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RESEARCH ARTICLE

Utilizing Nitroarenes and HCHO to Directly Construct Functional N-Heterocycles by Supported Cobalt/Amino Acid Relay Catalysis

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Abstract: Due to the generation of multiple intermediates during the nitroarene reduction, precise interception of single one to develop tandem reactions involving both C–C and C–N bond formations still remains a significant challenge. Herein, the relay catalysis of a supported bifunctional cobalt catalyst with *L*-proline has been successfully applied to establish a bran-new reductive annulation reaction of nitroarenes and formaldehyde, which enables direct and diverse construction of both symmetrical and unsymmetrical 1,3-diaryl imidazolines. It proceeds with operational simplicity, good substrate and functionality compatibility, and excellent step and atom-efficiency. Mechanistic studies reveal that the Co-catalyst exhibits a synergistic effect on the formation of key *N*-hydroxy imine, and the *L*-proline subsequently facilitates the key C–C bond formation. The current work opens a door to develop useful transformations with nitroarenes by reduction-interrupted strategy.

Introduction

Utilizing cheap and abundant feedstocks to step- and atom-economically produce functional products is always a dream of scientific community and industry. As a class of vital and bulk chemical raw materials, nitroarenes has been extensively employed to produce various arylamines by catalytic hydrogenation.^[1,2] In recent years, the construction of functional molecules via reductive functionalization of nitroarenes has attracted considerable attention. Advantageously, these transformations do not need pre-preparation of active anilines sensitive to many agents, thus avoiding tedious protection manipulations and improving the substrate and functionality compatibility. In this regard, except for the reductive *N*-formylation^[3] and *N*-alkylation^[4,5] of nitroarenes with carbonyl reagents (Figure 1a-1 and 1a-2), the construction of several types of *N*-heterocycles via reductive cyclization has also been nicely demonstrated, recently (Figure 1a-3).^[6,7] In terms of these transformations, they all apply the *in situ* formed arylamines arising from full hydrogenation of nitroarenes to form new C–N bonds. In contrast, due to the generation of multiple intermediates

during the nitroarene reduction (Figure 1a, nitrosoarenes, *N*-hydroxylamines, azoxybenzenes, azobenzenes, etc.),^[8] precise *in situ* interception of single hydroxyamine to develop tandem reactions involving both C–C and C–N bond formations still remains a significant challenge (Figure 1a-4), whereas such a concept offers a promising new direction to construct functional molecules that are inaccessible or difficult to prepare with the conventional approaches.

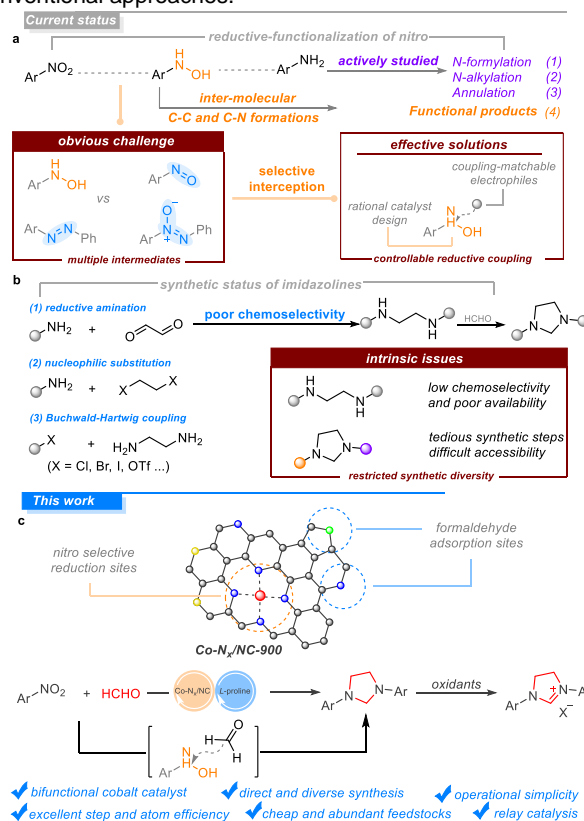


Figure 1. a) The advances and the challenge on reductive functionalization of nitroarenes. b) Conventional approaches for access to 1,3-diaryl imidazolines. c) Using nitroarenes and formaldehyde to construct 1,3-diaryl imidazolines by supported CoN_x/N with amino acid relay catalysis and the application to prepare *N*-heterocyclic carbene precursors (This work).

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N-aryl imidazolines constitute a class of highly important N-heterocycles, and they have been found to exhibit diverse interesting biological and therapeutic activities.^[9,10] Moreover, they are useful precursors^[11] for the preparation of N-heterocyclic carbene (NHC) catalysts,^[12-14] coordination ligands to transition metals,^[15-18] and functional materials.^[19-21] In general, *N*-aryl imidazolines are synthesized by the condensation of *N*¹,*N*²-diarylethane-1,2-diamines (DAEDAs) with formaldehyde or its surrogates (Figure 1b).^[22,23] However, such a synthesis often encounters the following key issues: (i) Restricted synthetic diversity due to the poor availability of requisite DAEDAs. As the DAEDAs are generally prepared by reductive amination of arylamines with oxalaldehyde (Figure 1b-1),^[24] nucleophilic substitution of 1,2-dihaloethanes with arylamines (Figure 1b-2), or Buchwald-Hartwig amination of aryl halides with ethane-1,2-diamine (Figure 1b-3),^[25] these protocols suffer from unavoidable generation of multiple by-products (e.g., 1,4-diphenylpiperazines, *N*-mono-, tri-, tetra-aryl substituted ethane-1,2-diamines) and easy occurrence of substrate decarbonylation or halogen elimination. (ii) Difficult catalyst reusability. In this context, the development of innovative strategies enabling direct and diverse construction of *N*-aryl imidazolines from cheap and abundant feedstocks, preferably with reusable base metal catalysts, would be highly desirable.

