ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Lu, Y. Liu, D. Liang and W. Xiao, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC00987F.

Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications

www.rsc.org/chemcomm

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION
Marilyn M. Olmstead, Alan L. Balch, Josep M. Poblet, Luis Echegoyen et al.
Reactivity differences of $Sc_3N@C_{2n}$ (2n = 68 and 80). Synthesis of the first methanofullerene derivatives of $Sc_3N@D_{5h}$-C_{80}

175 YEARS

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC00987F

Journal Name

COMMUNICATION

Practical heterogeneous photoredox/nickel dual catalysis for C-N and C-O coupling reactions†

3Received 00th April 20xx,
Accepted 00th May 20xx

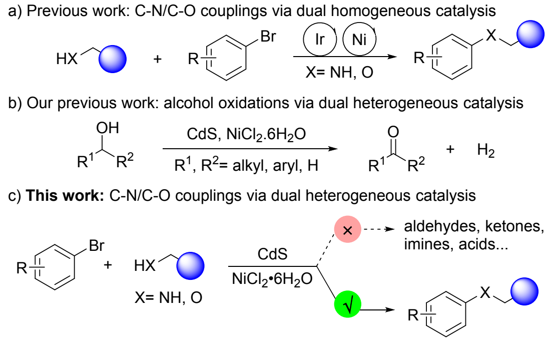
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yi-Yin Liu,[a] Dong Liang,[a] Liang-Qiu Lu*[a,b] and Wen-Jing Xiao[a,c]

Efficient C-N and C-O coupling reactions of aryl halides with amines and alcohols have been developed through the strategy of heterogeneous visible light photoredox and nickel dual catalysis. Obviously, the joint use of inexpensive and bench-stable CdS and nickel salts, together with mild reaction conditions, makes these two transformations attractive for the synthetic community. This heterogeneous dual catalysis system also proved to be successful in the ligand-free catalytic hydroxylation of aryl bromide with water as a nucleophile. The practicality of this protocol is further emphasized by the scaled-up reaction and the reusability of heterogeneous photocatalysts.

Visible light photoredox catalysis has attracted increasing attention from the synthetic community due to its powerful capacity in organic synthesis.[1] Generally, a photosensitizer is required for harvesting visible light energy and further promoting subsequent organic reactions.[2,3] Though great achievements have been made in the field of homogeneous visible light photocatalysis,[2] from the perspective of green and sustainable synthetic chemistry,[4] the exploitation of heterogeneous variants might be more practical and attractive for industry,[3] because, compared with the widely used Ir- or Ru-based photocatalysts, heterogeneous photocatalysts, including semiconductors such as TiO_2 and CdS, are usually much cheaper, more readily available and reusable. While, fewer efforts have been made for chemical bond formation in organic synthesis, albeit considerably more effort has been devoted to water splitting and hydrogen generation.[5] In 2012, König and coworkers developed a heterogeneous enantioselective α-alkylation of aldehydes by using the semiconductor CdS and a chiral secondary amine catalyst.[6] In 2017, Krauss, Weix and coworkers reported an impressive work on utilizing CdSe quantum dots (QDs) as efficient photocatalysts for carbon-carbon bond formzation along with a single case for carbon-nitrogen coupling.[7] Even though, the application of dual catalysis[8] using heterogeneous photocatalysts for C-heteroatom bond formation has been much less explored.[7,9,10]



Scheme 1 Coupling reactions via photoredox/nickel dual catalysis

Aromatic amines and ethers are important motifs prevalent in plenty of natural products, pharmaceuticals, and agrochemicals.[11] C-N and C-O coupling reactions of aryl halides with amines and alcohols, including the Buchwald-Hartwig and Ullmann coupling reactions through Pd and Cu catalysis, respectively, are among the most useful approaches to access these compounds.[13,14] In recent years, photoredox/Ni dual catalysis[15] has drawn increasing attention in the field of C-N[16] and C-O couplings[17] because it utilizes mild reaction conditions. Ir-based photocatalysts are indispensable for these transformations (Scheme 1, a). Recently, Xu and our lab cooperatively accomplished visible light-driven heterogeneous dehydrogenative oxidation of alcohols to carbonyls by merging CdS and Ni catalysis (Scheme 1, b).[18] Due to continuous interest in visible light photocatalysis[19] and transition metal catalysis,[20] we wish to further exploit the feasibility of this heterogeneous catalysis strategy for C-N and C-O coupling reactions of aryl halides with amines and alcohols (Scheme 1, c), albeit accompanying with the potential dehydrogenative oxidation of amines and alcohols.[21-23]

