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Note	

Nickel-Catalyzed Electrophilic Amination of the Biphenylene C–C σ-Bond

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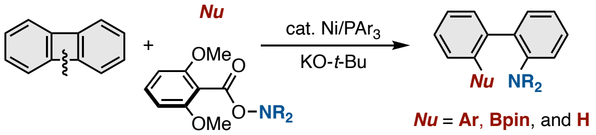
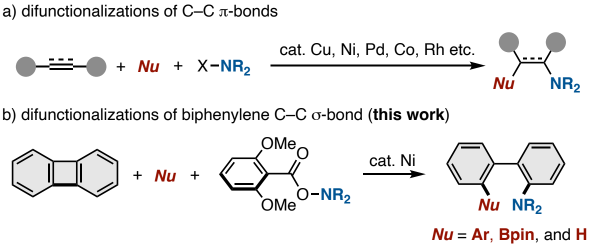
Supporting Information Placeholder



ABSTRACT: A nickel-catalyzed three-component carboamination of the biphenylene C–C σ-bond has been developed. Arylboronates and hydroxylamine derivatives work as carbon nucleophiles and nitrogen electrophiles, respectively, and the corresponding difunctionalized ring-opening products are obtained in good yields. The arylboronate nucleophile can be replaced with B_2pin_2 (boron nucleophile) and H–Si(OMe)$_3$ (hydride nucleophile), thus allowing for the aminoboration and hydroamination of the biphenylene C–C σ-bond under similar nickel catalysis.

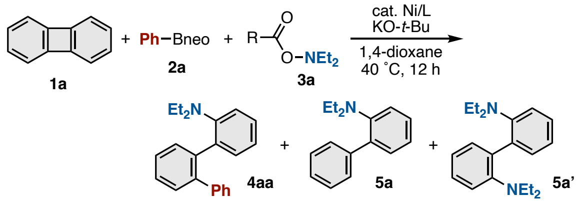
Amino groups are ubiquitously found in bioactive molecules, natural products, and organic functional materials, and their introduction to organic molecules is thus one of the most active research subjects in the synthetic community.[1] Numerous nucleophilic amination reactions with nitrogen-containing nucleophiles have been developed thanks to the electronegativity of nitrogen and the lone pair present in amino groups. The umpolung-enabled, electrophilic amination reaction using nitrogen electrophiles in the form of X–NR$_2$ (X = leaving groups) has recently received significant attention as a viable alternative to conventional nucleophilic amination reactions.[2] In particular, the nitrogen-umpolung-enabled, three-component cross-coupling aminative difunctionalization reactions of carbon-carbon π-bonds in alkenes and alkynes have greatly benefited from the development of various transition metal catalysts (Scheme 1a).[3] However, their applications to C–C σ-bonds still remain largely elusive despite their high synthetic potential for the deconstructive amination of organic skeletons.[4] Herein, we report such an electrophilic amination of the biphenylene C–C bond: a nickel-catalyzed carboamination of biphenylene with arylboronates and hydroxylamine derivatives is described (Scheme 1b). The arylboronate and hydroxylamine work as the carbon nucleophile and nitrogen electrophile, respectively, to form functionalized 2-aminobiphenyl products of structural importance in the field of material chemistry.[5] In addition, related aminoboration and hydroamination reactions using boron and hydride nucleophiles, respectively, are also disclosed. The obtained products can be easily synthesized by consecutive reactions of 2,2'-dibromobiphenyl, at first glance. However, the chemoselective stepwise transformations of the two Br groups are relatively difficult. Indeed, only the lithiation using BuLi under rigorously controlled conditions (low temperature, limited reaction stoichiometry, and/or microflow reactor) was allowed to be performed.[6] Thus, the facile approach to biphenyls with two different functional groups at the 2- and 2'-poitions is the apparently significant synthetic advantage of our protocol.

