

Cobalt-Catalyzed Intermolecular [2+2+2] Cycloaddition of Nitriles and Alkynes: Facile Synthesis of Polyarylpiperidines and Their Mechanochemical Cyclodehydrogenation to Nitrogen-Containing Polyaromatics

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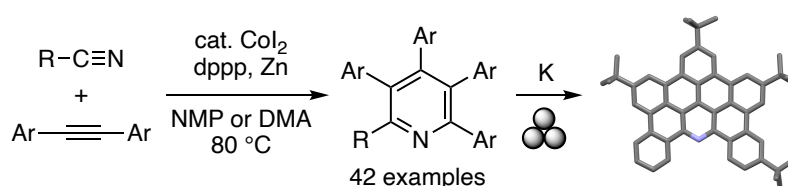
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Abstract

Transition metal-catalyzed [2+2+2] cycloaddition of nitriles and alkynes has been extensively developed as a straightforward and atom-economical synthetic approach to piperidines over the last several decades using various transition metal catalysts, both precious and non-precious. Despite this long history, cycloadditions of this type have often relied on the use of tethered diyne or cyanoalkyne as one of the reactants. Thus, examples of efficient, fully intermolecular catalytic [2+2+2] piperidine synthesis, especially those employing unactivated nitriles and internal alkynes leading to pentasubstituted piperidines, 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 without using a large excess of the nitrile. The present systems allow for the synthesis of broad range of polyarylated piperidines, many of which have not been previously accessed by the [2+2+2] manifold. Computational studies have supported a reaction pathway involving oxidative coupling of two alkynes, insertion of the nitrile into cobaltacyclopentadiene, and C–N reductive elimination, while shedding light on stepwise nature of the oxidative coupling and insertion processes. We also demonstrate that tetra- and pentaarylpiperidines can serve as precursors to hitherto unprecedented nitrogen-containing polycyclic aromatic hydrocarbons via mechanochemically assisted multifold reductive cyclodehydrogenation.



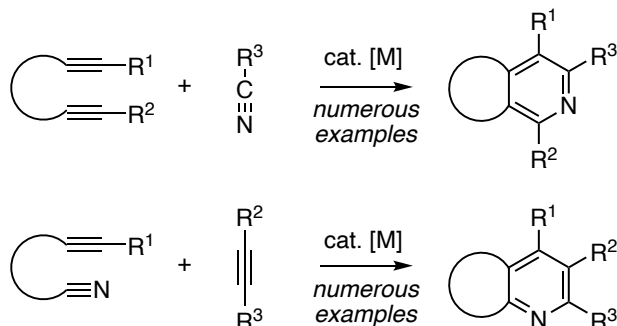
Introduction

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] cycloaddition to form benzene derivatives) and regioselectivity (Scheme 1a). Except for the stoichiometric variants involving the reaction between preformed zircona-^[13] and titanacycles,^[14] 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] For example, literature reports on the synthesis of pentarylpolyridines through catalytic [2+2+2] cycloaddition of aryl nitrile and diarylacetylene 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 1b). During the preparation of this manuscript, Wang and coworkers 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]

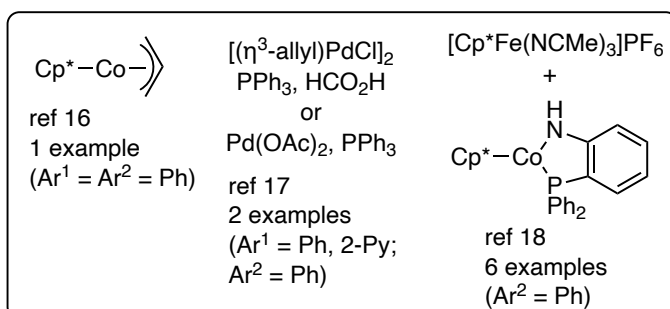
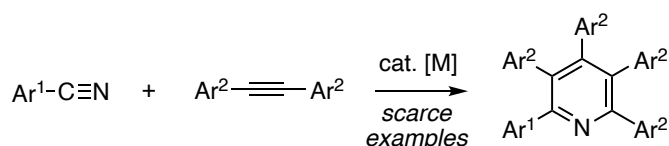
As a part of our continuing pursuit of low-valent cobalt–diphosphine catalyzed synthetic transformations^[19,20] we report herein that cobalt(II) iodide, 1,3-bis(diphenylphosphino)propane (dppp), and Zn in appropriate polar solvents give rise to simple, inexpensive, and highly robust catalytic systems for the fully intermolecular [2+2+2] cycloaddition of various aryl and alkyl nitriles with diarylacetylenes (Scheme 1c). 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, for the first time, multifold cyclodehydrogenation of tetra- and pentaarylpyridines enabled under mechanochemical conditions to form hitherto unprecedented types of nitrogen-containing polycyclic aromatic hydrocarbons (PAHs).

