesis of Polyarylpyridines and Their Mechanochemical Cyclodehydrogenation to Nitrogen-Containing Polyaromatics**

Chang-Sheng Wang[+]*, Qiao Sun*[+]*, Felipe García, Chen Wang,* and Naohiko Yoshikai**

Dedicated to Professor E. Peter Kündig on the occasion of his 75th birthday

Abstract: *The transition-metal-catalyzed [2+2+2] cycloaddition of nitriles and alkynes is an established synthetic approach to pyridines; however, these cycloadditions often rely on the use of tethered diynes or cyanoalkynes as one of the reactants. Thus, examples of efficient, fully intermolecular catalytic [2+2+2] pyridine synthesis, especially those employing unactivated nitriles and internal alkynes leading to pentasubstituted pyridines, remain scarce. Herein, we report on simple and inexpensive catalytic systems based on cobalt(II) iodide, 1,3-bis(diphenylphosphino)propane, and Zn that promote [2+2+2] cycloaddition of various nitriles and diarylacetylenes for the synthesis of a broad range of polyarylated pyridines. DFT studies support a reaction pathway involving oxidative coupling of two alkynes, insertion of the nitrile into a cobaltacyclopentadiene, and C-N reductive elimination. The resulting tetra- and pentaarylpyridines serve as precursors to hitherto unprecedented nitrogen-containing polycyclic aromatic hydrocarbons via mechanochemically assisted multifold reductive cyclodehydrogenation.*

Introduction

Transition-metal-catalyzed [2+2+2] cycloaddition between a nitrile and two alkynes represents a straightforward and atom-economical approach to the synthesis of multisubstituted pyridines,[1] which has found a number of applications in the synthesis of pyridine-containing complex natural products,[2] bioactive molecules,[3] and extended π-conjugated materials,[4] to name a few. Since the pioneering work of Wakatsuki and Yamazaki on CpCo complex-mediated/catalyzed reactions,[5] this cycloaddition has been extensively explored with the aid of various transition metal catalysts including cobalt,[6,7] nickel,[8] iron,[9] ruthenium,[10] rhodium,[11] and iridium,[12] in addition to stoichiometric variants using zirconium[13] and titanium[14] reagents. Despite the tremendous developments in the last decades, the majority of efficient catalytic [2+2+2] pyridine formations take advantage of using tethered diyne or cyanoalkyne as one of the starting materials to reduce the entropic penalty as well as to address the issues of chemoselectivity (e.g., competition with alkyne [2+2+2] cyclotrimerization) and regioselectivity (Scheme 1 a). Thus, examples of fully intermolecular [2+2+2] pyridine synthesis from unactivated nitriles and unactivated internal alkynes are surprisingly scarce. This problem, especially with respect to the cycloaddition involving diarylacetylenes, warrants attention in light of the significant interest in polyarylated pyridines for their optical/electronic properties and relevant applications.[15] In fact, literature reports on the synthesis of pentarylpyridines through [2+2+2] cycloaddition have been limited to those promoted by Cp*Co(η^3-allyl)[16] or palladium catalysts,[17] with only one or two examples for each catalyst (Scheme 1 b). During the preparation of this manuscript, Wang and co-workers reported a catalytic system comprised of iron and cobalt complexes for such cycloaddition, albeit using only diphenylacetylene and a limited scope of aryl nitriles.[18]

As a part of our pursuit of low-valent cobalt-diphosphine catalyzed synthetic transformations,[19,20] we report herein that cobalt(II) iodide, 1,3-bis(diphenylphosphino)propane (dppp), and Zn in polar solvents give rise to simple, inexpensive, and highly robust catalytic systems for the fully intermolecular [2+2+2] cycloaddition of various aryl and alkyl nitriles with diarylacetylenes (Scheme 1 c). The present systems allow for the synthesis of a diverse range of polyarylated pyridines without using large excess of the nitrile with respect to the alkyne (nitrile:alkyne = 1:1 to 1.5:1). Computational studies have suggested that the present [2+2+2] cycloaddition is initiated by oxidative coupling of two alkynes on cobalt, followed by nitrile insertion into cobaltacyclopentadiene and C-N reductive elimination. We have also demonstrated multifold cyclodehydrogenation of tetra- and pentaarylpyridines enabled under mechanochemical conditions to form hitherto unprecedented types of nitrogen-containing polycyclic aromatic hydrocarbons (PAHs).

---

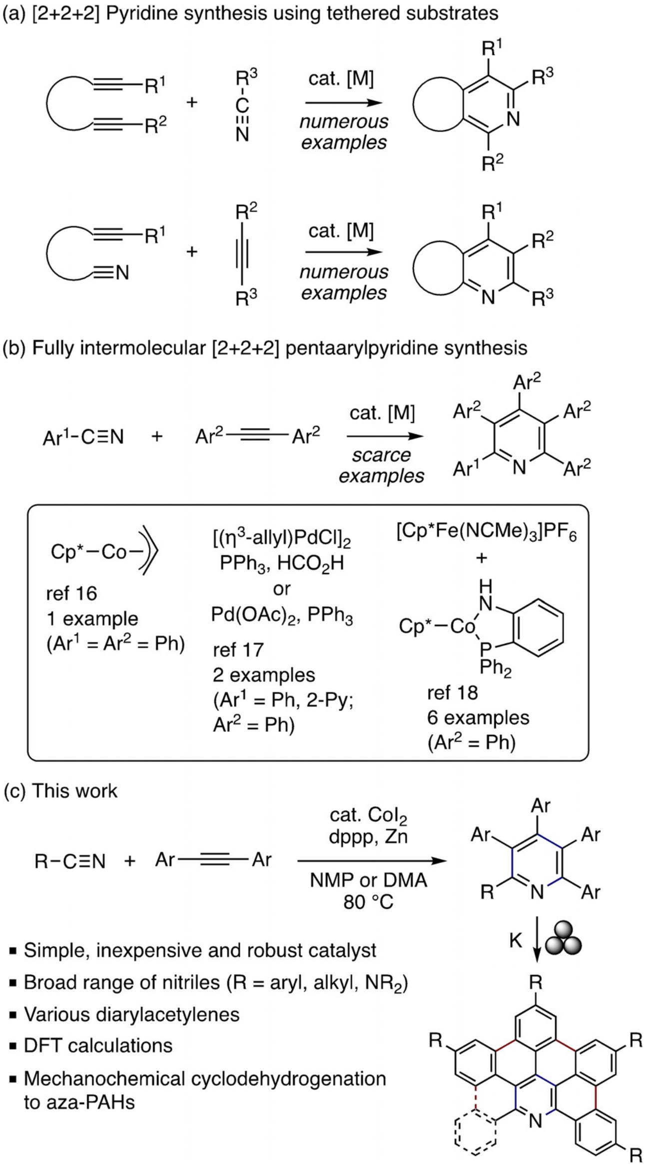
[*] Dr. C.-S. Wang,[+] Dr. Q. Sun,[+] Prof. F. García, Prof. N. Yoshikai
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: nyoshikai@ntu.edu.sg

Prof. C. Wang
Zhejiang Key Laboratory of Alternative Technologies for Fine Chemical Process, Shaoxing University
Shaoxing 312000 (P. R. China)
E-mail: wangchen@usx.edu.cn

[+] These authors contributed equally to this work.

