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Palladium-Catalyzed Amination of Chloromethylnaphthalene and Chloromethylanthracene Derivatives with Various Amines

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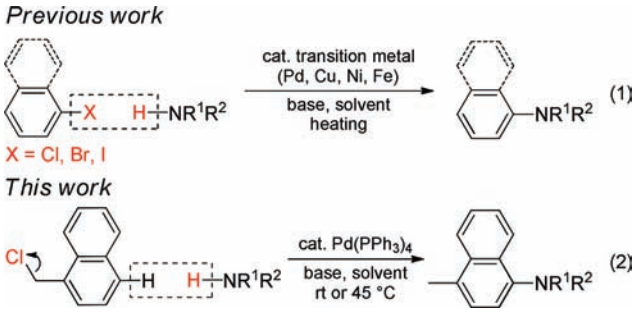
Supporting Information

ABSTRACT: Palladium-catalyzed amination of chloromethylnaphthalene and chloromethylanthracene derivatives to produce naphthylamines and anthrylamines in satisfactory to good yields has been developed. The unprecedented amination reactions proceeded smoothly under mild conditions in the presence of $Pd(PPh_3)_4$ as a catalyst.

The development of convenient and efficient methods for the synthesis of arylamines has attracted considerable attention. Arylamines represent an interesting structural motif that is frequently found in various bioactive molecules and functional materials.[1] Among C(aryl)−N bond-forming processes, the transition-metal-mediated amination of aryl halides with amines and amides using palladium,[2] copper,[3] nickel,[4] and iron[5] catalysts has recently emerged as an extremely powerful tool for the synthesis of aniline derivatives. As shown in eq 1,



the catalytic amination of aryl halides always occurs at the aromatic carbon linked to a halogen atom no matter which kind of catalyst is used. In addition, an excellent work reported by Hartwig and co-workers revealed that the reductive elimination reaction of a benzylpalladium amido complex containing the chelating ligand 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) can easily occur to form a C(alkyl)−N bond in benzylamine.[6]

Palladium-catalyzed amination of aryl halides with amines, namely, the Buchwald−Hartwig reaction, has been well-known as an area of intense research in the recent literature.[7,8] The Buchwald−Hartwig reaction was successfully utilized as a key reaction in natural product synthesis.[9] Herein, an unprecedented palladium-catalyzed amination of chloromethylnaphthalene and chloromethylanthracene derivatives with various amines is reported. As shown in eq 2, the palladium-catalyzed amination of 1-chloromethylnaphthalene with primary and secondary amines occurred at the para position to afford a 1-amino-4-methylnaphthalene derivative.

Initially, 1-chloromethylnaphthalene (**1a**) was used as a starting material to determine the scope of amine substrates under the optimized reaction conditions.[10] The results are shown in Table 1. The reaction of **1a** with the five- and six-membered cyclic amines pyrrolidine and piperidine proceeded smoothly to give the corresponding products **2a** and **2b** in moderate yields (62 and 66%, respectively). The use of the six-membered cyclic amines morpholine and thiomorpholine led to good yields of the corresponding products **2c** and **2d** (83 and 86%, respectively). Product **2e** was obtained in only 40% yield when the reaction of **1a** with 1-methylpiperazine was performed under the same reaction conditions (method A). Gratifyingly, the yield of **2e** was improved to 71% merely by changing the solvent from tetrahydrofuran (THF) to 1, 2-dimethoxyethane (DME). Decomposition of **1a** was observed when the noncyclic aliphatic amine diisopropylamine was examined (**2f**, 0%). However, the amination products **2g−i** were obtained in moderate to good yields when noncyclic aromatic amines *N*-methylaniline, 4-methyl-*N*-methylaniline, and 4-methoxy-*N*-methylaniline were tested (75, 81, and 65%, respectively). The reaction of **1a** with benzylamine, an aliphatic primary amine, gave the desired amination product **2j** in only 14% yield along with the normal nucleophilic substitution product *N*-benzyl-1-(naphthalen-1-yl)methanamine (**3**) and the dehalogenation product 1-methylnaphthalene (**4**) in yields of 30 and 43%, respectively. Subsequent investigations revealed that aromatic primary amines can be employed in this type of amination reaction under modified reaction conditions (method B). The product **2k** was isolated in 74% yield when a mixture of **1a** and aniline in DME was treated at 45 °C for 24 h. A relatively low yield was observed for the reaction of **1a** with 2-methylaniline (**2l**, 47%). The poor reactivity exhibited by 2-methylaniline was considered to be due to the steric effect of the *o*-methyl group in the aniline substrate. However, a *m*-methyl group in the aniline substrate did not influence the reaction yield, as product **2m** was obtained in 77% yield. A *m*-methoxy group in the aniline substrate, unlike the *m*-methyl group, strongly influenced the reaction process and resulted in a low yield of **2n** (45%). This result is perhaps due to the ability of the methoxy group to coordinate to palladium.[11] Product **2o** was isolated in low yield (38%) from the reaction of **1a** with 3-chloroaniline because **2o** acted as an aromatic secondary amine substrate that further reacted with **1a** to give the