Given the above issues, catalytic reductive annulation of nitroarenes and formaldehyde via sequential C–N and C–C bond formations would provide a highly practical way to access 1,3-diaryl imidazolines (Figure 1c), as both reactants are abundant and inexpensive, and water is generated as the by-product. However, the combination of nitroarenes with formaldehyde is seldom employed to construct N-heterocycles on account of the tendency to undergo more favorable reductive N-methylation reactions.^[4,5] Enlightened by the capability of atomically dispersed cobalt catalysts in nitro reduction,^[26-28] and the N-dopants in adsorbing HCHO and tuning the catalytic performance,^[29-32] we believe that the design of a suitable cobalt catalyst would offer a solution to precisely intercept one of multiple intermediates during the nitroarene reduction and realize the above synthetic purpose. Based on this idea, we wish herein to report a N-doped carbon-supported bifunctional cobalt catalyst (Co-N_x/NC-900), featuring atomically dispersed Co-species and abundant electron-rich nitrogen sites, and describe, for the first time, the relay catalysis of such a reusable catalyst with *L*-proline is successfully applied to directly and diversely construct 1,3-diaryl imidazolines from nitroarenes and formaldehyde with renewable formic acid as the reductant.^[33,34] This reaction proceeds with operational simplicity, good substrate and functionality compatibility, high step and atom efficiency, which offers a practical platform to access NHC precursors (Figure 1c).

Results and Discussion

At first, we prepared the catalyst (Co-N_x/NC-900) by pyrolysis of the bimetal-organic framework with a molar ratio of Co : Zn = 1 : 20 (Co₁Zn₂₀-BMOF) under flowing argon at 900 °C for 3 h, and the detailed procedure was described in the Supporting Information (SI, Scheme S1). In the X-ray diffraction (XRD) pattern of catalyst (Figure S2a), no obvious Co signal was observed. The Co 2p X-ray photoelectron spectroscopy (XPS) spectrum only showed characteristic peaks of CoN_x at 780.38 eV

and 782.33 eV (Figure S4c). Both of which indicate that no Co nanoparticles are formed in Co-N_x/NC-900. The aberration-corrected high-angle annular dark-field scanning transmission electron microscopy (AC HAADF-STEM) images confirmed that a small amount of Co atomic clusters and abundant cobalt single atoms (Co-SAs) arising from the pyrolysis of bimetallic MOF were highly dispersed in the catalyst (Figures 2a-b).

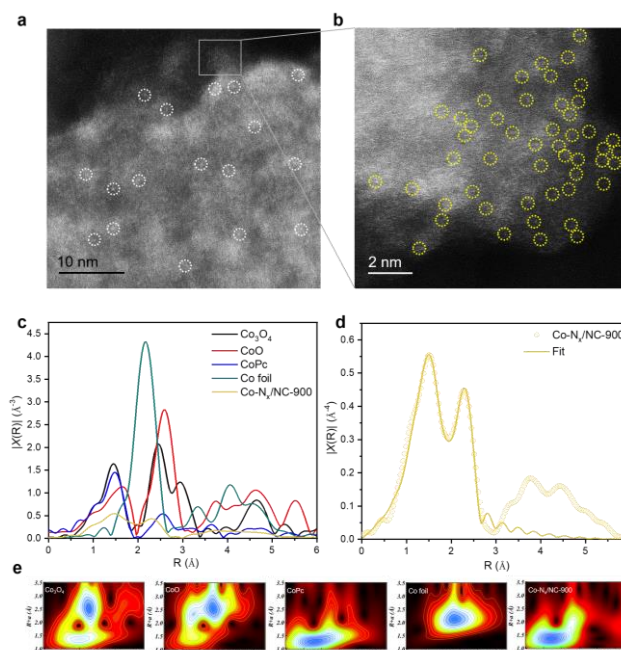


Figure 2. a-b) AC HAADF-STEM images of Co-N_x/NC-900. c) FT-EXAFS spectra in the R-space of Co₃O₄, CoO, CoPc, Co foil and Co-N_x/NC-900. d) Corresponding Co K-edge EXAFS fitting curve of Co-N_x/NC-900 in R space. e) Wavelet-transformed k³-weighted EXAFS spectra of Co₃O₄, CoO, CoPc, Co foil and Co-N_x/NC-900.

The X-ray absorption fine structure (XAFS) measurements were applied to further validate the coordination environment of the Co-species. Two distinct peaks at ca. 1.47 Å and 2.30 Å in the FT k³-weighted extended XAFS (EXAFS) spectrum (Figure 2c) contribute similarly to the CoPc and Co foil, respectively, indicating there are two completely different coordination environment of Co-species in Co-N_x/NC-900. Meanwhile, the coordination number of Co–N is ca. 4.90 and Co–Co is ca. 1.37 with mean bond lengths of 1.97 Å and 2.53 Å, respectively (Figure 2d and Table S1). The wavelet transform (WT) was further conducted to analyze the Co (Figure 2e) K-edge EXAFS oscillations. The WT maximum at 3.8 Å⁻¹ is assigned to the Co–N bonds, and the secondary signal at 7.4 Å⁻¹ arises from Co–Co bonds. Moreover, the N 1s XPS results show the existence of abundant electron-rich pyridinic and pyrrolic nitrogen species, which is caused by the sublimation of zinc during the pyrolysis (Figure S5c and Table S2). Based on the above results, the abundant Co-SAs (CoN₄) and a small number of atomic clusters are uniformly dispersed in the N-doped carbon support. Given this structure, we believe that a synergistic effect between atomically dispersed Co-species and N-dopants would exhibit promising catalytic performance for our synthetic purpose.