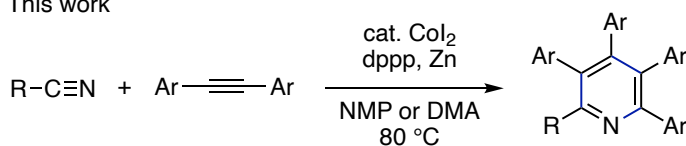
(a) [2+2+2] Pyridine synthesis using tethered substrates



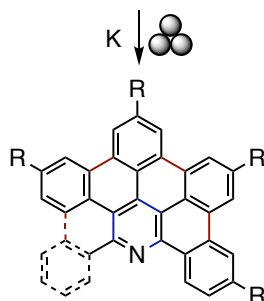
(b) Fully intermolecular [2+2+2] pentaarylpyridine synthesis



(c) This work



- Simple, inexpensive and robust catalyst
- Broad range of nitriles ($\text{R} = \text{aryl}, \text{alkyl}, \text{NR}_2$)
- Various diarylacetylenes
- DFT calculations
- Mechanochemical cyclodehydrogenation to aza-PAHs

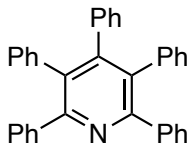


Scheme 1. Transition metal-catalyzed [2+2+2] cycloaddition of nitrile and alkynes.

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 CoI₂ (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 CoCl₂ or CoBr₂ as the precatalyst in place of CoI₂ led to a substantial drop in the yield of **3aa** (entries 5 and 6). A well-defined Co^I complex, CoCl(PPh₃)₃, also served as a viable precatalyst under otherwise identical conditions (entry 7). However, this complex did not promote the reaction at all when Zn was omitted (entry 8), implying that reduction of Co^I to Co⁰ was necessary for the catalytic activity. Screening of various ligands in combination with CoI₂ revealed that the present catalytic activity is unique to dppp. Thus, common diphosphine ligands such as dppm, dppe, dppb, and dppbz as well as monophosphine ligands such as PPh₃ barely promoted either pyridine-forming cycloaddition or benzene-forming cycloaddition (entries 9-13; see Table S1 for additional results). It was particularly surprising to us that the CoI₂/dppe/Zn system was completely ineffective (entry 10), as it is rather similar to the CoCl₂•6H₂O/dppe/Zn system developed by Okamoto for the cycloaddition between tethered diynes and nitriles.^[7b,c] With the CoI₂/dppp/Zn system, we were able to reduce the ratio of **1a** and **2a** to 1:1 without apparent decrease in the yield of **3aa** (79% isolated yield; entry 14), while further reduction to 1:2 (which corresponds to the theoretical stoichiometry) led to a drop to 52% yield (entry 15).

Table 1. [2+2+2] Cycloaddition of Benzonitrile (**1a**) and Diphenylacetylene (**2a**)^[a]

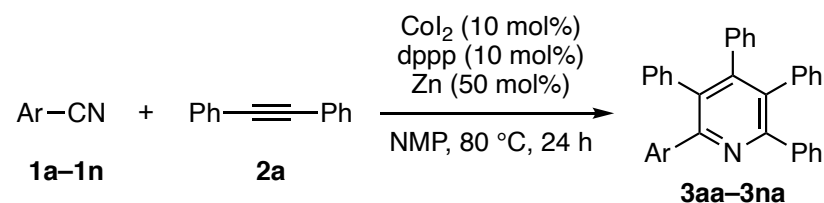
<div style="text-align: center;"><div>Ph-CN + Ph-C≡C-Ph</div><div>1a 2a</div><div>$\xrightarrow[\text{solvent, } T, 24 \text{ h}]{\text{CoX}_n (10 \text{ mol\%}) \text{ ligand } (10 \text{ mol\%}) \text{ Zn } (50 \text{ mol\%})}$</div><div><div></div><div>3aa</div></div></div>					
Entry	CoX _n	Ligand	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 hydrocarbamylation product (addition of DMF to **2a**) was obtained in 13% yield. [d] The reaction was performed without Zn. [e] 20 mol% of PPh₃ 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.

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 parent benzonitrile (**1a**) could be performed on a 3 mmol scale to afford the desired pyridine **3aa** in 83% yield (entry 1). Benzonitriles bearing various electron-donating or -withdrawing substituents (**1b–1f**) participated in the reaction to

afford the corresponding 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** in respectable yields (entries 12–14).

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), CoI₂ (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.