---

[a] CCNU-uOttawa Joint Research Centre, Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China. Email: luliangqiu@mail.ccnu.edu.cn
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, China
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, Shanghai 200032, China

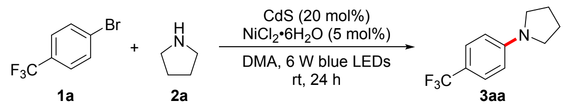
†Electronic supplementary information (ESI) available. See DOI: 10.1039/0000000000

View Article Online
DOI: 10.1039/C9CC00987F

We initially tested the heterogeneous C-N coupling reaction with 4-bromobenzotrifluoride and pyrrolidine. A quick investigation of Ni salts, ligands, solvents and light sources revealed that the combination of CdS, NiCl$_2$•6H$_2$O and DMA could provide the aniline product **3aa** in 83% yield under irradiation with 6 W blue LEDs, with no detection of oxidized by-products from pyrrolidine (entry 1). Control experiments indicated that both visible light, a photocatalyst and a nickel catalyst were all critical for this transformation (entries 2-4). The reaction performed under an aerobic atmosphere also did not yield any coupling product (entry 5). Varying the reaction solvent did not improve the result; among the solvents used, CH$_3$CN delivered the coupling product in 58% yield (entry 6). Other nickel salts also gave comparable yields (entry 7), but the lower cost of NiCl$_2$•6H$_2$O makes it a better choice.[24] Lowering the loading of CdS led to a dramatic decrease in efficiency (entry 8). The addition of the widely used bipyridine ligand had a negative effect on the efficiency of coupling reactions (entry 9). To our surprise, the base DABCO (entry 10), which was necessary in the dual Ir/Ni catalyst system, was found to completely inhibit the reaction.

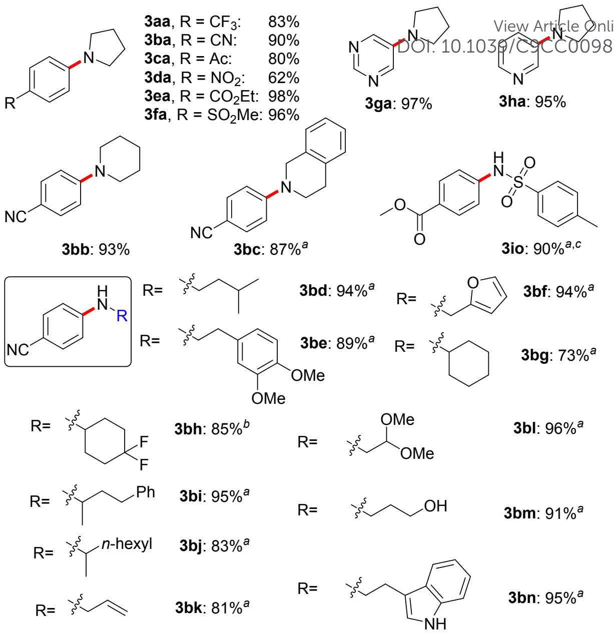
With the optimized conditions in hand, we started to evaluate the generality of this C-N coupling reaction (Scheme 2). As expected, the reaction with a series of substituted aryl bromides bearing a range of synthetically useful functional groups, such as cyano, nitro, ketone and ester moieties, proceeded well to furnish products **3ba**-**3fa** in 62-98% yields. Heteroaryl bromides, such as pyrimidine and pyridine, were also suitable for this transformation, delivering the corresponding products **3ga** and **3ha** in 97% and 95% yield, respectively. Next, a variety of primary and secondary amines were found to be successful in this heterogeneous C-N coupling protocol.