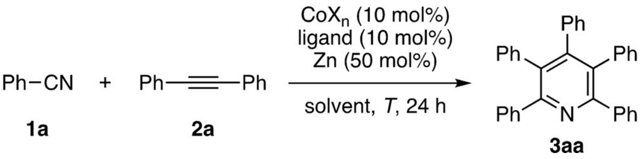
[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/10.26434/chemrxiv.13465697.v1).

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202017220.



Scheme 1. Transition-metal-catalyzed [2+2+2] cycloaddition of nitrile and alkynes.

Table 1: [2+2+2] Cycloaddition of benzonitrile (**1a**) and diphenylacetylene (**2a**).[a]



Entry	CoX$_n$	Ligand	Solvent	T [°C]	Yield [%][b]
1	CoI$_2$	dppp	NMP	120	53
2	CoI$_2$	dppp	DMF	120	47[c]
3	CoI$_2$	dppp	toluene	120	0
4	CoI$_2$	dppp	NMP	80	82 (80)
5	CoCl$_2$	dppp	NMP	80	25
6	CoBr$_2$	dppp	NMP	80	54
7	CoCl(PPh$_3$)$_3$	dppp	NMP	80	45
8[d]	CoCl(PPh$_3$)$_3$	dppp	NMP	80	0
9	CoI$_2$	dppm	NMP	80	4
10	CoI$_2$	dppe	NMP	80	0
11	CoI$_2$	dppb	NMP	80	0
12	CoI$_2$	dppbz	NMP	80	2
13[e]	CoI$_2$	PPh$_3$	NMP	80	0
14[f]	CoI$_2$	dppp	NMP	80	81 (79)
15[g]	CoI$_2$	dppp	NMP	80	52

[a] Unless otherwise noted, the reaction was performed using **1a** (0.5 mmol), **2a** (0.2 mmol), CoX$_n$ (10 mol%), ligand (10 mol%), and Zn (50 mol%) in 0.3 mL of solvent for 24 h. dppp = 1,3-bis(diphenylphosphino)propane; dppm = bis(diphenylphosphino)methane; dppe = 1,2-bis(diphenylphosphino)ethane; dppb = 1,4-bis(diphenylphosphino)butane; dppbz = 1,2-bis(diphenylphosphino)benzene. [b] Determined by GC using *n*-tridecane as an internal standard; isolated yield is shown in the parentheses. [c] The hydrocarbamoylation product (addition of DMF to **2a**) was obtained in 13% yield. [d] The reaction was performed without Zn. [e] 20 mol% of PPh$_3$ was used. [f] 0.2 mmol of **1a** and 0.2 mL of NMP were used. [g] 0.1 mmol of **1a** and 0.2 mL of NMP were used.

Results and Discussion

The present study commenced with screening of reaction conditions for the cycloaddition of benzonitrile (**1a**, 0.5 mmol) with diphenylacetylene (**2a**, 0.2 mmol). In the initial attempts, a catalytic system comprised of CoI$_2$ (10 mol%), dppp (10 mol%), and Zn dust (50 mol%) was found to promote the desired cycloaddition in NMP at 120 °C to afford, after 24 h, pentaphenylpyridine (**3aa**) in 53 % yield (Table 1, entry 1), along with a small amount (4%) of competitive cyclotrimerization product of **2a** (i.e. hexaphenylbenzene). The reaction also took place in DMF to give **3aa** in a comparable yield, which was accompanied by a small amount of byproduct arising from the addition of DMF to **2a** via carbamoyl C−H activation (entry 2).[20f] No pyridine formation was observed in toluene (entry 3). Lowering the temperature to 80 °C improved the yield of **3aa** to 82 % (80 % isolated yield; entry 4). The use of CoCl$_2$ or CoBr$_2$ in place of CoI$_2$ led to a substantial drop in the yield of **3aa** (entries 5 and 6). A well-defined Co^{I} complex, CoCl(PPh$_3$)$_3$, also served as a viable precatalyst under otherwise identical conditions (entry 7).[21] However, this complex failed to promote the reaction when Zn was omitted (entry 8), implying that reduction of Co^{I} to Co^{0} was necessary. Screening of various ligands revealed that the present catalytic activity is unique to dppp. Thus, common diphosphines such as dppm, dppe, dppb, and dppbz as well as monophosphines such as PPh$_3$ barely promoted the formation of either **3aa** or hexaphenylbenzene (entries 9–13; see Table S1 for additional results). It was particularly surprising to us that the CoI$_2$/dppe/Zn system was completely ineffective (entry 10), as it is rather similar to the systems developed by Cheng and Okamoto for the pyridine formation using tethered substrates.[7b–d] The ratio of **1a** and **2a** could be reduced to 1:1 without an apparent decrease in the yield of **3aa** (entry 14), while further reduction to 1:2 (which corresponds to the theoretical stoichiometry) led to a drop to 52 % yield (entry 15).

With the optimized catalytic system (Table 1, entry 14) in hand, we set out to explore the scope of the [2+2+2] cycloaddition. First, a variety of aryl nitriles were subjected to the reaction with **2a** (Table 2). The reaction of **1a** could be performed on a 3 mmol scale to afford **3aa** in 83 % yield

Table 2: [2+2+2] Cycloaddition of various aryl nitriles with **2a**.[a]

Entry	Ar	Product	Yield [%][b]
1	Ph (**1a**)	**3aa**	83[c]
2	4-MeC$_6$H$_4$ (**1b**)	**3ba**	72
3	4-MeOC$_6$H$_4$ (**1c**)	**3ca**	61
4	4-F$_3$CC$_6$H$_4$ (**1d**)	**3da**	62
5	4-Me(O)CC$_6$H$_4$ (**1e**)	**3ea**	76
6	4-NCC$_6$H$_4$ (**1f**)	**3fa**	61[d]
7	3-MeC$_6$H$_4$ (**1g**)	**3ga**	64
8	3-MeOC$_6$H$_4$ (**1h**)	**3ha**	78
9	2-MeC$_6$H$_4$ (**1i**)	**3ia**	43
10	2-FC$_6$H$_4$ (**1j**)	**3ja**	52
11	1-naphthyl (**1k**)	**3ka**	68
12	2-thienyl (**1l**)	**3la**	54
13	2-pyridyl (**1m**)	**3ma**	65
14	3-pyridyl (**1n**)	**3na**	76

[a] Unless otherwise noted, the reaction was performed using nitrile **1** (0.4 mmol), **2a** (0.4 mmol), CoI$_2$ (10 mol%), dppp (10 mol%), and Zn (50 mol%) in 0.4 mL of NMP at 80 °C for 24 h. [b] Isolated yield. [c] Isolated yield for a 3 mmol scale reaction. [d] 0.2 mmol of terephthalonitrile (**1f**) and 0.6 mmol of **2a** were used. Twofold cycloadduct was obtained in 7% yield.

