Letter

Well-designed N-Heterocyclic Carbene Ligands for Palladium-Catalyzed Denitrative C-N Coupling of Nitroarenes with Amines

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Well-designed *N*-Heterocyclic Carbene Ligands for Palladium-Catalyzed Denitrative C-N Coupling of Nitroarenes with Amines

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ABSTRACT: The C-N bond formation is one of the fundamental reactions in organic

chemistry due to the widespread presence of amine moieties in pharmaceuticals and

biologically active compounds. Palladium-catalyzed C-N coupling of haloarenes

represents one of the most efficient approaches to aromatic amines. Nitroarenes are ideal

alternative electrophilic coupling partners since they are cheap and readily available. The

denitration and cross-coupling using nitroarenes as the electrophilic partners is

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challenging because of the low reactivity of Ar-NO$_2$ bond towards oxidative addition. We

report here the C-N coupling of nitroarenes and amines using palladium/5-(2,4,6-

triisopropylphenyl)imidazolylidene[1,5-*a*]pyridines as the catalyst. The ligands are readily

available from commercial chemicals. The reaction shows broad substrate scope and

functional group tolerance. The method is applicable to both aromatic and aliphatic

amines, and a number of secondary and tertiary aromatic amines bearing various

functional groups were obtained in high yields.

KEYWORDS: palladium • *N*-heterocyclic carbene • nitroarenes • aniline • denitration •

C-N coupling

Arylamines are a privileged structural scaffold, which frequently occurs in opto-

electronic materials,[1] agrochemicals,[2] and pharmaceuticals.[3] The construction of C-N

bonds via copper-catalyzed Ullmann coupling[4] and palladium-catalyzed Buchwald-

Hartwig[5] coupling reactions of (pseudo)haloarenes and amines have been the most

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efficient and practical approaches to aromatic amines in modern synthetic chemistry.

Numerous efforts have been made in the development of more efficient ligands including

P-, *N*-, and *O*-donors.[6] Ethers, esters, and amides have also been studied as economic

and greener electrophilic partners in recent years.[7]

Nitroarenes are basic raw chemical materials for pharmaceutical, pesticide, and dye

industry. They are cheap and readily available from nitration of arenes.[8] In principle,

nitroarenes are ideal electrophilic partners for the manufacture of valuable aromatic

chemicals through metal-catalyzed cross-coupling reactions. Moreover, many

functionalized haloarenes especially bromo-and iodoarenes have to be prepared through

Sandmeyer-type reactions of anilines originated from nitroarenes. However, in this

context only quite limited success has been made due to the inertness of C-N bond

towards oxidative addition. In 2011, Wu et al reported rhodium-catalyzed C-O coupling of

nitroarenes and phenylboronic acids leading to aromatic ethers.[9] Later, the same C-O

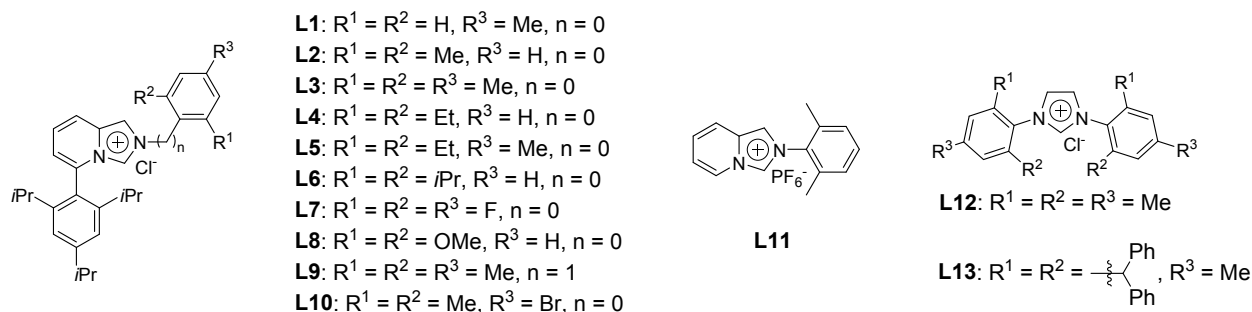coupling reactions was also achieved by using nano copper catalyst.[10] These C-O

coupling reactions are generally restricted to electron-deficient nitroarenes. Recently,