Scheme 1. Aminative Difunctionalizations Based on Electrophilic Amination



Optimization studies were commenced with biphenylene (**1a**; 0.15 mmol), phenylboronic acid neopentylglycolate (Ph-Bneo, **2a**; 0.30 mmol), and *O*-(2,6-dimethoxybenzoyl)-*N,N*-diethylhydroxylamine (**3a**; 0.18 mmol) to identify a suitable catalyst system (Table 1). On the basis of our previous work,[7] we initially attempted the reaction using copper catalysts, failing to observe any conversion of **1a**. Inspired by the high catalytic performance of nickel in the activation of biphenyl C–C σ-bond[8] as well as related electrophilic amination reactions with hydroxylamines,[9] we then focused on the Ni(II)-phosphine catalyst system. Pleasingly, the targeted ring-opening carboaminated product **4aa** was obtained in 56% ^{1}H-NMR yield when NiCl$_2$•DME/PPh$_3$ and KO-*t*-Bu were employed in 1,4-dioxane at 40 ˚C (entry 1). The ring-opening hydroaminated **5a** and diaminated byproduct **5a'** were also detected in 10% and 4% yield, respectively. Encouraged by this intriguing result, we investigated several phosphine ligands. While *meta*-substituted triarylphosphines and alkylphosphines negatively affected reaction efficiency (entries 2–5), the introduction of certain substituents at the *para*-position improved the yield, particularly with P(4-TMSC$_6$H$_4$)$_3$ (entries 6–9). Investigations of other reaction parameters revealed that the use of NiBr$_2$•DME and slightly higher loading of the carbon nucleophile **2a** (0.45 mmol) further increased the yield to 84% (entry 12). Additional ligand screening finally identified more bulky trimethylgermanyl-substituted[10] P(4-TMGC$_6$H$_4$)$_3$ to be the most performant, affording the desired **4aa** in 93% ^{1}H-NMR yield (84% isolated yield) at slightly higher reaction temperature (50 ˚C; entry 13). Meanwhile, we also noticed the following: the leaving group on the hydroxylamine was also critical, and the two MeO groups at the *ortho*-positions in **3a** were indispensable for satisfactory conversion of **1a** and high **4aa** selectivity over **5a/5a'** (entries 14–17);[11] Ph-B(OH)$_2$, Ph-Bpin, Ph-BF$_3$K, and (PhBO)$_3$ instead of **2a** were also tested to no avail. Other *tert*-butoxide bases (LiO-*t*-Bu and NaO-*t*-Bu) and weaker potassium bases (e.g., KOMe and K$_3$PO$_4$) dramatically decreased the yield (see the Supporting Information for details).

Table 1. Condition Optimization for the Ni-Catalyzed Carboamination of Biphenylene (1a) with Arylboronate 2a and Hydroxylamine 3a[a]



