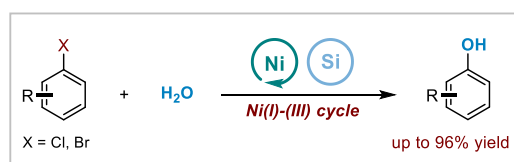


Ni(I)-Catalyzed Hydroxylation of Aryl Halides with Water under Thermal Catalysis

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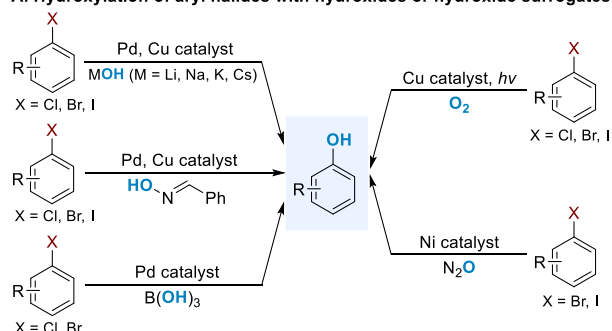
ABSTRACT: Although the nickel-catalyzed photochemical hydroxylation of aryl halides with water as the nucleophile has been studied, the hydroxylation with water under light-free conditions have not received attention. In this work, a highly effective hydroxylation of (hetero)aryl halides with water via Ni catalysis promoted by PhSiH₃ under thermal catalysis is reported. This methodology enables the hydroxylation of less-active aryl chlorides and aryl bromides with various functionalities, providing an efficient tool for the synthesis of diverse multifunctional pharmaceutically phenols and polyphenols, some of which are proven challenging to be synthesized using literature methods. Mechanism studies demonstrated that the addition of PhSiH₃ led to the formation of active Ni(I) species, which catalyze the subsequent reaction via a Ni(I)-Ni(III) cycle.

Phenols and their derivatives are important motifs founded in natural products, agrochemicals, pharmaceuticals and materials, which also are versatile intermediates for further transformation.¹ Although classic methods have been achieved for the synthesis of phenols,² one of the most valuable strategy is transition-metals-catalyzed hydroxylation of (hetero)aryl halides due to the abundance of aryl halides.³ Among them, the coupling reactions of aryl halides with alkali metal hydroxides (MOH) by Pd⁴ and Cu⁵ catalysis is successfully developed (Scheme 1, A). However, the requirement of strong inorganic bases or metal alkoxides caused the incompatibility of base-sensitive functional groups such as cyano, ester, and carbonyl groups.⁶ To bypass these limitations, the hydroxylation with benzaloxime,⁷ boric acid,⁸ O₂⁹ or N₂O¹⁰ as hydroxide surrogate by Pd, Cu and Ni catalysis have been developed recently (Scheme 1, A).

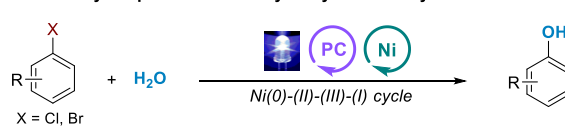
Different from the above approach, the use of water as the “OH” source and soluble organic amine as base catalyzed by earth-abundant metals is a novel strategy for the hydroxylation of aryl halides.^{11,12} Recently, MacMillan,¹³ Zhang¹⁴ and our group¹⁵ reported photoredox nickel-catalyzed hydroxylation of aryl halides with water using iridium complexes, boron-dipyrromethene derivatives (BODIPY), and heterogeneous organic semiconductor graphitic carbon nitride (g-C₃N₄) as photocatalyst respectively, which was considered to be a major advancement in this field (Scheme 1, B). Excited photocatalysts are proposed to generate Ni(III) intermediates to facilitate kinetically challenging reductive elimination of

Scheme 1. Transition-metals catalyzed hydroxylation of aryl halides

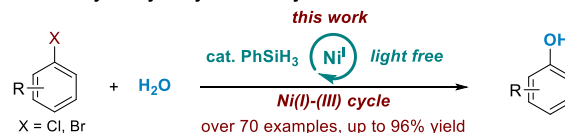
A. Hydroxylation of aryl halides with hydroxides or hydroxide surrogates



B. Ni-catalyzed photochemical hydroxylation of aryl halides with water



C. Ni-catalyzed hydroxylation of aryl halides with water via thermal catalysis

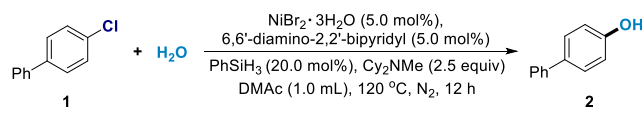


C–O bonds via a Ni(0/II/III/I) catalytic cycle in these reactions. Recent mechanistic studies on photoredox-nickel-catalyzed C–O coupling reactions have proved that Ni(I) species could be generated by the reduction of Ni(II) complex by photo-catalysts¹⁶ or via light-induced homo-cleavage of the excited Ni(II) complexes without external photosensitizers,¹⁷ which then catalyzes the reaction via Ni(I)-Ni(III) cycle. These photo-nickel synergistic system deliver a prevailing tool for further development of Ni(I) catalyzed coupling reactions.

