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# Reductive Coupling of Nitroarenes and HCHO for General Synthesis of Functional Ethane-1,2-diamines by a Cobalt Single Atom Catalyst

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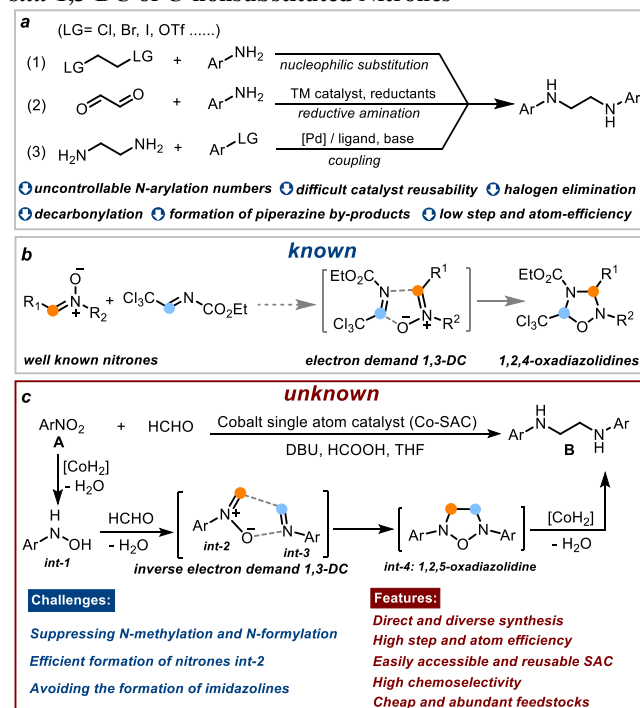
**KEYWORDS:** vicinal diamines, cobalt SAC, nitroarenes, reductive coupling, methanimine oxides

**ABSTRACT:** Despite the extensive applications, selective and diverse access to *N,N'*-diarylethane-1,2-diamines remains, to date, a challenge. Here, by developing a bifunctional cobalt single atom catalyst (Co<sub>SAC</sub>-N/NC), we present a general method for direct synthesis of such compounds via selective reductive coupling of cheap and abundant nitroarenes and formaldehyde, featuring good substrate and functionality compatibility, easily accessible base metal catalyst with excellent reusability, and high step and atom efficiency. Mechanistic studies reveal that the N-anchored cobalt single atoms (CoN<sub>4</sub>) serve as the catalytically active sites for the reduction processes, the N-doped carbon support enriches the HCHO to timely trap the *in situ* formed hydroxyamines and affords the requisite nitrones under weak alkaline conditions, and the subsequent inverse electron demand 1,3-dipolar cycloaddition of the nitrones and imines followed by hydrodeoxygenation of the cycloadducts furnishes the products. In this work, the concept of catalyst-controlled nitroarene reduction to *in situ* create specific building blocks is anticipated to develop more useful chemical transformations.

## INTRODUCTION

Among various vicinal diamines, ethane-1,2-diamines constitute a class of extremely important compounds, as they are frequently utilized as the key feedstocks for the synthesis of biomedical molecules,<sup>1</sup> chemical sensors,<sup>2</sup> and functional materials including polyamide fibers.<sup>3</sup> In addition, such compounds are also curing agents<sup>4</sup> of resins, bidentate ligands for catalysis<sup>5</sup> and organometallic chemistry,<sup>6</sup> and key precursors for the preparation of N-heterocyclic carbene (NHC) ligands.<sup>7</sup> Consequently, considerable attention has been directed toward the synthesis of the relevant compounds.<sup>8</sup> In contrast, selective and diverse construction of *N,N'*-diarylethane-1,2-diamines remains, to date, a challenge. In general, the synthesis could be realized by nucleophilic substitution of 1,2-dihaloethanes with anilines (Scheme 1a-1), reductive amination<sup>9</sup> of anilines with oxalaldehyde (Scheme 1a-2), palladium-catalyzed Buchwald-Hartwig amination of aryl halides with ethane-1,2-diamine (Scheme 1a-3).<sup>10</sup> However, these coupling strategies would encounter one or more issues, such as easy occurrence of decarbonylation and halogen elimination, difficult control of the N-arylation numbers, the generation of piperazine by-products, and difficult catalyst reusability. As such, it has resulted in a call for the development of new strategies enabling selective and diverse access to *N,N'*-diarylethane-1,2-diamines from easily available feedstocks, preferably with reusable catalyst.