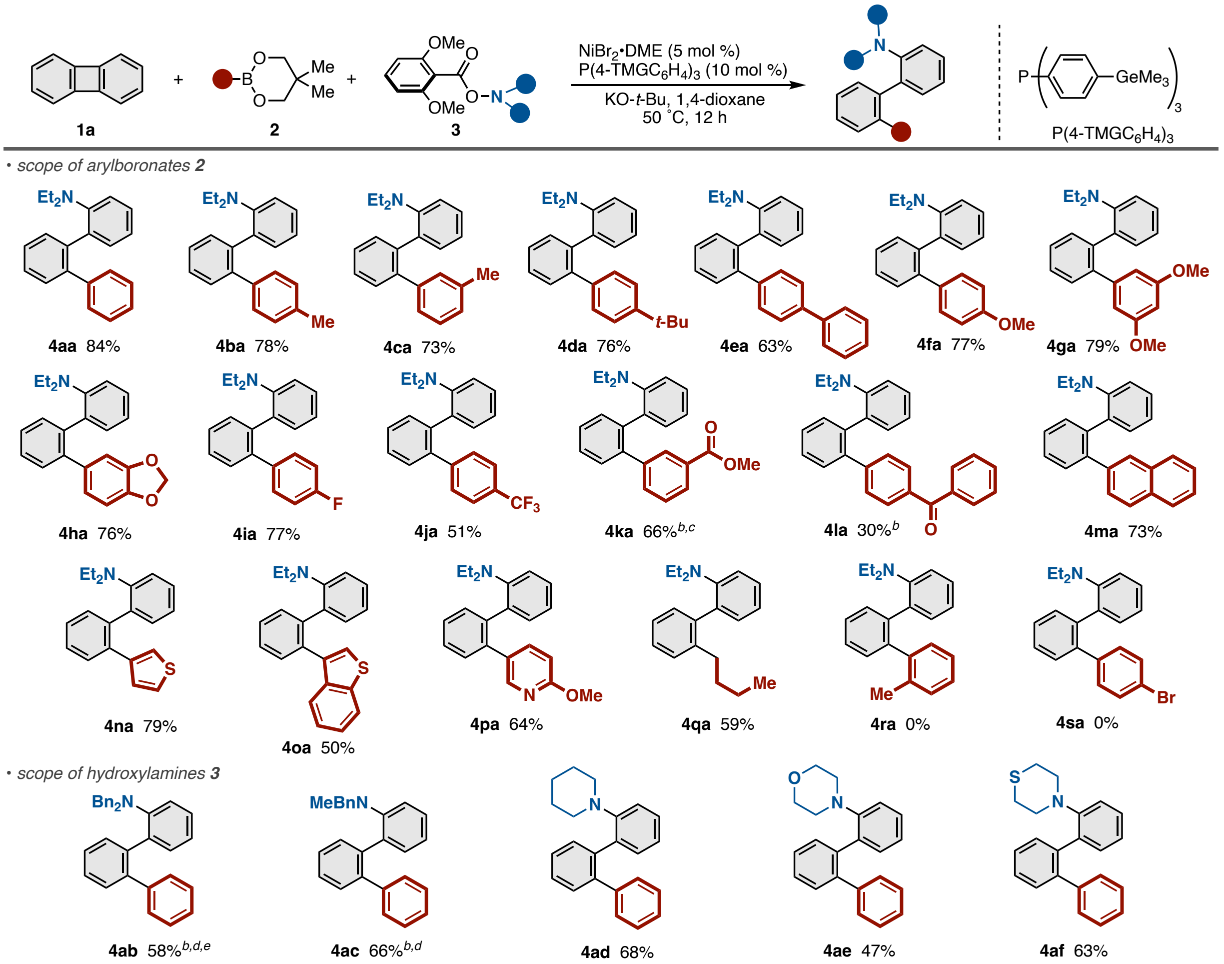
entry	Ni/L	R in **3**	yield (%)[b]	
			4aa	5a + 5a'
1	NiCl$_2$•DME PPh$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	56	10 + 4
2	NiCl$_2$•DME P(3,5-F$_2$C$_6$H$_3$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	(33)	6 + 1
3	NiCl$_2$•DME P[3,5-(*t*-Bu)$_2$C$_6$H$_3$]$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	33	7 + 0
4	NiCl$_2$•DME P(3,5-TMS$_2$C$_6$H$_3$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	47	7 + 1
5	NiCl$_2$•DME PCy$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	43	9 + 0
6	NiCl$_2$•DME P(4-MeOC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	54	25 + 6
7	NiCl$_2$•DME P(4-FC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	62	7 + 2
8	NiCl$_2$•DME P(4-*t*-BuC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	61	7 + 2
9	NiCl$_2$•DME P(4-TMSC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	66	7 + 1
10	NiBr$_2$•DME P(4-TMSC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	67	0 + 0
11	Ni(cod)$_2$ P(4-TMSC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	59	5 + 3
12[c]	NiBr$_2$•DME P(4-TMSC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	84	6 + 3
13[c,d]	NiBr$_2$•DME P(4-TMGC$_6$H$_4$)$_3$	2,6-(MeO)$_2$C$_6$H$_3$ (**3a**)	93 (84)	8 + 4
14[c,d]	NiBr$_2$•DME P(4-TMGC$_6$H$_4$)$_3$	Ph (**3a-Ph**)	35	6 + 5
15[c,d]	NiBr$_2$•DME P(4-TMGC$_6$H$_4$)$_3$	4-MeOC$_6$H$_4$ (**3a-OMe**)	47	6 + 6
16[c,d]	NiBr$_2$•DME P(4-TMGC$_6$H$_4$)$_3$	4-Me$_2$NC$_6$H$_4$ (**3a-NMe$_2$**)	0	0 + 13
17[c,d]	NiBr$_2$•DME P(4-TMGC$_6$H$_4$)$_3$	*t*-Bu (**3a-Piv**)	47	0 + 19

[a] Conditions: **1a** (0.15 mmol), **2a** (0.30 mmol), **3a** (0.18 mmol), Ni (0.0075 mmol, 5 mol %), L (0.015 mmol, 10 mol %), KO-*t*-Bu (0.30 mmol), 1,4-dioxane (1.0 mL), 40 ˚C, 12 h. [b] Estimated by ^{1}H-NMR with dibenzyl ether as the internal standard. Isolated yields are in parentheses. [c] With **2a** (0.45 mmol). [d] At 50 ˚C.