Inspired by the mechanistic studies, it is of great interest for the development of C–O coupling reactions under light-free conditions. This means that the use of light and photocatalysts would be avoided, while maintaining all the benefits of photoredox cross-coupling systems. Recently, Nocera reported Ni-catalyzed amination, etherification and esterification of aryl bromides under light-free conditions, providing new ideas for the development of C–O coupling reactions under light-free conditions.¹⁸ However, the substrates are limited to aryl bromines, and studies on coupling reactions involving more challenging aryl chlorides have not been reported. Furthermore, no experimental data on the presence of Ni(I) species are reported. Herein, we report a highly effective hydroxylation of less-active aryl chlorides and aryl bromides with water by Ni catalysis promoted by PhSiH₃ under thermal reaction conditions (Scheme 1, C). Mechanism studies verifies the formation of Ni(I) species by the reaction of Ni(II) complex with PhSiH₃, which catalyzes the subsequent C–O coupling reactions via a Ni(I)-Ni(III) cycle.

In our initial study, the hydroxylation of 4-chlorobiphenyl (**1**) with H₂O was chosen as the model reaction. As summarized in Table 1, examination of Ni salts, bases and solvents demonstrated the

Table 1. Optimization of reaction conditions^a

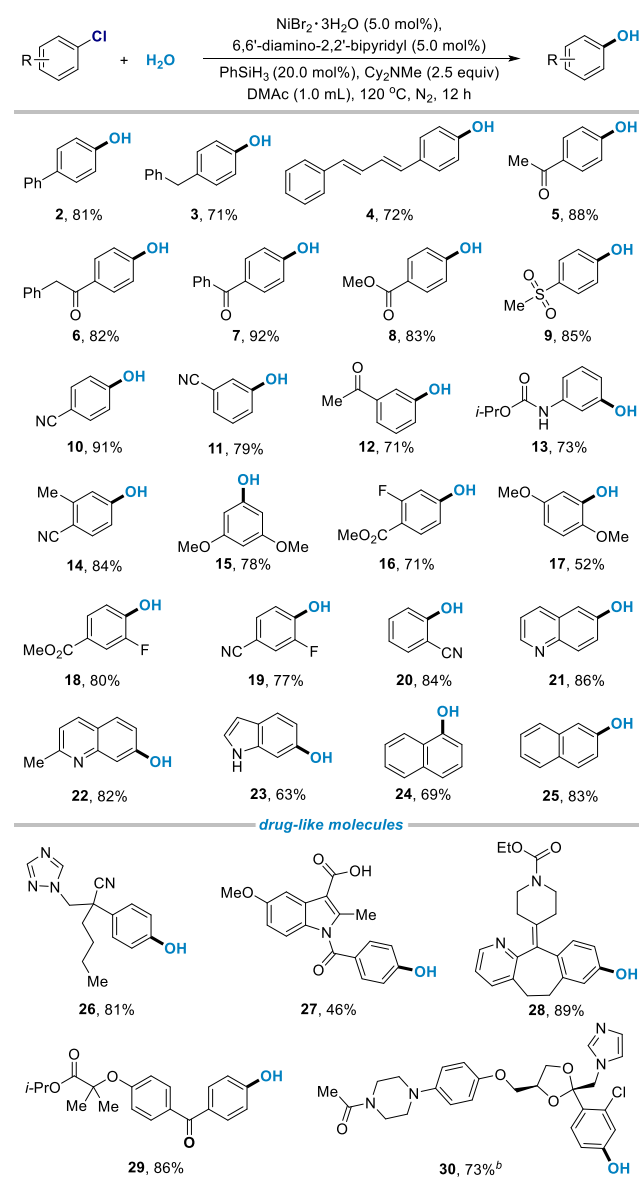


Entry	Deviation from the standard conditions	Yield of 2 (%)
1	Standard conditions	81
2	Zn instead of PhSiH ₃	32
3	No PhSiH ₃	0
4	NiCl ₂ ·6H ₂ O instead of NiBr ₂ ·3H ₂ O	63
5	NiI ₂ instead of NiBr ₂ ·3H ₂ O	72
6	Ni(OAc) ₂ instead of NiBr ₂ ·3H ₂ O	58
7	Et ₃ N instead of Cy ₂ NMe	54
8	DIPEA instead of Cy ₂ NMe	62
9	No NiBr ₂ ·3H ₂ O	0
10	No ligand	0
11	No base	0
12	Air instead of N ₂	0

^aStandard conditions: 4-chlorobiphenyl (0.5 mmol, 1.0 equiv), H₂O (50 equiv), NiBr₂·3H₂O (5.0 mol%), 6,6'-diamino-2,2'-bipyridyl (5.0 mol%), Cy₂NMe (2.5 equiv), PhSiH₃ (20.0 mol%), DMAc (1.0 mL), N₂, 120 °C, 12 h. Isolated yields are given. Cy₂NMe = *N,N*-dicyclohexylmethylamine, DMAc = *N,N*-dimethylacetamide, Et₃N = triethylamine, DIPEA = *N,N*-diisopropylethylamine.