With the availability of the Co-N_x/NC-900 material, we then employed it to test the reductive annulation reaction of nitroarene **A1** and formaldehyde (Table S3, see Figure S13 for model reaction). Gratifyingly, an optimal isolated yield of 1,3-diphenyl

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imidazoline **B1** (81%) was obtained when the reaction in 2 mL of pure tetrahydrofuran was conducted at 100 °C for 20 h by using 20 mg Co-N_x/NC-900 (2.82 wt%), 30 mol% of *L*-proline, and 5 equivalents of HCOOH (Table S3, entry 1).

After establishing the optimal reaction conditions, we then examined the substrate scope of the newly developed synthetic protocol. As illustrated in Figure 3, mono or di-substituted nitroarenes were initially employed to couple with formaldehyde. All the reactions proceeded smoothly and furnished the desired 1,3-diaryl imidazolines in moderate to excellent yields upon isolation (**B1**-**B22**). A vast range of functional groups (–Me, –Et, –OMe, –F, –Cl, –Br, –I, –CN, –CHO, ketyl, and ester) were well tolerated. Surprisingly, unsaturated cyano and carbonyl groups did not undergo reduction, and no hydrodehalogenation of the halogens was observed (**B4**-**B10**, **B15**-**B16**, and **B18**-**B20**). Importantly, the retention of these functionalities offers the potential for the elaboration of complex molecules via further chemical transformations. In comparison, nitroarenes with an electro-withdrawing group (eg., –CN, –CF₃, and ester) afforded much higher product yields (**B4**, **B6**, **B8**, **B11**, and **B14**-**B17**) than those containing a strong electron-donating alkoxy group (**B13**, **B19** and **B22**). Upon GC-MS analysis, this phenomenon is attributed to partial electron-rich nitroarenes undergoing reductive *N*-methylation to form the *N*-methyl and *N,N*-dimethylaniline by-products. Nitro-substituted *N*-heteroarenes also underwent efficient reductive annulation, delivering the desired *N*-heteroaryl imidazolines in moderate to good isolated yields (**B23**-**B31**).

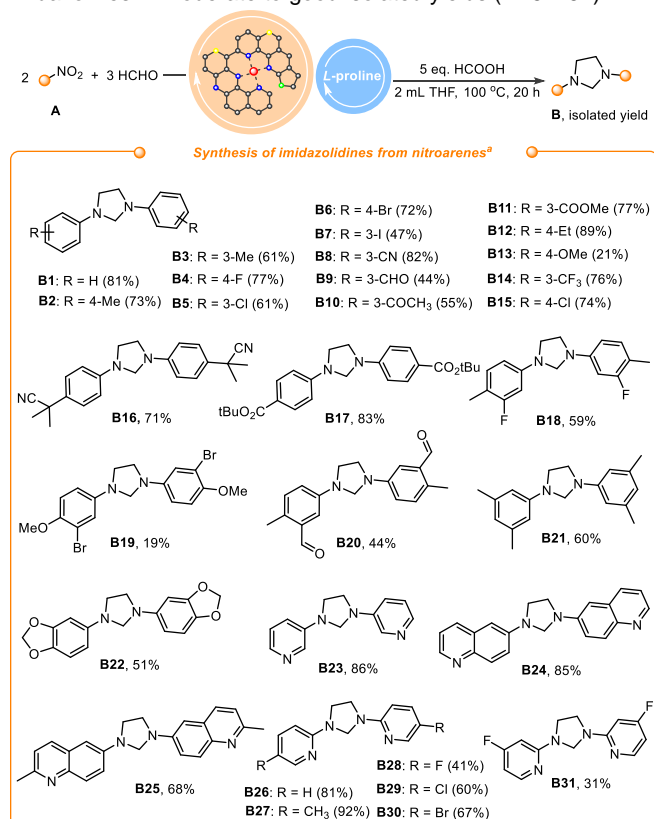


Figure 3. Synthesis of symmetrical 1,3-diaryl imidazolines from nitroarenes and formaldehyde. [a]Reaction conditions: nitroarene **A** (0.25 mmol), HCHO (2 eq.), catalyst (20 mg, 3.83 mol%), *L*-proline (30 mol%), HCOOH (5 eq.), and THF (2 mL), 100 °C, N₂, 20 h.

Encouraged by the successful synthesis of symmetrical 1,3-diaryl imidazolines, we subsequently turned our attention to the transformation employing two different nitroarenes to synthesize

unsymmetrical 1,3-diaryl imidazolines (Figure 4). In principle, the reaction generates one cross-coupling and two homocoupling products (**B**, **B'**, and **B''**), and each one has the maximum yield of 33%. Gratifyingly, by utilizing the different electronic properties of the substituents, we were able to obtain the desired cross-coupling products with the isolated yields higher than 30% in most cases (**B32**-**B35**, **B37**, **B39**, and **B41**-**B44**). The results of Figures 3-4 show that the developed chemistry offers a general approach to produce both symmetrical and unsymmetrical 1,3-diaryl imidazolines.