We next explored the reaction of benzonitrile (**1a**) with various alkynes (Table 3). Symmetrical diarylacetylenes bearing a series of electron-donating (alkyl, OMe) or -withdrawing (F, CO₂Et, COMe) substituents at the *para*-positions took part in the cycloaddition with **1a** 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, electron-donating *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 an unsymmetrical diarylacetylene such as 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 CoI₂/dppp system failed to engage a dialkylacetylene such as 4-octyne (**2l**) in the cycloaddition with **1a**. However, a modified catalytic system employing bis(dicyclohexylphosphino)methane (dcypm) and 1,2-dimethoxyethane (DME) instead of dppp and NMP, respectively, promoted the reaction to afford the desired pyridine **3al** in 63% yield (entry 11; see Table S2 for the optimization).

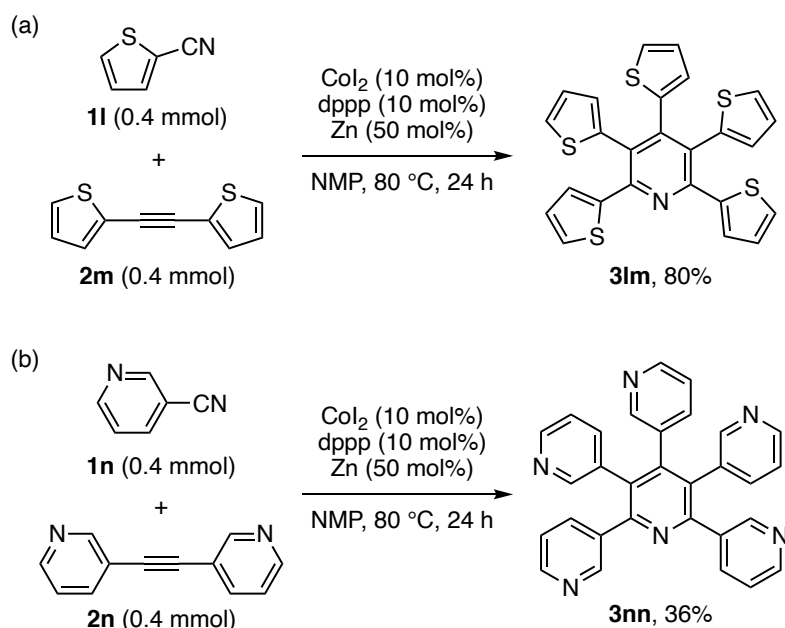
Table 3. [2+2+2] Cycloaddition of **1a** with Various Alkynes^[a]

$ \begin{array}{c} \text{Ph-CN} + \text{R} \equiv \text{R} \xrightarrow[\text{NMP, 80 } ^\circ\text{C, 24 h}]{\text{CoI}_2 \text{ (10 mol\%)} \\ \text{dppp (10 mol\%)} \\ \text{Zn (50 mol\%)}} \\ \textbf{1a} \qquad \qquad \textbf{2b-2l} \qquad \qquad \qquad \textbf{3ab-3al} \end{array} $			
Entry	R	Product	Yield [%] ^[b]
1	4-MeC ₆ H ₄ (2b)	3ab	65
2 ^[c]	4- <i>t</i> 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), CoI₂ (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.

The present catalytic system also proved effective for the cycloaddition of di(heteroaryl)acetylenes, as demonstrated by the synthesis of structurally interesting, symmetric penta(heteroaryl)pyridines (Scheme 2). Thus, the cycloaddition of 2-cyanothiophene (**1l**) and di(2-thienyl)ethyne (**2m**) afforded 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**), which remains unknown in the literature, could also be prepared from 3-cyanopyridine (**1n**) and di(3-pyridyl)ethyne (**2n**) albeit in a modest yield.



Scheme 2. Synthesis of penta(heteroaryl)pyridines.

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_3CN in place of MeCN was equally efficient and 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 participated in the reaction with **2a** to afford the 2-aminopyridine derivative **3aaa** in an excellent yield. As we observed for the reaction of PhCN (**1a**) and 4-octyne (**2l**; Table 3, entry 11), the reaction of **1p** and **2l** was achieved using the $\text{CoI}_2/\text{dcypm}$ system in DME in a moderate yield.

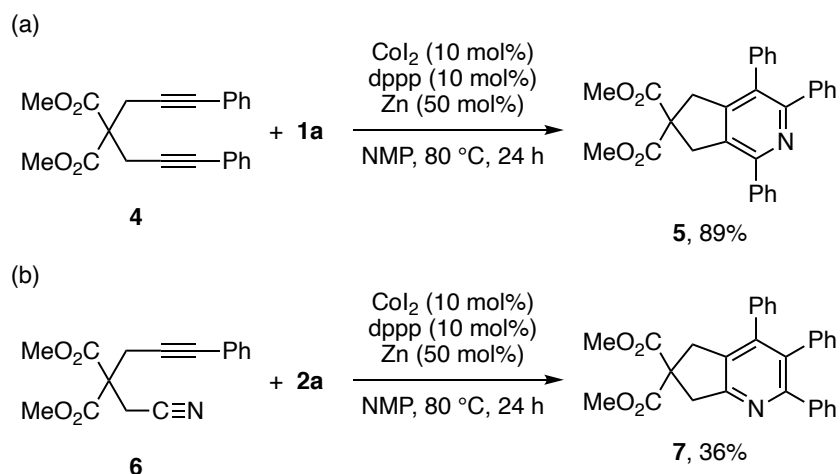
Table 4. [2+2+2] Cycloaddition of Alkyl Nitriles^[a]