combination of NiBr₂·3H₂O, 6,6'-diamino-2,2'-bipyridyl as the ligand and *N,N*-dicyclohexylmethylamine (Cy₂NMe) as the base in *N,N*-dimethylacetamide (DMAc) at 120 °C could give the best result, delivering the product with 81% isolated yield (entry 1).¹⁹ Reductants were found to play a crucial role in this reaction. Catalytic amount of PhSiH₃ exhibits the best efficiency, while other commonly used metal reductants such as Zn²⁰ resulted in low yields (entry 2). In the absence of PhSiH₃, there is no reaction (entry 3). In particular, among all the ligands examined,¹⁹ only 6,6'-diamino-2,2'-bipyridyl could give the desired products. The amine group on the bipyridine would facilitate the generation of the hydroxide nucleophile *in situ* from the coordinated water via hydrogen bonding and deprotonation.²¹ Although other Ni catalysts, including NiCl₂·6H₂O, NiI₂, Ni(OAc)₂ could also catalyze the reaction, but with low yields (entries 4-6). The choice of base also impacted on the reaction, the mild Cy₂NMe promoted the reaction significantly better than other

Scheme 2. Hydroxylation of aryl chlorides^a

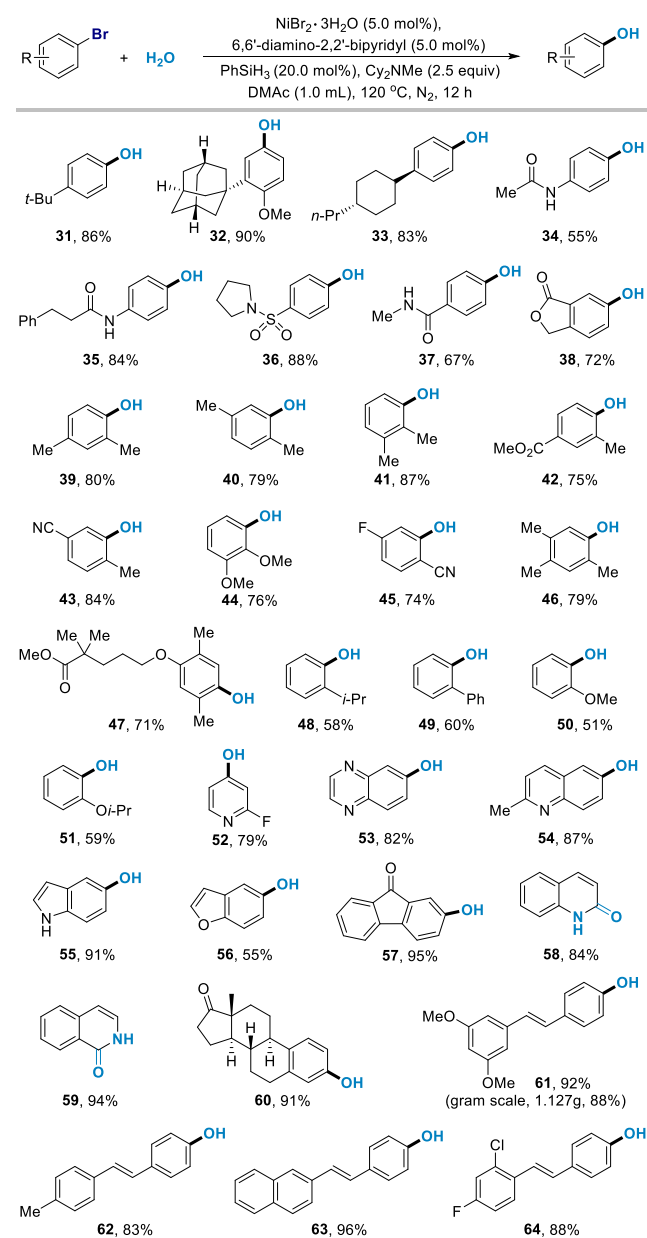


^aIsolated yields are given. For details, see SI. ^bH₂O (1.0 mL), Cy₂NMe (5.0 equiv), DMAc (3.0 mL), 24 h.

bases examined (entries 7-8). Control experiments demonstrate that the reaction could not proceed in the absence of nickel catalyst, ligand and base (entries 9-11). Furthermore, the reaction is deactivated under the presence of air (entry 12).

With the optimized reaction conditions in hand, the scope of cheaper but more challenging aryl chlorides were then investigated. As summarized in Scheme 2, aryl chlorides with a variety of functional groups reacted efficiently with water in this protocol, affording the desired phenols with high yields generally. For electron-neutral aryl chlorides, the corresponding phenols were obtained in good yields (2-4). Aryl chlorides with electron withdrawing substituent groups in *para*-position worked well, affording the desired products with good to excellent yields (5-10). Unfortunately, electron-rich aryl chloride such as *p*-MeO-substituted chlorobenzene was not suitable in this reaction. The *meta*-substituted aryl chlorides were also applicable (11-13) for this reaction. Disubstituted aryl chlorides