With optimized conditions (entry 13, Table 1), we next examined the scope of arylboronates **2** with **1a** and **3a** (Scheme 2). In addition to the model **2a**, electron-neutral (**4ba**–**ea**) and -rich (**4fa**–**ha**) substrates underwent the carboamination reaction smoothly. On the other hand, relatively low reactivity was observed when strongly electron-deficient arylboronate (**4ja**) was employed. The catalyst system was found to be compatible with ester and ketone functionalities to form the corresponding **4ka** and **4la** in acceptable yields. The naphthalene ring (**4ma**) as well as heteroarenes thiophene (**4na** and **4oa**) and pyridine (**4pa**) were also tolerated under our reaction conditions. Particularly noteworthy is the successful use of C(sp^3)-alkylboronate (**4qa**). The limitation is currently manifested in the sterically hindered *ortho*-substituted substrate (**4ra**) and the potentially reactive Ar-Br bond (**4sa**). The latter possibly suggests the intermediacy of electron-rich, low-valent Ni species in the catalytic cycle (vide infra). Meanwhile, some other hydroxylamines **3** were also viable partners: the deprotected *N*-benzyl substituent was tolerated (**4ab** and **4ac**); piperidine, morpholine, and thiomorpholine all were successfully coupled with **1a** and **2a** to afford the corresponding ring-opening arylaminated products **4ad**–**af** in good yields.

Under a slightly modified protocol using P(4-MeOC$_6$H$_4$)$_3$ instead of P(4-TMGC$_6$H$_4$)$_3$, B$_2$pin$_2$ also worked well as the boryl nucleophile to form aminoborated products **6** (Scheme 3a). This reaction also accommodated both acyclic (**6a**–**c**) and cyclic hydroxylamines (**6d**, **e**). The structure of **6b** was unambiguously confirmed by X-ray analysis (CCDC no. 2337750). Moreover, the boryl moiety in **6b** is a versatile handle in downstream transformations (Scheme 3b): the oxidation with NaBO$_3$ and Suzuki-Miyaura cross-coupling with 2-bromobenzothiophene provided the corresponding aminoalcohol **7** and (hetero)teraryl amine **8**, respectively, in acceptable yields. On the other hand, the ring-opening hydroamination product **5a** could also be selectively obtained from **1a**, HSi(OMe)$_3$, and **3a** (Scheme 3c). In this case, the major source of "H" in **5a** would be the hydrosilane, which was supported by a deuterium-labeling experiment with D$_2$SiPh$_2$ (Scheme 3d).[12]

Scheme 2. Nickel-Catalyzed Carboamination of Biphenylene (1a) with Arylboronates 2 and Hydroxylamines 3[a]



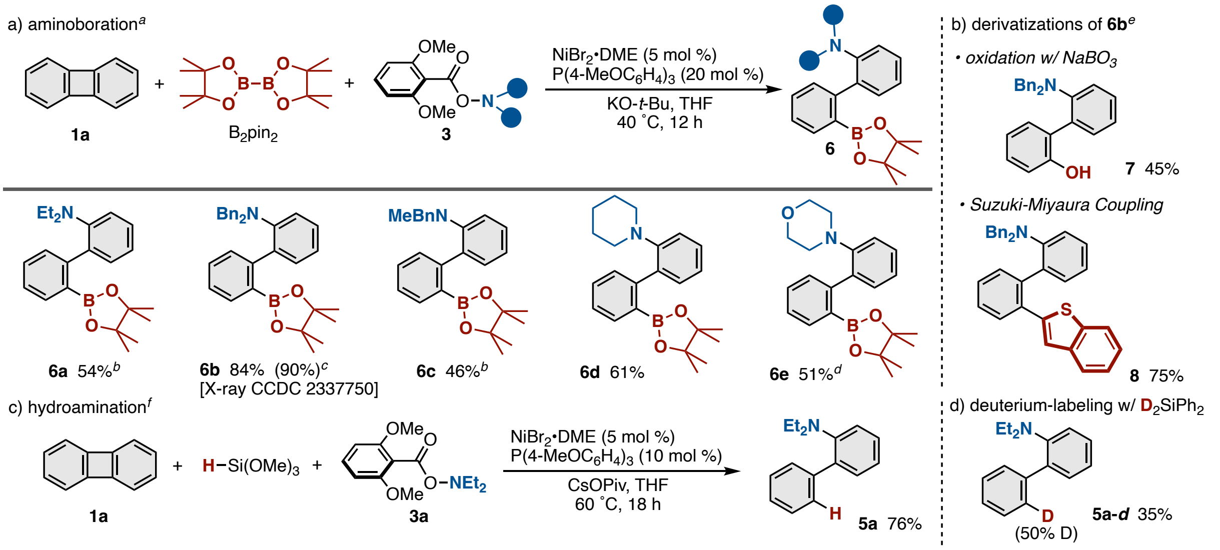
[a] Conditions: **1a** (0.15 mmol), **2** (0.45 mmol), **3** (0.18 mmol), NiBr$_2$•DME (0.0075 mmol), P(4-TMGC$_6$H$_4$)$_3$ (0.015 mmol), KO-*t*-Bu (0.30 mmol), 1,4-dioxane (1.0 mL), 50 °C, 12 h. Isolated yields are shown. [b] With **2** (0.60 mmol), NiBr$_2$•DME (0.015 mmol), P(4-TMGC$_6$H$_4$)$_3$ (0.030 mmol), and KO-*t*-Bu (0.45 mmol), for 18 h. [c] With PivO-NEt$_2$ (**3a-Piv**) instead of **3a**. [d] With P(4-TMSC$_6$H$_4$)$_3$ instead of P(4-TMGC$_6$H$_4$)$_3$. [e] With PivO-NBn$_2$ (**3b-Piv**) instead of **3b**.