R^1-CN 1o–1aa	+	$R^2-C\equiv C-R^2$ 2a–2c, 2l	$\xrightarrow[\text{DMA, 80 } ^\circ\text{C, 24 h}]{\text{CoI}_2 \text{ (5 mol\%)}, \text{dppp (5 mol\%)}, \text{Zn (25 mol\%)}}$	 3
<hr/>				
3oa (Ar = Ph), 90% ^[b]		[D₃]-3oa , 92% ^[b]		3pa , 89%
3ob (Ar = 4-MeC ₆ H ₄), 82% ^[b]				
3oc (Ar = 4- <i>t</i> BuC ₆ H ₄), 74% ^[b]				
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), CoI₂ (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] CoI₂ (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), CoI₂ (10 mol%), dcypm (10 mol%), and Zn (50 mol%) in DME at 100 °C.

The applicability of the present catalytic system to the cycloaddition of tethered substrates was briefly examined (Scheme 3). A diyne substrate capped with phenyl groups (**4**) underwent efficient cycloaddition with benzonitrile (**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 between diyne and nitrile. The reaction between a tethered cyanoalkyne **6** and diphenylacetylene (**2a**) also proved feasible, affording the 2,3,4-triarylpyridine derivative **7** albeit in a modest yield. This type of bimolecular cycloaddition leading to a bicyclic 2,3,4-triaryl-5,6-dialkylpyridine framework is also rare.^[8c]



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,21] The resulting cobaltacyclopentadiene may undergo [4+2] cycloaddition with nitrile to form the pyridine skeleton directly or go through stepwise bond formation processes involving nitrile insertion and C–N reductive elimination. On the other hand, the working mode of cobalt–diphosphine catalysts has not been studied computationally, while oxidative cyclization of a bis-alkyne complex has been proposed to be operative.^[7b,c]

In light of the above background, we explored the cycloaddition of **1a** and **2a** on two model low-valent cobalt complexes, namely, $[(\text{dppp})\text{Co}^0]$ and $[(\text{dppp})\text{Co}^{\text{I}}]^+$.^[22] In short, these studies have shown the following points. 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 than that of the alkyne/alkyne oxidative coupling and is unlikely to operate. 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 for the present cycloaddition. We describe the reaction pathways for the Co^0 complex below (Figure 1), and leave the detail of the Co^{I} -mediated reaction pathways in the Supporting Information (Figures S12 and S13).

Among a series of $(\text{dppp})\text{Co}^0$ complexes of **1a** and/or **2a**, the monoalkyne complex **CP_A** (spin state: doublet) was calculated to be the most stable (Figure S8). Note that the quartet spin state was found to be much higher in energy than the doublet state for a series of key intermediates and transition states along the reaction pathway (Figure S9). Note that the quartet spin state was found to be much higher in energy than the doublet state for a series of key intermediates along the reaction pathway (Figure S8). Coordination of the second molecule of **2a** to **CP_A** forms a tetrahedral bisalkyne complex **CP_{2A}** ($\Delta G = 7.8 \text{ kcal mol}^{-1}$), where the two alkyne ligands take twisted arrangement to avoid steric repulsion between the phenyl groups on the nearby carbons (C2 and C3). Subsequent oxidative coupling via **TS1**, with an activation energy of $24.7 \text{ kcal mol}^{-1}$ (from **CP_A**), leads to a metastable cobaltacycle intermediate **INT1** ($\Delta G = 13.4 \text{ kcal mol}^{-1}$). Reflecting the twisted orientation of the two alkyne ligands, **INT1** adopts a half-chair-like conformation (Figure 2). Notably, the metallacycle core of **INT1** is unsymmetrical, the Co–C1 bond (1.82 \AA) being distinctly shorter than the Co–C4 bond (1.97 \AA), which is also in line with higher Mayer bond order of the former (0.529) than the latter (0.332). The Co–C2 (1.96 \AA) and Co–C3 (2.04 \AA) distances are also unequal. These parameters, together with typical Co–C bond lengths ($1.92\text{--}1.99 \text{ \AA}$) in known cobaltacyclopentadiene complexes,^[23] suggest that the Co–C1 bond has a partial carbene-like character.^[24] **INT1** then undergoes facile bond reorganization and rearrangement via **TS2** ($\Delta G = 17.1 \text{ kcal mol}^{-1}$) to generate another, significantly more stable cobaltacycle **INT2** ($\Delta G = -5.7 \text{ kcal mol}^{-1}$). **INT2** has a distorted tetrahedral geometry and shows a clear structural feature of metallacyclopentadiene (Figure 2).^[25] Importantly, the potentially competing alkyne/nitrile oxidative coupling (**CP_A** to **TS6**) was found to require an activation energy ($29.9 \text{ kcal mol}^{-1}$) distinctly higher than that of the alkyne/alkyne oxidative coupling, producing an azacobaltacycle **INT7** ($\Delta G = 20.7 \text{ kcal mol}^{-1}$) in a significantly endergonic manner. As such, further reaction pathway of **INT7** was not considered.