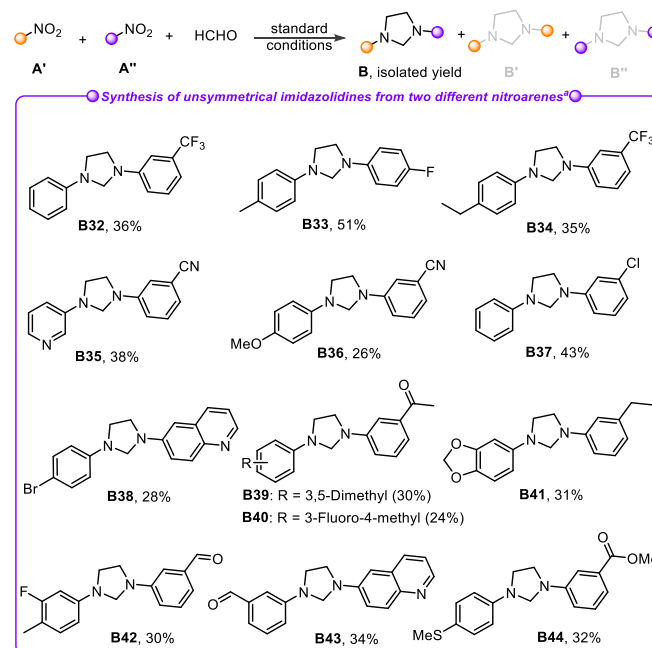


Figure 4. Synthesis of unsymmetrical 1,3-diaryl imidazolines from two different nitroarenes and formaldehyde. [a]Reaction conditions: nitroarenes **A'** (0.125 mmol), **A''** (0.125 mmol), HCHO (4 eq.), catalyst (20 mg, 7.66 mol%), *L*-proline (60 mol%), HCOOH (10 eq.), and THF (2 mL), 100 °C, N₂, 20 h.

To check the practicality of the synthetic method, the catalyst (Co-N_x/NC-900) recycling at full and half conversions of the model reaction was firstly examined (Figure S10). It was recycled to run the model reaction for 6 consecutive times. The activity and selectivity were very well retained, and no significant decrease of product yields was observed, which shows that the catalyst exhibits excellent cyclic durability. Meanwhile, the XRD, XPS and HAADF-STEM analysis of the reused catalyst unambiguously indicated that the catalyst structure has been maintained well after recycling (Figure S12).

As a class of promising compounds, thiourea derivatives are frequently utilized as synthetically useful building blocks and anti-inflammatory agents.^[35,36] We performed the model reaction by scaling up nitroarene **A1** from 0.25 mmol to 2.5 mmol to produce **B1** in a yield of 62%, and then prepared cyclic thiourea **B45** in 78% yield by treating **B1** with molecular sulfur S₈ under solvent-free conditions at 150 °C (Figure 5a).^[37] Further, the gram-scale syntheses of compounds **B6** and **B8** were also achieved by scaling up the nitroarenes to 10 mmol (Figure 5b). Considering that imidazolium salts are the precursors of NHCs extensively applied as organo-catalysts and coordination ligands to transition metals, we here were able to efficiently transform various imidazolines into the imidazolium salts via an oxidation process with NBS, NCS, or DDQ (Figure 5c, **C1**-**C13**),^[38] which

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demonstrates the potentials of the developed chemistry to be further applied in the field of organo and metal complex catalysis. It is important to note that, reasonable introduction of nitrogen atoms on the aromatic ring realized effective preparation of tridentate pyridine-NHC-pyridine pincer ligand precursors (**C10-C13**). Meanwhile, the synthetic protocol was successfully applied for the derivation of biomedically active molecules such as Ibuprofen derivatives **B46** and Adapalene derivatives **B47** (Figure 5d).

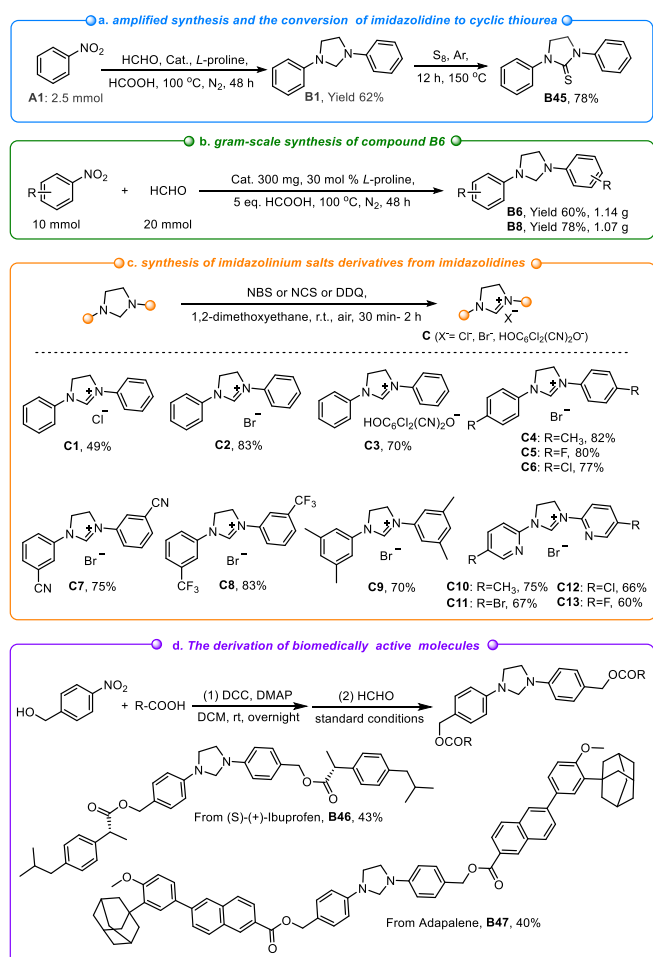


Figure 5. Synthetic applications. The detailed reaction conditions are indicated in "synthetic utility" in Supporting Information.