Table 1 Condition optimization for C-N coupling[a]



entry	variation from the standard conditions	yield (%)[b]
1[c]	none	83
2	no CdS	0
3	no NiCl$_2$·6H$_2$O	0
4	in the dark	0
5	in the air	0
6[c]	MeCN instead of DMA	58
7	NiCl$_2$·glyme instead of NiCl$_2$·6H$_2$O	80
8	2 mol% of CdS	12
9	5 mol% dtbbpy as ligand	56
10	2.0 eq. DABCO as base	trace

[a]Conditions: **1a** (1.0 mmol), **2a** (2.0 mmol, 2.0 equiv.), CdS (0.2 mmol, 20 mol%), NiCl$_2$•6H$_2$O (0.05 mmol, 5 mol%), and DMA (3.0 mL) under irradiation with 6 W blue LEDs. [b]Isolated yield of **3aa**. [c]No reaction occurred in other solvents, such as THF, DCM and CHCl$_3$. DMA: N,N-Dimethylacetamide; dtbbpy: dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine; LEDs: light-emitting diodes.



Reaction conditions: the same with entry 1 in Table 1; isolated yields. [a]Performed with DBU (2.0 mmol, 2.0 equiv.) at 55 °C. [b]Performed with DBU (4.0 mmol, 4.0 equiv.) at 55 °C. [c]Using aryl iodide instead of aryl bromide.

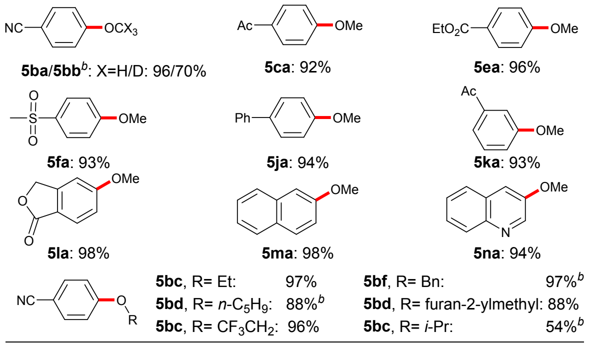
Scheme 2 Scope of the C-N coupling reaction

In most cases, 2.0 equiv. of DBU and an elevated reaction temperature were helpful to ensure the full conversion of aryl bromides. For example, piperidine and 1,2,3,4-tetrahydroisoquinoline were converted to the corresponding aniline derivatives **3bb** and **3bc** in 93% and 87% yield, respectively. Moreover, the direct use of amine hydrogen chloride salt and excess base were also successful, delivering the fluoride-bearing product **3bh** in good yield. Amines with functional groups, such as alkene and acetal, were well tolerated, delivering the desired products **3bk** and **3bl** in 81% and 96% yield, respectively. Interestingly, when aminoalcohol was used, chemoselective *N*-arylation occurred to produce an *N*-aryl amino alcohol **3bm** in 91% yield. The coupling reaction with tryptamine also resulted in the *N*-aryl product **3bn** with the nitrogen atom in the indole ring untouched. In addition to reactions with amines, the C-N coupling reaction with a sulfonamide also proceeded well. For instance, when methyl 4-iodobenzoate and *p*-toluenesulfonamide were subjected to standard conditions, the desired product **3io** was prepared in 90% yield. During the performance of C-N coupling reactions, we noticed that the photocatalyst was attracted to the surface of the magnetic stirrer (Figure S1, a-c). Then, we separated the CdS catalyst by simply removing the solution of crude product and then added Ni salt, aryl bromide, amine and DMA again to restart this C-N coupling reaction.[25] The CdS photocatalyst shows the same efficiency even after 10 cycles (Figure S1, a-c).

Inspired by the success of the C-N coupling reaction, we next chose to explore the heterogeneous C-O coupling reaction.[26] As highlighted in Scheme 3, a variety of functional groups on the benzene ring, such as cyano, ketone, ester and sulfone, in the para position were tolerated, giving corresponding products **5ca**-**5ja** in 92-96% yields. Variation in substituent position was also compatible