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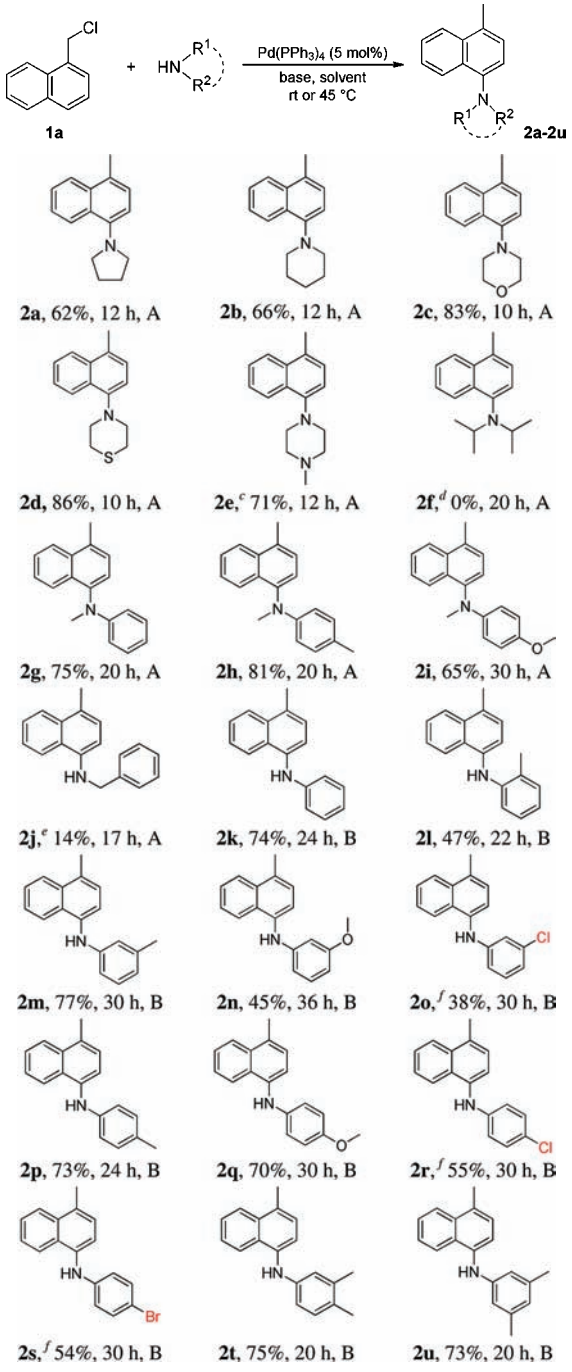
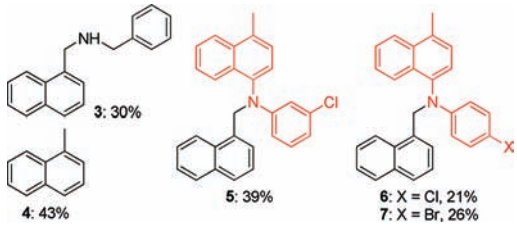
Table 1. Palladium-Catalyzed Regioselective Amination of 1-Chloromethylnaphthalene (1a) with Various Amines[a,b]