We then performed several control experiments to gain insight into the reaction mechanism. First, to elucidate the oxidation state of active Ni species, NiBr$_2$•DME and dppe (2.0 equiv to Ni) were treated with **2a** and KO-*t*-Bu (4.0 equiv to Ni) in THF-*d*$_8$, and the ^{31}P{^{1}H} NMR spectra change was monitored (Scheme 4a). The starting signal of free dppe (–13 ppm) rapidly disappeared within 5 min at room temperature, and a new signal at a lower field (44 ppm) was observed, which is tentatively assigned to Ni^0(dppe)$_2$, supported by the fact that a mixture of Ni(cod)$_2$ and dppe (2.0 equiv to Ni) also produced the same ^{31}P{^{1}H} NMR signal. Thus, the NiBr$_2$•DME catalyst precursor would be smoothly reduced to the Ni^0 species under the standard reductive conditions, which is also consistent with the result using Ni(cod)$_2$ in entry 11 of Table 1.[13] Thereafter, the biphenylene C–C σ-bond is known to undergo oxidative addition to Ni^{0}L$_n$ (L = PEt$_3$) species to form the corresponding nickelacycle at as low as 0 °C,[8a] and we conducted a stoichiometric reaction using Ni(cod)$_2$ and PEt$_3$ (Scheme 4b). Upon treatment with **2a**, **3a**, and KO-*t*-Bu, the in-situ generated nickelacycle **9-PEt$_3$** was converted to the carboaminated product **4aa**, indicating the key intermediacy of similar nickelacycles.[14] Finally, the direct reactivities of P(4-TMGC$_6$H$_4$)$_3$-coordinated nickelacycle **9-Ge** toward the arylboronate **2a** and hydroxylamine **3a** were examined (Scheme 4c). Although both **2a** and **3a** reacted individually with **9-Ge** to generate the corresponding hydroarylation product **10** and aminated products **5a**/**5a'**, respectively, the similar byproduct **10** was not detected at all under catalytic conditions (Table 1). On the other hand, the hydroaminated and diaminated **5a**/**5a'** were observed in the above-mentioned optimization studies, potentially suggesting the preferred combination of the hydroxylamine toward the nickelacycle intermediate under catalytic conditions.

On the basis of the above findings and literature knowledge, our proposed reaction mechanism (Scheme

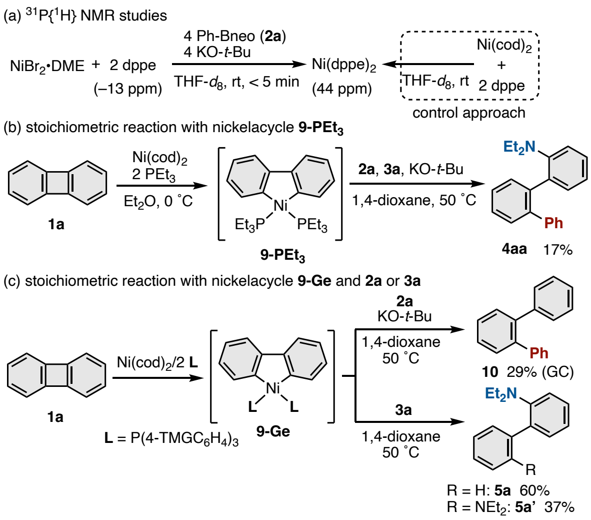
5) entails (1) initial reduction of $NiBr_2$•DME with **2** and KO-*t*-Bu to generate the active Ni(0) species **11**, (2) formation of nickelacycle **9-Ge** via oxidative addition of the C–C σ-bond of biphenylene **1a**, (3) electrophilic amination with the hydroxylamine **3** forming the ring-opening arylnickel species **12**, (4) transmetalation with the arylboronate **2**, and (5) reductive elimination from **13** to furnish the carboaminated product **4** along with the regeneration of the starting **11**. The observed hydroaminated and diaminated byproducts **5/5'** could arise from **12** and residual water or an additional hydroxylamine **3**.