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Nakao et al described palladium-catalyzed Suzuki coupling,[11] hydrodenitration,[12] and Buchwald-Hartwig amination of nitroarenes.[13] The success of such protocols has been attributed mainly to the use of sophisticated Buchwald biaryl monophosphines (BrettPhos).[14]

Bulky NHC ligands have proved to be useful ligands for palladium-catalyzed amination of haloarenes.[15] The use of bulky NHC ligands in place of BrettPhos is attractive taking account of their ease of availability and cost benefits.[16] We envisioned that well-designed bulky NHC ligands with strong electron-donating properties would be able to furnish the activation of C-N bonds of nitroarenes. Most likely, a NHC ligand geometrically resembling Buchwald-type biphenyl monophosphines would fulfil the challenging amination of nitroarenes. As a continuation of our NHC chemistry,[17] herein we report palladium-catalyzed denitrative C-N coupling reactions of nitroarenes with aromatic and aliphatic amines using 5-(2,4,6-triisopropylphenyl) imidazolylidene [1,5-*a*] pyridines as the ligands.

Scheme 1. Structural Illustration of the Ligand Precursors.

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L1: $R^1 = R^2 = H$, $R^3 = Me$, n = 0
L2: $R^1 = R^2 = Me$, $R^3 = H$, n = 0
L3: $R^1 = R^2 = R^3 = Me$, n = 0
L4: $R^1 = R^2 = Et$, $R^3 = H$, n = 0
L5: $R^1 = R^2 = Et$, $R^3 = Me$, n = 0
L6: $R^1 = R^2 = iPr$, $R^3 = H$, n = 0
L7: $R^1 = R^2 = R^3 = F$, n = 0
L8: $R^1 = R^2 = OMe$, $R^3 = H$, n = 0
L9: $R^1 = R^2 = R^3 = Me$, n = 1
L10: $R^1 = R^2 = Me$, $R^3 = Br$, n = 0

L11

L12: $R^1 = R^2 = R^3 = Me$

**L13**: $R^1 = R^2 = $ <Ph/Ph group>, $R^3 = Me$

The ligand precursors listed in Scheme 1 were prepared according to the general procedure of imidazolium salts.[18] The reaction of 4-nitroanisol and *p*-toluidine was initially investigated as the model reaction using 5 mol% Pd(acac)$_2$ as the catalyst in dioxane at 130 °C.[13] Unfortunately, no denitrative C-N coupling product was detected in the presence of the imidazolium salt (**L1**) bearing a *N*-*p*-tolyl substituent (Table 1, entry 1). To our delight, when **L2** bearing a *N*-2,6-dimethylphenyl substituent, the amination reaction successfully gave 4-methoxy-*N*-(*p*-tolyl)aniline **3aa** in 65% yield (Table 1, entry 2). An additional *para*-methyl of the *N*-phenyl group favors the coupling, and the reaction yield was increased to 76% (Table 1, entry 3). When the two *ortho* 2,6-substituents are replaced by two ethyl, the yield was sharply increased to 93%. The enhancement effect of the *para*-methyl was also observed for the bulkier ligands (Table 1, entry 4 *vs* 5). Bulkier

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ligand **L6** bearing two *ortho* *i*Pr groups led to a diminished yield (Table 1, entry 6).

Although bulkier ligand is expected to promote the reductive elimination, it disfavors the

oxidative addition of Ar-NO$_2$ bond. Other ligands such as **L7** and **L8** bearing fluoro and

methoxy substituents at two *ortho* positions resulted in no or low conversions (Table 1,

entries 7 and 8). The results illustrate that the electronic properties should also be

precisely tuned to balance the requirement of oxidative addition and reductive elimination

processes. The NHC ligand, **L5** electronically and sterically fits the denitrative coupling

of nitroarenes, resulting in the best catalyst.