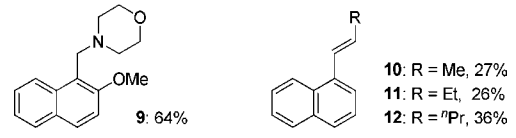


[a]Method A: **1a** (0.5 mmol), amine (2.0 equiv), NaH (4.0 equiv), and $Pd(PPh_3)_4$ (5 mol %) in THF (5 mL) at room temperature under a N_2 atmosphere. Method B: **1a** (0.5 mmol), amine (2.0 equiv), K_3PO_4 (2.0 equiv), and $Pd(PPh_3)_4$ (5 mol %) in DME (5 mL) at 45 °C under a N_2 atmosphere. [b]Isolated yields are shown. [c]DME was used as the solvent. [d]**1a** decomposed. [e]The normal substitution product **3** and dehalogenation product **4** were isolated in 30 and 43% yield, respectively. [f]Byproducts **5**, **6**, and **7** were isolated in 39, 21, and 26% yield, respectively.

nucleophilic substitution product *N*-(3-chlorophenyl)-4-methyl-*N*-(naphthalen-1-ylmethyl)naphthalen-1-amine (**5**) in 39% yield. Products **2p** and **2q** were obtained in satisfactory yields using aniline substrates bearing *p*-methyl or -methoxy groups (73 and 70% yield, respectively). Results similar to those for 3-chloroaniline were obtained when 4-chloro- and 4-bromoaniline were tested. Products **2r** and **2s** were obtained in yields of 55 and 54%, respectively, along with the byproducts *N*-(4-chlorophenyl)-4-methyl-*N*-(naphthalen-1-ylmethyl)naphthalen-1-amine (**6**) and *N*-(4-bromophenyl)-4-methyl-*N*-(naphthalen-1-ylmethyl)-naphthalen-1-amine (**7**) in 21 and 26% yield, respectively. Finally, dimethyl-substituted anilines 3,4-dimethylaniline and 3,5-dimethylaniline were examined, and the corresponding products **2t** and **2u** were obtained in yields of 75 and 73%, respectively.



Next, morpholine was used as an amine substrate to determine the scope of chloromethylnaphthalenes under the optimized reaction conditions.[10] The results are shown in Table 2. Unlike the reaction of 1-(chloromethyl)-2-methoxynaphthalene (**1c**) bearing a problematic *o*-methoxy group, the reactions of 1-(chloromethyl)-2-methylnaphthalene (**1b**) and 1-(chloromethyl)-3-methylnaphthalene (**1d**) proceeded smoothly to give the corresponding products **8b** and **8d** in yields of 78 and 63%, respectively. Product **8c** was isolated in 29% yield along with the normal nucleophilic substitution product 4-((2-methoxynaphthalen-1-yl)methyl)morpholine (**9**) in 64% yield. 1-Chloromethylnaphthalenes **1e–i** with phenyl groups linked at the benzylic position exhibited high reactivities, furnishing the corresponding products **8e–i** in moderate to good yields (67–88%). Notably, the Cl and Br atoms linked to the aromatic ring were maintained in the structures of the products **8g** and **8i** under the amination reaction conditions, suggesting that further manipulation may produce useful compounds. The applicability of 1-chloromethylnaphthalenes **1j–m** with alkyl groups linked at the benzylic position for this type of amination reaction were subsequently investigated. Products **8j–l** were obtained in moderate yields (60, 62, and 55%, respectively) along with *β*-hydride elimination products **10–12** in 27, 26, and 36% yield, respectively.[12] Surprisingly, **8m** was obtained in 89% yield as the sole product from the reaction of 1-(1-chloro-2-methylpropyl)naphthalene (**1m**) with morpholine. No *β*-hydride elimination product could be observed.