Scheme 3. Nickel-Catalyzed Boryl- and Hydroamination of Biphenylene (1a)

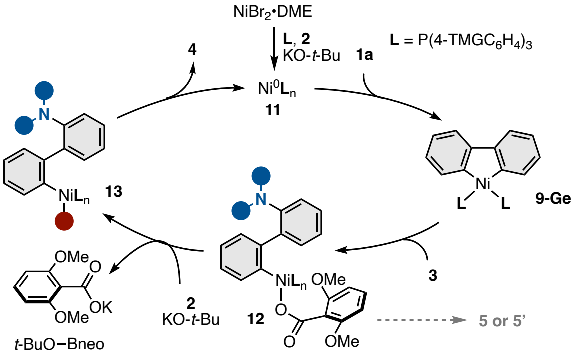


[a] Conditions: **1a** (0.15 mmol), B_2pin_2 (0.45 mmol), **3** (0.18 mmol), $NiBr_2$•DME (0.0075 mmol), $P(4-MeOC_6H_4)_3$ (0.030 mmol), KO-*t*-Bu (0.30 mmol), THF (1.0 mL), 40 ˚C, 12 h. Isolated yields are shown. [b] With B_2pin_2 (0.60 mmol), $NiBr_2$•DME (0.015 mmol), and $P(4-MeOC_6H_4)_3$ (0.060 mmol). [c] On a 1.0 mmol scale. [d] At 50 ˚C. [e] See the Supporting Information for detailed conditions. [f] Conditions: **1a** (0.15 mmol), $HSi(OMe)_3$ (0.45 mmol), **3a** (0.18 mmol), $NiBr_2$•DME (0.0075 mmol), $P(4-MeOC_6H_4)_3$ (0.015 mmol), CsOPiv (0.30 mmol), THF (1.0 mL), 60 ˚C, 18 h.

Scheme 4. Mechanistic Studies



Scheme 5. Proposed Mechanism



In summary, we have developed a nickel-catalyzed carboamination of biphenylene C–C σ-bond with arylboronates as the carbon nucleophiles and hydroxylamine derivatives as the nitrogen electrophiles to deliver the corresponding teraryl amines in good yields. The arylboronates can be replaced with B_2pin_2 (boron nucleophile) and hydrosilane (hydride) to enable the respective aminoboration and hydroamination. The key to success is the nitrogen-umpolung-enabled electrophilic amination strategy. To the best of our knowledge, this is one of only a handful of successful examples of electrophilic amination of C–C σ-bond. Further development of related catalysis systems capable of electrophilic amination of strong σ-bonds is ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{31}P{^{1}H} NMR spectra, ORTEP drawings, detailed optimization studies (PDF)

Accession Codes

CCDC 2337750 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(12) We performed the reaction in the presence of dehydrating reagent, such as MS4 Å and Na_2SO_4. However, the yield of **5a**/**5a-*d*** was reduced to <5%, and the deuterium content was not changed. We also confirmed that replacement of **3a** and $HSi(OMe)_3$ with simple $HNEt_2$ did not promote the ring-opening hydroamination of **1a** at all even under conditions using stoichiometric amounts of $Ni(cod)_2$ and $P(4\text{-}MeOC_6H_4)_3$.

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(14) In addition to **4aa**, the hydroaminated byproduct **5a**, tetraphenylene (dimer of **1a**), and simple biphenyl were also detected at 17%, 12%, and 28%, respectively. The use of $NiCl_2(PEt_3)_2$ as the catalyst precursor afforded **4aa** in 39% yield under otherwise identical conditions to those of entry 13 in Table 1.