Table 1. Optimization of reaction conditions.
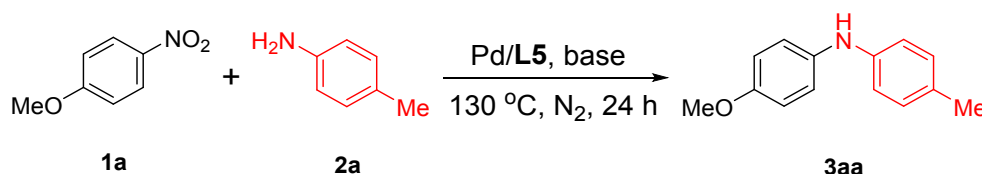
Entry	Ligand	Pd source	Base	Solvent	Yield/%
1	**L1**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	-
2	**L2**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	65
3	**L3**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	76
4	**L4**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	78
5	**L5**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	93
6	**L6**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	74
7	**L7**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	-
8	**L8**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	35
9	**L9**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	33
10	**L10**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	41
11	**L11**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	-
12	**L12**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	<5
13	**L13**	Pd(acac)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	<5
14	**L5**	Pd(OAc)$_2$	K$_3$PO$_4$·3H$_2$O	1,4-dioxane	70

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15	**L5**	$Pd_2(dba)_3$	$K_3PO_4 \cdot 3H_2O$	1,4-dioxane	60
16	**L5**	$Pd(acac)_2$	$K_3PO_4 \cdot 3H_2O$	DMF	-
17	**L5**	$Pd(acac)_2$	$K_3PO_4 \cdot 3H_2O$	toluene	78
18	**L5**	$Pd(acac)_2$	$K_3PO_4 \cdot 3H_2O$	*n*-heptane	90
19	**L5**	$Pd(acac)_2$	$K_3PO_4 \cdot 3H_2O$	MeCN	<5
20	**L5**	$Pd(acac)_2$	$K_3PO_4 \cdot 3H_2O$	MeOH	<5
21	**L5**	$Pd(acac)_2$	K_2CO_3	1,4-dioxane	<5
23	**L5**	$Pd(acac)_2$	Cs_2CO_3	1,4-dioxane	56
22	**L5**	$Pd(acac)_2$	KO^tBu	1,4-dioxane	-
24	**L5**	$Pd(acac)_2$	NEt_3	1,4-dioxane	<5
25	**L5**	$Pd(acac)_2$	DBU	1,4-dioxane	<5
26	**L5**	$Pd(acac)_2$	K_3PO_4	1,4-dioxane	61

Reaction conditions: 4-nitroanisol (0.3 mmol), *p*-toluidine (0.45 mmol), solvent (1.5 mL), [Pd] (5 mol%), **HL·Cl** (10 mol%), 130 °C, N_2, 24 h.

The imidazolium salt **L11** bearing no substituent at 5-position showed no activity.

Obviously, these results illustrate that both electronic and steric factors of two *N*-substituents are crucial to achieve clean amination of the nitroarene. For comparison, the commonly employed bulky NHC ligands IMes and IPr* (*N*,*N*-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) were also explored, and they were found to be not suitable ligands for the activation of the C-N bond (entries 12 and 13).