Table 3: [2+2+2] Cycloaddition of **1a** with various alkynes.[a]

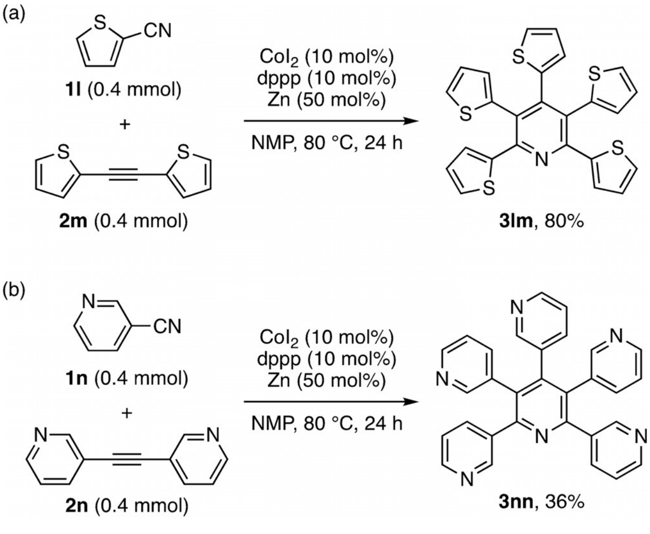
Entry	R	Product	Yield [%][b]
1	4-MeC$_6$H$_4$ (**2b**)	**3ab**	65
2[c]	4-*t*BuC$_6$H$_4$ (**2c**)	**3ac**	67
3[c]	4-MeOC$_6$H$_4$ (**2d**)	**3ad**	57
4	4-FC$_6$H$_4$ (**2e**)	**3ae**	71
5	4-EtO$_2$CC$_6$H$_4$ (**2f**)	**3af**	63
6	4-Me(O)CC$_6$H$_4$ (**2g**)	**3ag**	41
7	3-MeC$_6$H$_4$ (**2h**)	**3ah**	51
8	3-MeOC$_6$H$_4$ (**2i**)	**3ai**	84
9	3-Me$_2$NC$_6$H$_4$ (**2j**)	**3aj**	66
10	3,5-(MeO)$_2$C$_6$H$_3$ (**2k**)	**3ak**	86
11[d]	Pr (**2l**)	**3al**	63

[a] Unless otherwise noted, the reaction was performed using **1a** (0.4 mmol), alkyne **2** (0.4 mmol), CoI$_2$ (10 mol%), dppp (10 mol%), and Zn (50 mol%) in 0.4 mL of NMP at 80 °C for 24 h. [b] Isolated yield. [c] The reaction was performed using 0.6 mmol of **1a** for 72 h. [d] The reaction was performed using bis(dicyclohexylphosphino)methane (dcypm) and DME in place of dppp and NMP, respectively.

(entry 1). Benzonitriles bearing various electron-donating or -withdrawing substituents (**1b**–**1f**) participated in the reaction to afford the desired products **3ba**–**3fa** in 61–76% yields (entries 2–6). Note that terephthalonitrile (**1f**) was used as the limiting reagent with respect to **2a** in a ratio of 1:3, affording the cycloadduct **3fa** in 61% yield along with a small amount (7%) of twofold cycloaddition product (entry 6). The reaction also tolerated *meta*- (**1g** and **1h**) and *ortho*-substituted (**1i** and **1j**) benzonitriles (entries 7–10), while the latter reacted somewhat sluggishly probably due to the steric hindrance. 1-Naphthonitrile (**1k**) smoothly underwent the cycloaddition to give the product **3ka** in 68% yield (entry 11). Heteroaryl nitriles (**1l**–**1n**) were also well tolerated, affording thienyl- or pyridyl-substituted pentaarylpyridines **3la**–**3na** (entries 12–14).

We next explored the reaction of **1a** with various alkynes (Table 3). Symmetrical diarylacetylenes bearing electron-donating (alkyl, OMe) or -withdrawing (F, CO$_2$Et, COMe) substituents at the *para*-positions took part in the cycloaddition to afford the corresponding products **3ab**–**3ag** in moderate to good yields (entries 1–6), where only a small amount of the alkyne cyclotrimerization product was indicated by TLC analysis of the reaction mixture. Among these substituents, *t*-butyl and methoxy groups made the reaction somewhat sluggish, necessitating an increase in the nitrile/alkyne ratio to 1.5:1 and a prolonged reaction time of 72 h (entries 2 and 3). The reaction also tolerated diarylacetylenes bearing *meta*-substituents (**2h**–**2k**), affording pentaarylpyridines **3ah**–**3ak** in moderate to high yields (entries 7–10), while those bearing *ortho*-substituents such as 1,2-di-*o*-tolylethyne failed to undergo the cycloaddition. The reaction of ethyl 4-((4-methoxyphenyl)ethynyl)benzoate afforded an inseparable mixture of multiple pyridine regioisomers, despite the electronic difference between the two aryl groups (see Figure S2). The CoI$_2$/dppp system failed to engage 4-octyne (**2l**) in the cycloaddition with **1a**. However, a modified catalytic system employing bis(dicyclohexylphosphino)methane (dcypm) and 1,2-dimethoxyethane (DME) promoted the reaction to afford the desired pyridine **3al** in 63% yield (entry 11; see Table S2 for the optimization).

The present catalytic system also proved effective for the cycloaddition of di(heteroaryl)acetylenes, as demonstrated by the synthesis of structurally attractive, symmetric penta(heteroaryl)pyridines (Scheme 2). Thus, the cycloaddition of 2-cyanothiophene (**1l**) and di(2-thienyl)ethyne (**2m**) afforded