Subsequently, we conducted the mechanistic investigations by means of control experiments and DFT calculations. As shown in Figure 6a-1, the interruption of the model reaction after 20 min generated trace amount of product **B1** along with *N*-hydroxy imine **int-3**, imine **int-5** and *N*-oxide compound **int-6** (detected by HR-MS, Figure S16a-c). Noteworthy, these compounds were consumed up after completion of the reaction, indicating they serve as the reaction intermediates. Under the standard conditions, imine **int-5** can react with *m*-chloronitrobenzene to afford the homo and cross-coupling products **B5** and **B37** (Figure 6a-2 and Figure S17), and the reaction employing nitrosobenzene **int-1** or hydroxylamine **int-2** as the reactant produced product **B1** in 64% or 70% yield (Figure 6a-3 and Figure 6a-4). However, the

reaction of aniline and formaldehyde totally failed to afford product **B1** (Figure 6a-5). The results reveal that aniline, **int-1**, and **int-2** are also involved in the product formation, and they are the precursors of intermediates **int-3** and **int-5**. According to the matching principle of electronic property, **int-3** and **int-5** are the precursors for the formation of intermediate **int-6**. Further, replacing formaldehyde with glyoxal failed to produce **B1** (Figure 6a-6), implying that glyoxal as a reaction intermediate can be ruled out.

To figure out the role of key parameters on the formation of product **B1**, we conducted the comparison and formaldehyde-adsorption experiments (Figure 6b, Table S4 and Figure S14). Table S4 reveals that HCOOH as a reductant and Co-N_x/NC-900 as the catalyst are equally essential for the generation of **B1** (entries 1-4). Switching the reaction catalyst to Co(OAc)₂ or Co₁Zn₂₀-BMOF precursor led to no product generation (Table S4, entries 5-6). The absence of *L*-proline significantly lowered the product yield to 37% (Figure 6b, entry 2), and *N*-methylaniline and *N*-dimethylaniline became the major products, indicating that *L*-proline plays a key role on promoting the C–C bond formation to afford requisite intermediate **int-6**. Then, the poisoning experiment by introducing excess KSCN was conducted under the standard conditions, and no product was observed at all (Figure 6b, entry 3), which indicate that the highly dispersed CoN₄ species are the catalytic active sites. Meanwhile, the use of acid-etched Co-N_x/NC-900 gave a similar product yield (Figure 6b, entry 4), showing that the cobalt clusters do not affect the product formation. Further, the UV-Vis spectra reveal the excellent HCHO-adsorption capability of the catalyst (Figure S14), assigning to the contribution of large specific surface area (Figure S3a) and electron-rich nitrogen dopants (Figure S5c and Table S2),^[29,30] and the enriched formaldehyde ensures efficient formation of **int-3** and **int-5** to the greatest extent by timely capture the hydroxylamine **int-2**.

Further investigations were focused on the new C–C bond formation between **int-3** and **int-5**. We conducted the crossover reactions of *N*-hydroxyaniline and 4-cyano aniline (Figure 6c), two precursors allowing *in situ* formation of *N*-hydroxy imine **int-3** and imine with formaldehyde. The results show that the presence of HCOOH is indispensable to acquire the cross-coupling product **B48**, and the addition of *L*-proline significantly increased the product yield. Meanwhile, the Co-N_x/NC-900 has no effect on the product formation, indicating that the Co-catalyst is not involved in the C–C bond formation (entries 1-5). Notably, the presence of Co-N_x/NC-900 mainly resulted in the homocoupling product **B1** even the loading of 4-cyano aniline is two times of *N*-hydroxyaniline (Figure 6c, entries 6-8), indicating that the Co-catalyst in combination with HCOOH results in the reduction of *N*-hydroxyaniline to aniline and the more electron-rich aniline is favorable to condense with HCHO to afford requisite imine for the subsequent coupling with *N*-hydroxy imine **int-3** than 4-cyano aniline. Noteworthy, as shown in entries 4-5, no product **B1** formation indicates that the C–C bond formation from two *N*-hydroxy imines (**int-3**) is less likely. Further, pH-comparison experiments show that the acidity (grey polyline) of the reaction system plays a crucial role on the C–C bond formation (Figure S15), and there is no coordination between the cobalt catalyst and *L*-proline (Figures S18-20).