## Scheme 1. (a) Conventional Ways to Access *N,N'*-Diarylethane-1,2-diamines; (b) Electron Demand 1,3-DC of Conventional Nitrones; (c) Inverse Electron Demand *in situ* 1,3-DC of C-nonsubstituted Nitrones



As a class of unique building blocks with amphiphilic nature, nitrones have been applied to create various functional molecules via 1,3-dipolar cycloaddition (1,3-DC) with alkenes.<sup>11</sup> Interestingly, there is also one demonstration on normal electron demand 1,3-DC of the conventional nitrones with imines,<sup>12</sup> which enables efficient access to 1,2,4-oxadiazolidines (Scheme 1b). It is important to note that, for the purposes of isolation and storage, the introduction of suitable substituents on the imino carbon is essential to maintain stable electronic configuration of the nitrones. In contrast, methanimine oxides (Scheme 1c, **int-2**), namely imino carbon-nonsubstituted nitrones, remains yet unexplored in synthetic chemistry due to the poor stability. However, such active species would endow the potentials to construct functional molecules that are of difficult access with the conventional approaches.

In recent years, reductive functionalization of nitroarenes has been nicely applied to construct various functional molecules by employing fully hydrogenated anilines as the intermediates to form C–N bonds.<sup>13</sup> However, nitroarene reduction is a cascade process that produces multiple intermediates (i.e., nitrosobenzenes, hydroxylamines, azoxybenzenes, azobenzenes, phenylhydrazines, and anilines), precise utilization of partially hydrogenated one among them to develop tandem reaction remains a challenging but promising direction. Here, we anticipated that the introduction of HCHO into the nitroarene (**A**) reduction would be able to trap hydroxylamine **int-1** *in situ* via condensation, and generate nitrone **int-2** and imine **int-3** via its further reduction (Scheme 1c). Then, **int-2** and **int-3** preferentially undergo inverse electron demand 1,3-DC to form 1,2,5-oxadiazolidine **int-4** due to the sterically less-hindered stacking, and the catalytic hydrodeoxygenation of the cycloadduct **int-4** would offer a highly desirable way to access *N,N'*-diarylethane-1,2-diamine **B**. From both environmental and economic points of view, nitroarenes and HCHO are cheap and abundant feedstocks, water is the only by-product generating from the associated condensation and reduction processes, and the *in situ* utilization strategy avoids the pre-preparation of unstable nitrones and imines.

However, to achieve the above synthetic purpose involving both C–N and C–C bond formations, at least three challenges have to be addressed (Scheme 1c): (1) Under catalytic reduction conditions, the thermodynamically more favorable N-methylation<sup>13a,13c</sup> and N-formylation<sup>13c</sup> of nitroarene **A** into N-(di)methyl and N-formyl anilines should be suppressed. (2) A compatible reaction system is required to ensure efficient trap of hydroxylamine **int-1** with HCHO to form requisite nitrone **int-2**, and avoid the generation of other nitroarene reduction intermediates. (3) It is essential to prevent diamine **B** from condensing with HCHO to result in undesired imidazoline by-products.<sup>15</sup>

Single-atom catalysts (SACs), as a class of specific supported nanomaterials with isolated metal atoms, have received considerable attention due to the excellent catalytic performance.<sup>16</sup> Enlightened by the capability of cobalt catalyst in reduction of unsaturated chemical bonds<sup>13,17</sup> and the nitrogen-doped carbon materials in enrichment of HCHO by physical adsorption,<sup>18</sup> as well as the striking features of SACs in maximum utilization of metal atom-efficiency, we wish here to report the development of a N-doped carbon-supported cobalt single atom material (Co<sub>SA</sub>-N/NC), and describe, for the first time, its application as a bifunctional catalyst in direct and

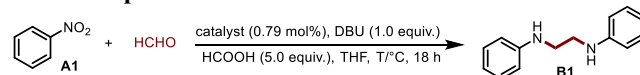
diverse construction of *N,N'*-diarylethane-1,2-diamines from cheap and abundantly available nitroarenes and HCHO.

## RESULTS AND DISCUSSION

Initially, we prepared the Co<sub>SA</sub>-N/NC catalyst through our designed procedure (Figure S1 in Supporting Information). Specifically, complex Co-TPP ((Tetraphenylporphinato)cobalt, 100 mg) was introduced into the solution of phenanthroline (200 mg) and carbon support (XC-72R, 1 g), and the mixture was stirred at room temperature for 30 minutes to afford the Co-TPP-Phen/C composite, which was pyrolyzed at 800 °C under argon protection to afford the catalyst material (Table S1). Advantageously, such an easily manipulated procedure allows ten-gram preparation of SACs in laboratory bench. The Co-content of Co<sub>SA</sub>-N/NC was determined as 0.386 wt% by inductively coupled plasma-optical emission spectroscopy (ICP-OES).