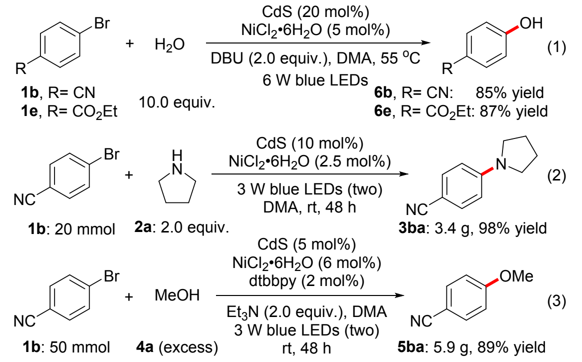
View Article Online
DOI: 10.1039/C9CC00987F

with the dual catalyst system, delivering the desired products **5ka** and **5la** in high yields. Naphthyl and quinolyl ether, **5ma** and **5na,** can also be produced in high yields under standard conditions. Given the great value of deuterium labeling in organic synthesis and the pharmaceutical industry,[27] we applied deuterated methanol in this C-O coupling reaction; the deuterium atom was incorporated into the product **5bb** with 70% yield (fully labelled methyl group). Moreover, many other alcohols, such as ethanol (**5bc**), *n*-pentanol (**5bd**), and fluoride-containing alcohol (**5be**) also reacted well with 4-bromobenzonitrile, delivering the desired products in 88-97% yields. The coupling reaction with isopropyl alcohol was also proven to be successful, albeit in a moderate yield (**5bh**, 54% yield). At the current stage, aryl bromides with electron-neutral and electron-rich substituents, as well as aniline, phenol and their analogs cannot participate in these C-N and C-O coupling reactions for unknown reasons. To our delight, brief condition optimization successfully provided the hydroxylated products **6b** and **6e** in high yields (eq. 1).[26] Different from previous reports, noble metal Ir-based photocatalysts[17a] and a special amino-containing bipyridine ligand[28] are not required in our case.



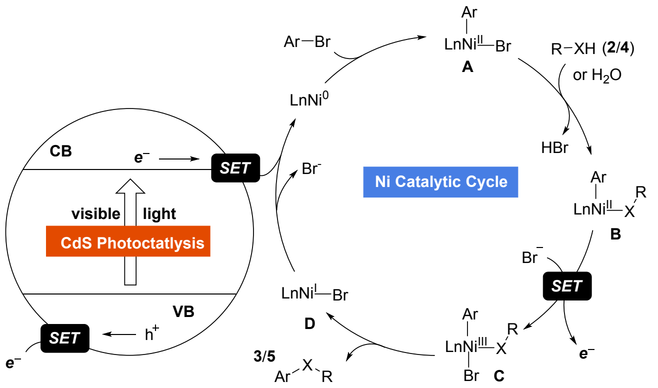
Reaction conditions: **1** (1.0 mmol), alcohol **2** (2.0 mL), CdS (0.05 mmol, 5 mol%), $NiCl_2•6H_2O$ (0.06 mmol, 6 mol%), dtbbpy (0.02 mmol, 2 mol%), Et_3N (2.0 mmol, 2.0 equiv.), and DMA (1.0 mL) under irradiation with 6 W blue LEDs; isolated yields. [b]Alcohol (5.0 equiv.) and DMA (3.0 mL) were used.

Scheme 3 Scope of the C-O coupling reaction



To emphasize the practicability of this heterogeneous catalysis system, we performed two scale-up reactions. As a result, the C-N coupling product can be achieved in 98% yield on a 20 mmol scale with half loading of catalysts, and the C-O coupling reaction can be scaled up to 50 mmol with 89% yield (eq. 2 and 3). Compared with traditional methods, this heterogeneous photoredox/Ni catalysis system offers an alternative and competitive choice featuring mild reaction conditions, easy operations and inexpensive catalysts.

Based on previous reports[16-18] and our experimental results, we proposed a plausible mechanism for the C-N and C-O coupling reactions of aryl bromides with amines, alcohols or water. As depicted in Scheme 4, oxidative addition of aryl bromides by a Ni(0) catalyst delivers an aryl Ni(II) species **A**, which is converted to another aryl Ni(II) intermediate **B** via ligand exchange with amines, alcohols or water. Meanwhile, heterogeneous photocatalyst CdS is excited by visible light. The oxidizing holes in the valence band (**VB**) of photoexcited CdS would abstract an electron from the Ni(II) species **B** to afford the Ni(III) species **C**, which is believed to be energetically favored to proceed with reductive elimination and produce the desired aryl amines, ethers and phenols. Finally, the conduction band (**CB**) of photoexcited CdS would reduce the Ni(I) to complex **D** to the active Ni(0) species by providing an electron, thus finishing the heterogeneous dual catalysis cycle.