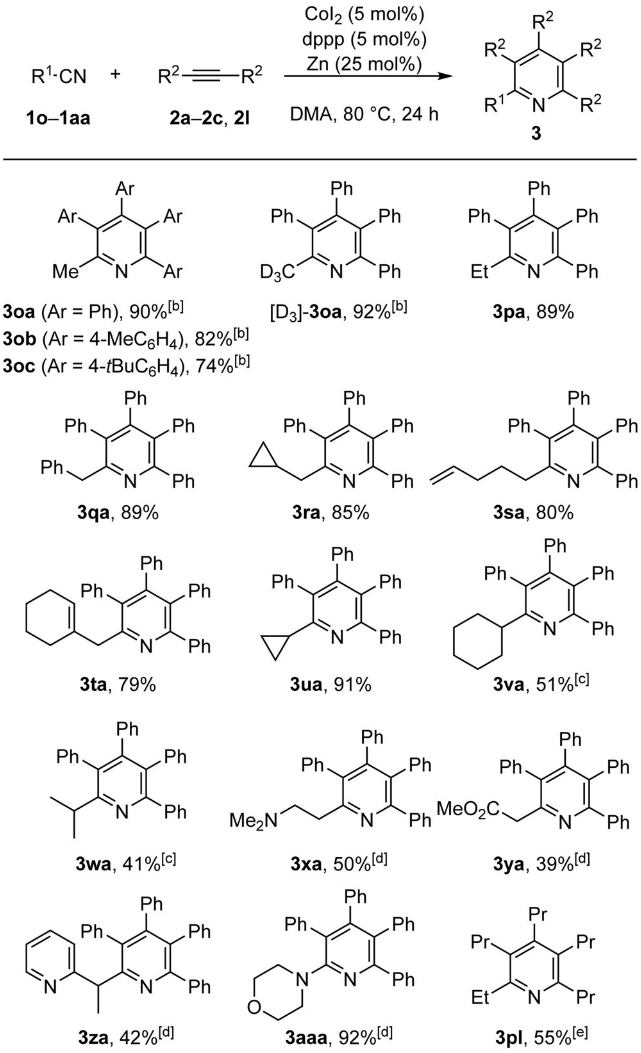


Scheme 2. Synthesis of penta(heteroaryl)pyridines.

penta(2-thienyl)pyridine (**3lm**) in 80% yield, which was previously synthesized via sequential Stille couplings[15a] or fivefold Suzuki–Miyaura coupling of pentachloropyridine.[15c] Penta(3-pyridyl)pyridine (**3nn**) could also be prepared from 3-cyanopyridine (**1n**) and di(3-pyridyl)ethyne (**2n**) albeit in a modest yield.

The scope of the [2+2+2] cycloaddition was further extended to alkyl nitriles (Table 4). We noted that the above catalytic system was only moderately effective for the reaction of MeCN (**1o**) and **2a**. With further optimization (see Table S3), a modified catalytic system comprised of CoI$_2$ (5 mol%), dppp (5 mol%), and Zn (25 mol%) in DMA was found to efficiently promote the reaction, at the expense of large excess MeCN (**1o**:**2a** = 5:1), affording the desired product **3oa** in 90% yield. MeCN could also be coupled with *para*-substituted diphenylacetylenes, affording **3ob** and **3oc** in good yields. The reaction using CD$_3$CN afforded **3oa**-d_3 in 92% yield. The reaction of propionitrile (**1p**) and **2a** was subjected to additional optimization (see Table S4) and was achieved in high yield (89%) at a lower nitrile/alkyne ratio of 1.5:1. This ratio was effective for a variety of other alkyl nitriles. Sterically unhindered alkyl and benzyl nitriles, including those bearing an olefin moiety, participated in the reaction with **2a** to afford the desired pyridine derivatives **3qa**–**3ua** in high yields. The reaction also tolerated sterically hindered secondary alkyl nitriles (see **3va** and **3wa**) as well as nitriles containing dialkylamino, ester, and pyridyl groups (see **3xa**–**3za**). Note that, among these 2-alkyl-3,4,5,6-tetraarylpyridines, only **3oa**, **3pa**, and **3qa** are known in the literature, reflecting the scarcity of relevant [2+2+2] cycloadditions.[16,18] A cyanamide derivative such as morpholine-4-carbonitrile (**1aa**) also reacted with **2a** to afford the 2-aminopyridine **3aaa** in an excellent yield. The reaction of **1p** and **2l** was achieved using the CoI$_2$/dcypm system to give the pentaalkylpyridine **3pl** in a moderate yield.

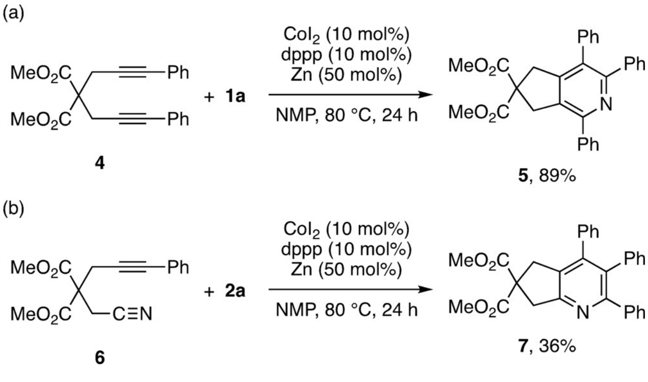
Table 4: [2+2+2] Cycloaddition of alkyl nitriles.[a]



3oa (Ar = Ph), 90%[b]
3ob (Ar = 4-MeC$_6$H$_4$), 82%[b]
3oc (Ar = 4-*t*BuC$_6$H$_4$), 74%[b]
[D$_3$]-**3oa**, 92%[b]
3pa, 89%
3qa, 89%
3ra, 85%
3sa, 80%
3ta, 79%
3ua, 91%
3va, 51%[c]
3wa, 41%[c]
3xa, 50%[d]
3ya, 39%[d]
3za, 42%[d]
3aaa, 92%[d]
3pl, 55%[e]

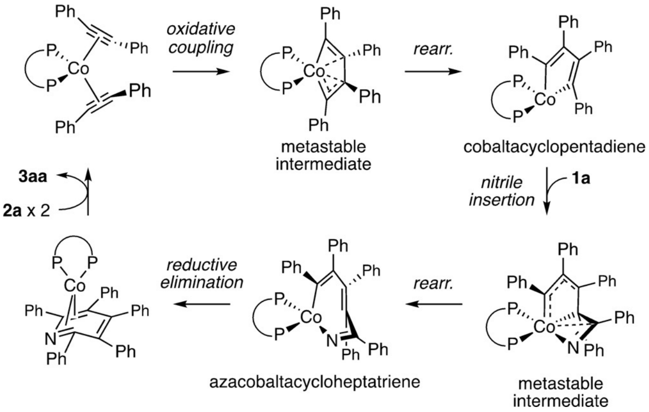
[a] Unless otherwise noted, the reaction was performed using nitrile **1** (0.6 mmol), alkyne **2** (0.4 mmol), CoI$_2$ (5 mol%), dppp (5 mol%), and Zn (25 mol%) in 0.4 mL of DMA at 80 °C for 24 h. The yields refer to isolated yields. [b] 2 mmol of nitrile was used. [c] The reaction was performed for 72 h. [d] CoI$_2$ (10 mol%), dppp (10 mol%), and Zn (50 mol%) were used. [e] The reaction was performed using propionitrile (2 mmol), 4-octyne (0.4 mmol), CoI$_2$ (10 mol%), dcypm (10 mol%), and Zn (50 mol%) in DME at 100 °C.