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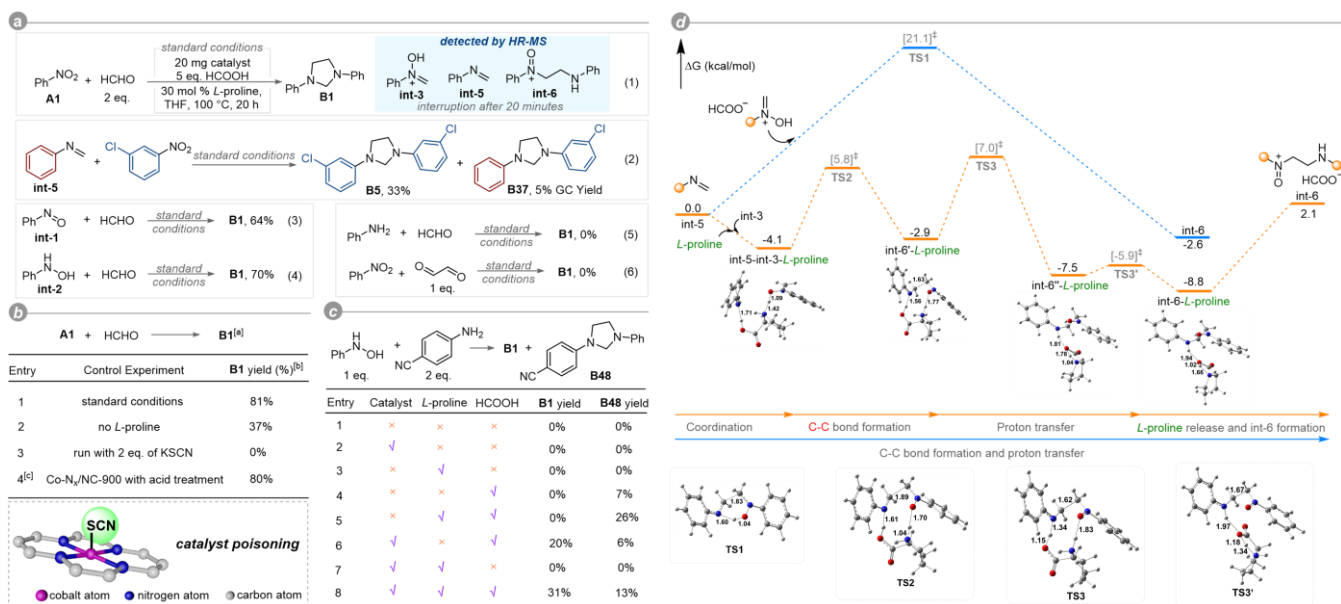


Figure 6. a) Control experiments. b) Verification experiments. [a] Reaction conditions: **A1** (0.25 mmol), HCHO (2 eq.), catalyst (20 mg), *L*-proline (30 mol %), HCOOH (5 eq.), and THF (2 mL), 100 °C, 20 h. [b] Determined by gas chromatography (GC) using *n*-hexadecane as an internal standard. [c] Co-N_x/NC-900 was etched as far as possible with 0.5 M H₂SO₄ aqueous solution at 80 °C for 12 h. c) Crossover reactions of *N*-hydroxyaniline and 4-cyano aniline. d) DFT calculations. (The detailed reaction conditions are indicated in “experimental procedure” in Supporting Information)

To reveal the role of *L*-proline on the formation of key C–C bond, DFT^[39] calculations were performed to compare the presumed pathways for the generation of *int-6* from *N*-hydroxy imine *int-3* and imine *int-5* at the B3LYP-D3(BJ)/6-311G** level, implemented in the Gaussian 16 package.^[40] Initiated with imine *int-5*, the potential energy surfaces (PESs) for the formation of *int-6* are shown in Figure 6d. In the absence of *L*-proline, the C–C bond-formation between *int-5* and *int-3* proceeds via a six-membered-ring transition state (**TS1**) with a barrier of 21.1 kcal/mol, and the reaction is exothermic by 2.6 kcal/mol. In contrast, the same PESs are analyzed under the assistance of *L*-proline (Figure 6d). Starting with the formation of complex *int-5-int-3-L-proline* by intermolecular hydrogen bonding interactions, which is exothermic by 4.1 kcal/mol, and the process for **TS2** is kinetically more favorable ($\Delta G^\ddagger = 9.9$ kcal/mol) as compared to the formation of **TS1** ($\Delta G^\ddagger = 21.1$ kcal/mol). Herein, the C–C bond formation accompanies with the proton transfer from the –N=OH⁺ unit to N-atom of *L*-proline, producing intermediate *int-6'-L-proline*. Then, *int-6'-L-proline* undergoes two consecutive proton transfer to form hydrogen-bonding complex *int-6-L-proline*, and this part of the PESs has low barrier of the entire path (9.9 kcal/mol for **TS3**, 1.6 kcal/mol for **TS3'**), corresponding to intermolecular proton transfer from the –COOH group of *L*-proline to the imino N-atom (*int-6'-L-proline* → *int-6''-L-proline*, $\Delta G = -4.6$ kcal/mol) and intramolecular proton transfer from the N-atom to the O-atom of *L*-proline (*int-6''-L-proline* → *int-6-L-proline*, $\Delta G = -1.3$ kcal/mol), respectively. Further dissociation of proline from *int-6-L-proline* to *int-6* undergoes a barrier of 10.9 kcal/mol.

Based on the above findings, a plausible reaction pathway for the formation of product **B1** is depicted in Figure 7. Initially, the Co-N_x sites on the catalyst surface bind active H-atoms from the decomposition of HCOOH,^[7,28,33-34] which results in catalytic transfer hydrogenation (CTH) of nitroarene **A1** to generate nitrosobenzene *int-1* and hydroxylamine *int-2*. Then, the catalyst-enriched formaldehyde timely traps *int-2* to afford *N*-hydroxy

imine *int-3* *in situ*. Noteworthy, being different from the conventional nitron *int-4* possessing a nucleophilic oxygen-site, *int-3* formed in acidic conditions undergoes carbo-nucleophilic addition to imine *int-5* resulting from CTH of *int-3* under the catalysis of *L*-proline, affording intermediate *int-6* through a new C–C bond formation. Finally, the CTH of *int-6* followed by dehydrative cyclization of DAEDA *int-7* with formaldehyde gives rise to imidazoline **B1**.