Scheme 3. Hydroxylation of aryl bromides^a



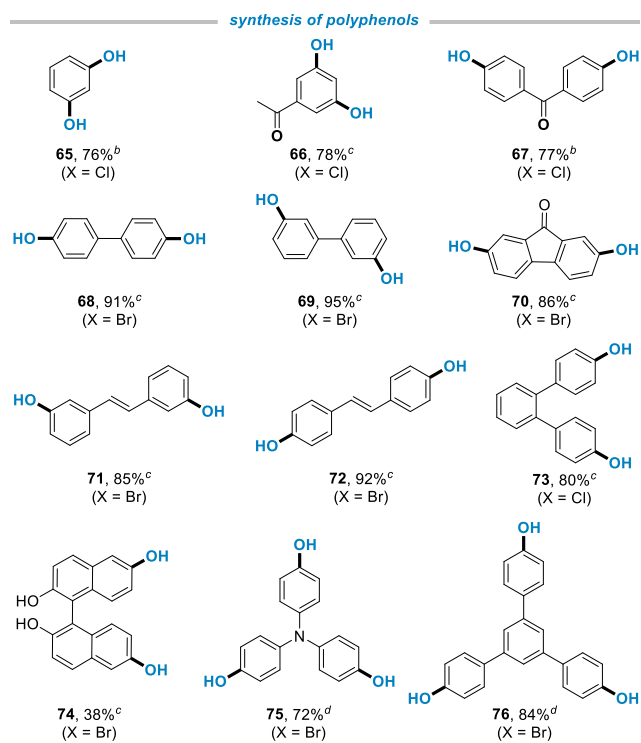
^aIsolated yields are given. For details, see SI.

bearing either electron-donating or electron-withdrawing groups were all suitable, providing the phenols with good yields (14-19). Notably, aryl chlorides with substitutes in *ortho*-position successfully coupled with water, delivering the desired phenols with high yields (17-20). Notably, these *ortho*-substituted substrates failed to provide the desired products under photoredox nickel-catalyzed hydroxylation, showcasing the good adaptability of steric hindrance of substrates in this reaction. Moreover, the use of a weak organic base enabled aryl chlorides with base-sensitive functional groups to react with water efficiently, delivering the phenols containing cyano, ketone, and ester group with high yields (8, 10-11, 14, 16, 18-20).²² The hydroxylation of heteroaryl chlorides containing quinoline (21, 22) and indole (23) proceed smoothly, affording the valuable phenols important in medicinal chemistry with 63-91% yields. Similarly, aryl chlorides with a fused ring were hydroxylated to give products (24, 25) in good yields. Furthermore, this methodology could be applied to the late-stage modification of drug-like molecules. As shown in Scheme 2, the corresponding chlorinated compounds from Chlorpropham (13), Myclobutanil (26), Indometacin (27), Loratadine (28), Fenofibrate (29), Ketoconazole (30) were all compatible under standard conditions, delivering the desired phenols with good to excellent yields. Therefore, this method allows easy access to phenols important in drug discovery, also providing a potential tool toward the modification of existing drug and synthesis of new drug molecules.

Aryl bromides have also been successfully applied to this hydroxylation. As summarized in Scheme 3, aryl bromides with a variety of functional groups reacted efficiently with water, exhibiting a wide substrate scope and a broad functional group compatibility. For electron-neutral, electron-rich and electron-deficient aryl bromides, the desired phenols were obtained with high yields in general (31-38). Significantly, the *ortho*-substituted aryl bromides with electron-donating or -withdrawing groups were all compatible, affording the phenols with -Me, -OMe, -CN, -*i*-Pr, -Ph and -*Oi*-Pr in the *ortho*-position (39-51) in good yields. These examples again showcased good adaptability to steric hindrance for substrates of this PhSiH_3 -promoted C-O coupling. Same as sterically hindered aryl chlorides, these *ortho*-substituted aryl bromides could not afford the desired products under photoredox nickel-catalyzed hydroxylation. In addition, various (hetero)aryl bromides containing pyridine, quinoxaline, quinoline, indole, benzofuran and fluorenone could couple efficiently with water, delivering the phenols with good to excellent yields (52-57). For 2-bromoquinoline and 1-bromoisoquinoline, the desired products existed as the lactam form (58, 59). To further demonstrate the application of this new hydroxylation, pterostilbene (61) and the derivatives of resveratrol (62-64), an important class of natural antioxidants and their derivatives, were prepared with this method in high yields. Furthermore, pterostilbene could be prepared at a gram scale (1.12 g, 88%), showcasing a possibility for the application of this reaction to the preparation of bioactive molecules.

To further demonstrate the applicability of this new hydroxylation, the application of this method in the synthesis of polyphenol was investigated (Scheme 4).²³ The dihydroxylated products (65-74) could be obtained with high yields under optimized reaction conditions.²⁴ It is worth noting that *trans*-stilbene derivatives, an important class of natural products with various biological activities, could be synthesized with this method.²⁵ Moreover, triple substituted aryl bromides were also well tolerated to this reaction, giving