$Pd(OAc)_2$ and $Pd_2(dba)_3$ are also applied to the amination, but both of them are less efficient (entries 14 and 15). The influence of solvents was also examined. The C-N coupling reaction could proceed smoothly in nonpolar and low polar solvents affording **3aa** in high yields, and polar solvents are not suitable for the reaction (entries 16-20). Reduction of nitrobenzene to aniline often occurred in polar solvents. Bases are also
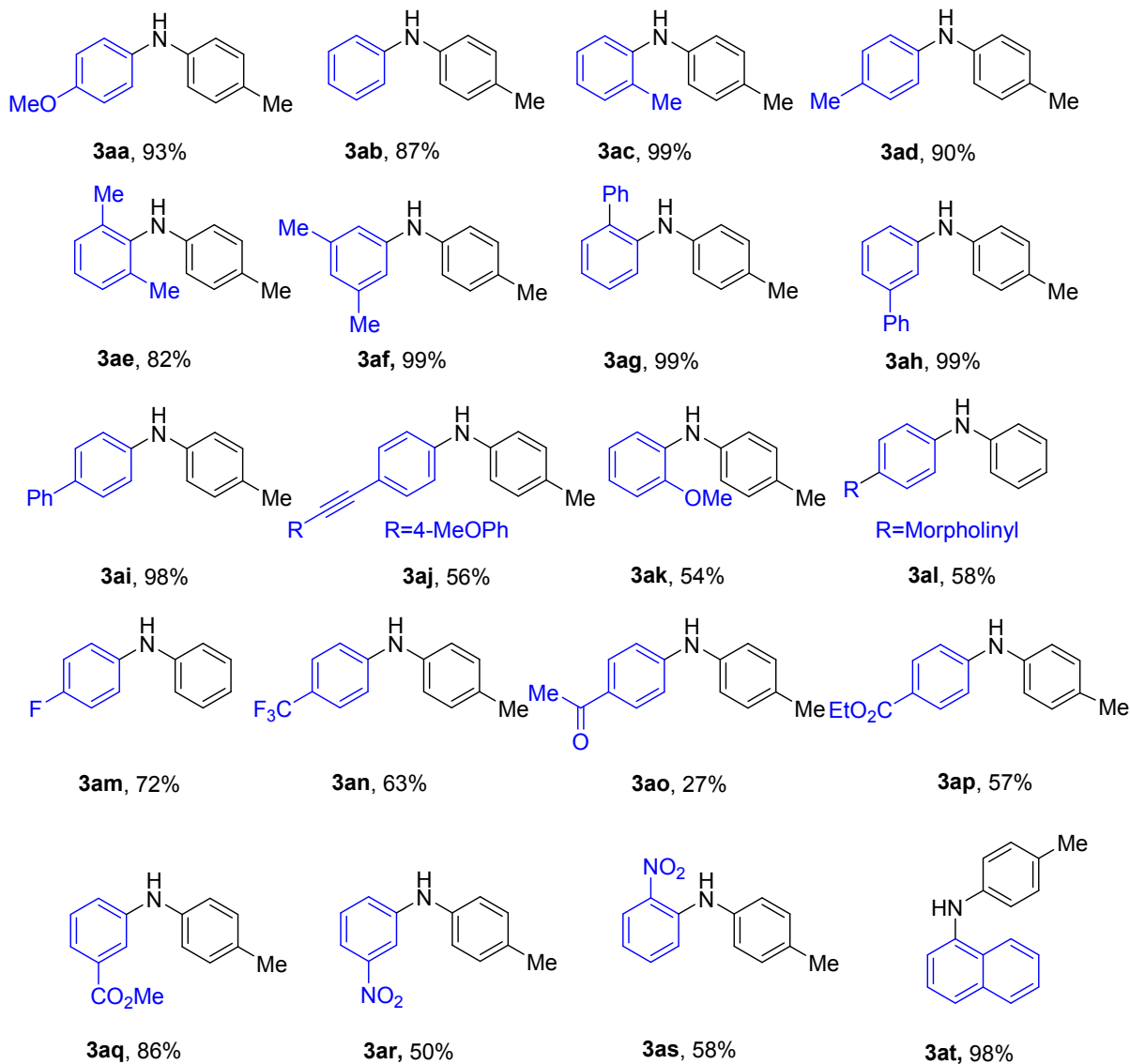
essential to the reaction, $K_3PO_4 \cdot 3H_2O$ is the best among the bases examined (entries 21-

26). The palladium-catalyzed amination of haloarenes often requires a strong base such

as KO^{t}Bu and NaO^{t}Bu et al.[19] We speculate that amines coordinated to the LPd(NO$_2$)Ar

species would be more easily deprotonated than their analogous LPd(X)Ar (X = halogen).

Although soluble organic bases are recently found to show enhancement effect,[20]

however, we found that organic bases favor the reduction of nitroarene to aniline other

than denitrative coupling. Finally, the optimized conditions were established to be 5 mol%

Pd(acac)$_2$ and 10 mol% **L5** in dioxane using $K_3PO_4 \cdot 3H_2O$ as the base.

Table 2. Scope of nitroarenes.