Scheme 4 Proposed mechanism for the C-N/C-O coupling

In conclusion, we have developed practical C-N and C-O coupling reactions of aryl halides with amines and alcohols through heterogeneous visible light photoredox and nickel dual catalysis. This protocol represents an alternative and competitive method to prepare aryl amines and ethers, compared with a dual homogeneous Ir/Ni catalyst system. In this work, only readily available and much less expensive CdS and nickel salts are required and this heterogeneous photocatalyst can even be reused many times. We believe that this dual catalysis strategy utilizing cheap and recyclable heterogeneous photocatalysts and inexpensive transition metals would make organic synthesis more practical and sustainable for industrial production.

We are grateful to the National Science Foundation of China (No. 21822103, 21820102003, 21772052, 21772053, 21572074 and 21472057), the Program of Introducing Talents of Discipline to Universities of China (111 Program, B17019), the Natural Science Foundation of Hubei Province (2017AHB047) and the International Joint Research Center for Intelligent Biosensing Technology and Health for support of this research.

Notes and references

1. (a) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.* 2011, **40**, 102-113. (b) J. Xuan and W.-J. Xiao, *Angew. Chem. Int. Ed.,* 2012, **51**, 6828-6838. (c) D. M. Schultz and T.

View Article Online
DOI: 10.1039/C9CC00987F

P. Yoon, *Science,* 2014, **343**, 985-993. (d) L. Marzo, S. K. Pagire, O. Reiser, and B. König, *Angew. Chem., Int. Ed.,* 2018, **57**, 10034-10072.