Scheme 4. Synthesis of polyphenols^a

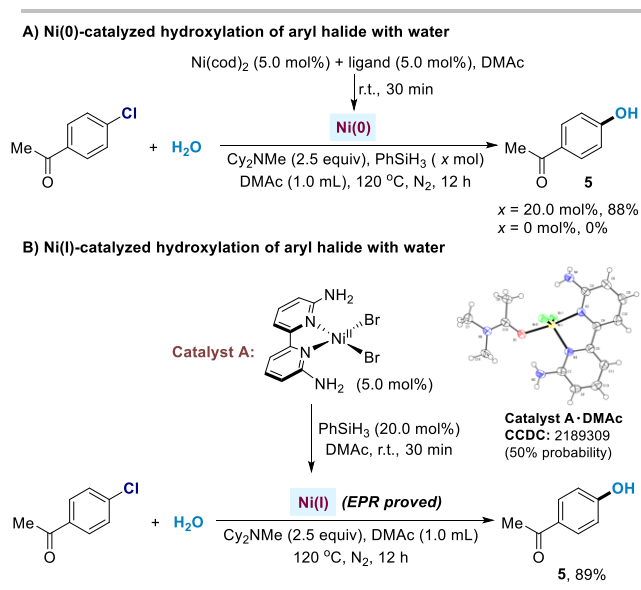


^aIsolated yields are given. ^bNiBr₂·3H₂O (10.0 mol%), 6,6'-diamino-2,2'-bipyridyl (10 mol%), H₂O (1.0 mL), Cy₂NMe (5.0 equiv), PhSiH₃ (40.0 mol%), DMAc (2.0 mL). ^cH₂O (1.0 mL), Cy₂NMe (5.0 equiv), DMAc (3.0 mL), 24 h. ^dH₂O (1.5 mL), Cy₂NMe (7.5 equiv), DMAc (4.5 mL).

triphenols with good yields (**75**, **76**). Substrate with both a bromide and chloride was converted to a mixture of phenols in this reaction conditions. The above successful examples fully demonstrates the great potential of this method in synthetic chemistry.

Preliminary mechanism studies were conducted to clarify the active Ni species in this catalytic system. As shown in Scheme 5, when

Scheme 5. Reactions aimed to probe the reaction mechanism



Ni(cod)₂ instead of NiBr₂·3H₂O was used as the catalyst under the standard conditions, the reaction proceeded with high yields. However, when PhSiH₃ was omitted, the desired product was not observed (Scheme 5, A). Next, the catalyst **A** (prepared from NiBr₂·3H₂O and 6,6'-diamino-2,2'-bipyridyl) and PhSiH₃ were stirred at room temperature for 30 minutes in the absence of substrates, and then stopped. Following introducing the substrate and carrying out the reaction for 12 hours, the product phenol was obtained with 89% yield (Scheme 5, B). Electron paramagnetic resonance (EPR) analysis of the mixture obtained from the above reaction of catalyst **A** with PhSiH₃ (in the absence of substrates) revealed a signal with $g_{zz} = 2.27$, $g_{yy} = 2.17$, $g_{xx} = 2.07$ (Figure 1),¹⁹ which indicates the formation of a Ni(I) species.²⁶ The above experiments indicate that the hydroxylation reaction would involve Ni(I) species and PhSiH₃ was required to achieve high yields.

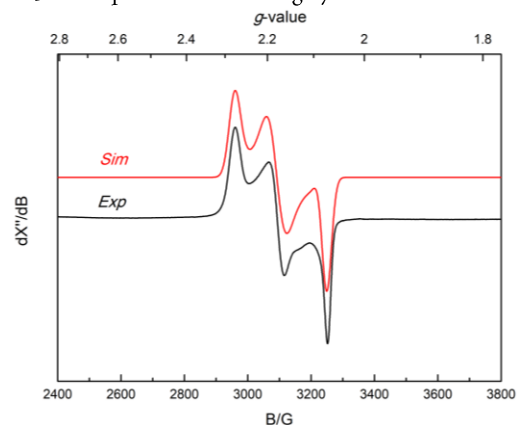
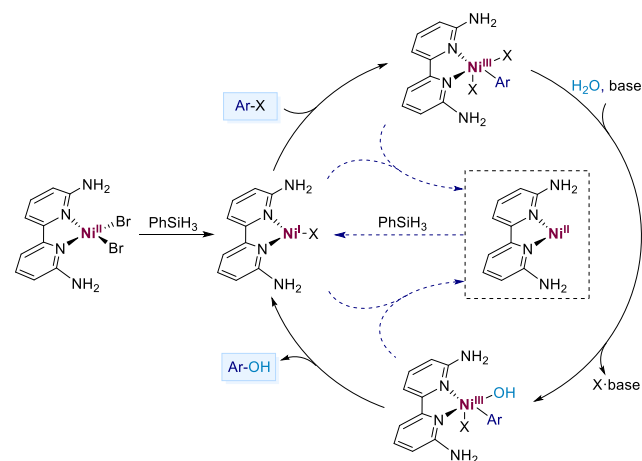


Figure 1. EPR spectrum of Ni(I) complex generated *in-situ* from Ni catalyst **A** with PhSiH₃.

Based on these results and recent research,^{16,18,26} this PhSiH₃-promoted catalytic coupling reaction was depicted in Scheme 6. First, the Ni(I) species was generated by the reduction of catalyst **A** with PhSiH₃. Then, aryl halides undergo an oxidative addition with Ni(I) complex to form Ni(III)-Ar intermediates. Amino moiety of the ligand acts as a base, facilitating the generation of the hydroxide nucleophile from the coordinated water. Then, Ni(III)-OH intermediates release the product phenol, while regenerating Ni(I) species, thus fulfilling the catalytic cycle. In addition, due to the formation of off-cycle catalytically inactive Ni(II) from the comproportionation of Ni(III) and Ni(I) species,^{16b} this species could be reduced to Ni(I)

Scheme 6. Proposed mechanism for hydroxylation reaction



again by PhSiH₃ to participate in the coupling reaction.