Nitroarenes

3aa, 93%   **3ab**, 87%   **3ac**, 99%   **3ad**, 90%

3ae, 82%   **3af,** 99%   **3ag**, 99%   **3ah**, 99%

R=4-MeOPh

R=Morpholinyl

3ai, 98%   **3aj**, 56%   **3ak**, 54%   **3al**, 58%

3am, 72%   **3an**, 63%   **3ao**, 27%   **3ap**, 57%

3aq, 86%   **3ar,** 50%   **3as**, 58%   **3at,** 98%
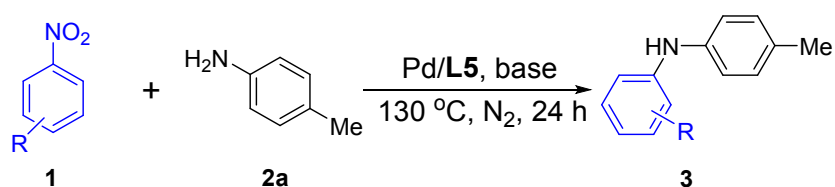
Nitroheteroarenes

3au, 48%   **3av**, 88%   **3aw**, 55%   **3ax**, 86%   **3ay**, 56%
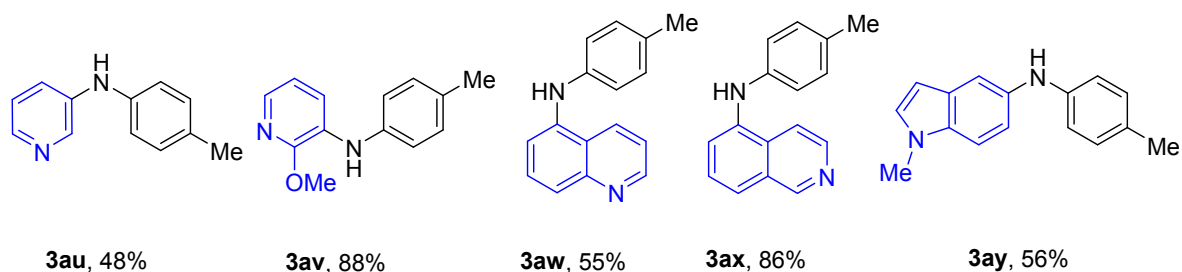
Reaction conditions: **1** (0.6 mmol), *p*-toluidine (1.5 equiv.), dioxane (3 mL), Pd(acac)$_2$ (5 mol%), **HL5·Cl** (10 mol%), K$_3$PO$_4$·3H$_2$O (3.0 equiv.), 130 °C, N$_2$, 24 h.

Under the optimized conditions, we explored the scope of nitroarenes through their reactions with *p*-toluidine, and the results are listed in Table 2. Various nitroarenes bearing methyl and phenyl at *o*-, *m*-, and *p*-positions worked well, affording diarylamines **3aa**-**3ai** in nearly quantitative yields. Even sterically hindered 1,3-dimethyl-2-nitrobenzene could be transformed to **3ae** in 82% yield. For comparison, Pd/Brettphos are not able to catalyse the coupling of ortho-substituted nitroarenes. Unsaturated substituent such as alkynyl is compatible, and **3aj** was afforded in 56% yield. Nitroarenes bearing strong electron-donating groups such as methoxy and amino gave the target products **3ak** and **3al** in good yields. The C-F bond in 4-nitro-1-fluorobenzene is tolerant giving the corresponding fluoro-containing diarylamine in good yield. Unfortunately, nitroarenes bearing chloro- and bromo functionalities were not successful because Ar-Cl and Ar-Br are more reactive than Ar-NO$_2$ bond with the Pd/NHC catalyst. In such cases, diarylamines containing a nitro group were generally obtained in excellent yields. Electro-withdrawing substituents such as ester, trifluoromethyl, acetyl, and nitro groups are well

compatible, and the corresponding secondary amines **3an**-**3as** were obtained in good

yields. In the cases of 1,2- and 1,3-dinitrobenzene, no double coupling products were

observed. It should be mentioned that 1,4-dintrobenzene is unreactive under the

optimized conditions, and only trace amount of the reduced product was observed. The

coupling of nitrobenzaldehyde derivatives also failed, and in such case only imine was

detected. Nitronaphthalene is a good coupling partner giving naphthalen-1-amine **3at** in

a quantitative yield. The coupling reaction is also applied to *N*-heterocyclic compounds.