The applicability of the present catalytic system to tethered substrates was briefly examined (Scheme 3). A diyne capped with phenyl groups (**4**) underwent cycloaddition with **1a** to afford the pentasubstituted pyridine **5** in 89% yield. Note that, despite the extensive previous studies, bicyclic pyridines bearing 2,3,6-triaryl substituents such as **5** have not been synthesized by bimolecular [2+2+2] cycloaddition. The reaction between a tethered cyanoalkyne **6** and **2a** also proved feasible, affording the 2,3,4-triarylpyridine derivative **7** albeit in a modest yield. This type of bimolecular cycloaddition is also rare.[8e]



Scheme 3. [2+2+2] Cycloaddition using tethered substrates.

To gain insight into the reaction pathway of the present [2+2+2] cycloaddition, we turned to density functional theory (DFT) calculations. The [2+2+2] pyridine formation promoted by CpCo^{I} catalysts has been studied computationally, and reaction pathways initiated by oxidative coupling of two alkyne molecules on Co^{I} have been identified.[7f,22] On the other hand, the working mode of cobalt-diphosphine catalysts remains unexplored, while oxidative coupling of alkynes on Co^{I} has been proposed.[7b–d] Here, we explored the cycloaddition of **1a** and **2a** on two model low-valent cobalt

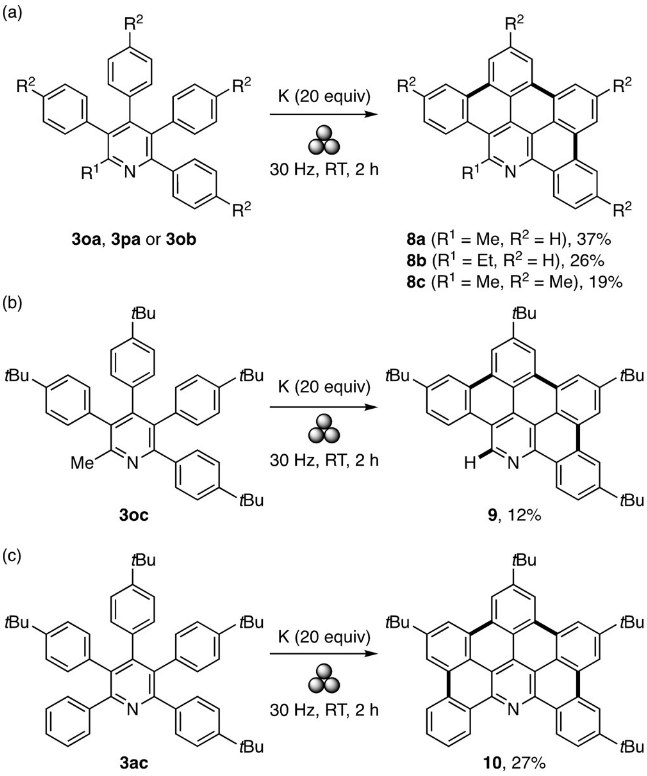


Scheme 4. Summary of the computationally revealed reaction pathway.

complexes, namely, [(dppp)Co^0] and [(dppp)Co^I]$^+$ (see the Supporting Information for detail).[23,24] In short, these studies have shown the following three major points (Scheme 4). Firstly, both the Co^0 and Co^I complexes can promote the reaction via oxidative coupling of two molecules of **2a** as the initial step, followed by insertion of **1a** into the cobaltacyclopentadiene and C-N reductive elimination. The potentially competing oxidative coupling of **1a** and **2a** requires a much higher activation barrier. Secondly, the activation barrier for the alkyne/alkyne oxidative coupling is distinctly lower for the Co^0 complex than for the Co^I complex, suggesting that a Co^0 species is more likely to serve as the active species. Thirdly, the alkyne oxidative coupling and the nitrile insertion proceed in a stepwise manner involving metastable metallacycle intermediates. Given that nitrile/alkyne oxidative coupling has been proposed to operate in some of the previously reported nickel- and iron-catalyzed [2+2+2] pyridine synthesis,[8a,9a] the difference among the neighboring first-row transition metal triad (i.e., Fe/Co/Ni) would deserve further theoretical investigation.

In light of Scholl-type cyclodehydrogenation of polyarylbenzenes as a well-established strategy to construct polycyclic aromatic hydrocarbons (PAHs),[25] it appears a natural idea to use tetra- and pentaarylpyridines as precursors to aza-PAHs[26] via analogous cyclodehydrogenation. However, to our best knowledge, no such transformation has been reported. The lack of precedence can be attributed to the electron-deficient nature and the basicity of a pyridine ring that would prevent the typical Scholl reaction employing Lewis or Brønsted acid. In this context, the reductive cyclodehydrogenation using potassium metal,[27] which has recently been utilized by Ito, Itami and co-workers for the conversion of azine-containing polyaromatic systems to aza-PAHs,[28] appeared attractive.

Adopting the reductive cyclodehydrogenation strategy powered by mechanochemistry,[29–32] we have successfully converted some of the tetra- and pentaarylpyridines described above into the corresponding aza-PAHs (Scheme 5). The threefold cyclodehydrogenation of 2,3,4,5-tetraaryl-6-alkylpyridines **3oa**, **3pa**, and **3ob** in the presence of potassium (20 equiv) under ball milling (30 Hz, 2 h) afforded the aza-PAHs **8a**–**8c** as poorly soluble light-yellow solids in 19–37 % yields, accompanied by tarry insoluble products with full conversion of the starting materials (Scheme 5a). Importantly, the reaction of **3oa** in toluene afforded **8a** in only 14 % yield (NMR), which could not be isolated due to byproducts arising from incomplete (single and twofold) cyclodehydrogenations. Curiously, the reaction of analogous tetraarylpyridine **3oc** afforded cyclodehydrogenation/demethylation product **9** as the only isolable compound (Scheme 5b). Finally, the fourfold cyclodehydrogenation of pentaarylpyridine **3ac** afforded the aza-PAH **10** in 27 % yield (Scheme 5c), whereas no detectable amount of **10** could be obtained by the reaction in toluene. The failure of the solution-phase syntheses of the aza-PAHs might be ascribed to the inhomogeneity of the reaction mixture and the decreased solubility of partially cyclodehydrogenated intermediates.



Scheme 5. Mechanochemically assisted cyclodehydrogenation of tetra- and pentaarylpyridines to nitrogen-containing PAHs.