The cobaltacyclopentadiene **INT2** accepts either side-on or end-on coordination of **1a** to form **INT3** ($\Delta G = 9.0 \text{ kcal mol}^{-1}$) or **INT3'** ($\Delta G = -4.8 \text{ kcal mol}^{-1}$), respectively, which features square-pyramidal geometry with C4 at the apical site. The former complex is connected to an insertion transition state **TS3** with an overall activation barrier of 19.1 kcal

mol⁻¹ (from **INT2**), leading to a metastable intermediate **INT4** ($\Delta G = 4.3$ kcal mol⁻¹). **INT4** features a fused azametallabicyclic structure,^[7f,10d,21a,b] with the Co–C1 bond (2.05 Å) at the junction. Partial carbene-like nature of the Co–C4 bond is suggested from the geometry around Co and C2–C4 (Figure 2). **INT4** undergoes a rearrangement involving Co–C1 bond cleavage via **TS4** with a small activation barrier (2.0 kcal mol⁻¹), affording a more stable azacobaltacycloheptadiene **INT5** ($\Delta G = -4.3$ kcal mol⁻¹). Note that all attempts to locate a transition state for direct [4+2] cycloaddition between **INT2** and **1a** failed, converging to the transition state of nitrile insertion. Finally, C–N reductive elimination of **INT5** occurs via **TS5** with a relatively small activation energy (8.3 kcal mol⁻¹) to give an η^4 -type product complex **INT6**, followed by ligand exchange with **2a** to release **3aa** and regenerate **CP_A**.

While the overall reaction pathway described above conforms to the commonly proposed mechanistic framework involving alkyne/alkyne oxidative coupling and nitrile insertion into cobaltacyclopentadiene,^[7b,c] the present calculations have revealed nontrivial stepwise nature of the elementary steps (i.e., oxidative coupling and nitrile insertion). Given that nitrile/alkyne oxidative coupling has been proposed as a plausible operative mechanism for 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.

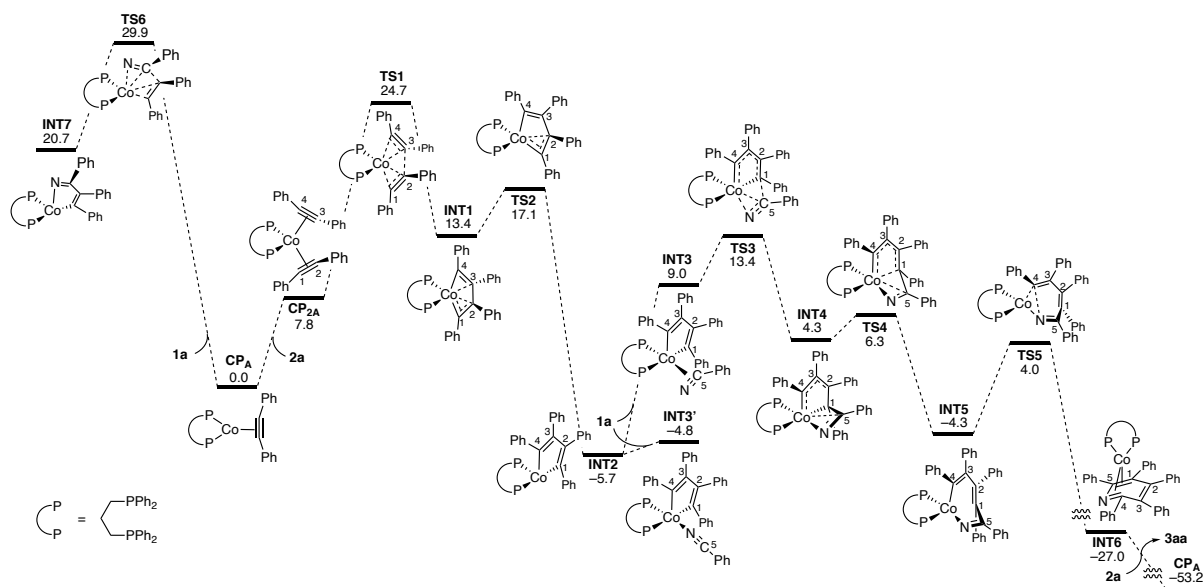


Figure 1. Gibbs free energy diagram of the [2+2+2] cycloaddition of benzonitrile (**1a**) and diphenylacetylene (**2a**) on [(dppp)Co⁰] calculated at the SMD(NMP)-M06L/6-311++G(2df,2p)-SDD(Co)/M06L/6-31G(d)-SDD(Co) level.