3-Nitropyridines could couple with *p*-toluidine giving **3au** and **3av** in 48% and 88% yields,

respectively. Similarly, 5-nitroquinoline and 5-nitroisoquinoline are suitable substrates,

and their corresponding coupling products **3aw** and **3ax** were obtained in 55% and 86%

yields, respectively. However, under the same conditions the coupling of 8-nitroquinoline

was not successful. The above results illustrate that electron-deficient nitroarenes

generally disfavor the denitrative C-N coupling reactions. The present Pd/NHC catalyst are

more efficient for both electron-rich and electron-deficient nitroarenes than previously reported

Pd/Brettphos[11] under similar conditions, which can be ascribed to the smaller activation barrier

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for the oxidative addition of Ar-NO$_2$ to (NHC)Pd(0) than that of (BrettPhos)Pd(0).[16d] In addition, NHCs are better to resist oxidation than phosphine ligands, and thus low loading of the NHC ligand was allowed.

We next explored the scope of primary and secondary anilines bearing different functional groups. Various electron-rich, electron-poor, *ortho*-substituted, and heteroaryl amines were cross-coupled successfully with 1-nitronaphthalene, and the results were summarized in Table 3. Generally, mono- and dialkyl-substituted anilines are good coupling partners, and their corresponding diarylamnies **4aa**-**4ad** were isolated in nearly quantitative yields. The coupling reaction showed obvious steric effect for 2,6-disubstituted anilines. The transformation involving 2,6-diethylaniline proceeded efficiently giving their corresponding secondary amines **4ae** and **4af** in 70 and 80% yields, respectively, but the more hindered 2,6-diisopropylaniline was less reactive. Thus, the reaction of 1-nitronaphthalene and 2,6-diisopropylaniline afforded **4ag** in only 63% yield.

The electron-rich anilines bearing methoxy, phenoxy, and amino groups at *ortho* or *para*-positions are quite active giving the desired products **4ah**-**4aj** in up to 94% yields.

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However, unprotected 4-aminophenol gave a complicated mixture. Interestingly, 3,4-

difluoroaniline was afforded in 97% with two fluoro unreacted. Again, haloanilines are not

compatible since Ar-X (X = Cl, Br, and I) bonds are more reactive than Ar-NO_2.

Palladium-catalyzed denitrative coupling is also applied to anilines bearing electron-

withdrawing substituents such as ester, acetyl, cyanide, and CF_3 to give **4am**-**4at**. The

yields of the coupling products are dependent upon the substitution positions. For

example, under the same conditions the reaction of ethyl 4-aminobenzoate and

nitronaphthalene afforded **4aq** in 93% yield, whereas methyl 2-aminobenzoate gave **4ao**

in only 32% yield. Generally, the electron-deficient anilines are less reactive probably due

to reduced coordination abilities to palladium center of the amines. We next explored the

possibility of secondary aromatic amines, and found both *N*-methyl and *N*-ethylaniline

could successfully couple with 1-nitronaphthalene furnishing tertiary amines **4au** and **4av**

in 71% and 28% yields, respectively. Cyclic indoline is a good secondary nucleophilic

amination reagent. The influence of steric hindrance is also remarkable for the coupling

reactions of 1,3-dimethyl-2-nitrobenzene and 2-nitrobiphenyl with 2,6-dimethylaniline and

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2,6-diethylaniline. The yields of **4ax**-**4bb** vary depending upon the bulkiness of the substituents.

A variety of aliphatic chain and cyclic, primary and secondary amines were further studied. *n*-Butylamine, *n*-hexylamine, and benzylamine were successfully *N*-arylated with 1-nitronaphthalene in almost quantitative yields. Cyclic primary amine such as cyclohexylamine was transformed to *N*-cyclohexylnaphthalen-1-amine **4bg** in up to 98% yield. In addition, the coupling reaction was amenable to pyrrolidine, piperidine, morpholine, and azepane, which are pharmaceutically important building blocks, to give the products **4bh**-**4bm** in high yields. It should be noted that Ph_2NH and Et_2NH are not reactive, and thus the secondary amines listed in Tables 2 and 3 were selectively obtained. Obviously, the Pd/NHC catalyst is more suitable for the coupling of primary aromatic and aliphatic amines. In contrast, Ph_2NH is able to couple with various nitroarenes delivering triarylamines in good yields when Pd/Brettphos was employed under similar conditions.[13] Probably, the pocket-shaped imidazolylidene [1,5-*a*] pyridine ligands would inhibit the coordination of diarylamine.