In summary, we have developed a catalytic hydroxylation of aryl halides with water via a Ni(I)-Ni(III) cycle under thermal reaction conditions. PhSiH₃ was proved to play an important role to promote the cross-coupling reaction. This method affords a valuable tool for the efficient synthesis of challenging diverse multifunctional phenols and polyphenols. Mechanism studies demonstrated that the addition of PhSiH₃ led to the formation of active Ni(I) species, which then catalyze the subsequent reaction via a Ni(I)-Ni(III) cycle.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett>.

Experimental details, characterization data, and NMR spectra of isolated compounds (PDF)

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Notes

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REFERENCES

- (1) Rappoport, Z. *The Chemistry of Phenols*, Wiley-VCH, Weinheim, **2003**.
- (2) For a review on manufacturing phenol, see: (a) Arpe, H.-J. *Industrial Organic Chemistry*, 5th ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2010**, pp 359-374; for S_NAr reactions of activated aryl halides to form phenols. (b) Feldman, D.; Segal-Lew, D.; Rabinovitz, M. Nucleophilic aromatic substitution by hydroxide ion under phase-transfer catalysis conditions; fluorine displacement in polyfluorobenzene derivatives. *J. Org. Chem.* **1991**, *56*, 7350-7354. (c) Rogers, J. F.; Green, D. M. Mild conversion of electron deficient aryl fluorides to phenols using 2-(methylsulfonyl)ethanol. *Tetrahedron Lett.* **2002**, *43*, 3585-3587. (d) Fier, P. S.; Maloney, K. M. Direct conversion of haloarenes to phenols under mild, transition-metal-free conditions. *Org. Lett.* **2016**, *18*, 2244-2247.
- (3) For reviews on metal-catalyzed hydroxylation of (hetero)aryl halides, see: (a) Willis, M. C. Palladium-catalyzed coupling of ammonia and hydroxide with aryl halides: The direct synthesis of primary anilines and phenols. *Angew. Chem. Int. Ed.* **2007**, *46*, 3402-3404. (b) Alonso, D. A.; Najera, C.; Pastor, I. M.; Yus, M. Transition-metal-catalyzed synthesis of hydroxylated arenes. *Chem. Eur. J.* **2010**, *16*, 5274-5284. (c) Enthaler, S.; Company, A. Palladium-catalysed hydroxylation and alkoxylation. *Chem. Soc. Rev.* **2011**, *40*, 4912-4924.
- (4) For Cu-catalyzed hydroxylation, see: (a) Tlili, A.; Xia, N.; Monnier, F.; Taillefer, M. A very simple copper-catalyzed synthesis of phenols employing hydroxide salts. *Angew. Chem. Int. Ed.* **2009**, *48*, 8725-8728. (b) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. Synthesis of phenol, aromatic ether, and benzofuran derivatives by copper-catalyzed hydroxylation of aryl halides. *Angew. Chem. Int. Ed.* **2009**, *48*, 8729-8732. (c) Yang, D.; Fu, H. A simple and practical copper-catalyzed approach to substituted phenols from aryl halides by using water as the solvent. *Chem. Eur. J.* **2010**, *16*, 2366-2370. (d) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. Lithium pipecolinate as a facile and efficient ligand for copper-catalyzed hydroxylation of aryl halides in water. *Chem. Comm.* **2010**, *46*, 4767-4769. (e) Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. Highly efficient synthesis of phenols by copper-catalyzed hydroxylation of aryl iodides, bromides, and chlorides. *Org. Lett.* **2011**, *13*, 4340-4343. (f) Thakur, K. G.; Sekar, G. D-Glucose as green