With the availability of the Co<sub>SA</sub>-N/NC, we then applied it to run the reductive coupling of nitrobenzene **A1** and HCHO by using formic acid as the hydrogen donor (model reaction), and aimed to screen an optimal system toward the formation *N,N'*-diphenylethane-1,2-diamines **B1**. First, by performing the reaction in THF at 120 °C for 18 h, the influence of various acid and base additives (entries 2, 4-12, Table S2 in SI) was tested, and the use of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) showed to be the best choice. Then, in the presence of 1 equivalent of DBU, the evaluation of potential catalysts revealed that only the use of Co<sub>SA</sub>-N/NC can afford the desired product **B1** in 58% (entries 1-4, Table 1). Further screening showed that a slight increase of reaction temperature to 130 °C is sufficient to improve the product yield to 78% upon isolation (Table 1, entries 5-6), and the combination of Co<sub>SA</sub>-N/NC and DBU is essential to constitute an efficient reaction system (entries 7-8, Table 1). However, switching THF to other solvents resulted in either low yields or no product formation (entries 14-16, Table S2).

**Table 1. Optimization of the Reaction Conditions.<sup>a</sup>**

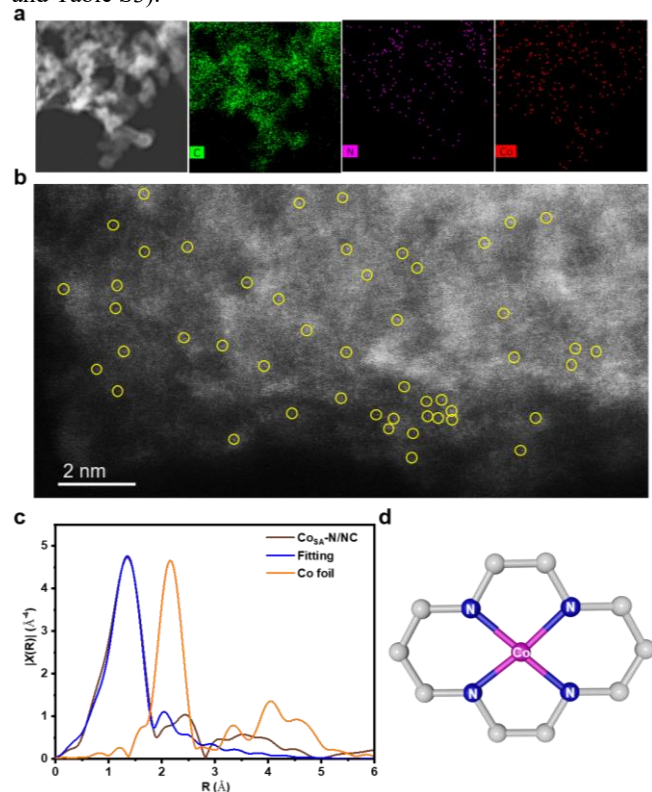


entry	catalyst	additive	temperature/°C	yield <sup>b</sup>
1	Co <sub>SA</sub> -N/NC	DBU	120	58%
2	Co-TPP/NC	DBU	120	0%
3	Co-TPP	DBU	120	0%
4	[Cp*IrCl <sub>2</sub> ] <sub>2</sub>	DBU	120	0%
5	Co <sub>SA</sub> -N/NC	DBU	130	78%
6	Co <sub>SA</sub> -N/NC	DBU	110	21%
7	-	DBU	130	0%
8	Co <sub>SA</sub> -N/NC	-	130	0%

<sup>a</sup>Reaction conditions: nitrobenzene **A1** (0.25 mmol), HCHO (0.25 mmol), catalyst (0.79 mol%), additive (0.25 mmol), HCOOH (1.25 mmol), and solvent (2 mL). <sup>b</sup>Isolated yield.

To understand the catalyst structure-performance relationship, we conducted detailed spectroscopic characterization of the Co<sub>SA</sub>-N/NC, and the results are summarized in Figure 1. The high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) and corresponding elemental mappings show that the Co and N species in Co<sub>SA</sub>-N/NC are uniformly distributed throughout the carbon support (Figure 1a). Further, the aberration-corrected HAADF-STEM (AC HAADF-STEM) image confirms that the Co single atoms

highlighted by yellow circles are atomically dispersed in the N-doped carbon matrix, and there are no agglomerated cobalt nanoparticles (Co NPs), which is consistent with the results of X-ray diffraction (XRD) pattern, wherein only two broad diffraction peaks ascribed to carbon can be observed (Figure 1b, Figure S2). From the X-ray photoelectron spectroscopy (XPS) spectra of Co 2p, the peaks with binding energy at 780.2 eV and 796.2 eV are ascribed to Co 2p<sub>3/2</sub> and Co 2p<sub>1/2</sub>, respectively (Figure S3a), which shows that the valence state of the cobalt in Co<sub>OSA</sub>-N/NC is +2.<sup>17d</sup> No signals accountable for metallic cobalt (Figure S3a) are found. On the other hand, the binding energy of N 1s in Co<sub>OSA</sub>-N/NC reveals the presence of pyrrolic nitrogen and pyridinic nitrogen<sup>18b,19</sup> (Figure S3b and Table S3).