The planarized structure of the novel aza-PAH **10** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1a).[33] The C−C bonds connecting the pyridine ring and the peripheral benzene rings (bonds **a**–**e**) have average length of 1.444 Å, which is shorter than that of the corresponding bonds in penta(*p*-tolyl)pyridine (1.494 Å),[15c] reflecting the extended π-conjugation. Meanwhile, as expected from the Clar structure[34] of **10**, these and the newly formed C−C bonds (bonds **f**–**i**; average length 1.469 Å) are distinctly longer than that of the C−C bonds in the rings **A**–**E** (average 1.400 Å). The molecular packing of **10** displayed a face-to-face antiparallel π-π stacked pair with a 3.31 Å-distance between the C4 positions of the pyridine rings, which is sandwiched by two other molecules of **10** through C−H/π interactions (Figure 1b and Figure S4).

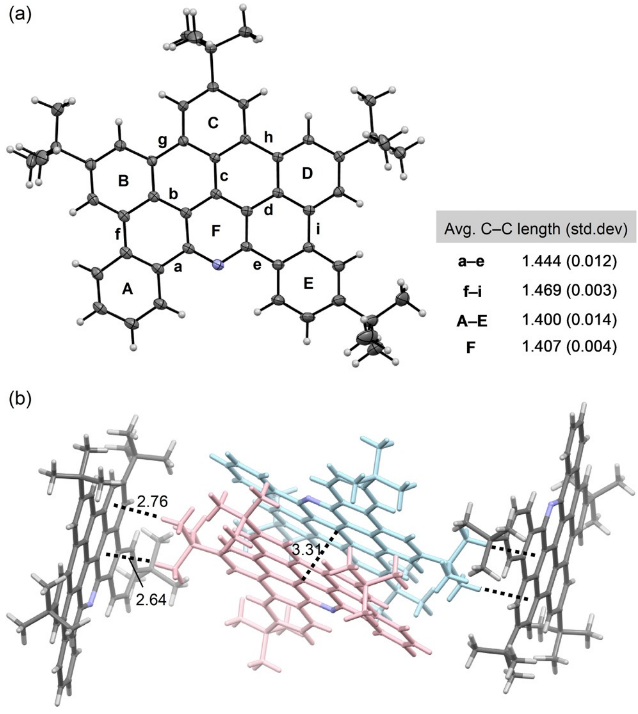


Figure 1. a) ORTEP representation of **10** (thermal ellipsoids at the 50% probability). Solvent molecule (THF) is omitted for clarity. b) Molecular packing in the single-crystal X-ray structure of **10**. Distances are in Å.

Figure 2 shows the UV-vis absorption and emission spectra of the aza-PAHs **8a** and **10**. Similar to their hydrocarbon analogues,[35] **8a** and **10** displayed the absorption spectra featuring high degree of fine structure in the ranges of 290–402 nm and 304–430 nm, respectively, where the absorption peaks may be designated as α, β, or para-bands. With TD-DFT calculations of the optimized structures, the lowest transition energies of **8a** and **10** were calculated to be 379 nm and 405 nm, respectively (see Tables S7 and S8). The emission spectra of **8a** and **10** were characterized by multiple peaks (407, 432, and 457 nm for **8a**; 435, 462, and 494 nm for **10**) with rather small Stokes shift (< 10 nm), reflecting their rigid molecular structures. The emission quantum yields were determined to be 0.27 and 0.47 for **8** and **10**, respectively.

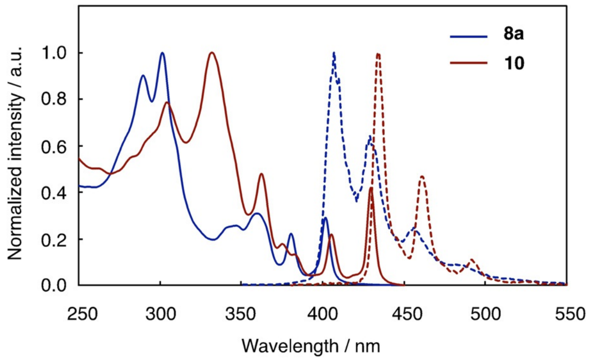


Figure 2. UV-vis absorption (solid lines) and emission (dashed lines) spectra of **8a** and **10** in CH_2Cl_2 (excitation wavelengths: 301 nm for **8a** and 331 nm for **10**).

Conclusion

In summary, we have developed highly robust cobalt-based catalytic systems for the fully intermolecular [2+2+2] cycloaddition of nitrile and internal alkynes. Thus, simple and inexpensive catalysts generated from CoI_2, dppp, and Zn have enabled the preparation of monocyclic tetra- and pentarylpyridines with an unprecedented level of structural diversity. DFT calculations supported a reaction pathway involving oxidative coupling of two alkyne molecules, insertion of nitrile into cobaltacyclopentadiene, and C-N reductive elimination, while demonstrating stepwise nature of the oxidative coupling and nitrile insertion steps. Furthermore, we have also demonstrated the power of mechanochemistry in forging hitherto unknown types of aza-PAHs through multifold reductive cyclodehydrogenation of polyarylated pyridines. Taken together, the present studies would stimulate further development and mechanistic study of intermolecular [2+2+2] pyridine formation as well as the use of polyarylated pyridines as precursors to nitrogen-doped nanographenes.[24]

Acknowledgements

This work was supported by the Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2016-T2-2-043 to N.Y.) and Tier 1 (RG114/18 to N.Y.), Zhejiang Provincial Natural Science Foundation of China (Grant LY18B020007 to C.W.), and A*STAR (AME IRG A1783c0003 and A2083c0050 to F.G.). We thank Dr. Yongxin Li for his assistance with X-ray crystallographic analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloaddition · homogeneous catalysis · mechanochemistry · polycyclic aromatic compounds · pyridines

---

[1] a) J. A. Varela, C. Saa, *Chem. Rev.* **2003**, *103*, 3787 – 3801; b) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307 – 2327; c) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085 – 1094; d) G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430 – 3444.

[2] a) N. Nicolaus, H.-G. Schmalz, *Synlett* **2010**, 2071 – 2074; b) C. Yuan, C. T. Chang, A. Axelrod, D. Siegel, *J. Am. Chem. Soc.* **2010**, *132*, 5924 – 5925.

[3] a) B. L. Gray, X. Wang, W. C. Brown, L. Kuai, S. L. Schreiber, *Org. Lett.* **2008**, *10*, 2621 – 2624; b) G. Schäfer, J. Milić, A. Eldahshan, F. Götz, K. Zühlke, C. Schillinger, A. Kreuchwig, J. M. Elkins, K. R. Abdul Azeez, A. Oder, M. C. Moutty, N. Masada, M. Beerbaum, B. Schlegel, S. Niquet, P. Schmieder, G. Krause, J. P. von Kries, D. M. Cooper, S. Knapp, J. Rademann, W. Rosenthal, E. Klussmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12187 – 12191; *Angew. Chem.* **2013**, *125*, 12409 – 12413.

[4] J. Klívar, A. Jancarik, D. Saman, R. Pohl, P. Fiedler, L. Bednarova, I. Stary, I. G. Stara, *Chem. Eur. J.* **2016**, *22*, 14401 – 14405.