The success in obtaining naphthylamines via palladium-catalyzed amination of chloromethylnaphthalenes encouraged us to examine the reaction of 9-chloromethylanthracene (**13**) with various amines, and the results are summarized in Table 3. When the palladium-catalyzed amination reactions of **13** with *N*-methylaniline, *N*-ethylaniline, *N*-allylaniline, 4-methyl-*N*-methylaniline, and 4-methoxy-*N*-methylaniline were performed in DME using NaO^tBu as a base for 12 h (method D), the corresponding amination products **14a–e** were obtained in moderate yields (48–55%). The cyclic secondary amine morpholine exhibited higher reactivity than the *N*-alkyl-substituted anilines, affording the desired product **14f** in 60%

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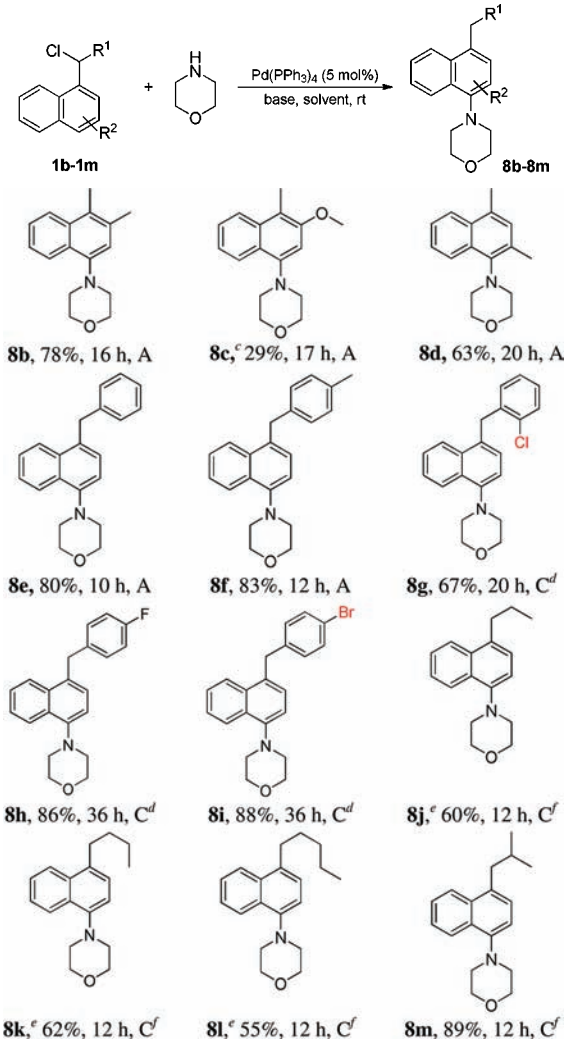
Table 2. Palladium-Catalyzed Regioselective Amination of Chloromethylnaphthalene Derivatives with Morpholine[a,b]



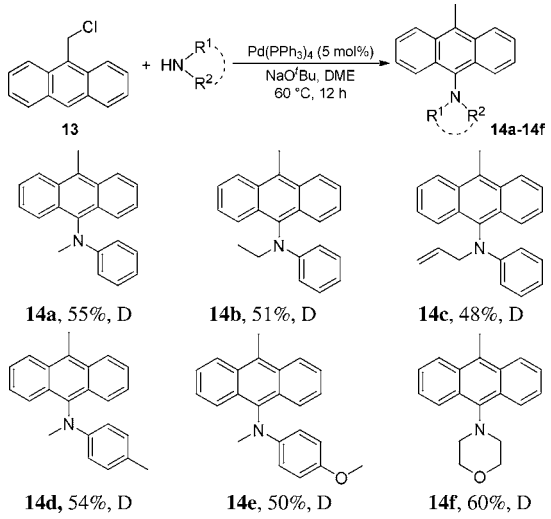
[a]Method A: **1b–i** (0.5 mmol), amine (2.0 equiv), NaH (4.0 equiv), and $Pd(PPh_3)_4$ (5 mol %) in THF (5 mL) at room temperature under a N_2 atmosphere. Method C: **1g–m** (0.5 mmol), amine (1.2 equiv), NaO^{t}Bu (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol %) in THF or DMSO (5 mL) at room temperature under a N_2 atmosphere. [b]Isolated yields are shown. [c]The normal nucleophilic substitution product **9** was isolated in 64% yield. [d]THF was used as the solvent. [e]β-H elimination products **10**, **11**, and **12** were also isolated in 27, 26, and 36% yield, respectively. [f]DMSO was used as the solvent.

yield. The relatively low yields of **14a–f** obtained may be attributed to the instability of **13** under the reaction conditions.