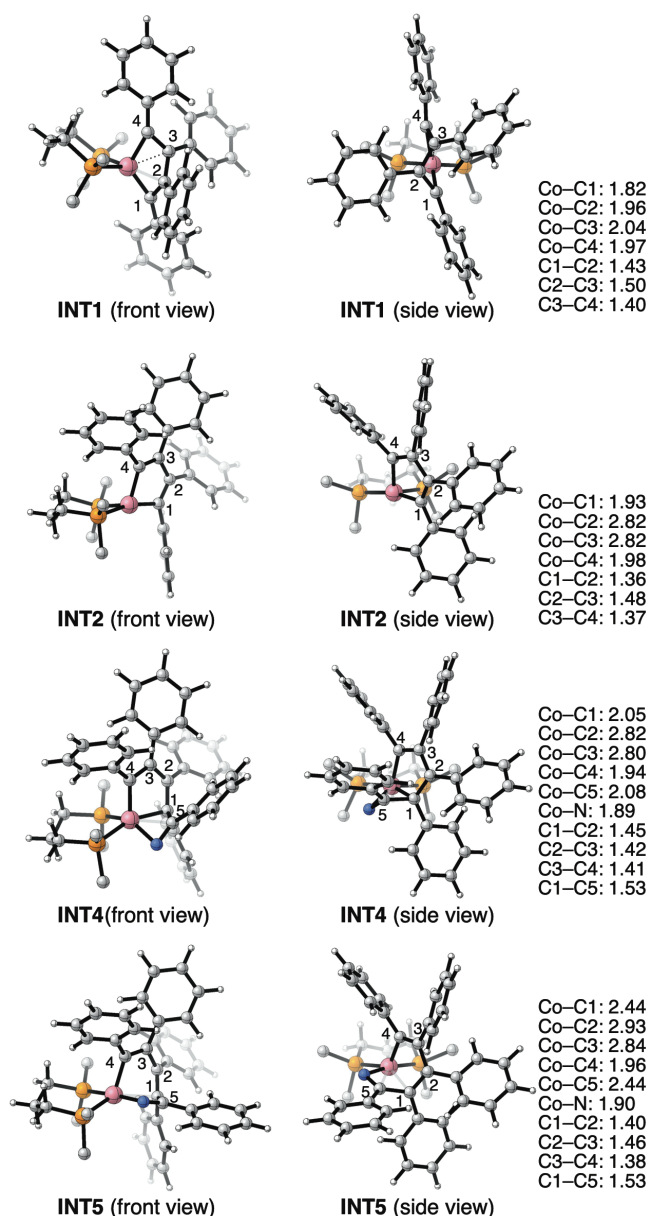
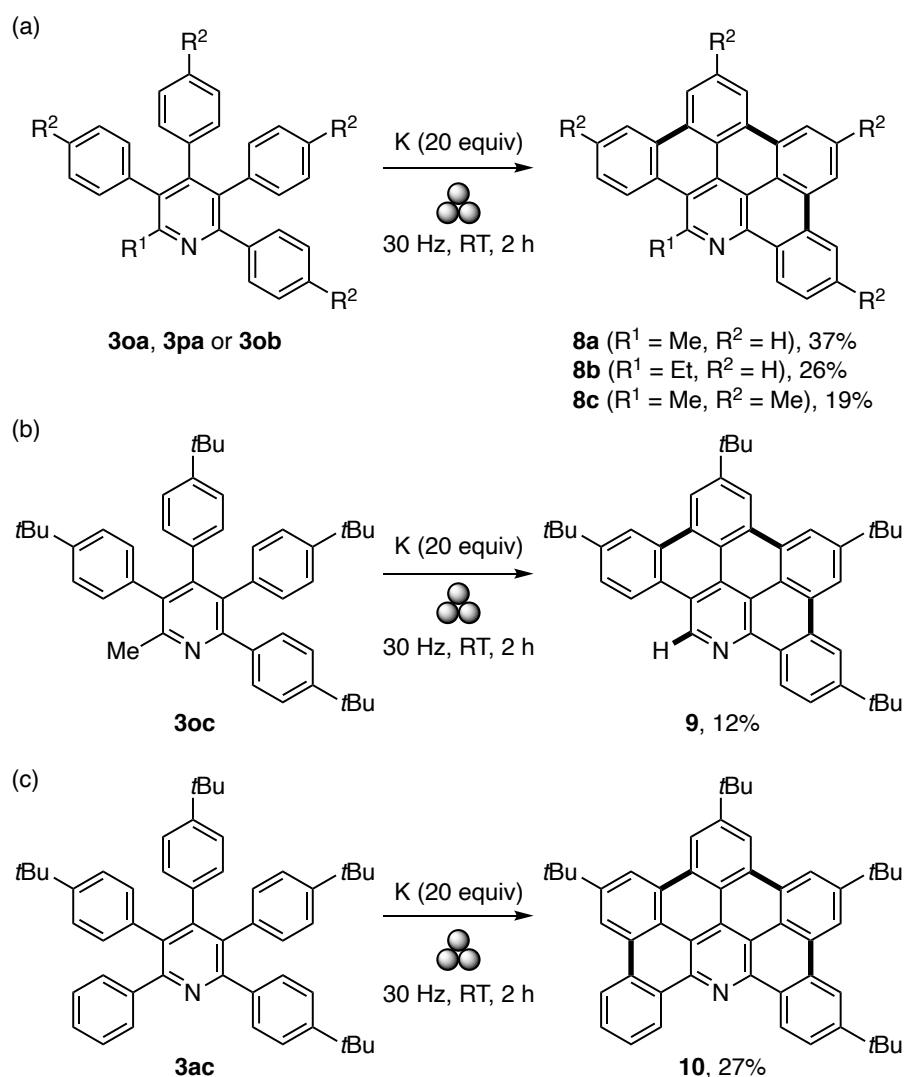