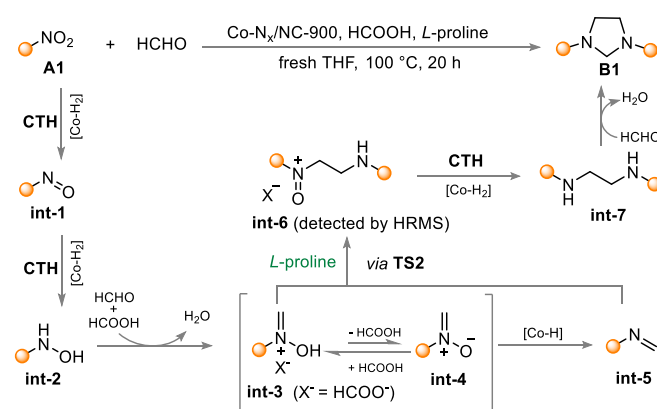


Figure 7. Plausible reaction pathway.

Conclusion

In summary, by developing a nitrogen-doped graphitic carbon-supported bifunctional cobalt catalyst with atomically dispersed Co-sites, the relay catalysis of such a reusable catalyst with *L*-proline has been successfully applied to establish a new reductive annulation reaction of nitroarenes and formaldehyde, which enables direct and diverse construction of both symmetrical and unsymmetrical 1,3-diaryl imidazolines with the features of

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operational simplicity, high step- and atom-efficiency, and good substrate and functionality compatibility. Upon a simple oxidation, the obtained products can be transformed into the N-heterocyclic carbene precursors widely applied in organometallic chemistry and catalysis. Mechanistic studies reveal that the Co-catalyst plays a crucial role on the formation of key N-hydroxy imine by a synergistic effect of the nitroarene reduction and the enrichment of HCHO to timely trap the *in situ* formed hydroxyamines, and the L-proline subsequently facilitates the C–C bond formation to afford requisite *N*¹,*N*²-diarylethane-1,2-diamines for the generation of target imidazolines. The developed chemistry opens a door to further develop valuable transformations with nitroarenes by reduction-interrupted strategy.

Acknowledgements

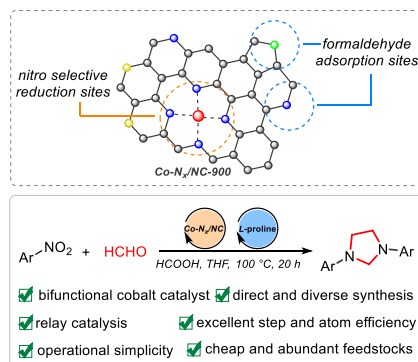
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Keywords: Nitroarenes and formaldehyde • Reductive coupling • Imidazolines • N-heterocyclic carbene ligands • Relay catalysis • Precise interception