2. For selected reviews on homogenous visible light photocatalysis with transition metal complexes, see: (a) C. K. Prier, D. A. Rankic, and D. W. C. MacMillan, *Chem. Rev.,* 2013, **113**, 5322-5363. With organic dyes, see: (b) N. A. Romero and D. A. Nicewicz, *Chem. Rev.,* 2016, **116**, 10075-10166.
3. For selected reviews on heterogeneous visible light photocatalysis with semiconductors, see: (a) M. Cherevatskaya, and B. König. *Russ. Chem. Rev.,* 2014, **83**, 183-195. (b) X. Lang, X. Chen, and J. Zhao, *Chem. Soc. Rev.,* 2014, *43*, 473-486. (c) J. Chen, J. Cen, X. Xu, and X. Li, *Catal. Sci. Technol.,* 2016, **6**, 349-362.
4. (a) I. T. Horváth and M. M. Kirchhoff, *Acc. Chem. Res.* 2002, **35**, 686-694. (b) I. T. Horváth and P. T. Anastas, *Chem. Rev.* 2007, **107**, 2169-2173.
5. (a) X. Chen and S. S. Mao, *Chem. Rev.,* 2007, **107**, 2891-1959. (b) R. M. Navarro Yerga, M. C. Álvarez-Galván, F. del Valle, J. A. Villoria de La Mano, and J. L. G. Fierro, *ChemSusChem.*, 2009, **2**, 471-485 (c) A. Kudo and Y. Miseki, *Chem. Soc. Rev.,* 2009, **38**, 253-278.
6. M. Cherevatskaya, M. Neumann, S. Füldner, C. Harlander, S. Kümmel, S. Dankesreiter, A. Pfitzner, K. Zeitler, and B. König, *Angew. Chem. Int. Ed.,* 2012, **51**, 4062-4066.
7. J. A. Caputo, L. C. Frenette, N. Zhao, K. L. Sowers, T. D. Krauss, and D. J. Weix, *J. Am. Chem. Soc.*, 2017, **139**, 4250-4253.
8. (a) M. N. Hopkinson, B. Sahoo, J.-L. Li, and F. Glorius, *Chem. Eur. J.,* 2014, **20**, 3874-3886. (b) K. L. Skubi, T. R. Blum, and T. P. Yoon, *Chem. Rev.,* 2016, **116**, 10035-10074.
9. (a) F. Parrino, A. Ramakrishnan, and H. Kisch, *Angew. Chem.Int. Ed.,* 2008, **47**, 7107-7109. (b) X. Chen, J. Zhang, X. Fu, M. Antonietti, and X. Wang, *J. Am. Chem. Soc.* 2009, **131**, 11658-11659. (c) Y. Zhang, N. Zhang, Z.-R. Tang, and Y.-J. Xu, *Chem. Sci.,* 2012, **3**, 2812-2822; (d) V. T. Bhat, P. A. Duspara, S. Seo, N. S. B. A. Bakar, and M. F. Greaney, *Chem. Commun.,* 2015, **51**, 4383-4385.
10. For selected examples on Quantum Dots catalyzed organic reactions, see: (a) X.-B. Li, Z.-J. Li, Y.-J. Gao, Q.-Y. Meng, S. Yu, R.-G. Weiss, C.-H. Tung, and L.-Z. Wu, *Angew. Chem. Int. Ed.,* 2014, **53**, 2085-2089. (b) L.-M. Zhao, Q.-Y. Meng, X.-B. Fan, C. Ye, X.-B. Li, B. Chen, V. Ramamurthy, C.-H. Tung, and L.-Z. Wu, *Angew. Chem. Int. Ed.,* 2017, **56**, 3020-3024. (c) Z. Zhang, K. Edme, S. Lian, E. A. Weiss, *J. Am. Chem. Soc.* 2017, **139**, 4246-4249.
11. (a) S. A. Lawrence, Amines: Synthesis Properties and Applications (Cambridge Univ. Press, Cambridge, 2004); b) A. Ricci, Amino Group Chemistry: From Synthesis to the Life Sciences (Wiley-VCH, Weinheim, 2008).
12. (a) H. Fuwa, Total Synthesis of Marine Polycyclic Ether Natural Products. In Toxins and Biologically Active Compounds from Microalgae, Volume 1; CRC Press: Boca Raton, FL, 2014, 348. (b) E. N. Pitsinos, V. P. Vidali, and E. A. Couladouros, *Eur. J. Org. Chem.,* 2011, 1207-1222. (c) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, and N. Winssinger, *Angew. Chem. Int. Ed.,* 1999, **38**, 2096-2152.
13. (a) J. P. Wolfe, S. Wagaw, J. - F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.,* 1998, **31**, 805-818. (b) J. F. Hartwig, *Acc. Chem. Res.,* 1998, **31**, 852-860. (c) P. Ruiz-Castillo, and S. L. Buchwald, *Chem. Rev.,* 2016, **116**, 12564-12649.
14. (a) S. V. Ley, and A. W. Thomas, *Angew. Chem. Int. Ed.,* 2003, **42**, 5400-5449 (b) C. Sambiagio, S. P. Marsden, A. J. Blacker, and P. C. McGowan, *Chem. Soc. Rev.,* 2014, **43**, 3525-3550.