**Figure 1.** Characterization of the Co<sub>OSA</sub>-N/NC catalyst. (a) HAADF-STEM and corresponding EDX elemental mappings of Co, N, and C; (b) aberration-corrected HAADF-STEM image; (c) FT-EXAFS spectra of Co<sub>OSA</sub>-N/NC and Co foil; (d) suggested atomic structure model of Co<sub>OSA</sub>-N/NC.

Then, X-ray absorption fine structure (XAFS) measurement was applied to thoroughly investigate the coordination environment of the cobalt in the Co<sub>OSA</sub>-N/NC (Figure S4-S6). As shown in Figure 1c, one main peak at ca. 1.37 Å in the FT k<sup>3</sup>-weighted EXAFS spectrum of Co<sub>OSA</sub>-N/NC contributes a significant difference to the peaks of Co foil at 2.16 Å. Meanwhile, the EXAFS fitting suggests that the coordination number of Co is ca. 4.34 with a mean bond length of 1.89 Å (Figure 1d, Table S4), thus the CoN<sub>4</sub> is believed to be the catalytically active metal center. The wavelet transform (WT) analysis reveals powerful resolution in both k and R spaces, and the WT maximum at 3.8 Å<sup>-1</sup> for Co<sub>OSA</sub>-N/NC can be attributed to the Co–N bonding with CoPc as a reference. Simultaneously, no intensity maximum at 7.4 Å<sup>-1</sup> is detected as referred to the

WT plots of Co foil, CoO, and Co<sub>3</sub>O<sub>4</sub>, implying the Co–Co bonds are negligible in Co<sub>OSA</sub>-N/NC (Figure S4c).

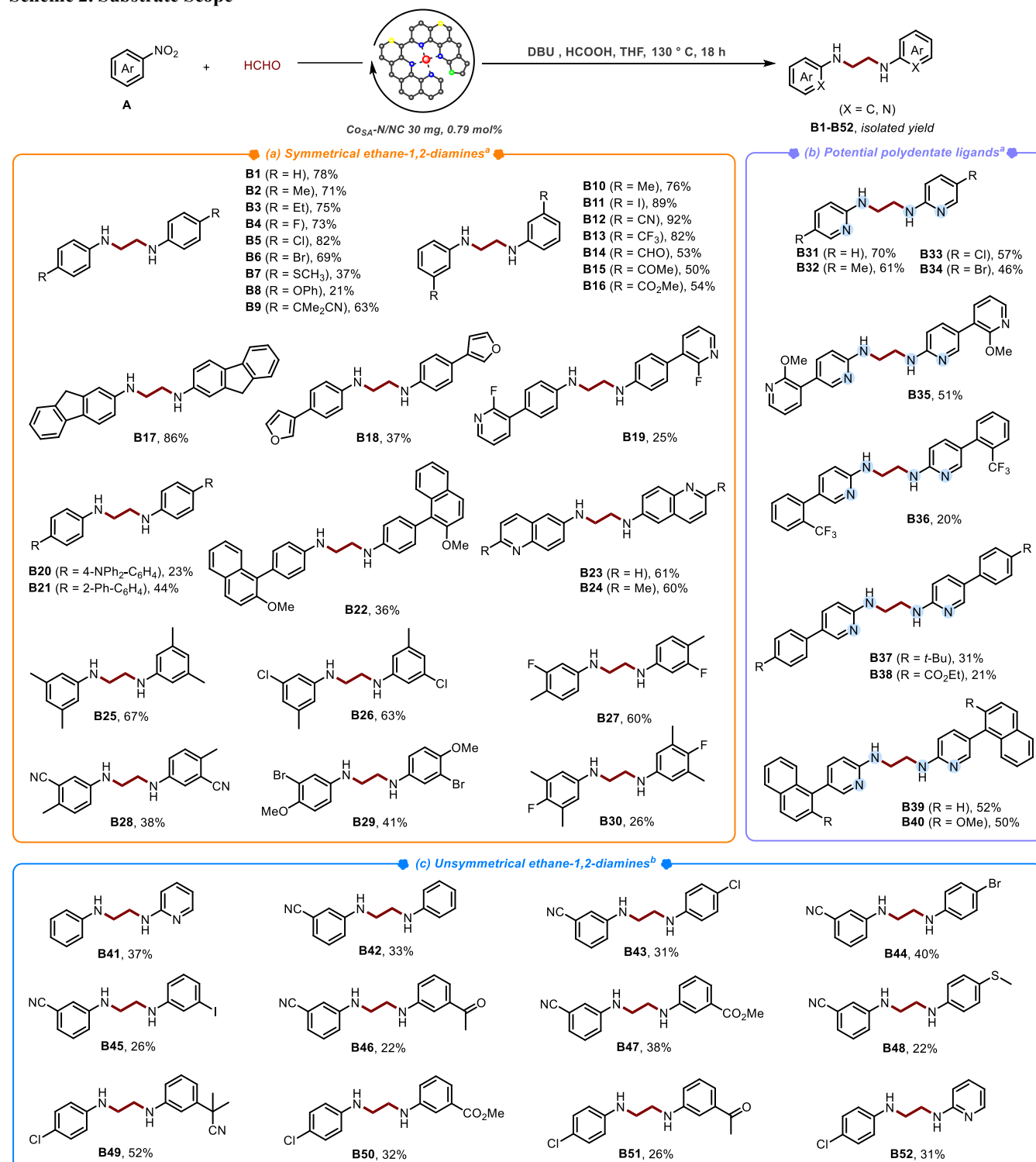
After establishing the optimal reaction system, we set out to test the substrate scope of the newly developed catalytic transformation. As illustrated in Scheme 2a (left), a vast ranges of nitroarenes were tested, and all the reactions proceeded smoothly to furnish the desired *N,N'*-diarylethane-1,2-diamines in moderate to excellent yields upon isolation. A series of functionalities (alkyl, -SMe, -CN, -CHO, halogen, phenoxy, ketyl, and ester) on the aryl ring are well tolerated, and no hydrodehalogenation and reduction of unsaturated groups (**B2-16**) were observed. The retention of these functionalities offers the basis for the elaboration of luxuriant molecule frameworks via further chemical transformations. Noteworthy, nitroarenes bearing an electro-withdrawing group (CN, CF<sub>3</sub>, and halogens) afforded much higher isolated yields (**B4-6**, **B9**, and **B11-13**) than those containing a strong electron-donating group (**B7-8**), which is assigned to electron-rich nitroarenes undergoing partial reductive N-methylation side reaction. Subsequently, nitroarenes (**A17-22** in Scheme S1) bearing an optoelectronic material-relevant motif also underwent efficient reductive coupling to afford the desired products (**B17-22**) in excellent yields, which offer the basis for further development of functional materials. In addition to nitroarenes, nitroheteroarenes were also amenable to the transformation, delivering the desired products in reasonable yields (**B23-24**), nitroarenes bearing two or three substituents smoothly afforded the polysubstituted products (**B25-30**).