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Finally, heteroarylamines such as 3-aminopyridine, 5-aminoquinoline, 3-aminocarbazole, and 3-aminothiophene derivatives were coupled with 1-nitronaphthalene successfully in excellent yields.

Table 3. Scope of amines
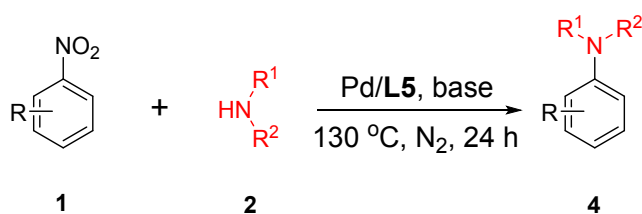
Aromatic amines
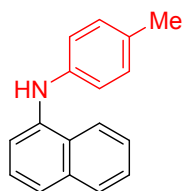
3at, 98%
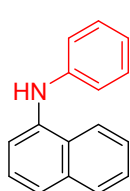
4aa, 99%
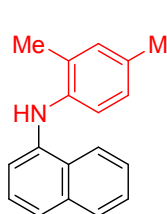
4ab, 93%
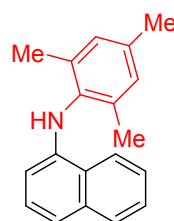
4ac, 90%
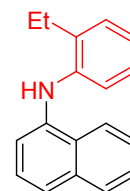
4ad, 97%
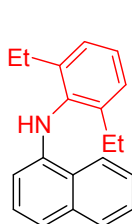
4ae, 70%
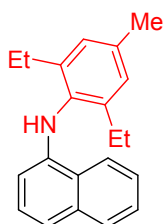
4af, 80%
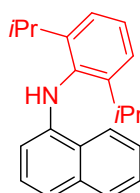
4ag, 63%
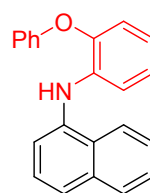
4ah, 87%
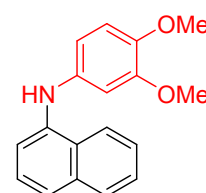
4ai, 94%
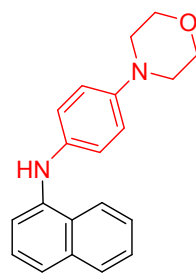
4aj, 94%
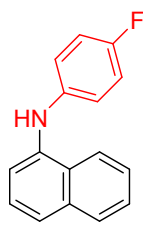
4ak, 89%
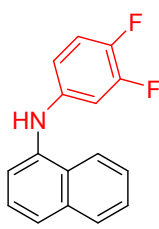
4al, 97%
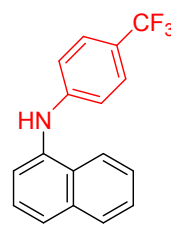
4am, 80%
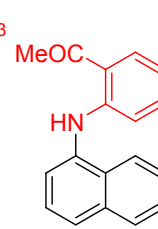
4an, 59%
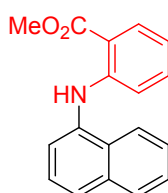
4ao, 32%
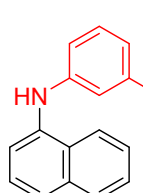
4ap, 62%
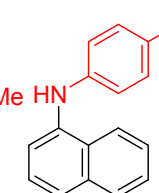
4aq, 93%
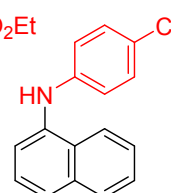
4ar, 70%
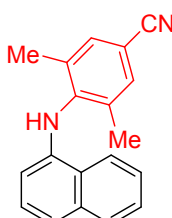
4as, 82%
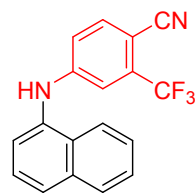
4at, 87%
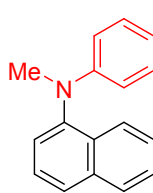
4au, 71%
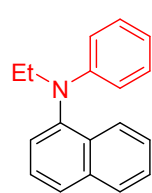
4av, 28%
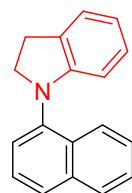
4aw, 92%
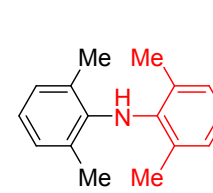
4ax, 60%
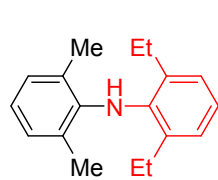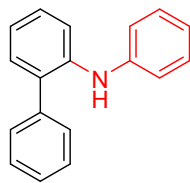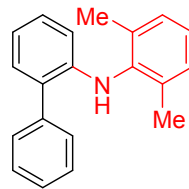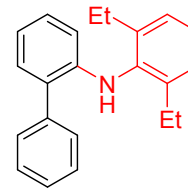
4ay, 21%   **4az**, 94%   **4ba**, 40%   **4bb**, 18%