Figure 2. Structures of selected cobaltacycle intermediates. The phenyl groups of dppp are truncated for clarity. The distances are in Å.

In light of Scholl-type cyclodehydrogenation of polyarylbenzenes as a well-established and widely practiced strategy to construct polycyclic aromatic hydrocarbons (PAHs),^[26] it appears a natural idea to use tetra- and pentaarylpyridines as precursors to aza-PAHs^[27] via analogous cyclodehydrogenation. However, to our best knowledge, no single example of such a transformation has been reported to date. This is somewhat surprising but understandable, because the electron-deficient nature and the basicity of a pyridine ring would prevent the oxidative Scholl reaction typically employing Lewis or Brønsted acid. In this context, the reductive cyclodehydrogenation using potassium metal,^[28] which has recently been utilized by

Ito, Itami and coworkers for the conversion of azine-containing polyaromatic systems to aza-PAHs,^[29] appeared attractive.

Adopting the reductive cyclodehydrogenation strategy powered by mechanochemistry,^[30-32] we have successfully converted some of the tetra- and pentaarylpyridines described above into the corresponding aza-PAH derivatives (Scheme 4). The threefold cyclodehydrogenation of 2,3,4,5-tetraaryl-6-alkylpyridines **3oa**, **3pa**, and **3ob** in the presence of potassium (20 equiv) proceeded under ball milling (30 Hz, 2 h) to afford the corresponding aza-PAHs **8a–8c** as poorly soluble light-yellow solids in 19–37% yields (Scheme 4a). Importantly, the reaction of **3oa** in toluene afforded **8a** in only 14% yield (NMR), which could not be isolated in a pure form due to accompanying byproducts arising from incomplete (single and twofold) cyclodehydrogenations. Curiously, the mechanochemical reaction of analogous tetraarylpyridine **3oc** afforded cyclodehydrogenation/demethylation product **9** as the only isolable compound (Scheme 4b). Finally, the fourfold cyclodehydrogenation of pentaarylpyridine **3ac** afforded the corresponding aza-PAH **10** in 27% yield (Scheme 4c). Note that the reaction of **3ac** in toluene failed to give **10** in a detectable amount. We speculate that the failure of the solution-phase syntheses of the aza-PAHs is mainly ascribed to the inhomogeneity of the reaction mixture and the decreased solubility of partially cyclodehydrogenated intermediates, which represent problems that can be effectively addressed under mechanochemical conditions.



Scheme 4. Mechanochemically assisted cyclodehydrogenation of tetra- and pentaarylpiperidines to nitrogen-containing PAHs.

The planarized structure of the novel aza-PAH **10** was unambiguously confirmed by X-ray crystallographic analysis (Figure 3a).^[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 the known structure of 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 distance between the C4 positions of the pyridine rings of 3.31 Å, which is sandwiched by two other molecules of **10** through C–H/ π interactions (Figure 3b and Figure S4).