Encouraged by the above successful examples, we then focused on the transformation of 2-nitropyridines into potential tetradentate N-ligands (Scheme 2b, right), a class of highly valuable compounds that are applicable for organometallic chemistry and catalysis. All the 2-nitropyridines underwent efficient reductive coupling, giving the *N,N'*-di(pyridin-2-yl)ethane-1,2-diamines in reasonable to high yields (**B31-40**).

Further, we explored the synthesis of unsymmetrical products by employing two different nitroarenes (Scheme 2c, bottom). In principle, the reaction generates two homocoupling and one cross-coupling products, and each one has a maximum yield of 33.3% according to the distribution law. Here, we were able to obtain the cross-coupling products with desirable yields higher than 30% in most cases by simple flash chromatography (**B41-44**, **B47**, **B49-50**, **B52**). Thus, the results shown in Scheme 2 indicate that the developed chemistry offers a general approach for the synthesis of both symmetrical and unsymmetrical *N,N'*-diarylethane-1,2-diamines.

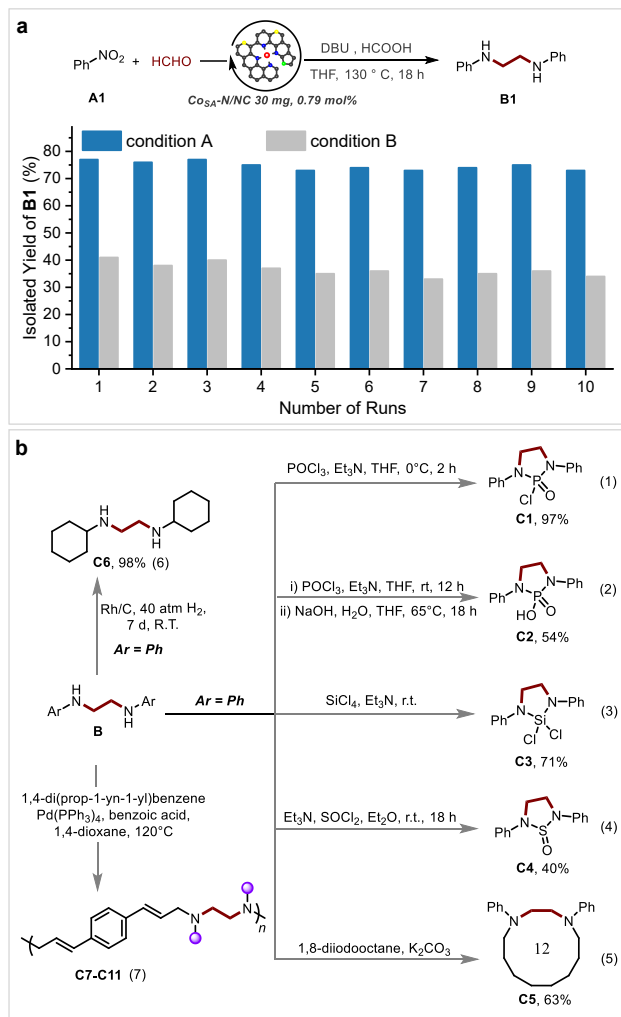
To examine the stability and reusability of the newly developed catalyst, we then investigated the catalyst recycling at full and half conversions of the model reaction. As illustrated in Scheme 3a, the Co<sub>OSA</sub>-N/NC could be reused at least for ten runs, as the product yields of **B1** did not show a significant decline. Similarly, recycling experiments conducted at half conversion also showed an excellent catalyst stability. XRD analysis of the reused catalyst unambiguously shows that the catalyst structure maintains well (Figure S2). Further XPS analyses show that the Co 2p, N 1s, and C 1s XPS spectra of Co<sub>OSA</sub>-N/NC are similar with the fresh one (Figure S3), which also proves the good stability of the developed catalyst. The slight deviation in the N spectra is assigned to the adsorption of organic molecules on the catalyst surface after the reaction.<sup>16c</sup>