15. For related reviews, see: (a) M. D. Levin, S. Kim, and F. D. Toste, *ACS Cent. Sci.,* 2016, **2**, 293-301. (b) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052. For two pioneering works on dual photoredox/Ni catalysis, see: (c) J. C. Tellis, D. N. Primer, and G. A. Molander, *Science,* 2014, **345**, 433-436. (d) Z. Zuo, D. T. Ahneman, J. Chu, J. A. Terrett, A. G. Doyle, and D. W. C. MacMillan, *Science,* 2014, **345**, 437-440.
16. (a) S. Z. Tasker, and T. F. Jamison, *J. Am. Chem. Soc.,* 2015, **137**, 9531-9534. (b) E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, and D. W. C. MacMillan, *Science*, 2016, **353**, 279-283. (c) M. S. Oderinde, N. H. Jones, A. Juneau, M. Frenette, B. Aquila, S. Tentarelli, D. W. Robbins, and J. W. Johannes, *Angew. Chem. Int. Ed.,* 2016, **55**, 13219-13223. (d) T. Kim, S. J. McCarver, C. Lee, and D. W. C. MacMillan, *Angew. Chem., Int. Ed.,* 2018, **57**, 3488-3492. (e) Y. Du, R. M. Pearson, C. H. Lim, S. M. Sartor, M. D. Ryan, H. S. Yang, N. H. Damrauer and G. M. Miyake, *Chem.–Eur.J.*, 2017, **23**, 10962-10968. (f) Z. Huang, K. Xie, G. Meng, J. Ma, D. Xue and J. Yang, CN108409618, 2018, A. For the nickel catalyzed C-N coupling with near UV light, see: (g) C. H. Lim, M. Kudisch, B. Liu, and G. M. Miyake, *J. Am. Chem. Soc.*, 2018, **140**, 7667-7673. For the C-N coupling with dual nickel/electrochemical catalysis, see: (h) C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan and P. S. Baran, Angew. Chem., Int. Ed., 2017, 56, 13088-13093.
17. (a) J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff, and D. W. C. MacMillan, *Nature*, 2015, **524**, 330-334. (b) E. R. Welin, C. Le, D. M. Arias-Rotondo, J. K. McCusker, and D. W. C. MacMillan, *Science*, 2017, **355**, 380-385.
18. Z. Chai, T.-T. Zeng, Q. Li, L.-Q. Lu, W.-J. Xiao, and D. Xu, *J. Am. Chem. Soc.,* 2016, **138**, 10128-10131.
19. (a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, and W.-J. Xiao, *Acc. Chem. Res.,* 2016, **49**, 1911−1923. (b) W. Ding, L.-Q. Lu, Q.-Q. Zhou, Y. Wei, J.-R. Chen, and W.-J. Xiao, *J. Am. Chem. Soc.,* 2017, **139**, 63-66. (c) Y.-Y. Liu, X.-Y. Yu, J.-R. Chen, M.-M. Qiao, X. Qi, D.-Q. Shi, and W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2017, **56**, 9527-9531.
20. (a) L.-Q. Lu, T.-R. Li, Q. Wang, and W.-J. Xiao, *Chem. Soc. Rev.,* 2017, **46**, 4135-4149. (b) M.-M. Li, Y. Wei, J. Liu, H.-W. Chen, L.-Q. Lu, and W.-J. Xiao, *J. Am. Chem. Soc.*, 2017, **139**, 14707-14713.
21. (a) T. Mitkina, C. Stanglmair, W. Setzer, M. Gruber, H. Kisch, and B. König, *Org. Biomol. Chem.,* 2012, **10**, 3556-3561. (b) W. Zhao, C. Liu, L. Cao, X. Yin, H. Xu, B. Zhang, *RSC Adv.,* 2013, **3**, 22944-22948.
22. N. Zhang, Y. Zhang, X. Pan, X. Fu, S. Liu, and Y.-J. Xu, *J. Phys. Chem. C,* 2011, **115**, 23501-23511.
23. G. Han, Y.-H. Jin, R. A. Burgess, N. E. Dickenson, X.-M. Cao, and Y. Sun, *J. Am. Chem. Soc.*, 2017, **139**, 15584-15587.
24. Price of $NiCl_2 \bullet 6H_2O$ vs $NiCl_2 \bullet$glyme: 26.1 vs 473.8 CNY/g, Price of CdS vs 5.1 vs 10,296 CNY/g. data from Sigma-Aldrich.
25. Re-starting the C-N coupling reaction without addition of $NiCl_2 \bullet 6H_2O$ failed, indicating that the Ni catalyst is homogeneous in solution.
26. Please see the details of condition optimizations for C-O coupling reactions in the Supporting Information.
27. (a) B. Belleau, J. Burba, M. Pindell, and J. Reiffenstein, *Science*, 1961, **133**, 102-104. (b) T. G. Gant, *J. Med. Chem.,* 2014, **57**, 3595-3611. (c) A. Mullard, *Nat. Rev. Drug Discov.*, 2016, **15**, 219-221.
28. L. Yang, Z. Huang, G. Li, W. Zhang, R. Cao, C. Wang, J. Xiao, and D. Xue, *Angew. Chem. Int. Ed.*, 2018, **57**, 1968-1972.

View Article Online
DOI: 10.1039/C9CC00987F

Table of Contents Entry