- ligand for selective copper-catalyzed phenol synthesis from aryl halides with an easy catalyst removal. *Chem. Comm.* **2011**, 47, 6692-6694. (g) Jia, J.; Jiang, C.; Zhang, X.; Jiang, Y.; Ma, D. CuI-catalyzed hydroxylation of aryl bromides under the assistance of 5-bromo-2-(1H-imidazol-2-yl)pyridine and related ligands. *Tetrahedron Lett.* **2011**, 52, 5593-5595. (h) Xiao, Y.; Xu, Y.; Cheon, H. S.; Chae, J. Copper(II)-catalyzed hydroxylation of aryl halides using glycolic acid as a ligand. *J. Org. Chem.* **2013**, 78, 5804-5809. (i) Ding, G.; Han, H.; Jiang, T.; Wu, T.; Han, B. Heterogeneous copper-catalyzed hydroxylation of aryl iodides under air conditions. *Chem. Comm.* **2014**, 50, 9072-9075. (j) Wang, Y.; Zhou, C.; Wang, R. Copper-catalyzed hydroxylation of aryl halides: Efficient synthesis of phenols, alkyl aryl ethers and benzofuran derivatives in neat water. *Green Chem.* **2015**, 17, 3910-3915. (k) Xia, S.; Gan, L.; Wang, K.; Li, Z.; Ma, D. Copper-catalyzed hydroxylation of (hetero)aryl halides under mild conditions. *J. Am. Chem. Soc.* **2016**, 138, 13493-13496.
- (5) For Pd-catalyzed hydroxylation, see: (a) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. The selective reaction of aryl halides with KOH: Synthesis of phenols, aromatic ethers, and benzofurans. *J. Am. Chem. Soc.* **2006**, 128, 10694-10695. (b) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. Practical imidazole-based phosphine ligands for selective palladium-catalyzed hydroxylation of aryl halides. *Angew. Chem. Int. Ed.* **2009**, 48, 918-921. (c) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. Palladium-catalyzed hydroxylation of aryl halides under ambient conditions. *Angew. Chem. Int. Ed.* **2009**, 48, 7595-7599. (d) Dumrath, A.; Wu, X.; Neumann, H.; Spannenberg, A.; Jackstell, R.; Beller, M. Recyclable catalysts for Palladium-catalyzed C–O coupling reactions, Buchwald–Hartwig aminations, and Sonogashira reactions. *Angew. Chem. Int. Ed.* **2010**, 49, 8988-8992. (e) Yu, C.-W.; Chen, G. S.; Huang, C.-W.; Chern, J.-W. Efficient microwave-assisted Pd-catalyzed hydroxylation of aryl chlorides in the presence of carbonate. *Org. Lett.* **2012**, 14, 3688-3691. (f) Lavery, C. B.; Rottaloria, N. L.; McDonald, R.; Stradiotto, M. Pd₃dba₃/bippphos: A robust catalyst system for the hydroxylation of aryl halides with broad substrate scope. *Adv. Synth. Catal.* **2013**, 355, 981-987. (g) Santanilla, A. B.; Christensen, M.; Campeau, L. C.; Davies, I. W.; Dreher, S. D. P₂Et Phosphazene: A mild, functional group tolerant base for soluble, room temperature Pd-catalyzed C–N, C–O, and C–C cross-coupling reactions. *Org. Lett.* **2015**, 17, 3370-3373.
- (6) (a) Mann, G.; Hartwig, J. F. Palladium alkoxides: Potential intermediacy in catalytic amination, reductive elimination of ethers, and catalytic etheration. Comments on alcohol elimination from Ir(III). *J. Am. Chem. Soc.* **1996**, 118, 13109-13110. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. Palladium-catalyzed C–O coupling involving unactivated aryl halides. Sterically induced reductive elimination to form the C–O bond in diaryl ethers. *J. Am. Chem. Soc.* **1999**, 121, 3224-3225.
- (7) (a) Fier, P. S.; Maloney, K. M. Synthesis of complex phenols enabled by a rationally designed hydroxide surrogate. *Angew. Chem. Int. Ed.* **2017**, 56, 4478-4482. (b) Fier, P. S.; Maloney, K. M. Reagent design and ligand evolution for the development of a mild Copper-catalyzed hydroxylation reaction. *Org. Lett.* **2017**, 19, 3033-3036.
- (8) Song, Z.-Q.; Wang, D.-H. Palladium-catalyzed hydroxylation of aryl halides with boric acid. *Org. Lett.* **2020**, 22, 8470-8474.
- (9) Zhang, X.; Wu, G.; Gao, W.; Ding, J.; Huang, X.; Liu, M.; Wu, H. Synergistic photo-copper-catalyzed hydroxylation of (hetero)aryl halides with molecular oxygen. *Org. Lett.* **2018**, 20, 708-711.
- (10) Vaillant, F. L.; Calbet, A. M.; González-Pelayo, S.; Reijerse, E. J.; Ni, S.; Busch, J.; Cornella, J. Catalytic synthesis of phenols with nitrous oxide. *Nature* **2022**, 604, 677-683.
- (11) For photocatalytic direct hydroxylation of arenes with water, see: Zheng, Y.-W.; Chen, B.; Ye, P.; Feng, K.; Wang, W.; Meng, Q.-Y.; Wu, L.-Z.; Tung, C.-H. Photocatalytic hydrogen-evolution cross-couplings: Benzene C–H amination and hydroxylation. *J. Am. Chem. Soc.* **2016**, 138, 10080-10083.
- (12) Yang, L. Xue, D. Transition-metal-catalyzed hydroxylation reaction of aryl halide for the synthesis of phenols. *Synlett* **2021**, 32, 1891-1896.
- (13) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **2015**, 524, 330-334. (Two example with medium yields of phenols).
- (14) Wang, K.; Tong, M.; Yang, Y.; Zhang, B.; Liu, H.; Li, H.; Zhang, F. Visible light-catalytic hydroxylation of aryl halides with water to phenols by carbon nitride and nickel complex cooperative catalysis. *Green Chem.* **2020**, 22, 7417-7423.
- (15) Yang, L.; Huang, Z.; Li, G.; Zhang, W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. Synthesis of phenols: Organophotoredox/nickel dual catalytic hydroxylation of aryl halides with water. *Angew. Chem. Int. Ed.* **2018**, 57, 1968-1972.