## Scheme 2. Substrate Scope



Subsequently, we explored the synthetic utility of the developed chemistry. Through nucleophilic substitution, the reaction of compound **B1** and phosphoryl trichloride generated the five-membered heterocycle **C1** with a phosphoryl chloride motif in excellent yield (Scheme 3b-1), which can be converted into the phosphate **C2** via hydrolysis (Scheme 3b-2). Similarly, the reactions of compound **B1** with perchlorosilane and sulfurous dichloride produced the diazasilolidine **C3** and thiazolidine 1-oxide **C4** at room temperature, respectively (Scheme 3b-3 and 3b-4), and the cyclization of **B1** and 1,8-diiodooctane afforded 1,4-diazacyclododecane **C5** in 63% yield (Scheme 3b-5). Further, compound **B1** underwent rhodium-catalyzed full hydrogenation to deliver *N,N'*-dicyclohexylethane-1,2-diamine **C6** in excellent yield (Scheme 3b-6). By cooperative catalysis of Pd(0)/benzoic acid, different ethane-1,2-diamines (**B1**, **B12**, **B16**, **B29**, **B34**) underwent efficient migratory hydroamination of 1,4-di(prop-1-yn-1-yl)benzene, affording the polymers (**C7-C11**) containing allylic amine motifs (Scheme 3b-7 and Figure S7,S8a).<sup>3d</sup> The UV-vis absorption of these products in diluted THF solution falls in the range of 236–400 nm (Figure S8b), which is assigned to the  $\pi$ - $\pi^*$  transitions in the aromatic portion of the molecules. Correspondingly, the solution emission color ranges from blue to yellow owing to the different electronic effect of the substituents (Figure S8c). Compound **C11** with large conjugated structure had a strong emission at 515 nm with an intensity of ~5 fold higher than others. These results show that these compounds have potential to be applied in developing optoelectronic materials.

**Scheme 3. Synthetic Utility. (a) Catalyst-recycling Experiment<sup>d</sup>; (b) Derivatization of Ethane-1,2-diamines**



<sup>d</sup>Reaction condition A: the reaction of **A1** (0.25 mmol), HCHO (0.25 mmol), HCOOH (1.25 mmol), and catalyst (30 mg, 0.79 mol %) in THF (2 mL) was performed at 130 °C for 18 h under N<sub>2</sub> protection. Reaction condition B: the same as “A” for 1 h.