[5] a) Y. Wakatsuki, H. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1973**, 280; b) Y. Wakatsuki, H. Yamazaki, *Tetrahedron Lett.* **1973**, *14*, 3383–3384.

[6] For early and recent reviews, see: a) H. Bönnemann, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 505–515; *Angew. Chem.* **1978**, *90*, 517–526; b) K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556; *Angew. Chem.* **1984**, *96*, 525–541; c) H. Bönnemann, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 248–262; *Angew. Chem.* **1985**, *97*, 264–279; d) V. Gandon, *Transition-Metal-Mediated Aromatic Ring Construction* (Ed.: K. Tanaka), Wiley, Hoboken, **2013**, chap. 1; e) T. Gläsel, M. Hapke, *Cobalt Catalysis in Organic Synthesis* (Eds.: M. Hapke, G. Hilt), Wiley-VCH, Weinheim, **2020**, chap. 9.

[7] a) A. Gutnov, B. Heller, C. Fischer, H. J. Drexler, A. Spannenberg, B. Sundermann, C. Sundermann, *Angew. Chem. Int. Ed.* **2004**, *43*, 3795–3797; *Angew. Chem.* **2004**, *116*, 3883–3886; b) H.-T. Chang, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2007**, *9*, 505–508; c) K. Kase, A. Goswami, K. Ohtaki, E. Tanabe, N. Saino, S. Okamoto, *Org. Lett.* **2007**, *9*, 931–934; d) A. Goswami, K. Ohtaki, K. Kase, T. Ito, S. Okamoto, *Adv. Synth. Catal.* **2008**, *350*, 143–152; e) A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert, V. Gandon, *Angew. Chem. Int. Ed.* **2009**, *48*, 1810–1813; *Angew. Chem.* **2009**, *121*, 1842–1845; f) M. Hapke, N. Weding, A. Spannenberg, *Organometallics* **2010**, *29*, 4298–4304; g) P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, V. Gandon, *Chem. Eur. J.* **2012**, *18*, 4337–4344; h) I. Thiel, H. Jiao, A. Spannenberg, M. Hapke, *Chem. Eur. J.* **2013**, *19*, 2548–2554.

[8] a) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031; b) P. Kumar, S. Prescher, J. Louie, *Angew. Chem. Int. Ed.* **2011**, *50*, 10694–10698; *Angew. Chem.* **2011**, *123*, 10882–10886; c) R. M. Stolley, M. T. Maczka, J. Louie, *Eur. J. Org. Chem.* **2011**, 3815–3824; d) R. M. Stolley, H. A. Duong, D. R. Thomas, J. Louie, *J. Am. Chem. Soc.* **2012**, *134*, 15154–15162; e) X. You, X. Xie, G. Wang, M. Xiong, R. Sun, H. Chen, Y. Liu, *Chem. Eur. J.* **2016**, *22*, 16765–16769.

[9] a) C. Wang, X. Li, F. Wu, B. Wan, *Angew. Chem. Int. Ed.* **2011**, *50*, 7162–7166; *Angew. Chem.* **2011**, *123*, 7300–7304; b) B. R. D'Souza, T. K. Lane, J. Louie, *Org. Lett.* **2011**, *13*, 2936–2939; c) T. K. Lane, B. R. D'Souza, J. Louie, *J. Org. Chem.* **2012**, *77*, 7555–7563; d) C. Wang, D. Wang, F. Xu, B. Pan, B. Wan, *J. Org. Chem.* **2013**, *78*, 3065–3072; e) N. A. Spahn, M. H. Nguyen, J. Renner, T. K. Lane, J. Louie, *J. Org. Chem.* **2017**, *82*, 234–242.

[10] a) Y. Yamamoto, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6189–6190; b) Y. Yamamoto, S. Okuda, K. Itoh, *Chem. Commun.* **2001**, 1102–1103; c) J. A. Varela, L. Castedo, C. Saa, *J. Org. Chem.* **2003**, *68*, 8595–8598; d) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605–613; e) Y. Yamamoto, K. Kinpara, H. Nishiyama, K. Itoh, *Adv. Synth. Catal.* **2005**, *347*, 1913–1916; f) Y. Yamamoto, K. Kinpara, R. Ogawa, H. Nishiyama, K. Itoh, *Chem. Eur. J.* **2006**, *12*, 5618–5631; g) S. Medina, G. Dominguez, J. Perez-Castells, *Org. Lett.* **2012**, *14*, 4982–4985; h) J.-F. Tan, C. T. Bormann, F. G. Perrin, F. M. Chadwick, K. Severin, N. Cramer, *J. Am. Chem. Soc.* **2019**, *141*, 10372–10383.

[11] a) Y. Komine, A. Kamisawa, K. Tanaka, *Org. Lett.* **2009**, *11*, 2361–2364; b) T. Shibata, T. Uchiyama, K. Endo, *Org. Lett.* **2009**, *11*, 3906–3908; c) Y. Komine, K. Tanaka, *Org. Lett.* **2010**, *12*, 1312–1315; d) K. Murayama, Y. Sawada, K. Noguchi, K. Tanaka, *J. Org. Chem.* **2013**, *78*, 6202–6210; e) K. Kashima, M. Ishii, K. Tanaka, *Eur. J. Org. Chem.* **2015**, 1092–1099.

[12] a) G. Onodera, Y. Shimizu, J. N. Kimura, J. Kobayashi, Y. Ebihara, K. Kondo, K. Sakata, R. Takeuchi, *J. Am. Chem. Soc.* **2012**, *134*, 10515–10531; b) R. Takeuchi, S. Fujisawa, Y. Yoshida, J. Sagano, T. Hashimoto, A. Matsunami, *J. Org. Chem.* **2018**, *83*, 1852–1860.

[13] a) T. Takahashi, F.-Y. Tsai, M. Kotora, *J. Am. Chem. Soc.* **2000**, *122*, 4994–4995; b) T. Takahashi, F. Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067.

[14] a) D. Suzuki, R. Tanaka, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **2002**, *124*, 3518–3519; b) D. Suzuki, Y. Nobe, Y. Watai, R. Tanaka, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7474–7479; c) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780.

[15] a) S. L. Gholap, P. Hommes, K. Neuthe, H. U. Reissig, *Org. Lett.* **2013**, *15*, 318–321; b) C. Doebelin, P. Wagner, F. Bihel, N. Humbert, C. A. Kenfack, Y. Mely, J. J. Bourguignon, M. Schmitt, *J. Org. Chem.* **2014**, *79*, 908–918; c) S. Reimann, P. Ehlers, A. Petrosyan, S. Kohse, A. Spannenberg, A. E. Surkus, T. V. Ghochikyan, A. S. Saghyan, S. Lochbrunner, O. Kühn, R. Ludwig, P. Langer, *Adv. Synth. Catal.* **2014**, *356*, 1987–2008; d) S. Suzuki, Y. Segawa, K. Itami, J. Yamaguchi, *Nat. Chem.* **2015**, *7*, 227–233; e) T. Asako, W. Hayashi, K. Amaike, S. Suzuki, K. Itami, J. Yamaguchi, *Tetrahedron* **2017**, *73*, 3669–3676.