To explore the mechanism of this type of amination reaction, a mixture of **1e** and morpholine was treated under method A conditions for a short time (1 h). The result is shown in Scheme 1. As expected, an aminative dearomatization product, **15**, was isolated in 30% yield. Product **15** was quite stable under neutral and acidic conditions at room temperature but could easily change into the isomer **8e** (see Table 2) under strongly basic conditions.

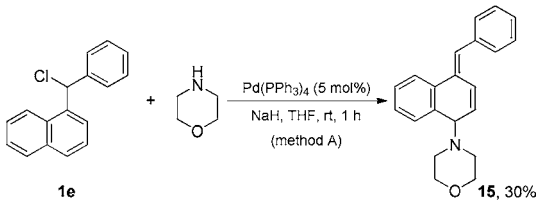
A plausible mechanism for the palladium-catalyzed amination of chloromethylnaphthalene and chloromethylanthracene derivatives with amines is shown in Scheme 2. The oxidative addition of **1a** to a Pd(0) species could produce the η^3-allylpalladium chloride intermediate **A**, which could isomerize

Table 3. Palladium-Catalyzed Regioselective Amination of 9-Chloromethylanthracene (13) with Various Amines[a,b]

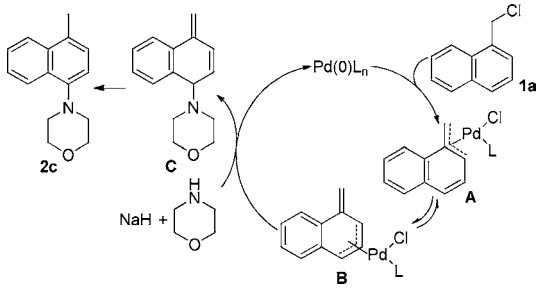


[a]Method D: **13** (0.5 mmol), amine (1.2 equiv), NaO^{t}Bu (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol %) in DME (5 mL) at 60 °C under a N_2 atmosphere. [b]Isolated yields are shown.

Scheme 1. Palladium-Catalyzed Regioselective Amination of 1-(Chloro(phenyl)methyl)naphthalene (1e) with Morpholine



Scheme 2. Proposed Mechanism for the Palladium-Catalyzed Amination of Chloromethylnaphthalene and Chloromethylanthracene Derivatives with Amines



to η^3-allylpalladium chloride intermediate **B**. The Tsuji–Trost-type nucleophilic substitution reaction of intermediate **B** with morpholine in the presence of NaH as a base could produce dearomatization product **C** and regenerate the Pd(0) catalyst.[13] The product **C** could undergo a 1,5-prototropic shift under basic reaction conditions to give the para-aminated product **2c**.[14]

In summary, we have developed a novel and general catalytic method for the conversion of chloromethylnaphthalene and chloromethylanthracene derivatives to naphthylamines and anthrylamines using $Pd(PPh_3)_4$ as a catalyst. The methyl group in the structures of products **2a–e**, **2g–u**, and **14a–f** should easily be transformed into various functional groups, which would make these products more useful in organic

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synthesis. The commercial availability of the catalyst, mild reaction conditions, experimental simplicity, and broad substrate scope are the features of the catalytic method presented in the current paper. Further studies focusing on the theoretical explanation of the reaction mechanism and the extension of the reaction scope using oxygen-, phosphorus-, and sulfur-containing nucleophiles are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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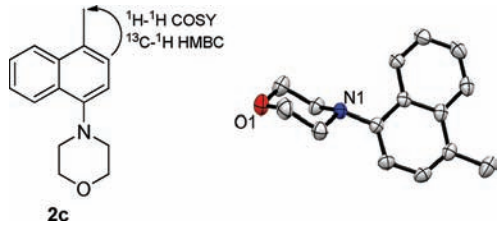
(14) The structural assignment was based on the analysis of 1D (^{1}H and ^{13}C) and 2D (^{1}H−^{1}H COSY and ^{13}C−^{1}H HMBC) NMR spectra. For example, the connection of product **2c** was obtained from ^{1}H−^{1}H COSY and ^{13}C−^{1}H HMBC spectra, and **2c** was further identified by a determination of its X-ray structure.



2c

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