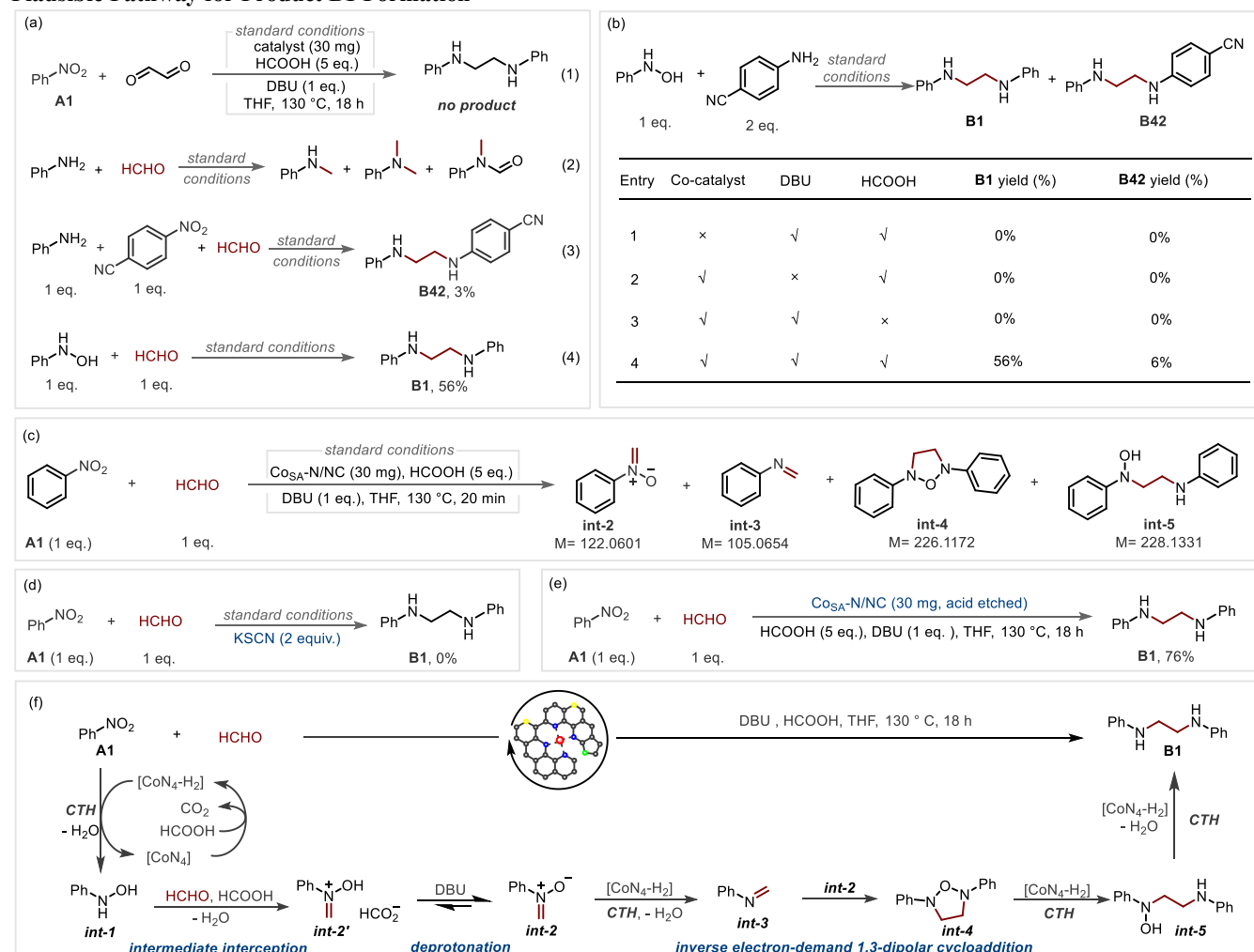
To gain mechanistic insights into the reaction, we conducted various control experiments. As shown in Scheme 4a-1, replacing HCHO with glyoxal failed to produce **B1**, showing that glyoxal is not a reaction intermediate. The reaction of aniline and formaldehyde under standard conditions only resulted in the *N*-methyl and *N*-formyl products (Scheme 4a-2), whereas the reaction of 4-nitrobenzotrile and aniline produced the unsymmetric ethane-1,2-diamine **B42** in 3% yield (Scheme 4a-3 and Figure S12), these two experiments prove the indispensable role of the partially hydrogenated nitroarenes in affording the desired ethane-1,2-diamines. The low yield of **B42** is rationalized as the electron-deficient hydroxylamine arising from the reduction of 4-nitrobenzotrile disfavoring the condensation with HCHO to afford the nitron, thus the aniline tends to undergo reductive *N*-methylation and *N*-formylation. This phenomenon discloses that a matchable generating rate between the nitrones and imines plays a crucial role in determining the reaction chemo-selectivity. Moreover, hydroxylamine reacted with HCHO to give product **B1** in 56% yield (Scheme 4a-4). The results show that the imine and nitron, deriving from the condensation of hydroxylamine with HCHO under alkaline conditions, are the key reaction intermediates.

Then, we studied the cross-coupling of hydroxylamine and 4-cyanoaniline, two precursors for *in situ* generation of nitron

and imine with HCHO, respectively (Scheme 4b). The results reveal that the Co<sub>SA</sub>-N/NC catalyst, HCOOH, and DBU are all indispensable for the formation of ethane-1,2-diamines (entries 1-4). Under the standard conditions, the reaction preferentially afforded product **B1** over compound **B42** (entry 4) even in the presence of excess 4-cyanoaniline, indicating that the formation of aniline-derived imine is faster than 4-cyanoaniline-derived imine, and the cobalt catalyst is involved in the catalytic transfer hydrogenation (CTH) processes. Further, the HR-MS analysis of the model reaction interrupted at 20 min indicated the generation of nitron **int-2**, imine **int-3**, cycloadduct **int-4**, and the open-ring compound **int-5** (Scheme 4c, see the HR-MS in Figure S13). Noteworthy, these compounds were consumed up after completion of the reaction, suggesting that they are all the reaction intermediates. All the results are in good agreement with the envisioned reaction pathway in Scheme 1c.