- [1] R. V. Jagadeesh, A.-E. Surkus, H. Junge, M.-M. Pohl, J. Radnik, J. Rabeah, H. Huan, V. Schünemann, A. Brückner, M. Beller, *Science* **2013**, *342*, 1073–1076.
- [2] G. Wienhöfer, I. Sorribes, A. Boddien, F. Westerhaus, K. Junge, H. Junge, R. Llusar, M. Beller, *J. Am. Chem. Soc.* **2011**, *133*, 12875–12879.
- [3] N. Shen, S.-J. Zhai, C. W. Cheung, J.-A. Ma, *Chem. Commun.* **2020**, *56*, 9620–9623.
- [4] P. Zhou, L. Jiang, F. Wang, K. Deng, K. Lv, Z. Zhang, *Sci. Adv.* **2017**, *3*, e1601945.
- [5] L. Wang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2019**, *58*, 5417–5421.
- [6] T. Schwob, R. A Kempe, *Angew. Chem. Int. Ed.* **2016**, *55*, 15175–15179.
- [7] P. Ryabchuk, T. Leischner, C. Kreyenschulte, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2020**, *59*, 18679–18685.
- [8] a) M. L. Ploeger, A. Darù, J. N. Harvey, X. Hu, *ACS Catal.* **2020**, *10*, 2845–2854; b) T. Schwob, M. Ade, R. Kempe, *ChemSusChem* **2019**, *12*, 3013–3017; c) H.-U. Blaser, H. Steiner, M. Studer, *ChemCatChem* **2009**, *1*, 210–221.
- [9] D. R. Bazanov, N. V. Pervushin, E. V. Savin, M. D. Tsymlakov, A. I. Maksutova, S. E. Sosonyuk, G. S. Kopeina, N. A. Lozinskaya, *Med. Chem. Res.* **2021**, *30*, 2216–2227.
- [10] A. G. Woolfork, K. Suh, M. Weigand, D. S. Hage, *J. Pharm. Biomed. Anal.* **2021**, *202*, 114135.
- [11] J. P. Coyle, E. R. Sirianni, I. Korobkov, G. P. Yap, G. Dey, S. T. Barry, *Organometallics* **2017**, *36*, 2800–2810.
- [12] P. Bellotti, M. Koy, M. N. Hopkinson, F. Glorius, *Nat. Rev. Chem.* **2021**, *5*, 711–725.
- [13] K.-Q. Chen, H. Sheng, Q. Liu, P.-L. Shao, X.-Y. Chen, *Sci. China Chem.* **2021**, *64*, 7–16.
- [14] X.-Y. Chen, Z.-H. Gao, S. Ye, *Acc. Chem. Res.* **2020**, *53*, 690–702.
- [15] M. Koy, P. Bellotti, M. Das, F. Glorius, *Nat. Catal.* **2021**, *4*, 352–363.
- [16] F. Nagra, C. S. J. Cazin, *Chem. Soc. Rev.* **2021**, *50*, 3094–3142.
- [17] Q. Chen, Q. Liu, J. Xiao, X. Leng, L. Deng, *J. Am. Chem. Soc.* **2021**, *143*, 19956–19965.
- [18] L. Kong, J. Morvan, D. Pichon, M. Jean, M. Albalat, T. Vives, S. Colombel-Rouen, M. Giorgi, V. Dorcet, T. Roisnel, *J. Am. Chem. Soc.* **2020**, *142*, 93–98.
- [19] M. Franz, S. Chandola, M. Koy, R. Zielinski, H. Aldahhak, M. Das, M. Freitag, U. Gerstmann, D. Liebig, A. K. Hoffmann, *Nat. Chem.* **2021**, *13*, 828–835.
- [20] D. E. Westmoreland, R. López-Arteaga, E. A. Weiss, *J. Am. Chem. Soc.* **2020**, *142*, 2690–2696.
- [21] S. Ibáñez, M. Poyatos, E. Peris, *Acc. Chem. Res.* **2020**, *53*, 1401–1413.
- [22] X. Frogneux, E. Blondiaux, P. Thuéry, T. Cantat, *ACS Catal.* **2015**, *5*, 3983–3987.
- [23] X.-Y. Li, S.-S. Zheng, X.-F. Liu, Z.-W. Yang, T.-Y. Tan, Y. Ao, L.-N. He, *ACS Sus. Chem. Eng.* **2018**, *6*, 8130–8135.
- [24] G. R. Qiang, X. M. Wu, Q. Wang, W. Pei, *Chin. Chem. Lett.* **2007**, *18*, 1469–1470.
- [25] R. Dorel, C. P. Grugel, A. M. Haydl, *Angew. Chem. Int. Ed.* **2019**, *58*, 17118–17129.
- [26] G. Zhang, F. Tang, X. Wang, L. Wang, Y.-N. Liu, *ACS Catal.* **2022**, *12*, 5786–5794.
- [27] H. Jin, P. Li, P. Cui, J. Shi, W. Zhou, X. Yu, W. Song, C. Cao, *Nat. Commun.* **2022**, *13*, 723.
- [28] X. Cui, W. Li, P. Ryabchuk, K. Junge, M. Beller, *Nat. Catal.* **2018**, *1*, 385–397.
- [29] C. Su, K. Liu, J. Guo, W. Ma, H. Li, Z. Zeng, L. Li, *Surf. Interfaces* **2021**, *24*, 101038.
- [30] E. Lepre, S. Rat, C. Cavedon, P. H. Seeberger, B. Pieber, M. Antonietti, N. Lopez-Salas, *Angew. Chem. Int. Ed.* **2023**, *62*, e202211663.
- [31] W. Ye, S. Chen, Y. Lin, L. Yang, S. Chen, X. Zheng, Z. Qi, C. Wang, R. Long, M. Chen, *Chem* **2019**, *5*, 2865–2878.
- [32] X. Wei, S. Song, W. Cai, X. Luo, L. Jiao, Q. Fang, X. Wang, N. Wu, Z. Luo, H. Wang, *Chem* **2023**, *9*, 181–197.
- [33] R. Xie, W. Mao, H. Jia, J. Sun, G. Lu, H. Jiang, M. Zhang, *Chem. Sci.* **2021**, *12*, 13802–13808.
- [34] H. Ning, Y. Chen, Z. Wang, S. Mao, Z. Chen, Y. Gong, Y. Wang, *Chem* **2021**, *7*, 3069–3084.
- [35] C. T. Supuran, A. Scozzafava, B. C. Jurca, M. A. Ilies, *Eur. J. Med. Chem.* **1998**, *33*, 83–93.
- [36] H. Kogen, K. Tago, M. Arai, E. Minami, K. Masuda, T. Akiyama, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1347–1350.
- [37] M. K. Denk, S. Gupta, J. Brownie, S. Tajammul, A. J. Lough, *Chem. Eur. J.* **2001**, *7*, 4477–4486.
- [38] A. Salerno, C. Caterina, I. A. Perillo, *Synth. Commun.* **2000**, *30*, 3369–3382.
- [39] R. G. Parr, W. Yang, *Density-Functional Theory of Atoms and Molecules* (Oxford Univ. Press, **1989**).
- [40] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, et al. *Gaussian 16 Rev. C.01* **2016**.

RESEARCH ARTICLE

Utilizing Nitroarenes and HCHO to Directly Construct Functional N-Heterocycles by Supported Cobalt/Amino Acid Relay Catalysis

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The relay catalysis of a supported bifunctional cobalt catalyst and L -proline has been applied to establish a new reductive annulation reaction of nitroarenes and formaldehyde, which enables direct and diverse construction of 1,3-diaryl imidazolines. Mechanistic studies reveal that the Co-catalyst exhibits a synergistic effect on the formation of requisite N -hydroxy imines, and the L -proline subsequently facilitates the key C–C bond formation.