[16] H. Nehl, *Chem. Ber.* **1994**, *127*, 2535–2537.

[17] J. Uhm, H. W. An, *J. Korean Chem. Soc.* **2001**, *45*, 268–273.

[18] Y. Xie, C. Wu, C. Jia, C.-H. Tung, W. Wang, *Org. Chem. Front.* **2020**, *7*, 2196–2201.

[19] a) W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, 3537–3562; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208–1219; c) P. Gandeepan, C. H. Cheng, *Acc. Chem. Res.* **2015**, *48*, 1194–1206; d) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498–525; e) P. Röse, G. Hilt, *Synthesis* **2016**, *48*, 463–492; f) N. Yoshikai, *Synthesis* **2019**, *51*, 135–141.

[20] a) J. Yang, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 16748–16751; b) J. Yang, A. Rerat, Y. J. Lim, C. Gosmini, N. Yoshikai, *Angew. Chem. Int. Ed.* **2017**, *56*, 2449–2453; *Angew. Chem.* **2017**, *129*, 2489–2493; c) C. Wu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2018**, *57*, 6558–6562; *Angew. Chem.* **2018**, *130*, 6668–6672; d) J. Yang, Y. Shen, Y. J. Lim, N. Yoshikai, *Chem. Sci.* **2018**, *9*, 6928–6934; e) W. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2019**, *58*, 2500–2504; *Angew. Chem.* **2019**, *131*, 2522–2526; f) C. S. Wang, S. Di Monaco, A. N. Thai, M. S. Rahman, B. P. Pang, C. Wang, N. Yoshikai, *J. Am. Chem. Soc.* **2020**, *142*, 12878–12889.

[21] For the use of $CoCl(PPh_3)_3$ as a catalyst for alkyne cyclotrimerization, see: a) P. Jungk, F. Fischer, I. Thiel, M. Hapke, *J. Org. Chem.* **2015**, *80*, 9781–9793; b) L. D. Field, A. J. Ward, P. Turner, *Aust. J. Chem.* **1999**, *52*, 1085–1092; c) K. P. Angermund, P. Betz, H. Butenschön, *Chem. Ber.* **1993**, *126*, 713–724.

[22] a) G. Dazinger, M. Torres-Rodrigues, K. Kirchner, M. J. Calhorda, P. J. Costa, *J. Organomet. Chem.* **2006**, *691*, 4434–4445; b) A. A. Dahy, K. Yamada, N. Koga, *Organometallics* **2009**, *28*, 3636–3649; c) A. A. Dahy, N. Koga, *J. Organomet. Chem.* **2010**, *695*, 2240–2250; d) A. M. Rodriguez, C. Cebrian, P. Prieto, J. I. Garcia, A. de la Hoz, A. Diaz-Ortiz, *Chem. Eur. J.* **2012**, *18*, 6217–6224.

[23] All the DFT calculations were performed using Gaussian 09 program package. See the Supporting Information for the details of the computational methods and results.

[24] For the generation of diphosphine-ligated Co^I and Co^0 species through reduction by Zn, see: M. R. Friedfeld, H. Zhong, R. T. Ruck, M. Shevlin, P. J. Chirik, *Science* **2018**, *360*, 888–893.

[25] a) M. Grzybowski, K. Skonieczny, H. Butenschon, D. T. Gryko, *Angew. Chem. Int. Ed.* **2013**, *52*, 9900–9930; *Angew. Chem.* **2013**, *125*, 10084–10115; b) M. Grzybowski, B. Sadowski, H. Butenschon, D. T. Gryko, *Angew. Chem. Int. Ed.* **2020**, *59*, 2998–3027; *Angew. Chem.* **2020**, *132*, 3020–3050.

[26] a) X.-Y. Wang, X. Yao, A. Narita, K. Müllen, *Acc. Chem. Res.* **2019**, *52*, 2491 – 2505; b) M. Stépień, E. Gońka, M. Żyla, N. Sprutta, *Chem. Rev.* **2017**, *117*, 3479 – 3716.

[27] a) P. Schlichting, U. Rohr, K. Müllen, *J. Mater. Chem.* **1998**, *8*, 2651 – 2655; b) D. T. Gryko, J. Piechowska, M. Galezowski, *J. Org. Chem.* **2010**, *75*, 1297 – 1300; c) M. Rickhaus, A. P. Belanger, H. A. Wegner, L. T. Scott, *J. Org. Chem.* **2010**, *75*, 7358 – 7364.

[28] K. P. Kawahara, W. Matsuoka, H. Ito, K. Itami, *Angew. Chem. Int. Ed.* **2020**, *59*, 6383 – 6388; *Angew. Chem.* **2020**, *132*, 6445 – 6450.

[29] For selected reviews, see: a) T. Friščić, C. Mottillo, H. M. Titi, *Angew. Chem. Int. Ed.* **2020**, *59*, 1018 – 1029; *Angew. Chem.* **2020**, *132*, 1030 – 1041; b) D. Tan, F. García, *Chem. Soc. Rev.* **2019**, *48*, 2274 – 2292; c) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080 – 3094; d) J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435 – 1443; e) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13 – 19.

[30] For examples of mechanochemical synthesis of PAHs, see: a) G. Báti, D. Csókás, T. Yong, S. M. Tam, R. R. S. Shi, R. D. Webster, I. Pápai, F. García, M C. Stuparu, *Angew. Chem. Int. Ed.* **2020**, *59*, 21620 – 21626; *Angew. Chem.* **2020**, *132*, 21804 – 21810; b) C. Wang, M. Hill, B. Theard, J. Mack, *RSC Adv.* **2019**, *9*, 27888 – 27891; c) Y. Zhao, S. V. Rocha, T. M. Swager, *J. Am. Chem. Soc.* **2016**, *138*, 13834 – 13837.

[31] We also made attempts to perform the present [2+2+2] cycloaddition under mechanochemical conditions, which however did not meet with success.

[32] For other failed attempts on cyclodehydrogenation of **3oa**, see the Supporting Information.

[33] Deposition Number 2050264 (**10**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[34] M. Solà, *Front. Chem.* **2013**, *1*, 22.

[35] a) R. Rieger, K. Müllen, *J. Phys. Org. Chem.* **2010**, *23*, 315 – 325; b) A.-K. Steiner, K. Y. Amsharov, *Angew. Chem. Int. Ed.* **2017**, *56*, 14732 – 14736; *Angew. Chem.* **2017**, *129*, 14926 – 14931.

Manuscript received: January 6, 2021
Accepted manuscript online: February 8, 2021
Version of record online: March 12, 2021