Aliphatic amines
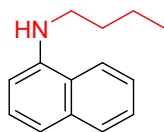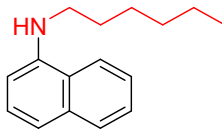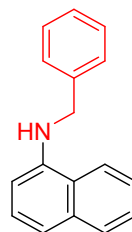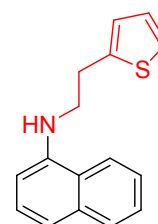
4bc, 92%   **4bd**, 98%   **4be**, 97%   **4bf**, 91%
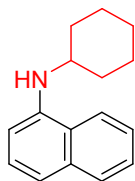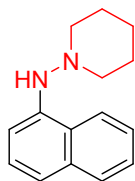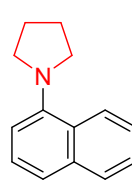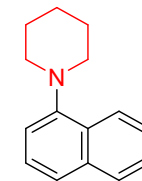
4bg, 98%   **4bh**, 86%   **4bi**, 96%   **4bj**, 90%
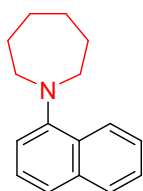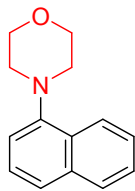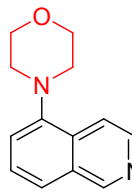
4bk, 74%   **4bl**, 84%   **4bm**, 56%

Heteroaryl amines
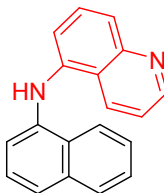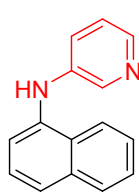
4bn, 87%   **4bo**, 93%   **4bp**, 97%   **4bq,** 76%

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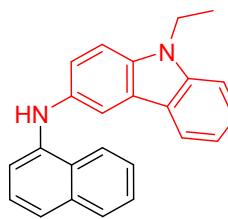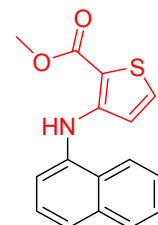
Reaction conditions: **1** (0.6 mmol), **2** (1.5 equiv), dioxane (3 mL), Pd(acac)$_2$ (5 mol%), **HL5·Cl** (10 mol%), K$_3$PO$_4$·3H$_2$O (3.0 equiv), 130 ºC, N$_2$, 24 h.

In summary, we have demonstrated that the combination of palladium and the NHC ligands *in situ* generated from 5-(2,4,6-triisopropylphenyl)imidazolium[1,5-*a*]pyridines are able to catalyze the dinitrative C-N coupling of nitroarenes and amines leading to diarylamines and *N*-alkylanilines in good to excellent yields. The ligands are readily prepared from inexpensive and commercially available starting materials, and the present protocol shows broad scopes for both electrophilic and nucleophilic partners and wide functional group tolerance. The coupling reaction proceeded without the need of strong bases, that expands the scope for base-sensitive substrates. It offers an alternative practical approach to prepare secondary and tertiary aromatic amines. In addition, the present work also demonstrates that the potential application of well-designed NHC ligands with appropriate electronic and steric properties would be expected for the activation of inert chemical bonds.

ASSOCIATED CONTENT

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Detailed experimental procedures; characterization data; and copies of [1] H, ^{19}F,

and ^{13}C NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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