To identify the catalytically active sites of the catalyst, the poisoning experiment with 2 equivalents of KSCN under standard conditions led to no product formation, whereas acid-etched Co<sub>SA</sub>-N/NC still gave an excellent product yield, the results prove that the atomically dispersed CoN<sub>4</sub> species serve as the catalytically active sites (Scheme 4d and 4e). Then, the adsorption-experiment reveals that the Co-catalyst has a remarkable adsorbing capability toward formaldehyde (Figure S9), owing to the contribution of electron-rich N-dopants

**Scheme 4. (a–c) Control Experiments; (d) KSCN Poisoning Experiment; and (e) Activity of Acid-Etched Co<sub>SA</sub>-N/NC; (f) Plausible Pathway for Product B1 Formation**



(Figure S3b and Table S3), and the enriched HCHO ensures timely trap of hydroxyamine **int-1** to form requisite nitron **int-2** and imine **int-3**. Meanwhile, comparative experiments showed that the DBU exhibited the best selectivity for the formation of **B1** (Figure S10), as such a base is beneficial to the nitron formation by providing a weak alkaline environment (PH = 8), and it also does not act as a nucleophile to react with the reaction intermediates. Subsequently, we studied the effect of DBU concentration. As shown in Figure S11, the use of 1 equivalent of DBU (0.12 M) showed to be the best choice as the imidazoline *by*-products were effectively suppressed.

Based on the above findings, a plausible reaction pathway on the formation of product **B1** is depicted in Scheme 4f. Initially, the catalyst-induced decomposition of formic acid affords the reductive H-species adsorbed on the CoN<sub>4</sub> sites (CoN<sub>4</sub>-H<sub>2</sub>), which is able to run catalytic transfer hydrogenation (CTH)<sup>13</sup> of nitrobenzene **A1** to form hydroxyamine **int-1**. Then, the HCHO enriched by the N-doped carbon support timely traps **int-1** to generate salt **int-2'** via condensation and nitron **int-2** via DBU-induced neutralization of **int-2'**. Further, the inverse electron demand 1,3-DC (Figure S14) between **int-2** and imine **int-3** deriving from CTH of **int-2** gives the cycloadduct **int-4**. Finally, the CTH of **int-4** into ring-opening compound **int-5** followed by reductive deoxygenation of **int-5** gives rise to the desired product **B1**.

## CONCLUSIONS

In conclusion, by developing a bifunctional cobalt single atom catalyst (Co<sub>SA</sub>-N/NC), we have successfully applied it to develop a new reductive coupling reaction of cheap and abundant nitroarenes and formaldehyde involving both C–C and C–N bond formations. The catalytic transformation features good substrate and functionality compatibility, high step and atom efficiency, easily accessible catalyst with excellent reusability, which offers a practical platform for general synthesis of both symmetrical and unsymmetrical *N,N'*-diarylethane-1,2-diamines with the potential to be applied in numerous fields. Mechanistic studies reveal that the cobalt single atoms are the active sites for the transfer hydrogenation processes, the N-doped carbon support enriches the HCHO to timely trap the *in situ* formed hydroxyamines and affords the requisite nitrones in the presence of DBU, and the subsequent inverse electron demand 1,3-dipolar cycloaddition of the nitrones and imines followed by reductive deoxygenation of the cycloadducts gives rise to the desired products. The concept of catalyst-controlled nitroarene reduction to *in situ* create specific building blocks is anticipated to develop more useful tandem reactions.

## ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

Additional experimental details, materials, methods, and <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra for all compounds (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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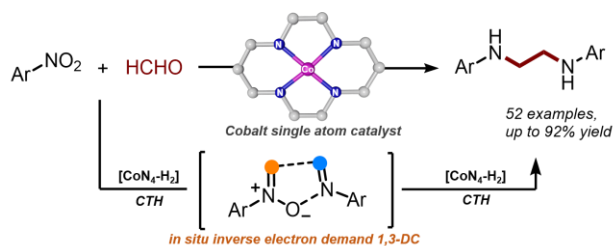
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# Reductive Coupling of Nitroarenes and HCHO for General Synthesis of Functional Ethane-1,2-diamines by a Cobalt Single Atom Catalyst

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- ☑ cheap and abundant feedstocks
- ☑ easily accessible SA catalyst with reusability
- ☑ direct and diverse synthesis
- ☑ excellent chemoselectivity
- ☑ high step and atom efficiency