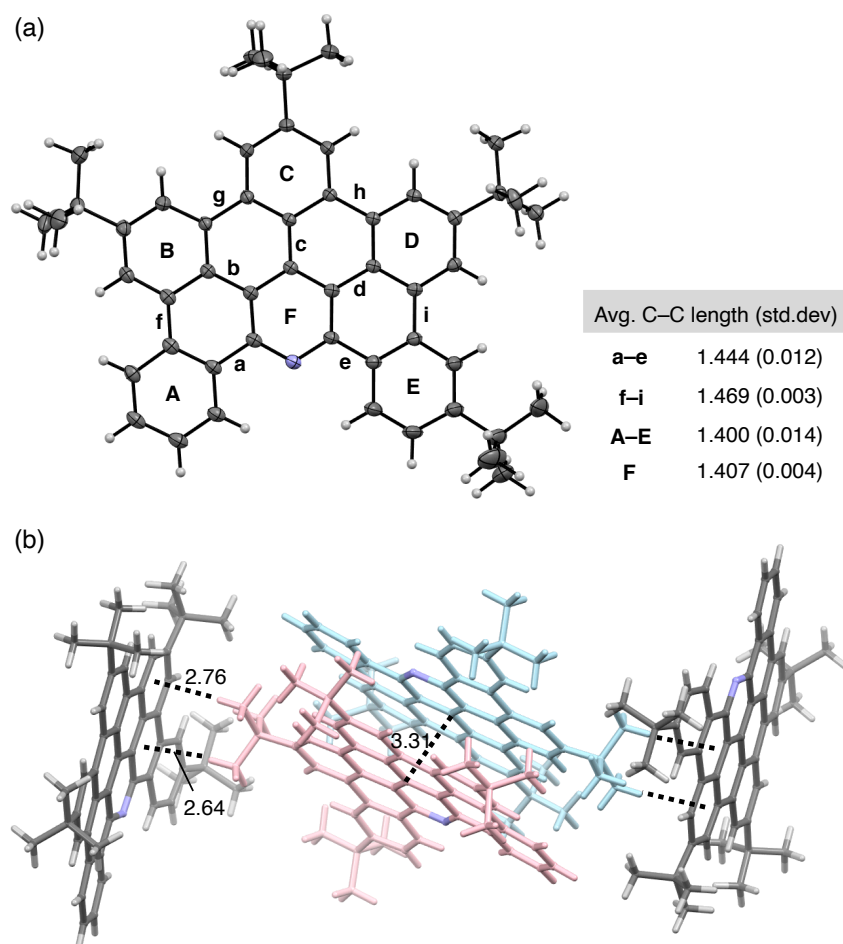


Figure 3. (a) ORTEP representation of **10** (thermal ellipsoids at the 50% probability). Solvent molecule (THF) is omitted for clarity. (b) Molecular packing in single crystal X-ray structure of **10**. Distances are in Å.

Figure 4 shows the UV-vis absorption and emission spectra of the aza-PAHs **8a** and **10**. Similar to their known 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. Mechanochemical synthesis of a greater variety of aza-PAHs from polyarylpyridines and exploration of their optical and electronic properties are currently underway.

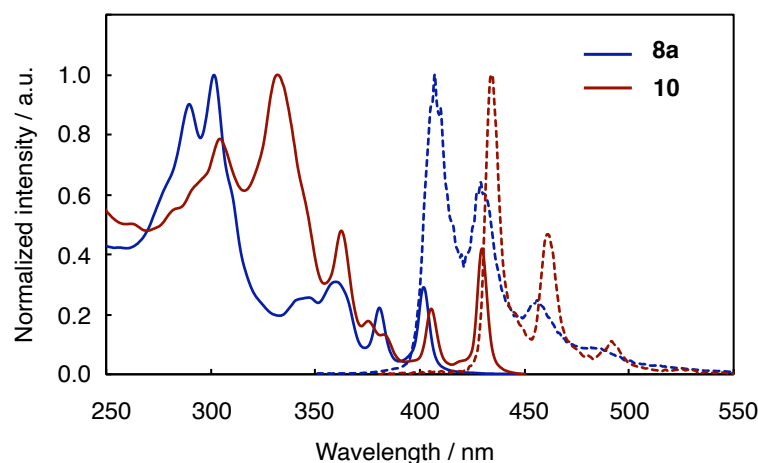


Figure 4. UV-vis absorption (solid lines) and emission (dashed lines) spectra of **8a** and **10** in CH₂Cl₂ (excitation wavelengths: 301 nm for **8a** and 331 nm for **10**).

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 for the synthesis of pentasubstituted pyridines. Thus, simple and inexpensive catalysts generated from CoI₂, dppp, and Zn have enabled the preparation of monocyclic tetra- and pentarylpyridines with an unprecedented level of structural diversity. DFT calculations supported the often-proposed reaction pathway involving oxidative coupling of two alkyne molecules, insertion of nitrile into cobaltacyclopentadiene, and C–N reductive elimination, while providing insight into the mechanistic subtlety of each of the elementary 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.

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