- (16) (a) Shields, B. J.; Kudisch, B.; Scholes, G. D.; Doyle, A. G. Long-lived charge-transfer states of nickel(II) aryl halide complexes facilitate bimolecular photoinduced electron transfer. *J. Am. Chem. Soc.* **2018**, 140, 3035-3039. (b) Sun, R.; Qin, Y.; Ruccolo, S.; Schnedermann, C.; Costentin, C.; Nocera, D. G. Elucidation of a redox-mediated reaction cycle for nickel-catalyzed cross coupling. *J. Am. Chem. Soc.* **2019**, 141, 89-93. (c) Cagan, D. A.; Bím, D.; Silva, B.; Kazmierczak, N. P.; McNicholas, B. J.; Hadt, R. G. Elucidating the mechanism of excited-state bond homolysis in nickel-bipyridine photoredox catalysts. *J. Am. Chem. Soc.* **2022**, 144, 6516-6531. (d) Ting, S. I.; Williams, W. L.; Doyle, A. G. oxidative addition of aryl halides to a Ni(I)-bipyridine complex. *J. Am. Chem. Soc.* **2022**, 144, 5575-5582.
- (17) (a) Yang, L.; Lu, H.-H.; Lai, C.-H.; Li, G.; Zhang, W.; Cao, R.; Liu, F.; Wang, C.; Xiao, J.; Xue, D. Light-promoted nickel catalysis: Etherification of aryl electrophiles with alcohols catalyzed by a Ni^{II}-aryl complex. *Angew. Chem. Int. Ed.* **2020**, 59, 12714-12719. (b) Li, G.; Yang, L.; Liu, J.-J.; Zhang, W.; Cao, R.; Wang, C.; Zhang, Z.; Xiao, J.; Xue, D. Light-promoted C–N coupling of aryl halides with nitroarenes. *Angew. Chem. Int. Ed.* **2021**, 60, 5230-5234. (c) Song, G.; Yang, L.; Li, J.-S.; Tang, W.-J.; Zhang, W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. Chiral arylated amines via C–N coupling of chiral amines with aryl bromides promoted by light. *Angew. Chem. Int. Ed.* **2021**, 60, 21536-21542. (d) Abderrazak, Y.; Bhattacharyya, A.; Reiser, O.; Visible-light-induced homolysis of earth-abundant metal-substrate complexes: A complementary activation strategy in photoredox catalysis. *Angew. Chem. Int. Ed.* **2021**, 60, 21100-21115. (e) Wenger, O. S. Photoactive nickel complexes in cross-coupling catalysis. *Chem. Eur. J.* **2021**, 27, 2270-2278.
- (18) Sun, R.; Qin, Y.; Nocera, D. G. General paradigm in photoredox nickel-catalyzed cross-coupling allows for light-free access to reactivity. *Angew. Chem. Int. Ed.* **2020**, 59, 9527-9533.
- (19) For details, see Supporting Information.
- (20) (a) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing conventional carbon nucleophiles with electrophiles: Nickel-catalyzed reductive alkylation of aryl bromides and chlorides. *J. Am. Chem. Soc.* **2012**, 134, 6146-6159. (b) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. An improved system for the aqueous Lipshutz-Negishi cross-coupling of alkyl halides with aryl electrophiles. *Angew. Chem. Int. Ed.* **2016**, 55, 1849-1853.
- (21) For leading examples for water activation by the hangman construct, see: (a) Dempsey, J. L.; Esswein, A. J.; Manke, D. R.; Rosenthal, J.; Soper, J. D.; Nocera, D. G. Molecular Chemistry of consequence to renewable energy. *Inorg. Chem.* **2005**, 44, 6879-6892. (b) Dogutan, D. K.; McGuire, R.; Jr.; Nocera, D. G. Electrocatalytic water oxidation by cobalt(III) hangman β -octafluoro corroles. *J. Am. Chem. Soc.* **2011**, 133, 9178-9180.
- (22) (a) Harris, M. C.; Huang, X.; Buchwald, S. L. Improved functional group compatibility in the palladium-catalyzed synthesis of aryl amines. *Org. Lett.* **2002**, 4, 2885-2888. (b) Sperry, J. B.; Price Wigglesworth, K. E.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Piatnitski Chekler, E. L.; Langille, J.; Coe, J. W. Kiloscale Buchwald-Hartwig amination: Optimized coupling of base-sensitive 6-bromoisoquinoline-1-carbonitrile with (S)-3-amino-2-methylpropan-1-ol. *Org. Process Res. Dev.* **2014**, 18, 1752-1758. (c) Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D. Oxalic diamides and tert-butoxide: Two types of ligands enabling practical access to alkyl aryl ethers via Cu-catalyzed coupling reaction. *J. Am. Chem. Soc.* **2019**, 141, 3541-3549.
- (23) (a) Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angew. Chem. Int. Ed.* **2011**, 50, 586-621. (b) Estrela, J. M.; Mena, S.; Obrador,

E.; Benlloch, M.; Castellano, G.; Salvador, R.; Dellinger, R. W. Polyphenolic phytochemicals in cancer prevention and therapy: Bioavailability versus bioefficacy. *J. Med. Chem.* **2017**, *60*, 9413-9436.

(24) (a) Shen, T.; Wang, X.-N.; Lou, H.-X. Natural stilbenes: An overview. *Nat. Prod. Rep.* **2009**, *26*, 916-935. (b) Duy Vo, D.; Eloffsson, M. Total synthesis of viniferifuran, resveratrol-piceatannol hybrid, anigopreissin A and analogues-investigation of demethylation strategies. *Adv. Synth. Catal.* **2016**, *358*, 4085-4092.

(25) Fantacuzzi, M.; Amoroso, R.; Carradori, S.; Filippis, B. D. Resveratrol-based compounds and neurodegeneration: Recent insight in multitarget therapy. *Eur. J. Med. Chem.* **2022**, *233*, 114242.

(26) Na, H.; Mirica, L. M. Deciphering the mechanism of the Ni-photocatalyzed C–O cross-coupling reaction using a tridentate pyridinophane ligand. *Nat. Commun.* **2022**, *13*, 1313.
