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# Highly Efficient Aminocarbonylation of Iodoarenes at Atmospheric Pressure Catalyzed by a Robust Acenaphthoimidazolyidene Allylic Palladium Complex

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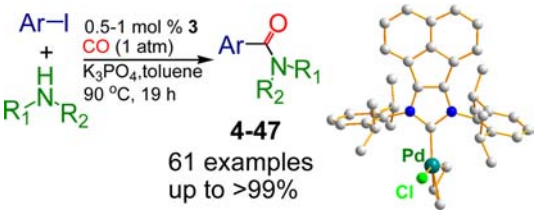
## ABSTRACT




**A robust allylic palladium−NHC complex was developed and exhibited extremely high catalytic activity toward aminocarbonylation of various (hetero)aryl iodides under atmospheric carbon monoxide pressure, in which a broad range of secondary and primary amines were well tolerated. In addition, the concise synthesis of an anticancer drug tamibarotene was accomplished even in a gram scale, further highlighting the practical applicability of the protocol.**

Significant efforts have been devoted to the development of transition metal catalyzed cross-coupling reactions,[1] which have been considered the most powerful protocols to construct C−C or C−N bonds. Among them,[2] the palladium-catalyzed aminocarbonylation reactions are less studied and consititute an indispensable highly regioselective methodology to synthesize amides,[3] which broadly exist in bioactive drugs (Figure 1), polymers, and natural products.[4] Although some progress has been achieved along with the development of various catalysts containing phosphine ligands (Figure 2),[5−7] their applicability is still hindered by the following aspects: (1) high catalyst loadings (usually 2−10 mol %), (2) high temperatures (100−150 °C in general), (3) high pressure of carbon monoxide (up to 180 psi), and (4) tedious handle steps are required to avoid oxidization of the highly air sensitive phosphines. Moreover, the most essential obstacle is that the activity of the catalysts toward oxidative addition of aryl halides is hindered by the strong bonding ability of

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CO ($\pi$ acceptor) to the Pd center.[6] As one kind of strong $\sigma$-donor and weak $\pi$-acceptor, N-heterocyclic carbenes (NHCs) represent robust ligands and could accelerate the oxidation addition of transition metals into aryl halides.[8] However, to the best of our knowledge, there is only one example on the aminocarbonylation catalyzed by Pd-NHCs, in which up to a 10 mol % catalyst was required to achieve moderate yields.[7e] In comparison with imidazole ylidenes, the less intensively studied ylidenes derived from benzimidazolium and acenaphthoimidazolium salts behave differently;[9] as stronger $\sigma$-donors and weaker $\pi$-acceptors they may further increase the electron density of the catalytic center and facilitate the oxidative addition even under an excess of CO atmosphere. Therefore, we are interested in exploring the possibility of the catalytic activity enhancement by using Pd-NHC complexes based on acenaphthoimidazolium salts in the aminocarbonylation reactions.

Following our recent research interests in the synthesis of metal complexes and their potential applications in catalysis and soft matter aspects,[10−12] robust palladium NHC complexes **2** based on $\pi$-extended sterically bulky imidazolium salts were synthesized and exhibited very high catalytic activity toward the amination and Suzuki−Miyaura cross-coupling of sterically hindered (hetero-) aryl halides in excellent yields.[12a,b] In addition, we have successfully developed a straightforward, efficient, and practical hydration protocol to access a variety of primary (hetero)aromatic amides from the corresponding organonitriles in water catalyzed by $K_2CO_3$ under microwave irradiation.[13] To further extend these works, herein, we synthesized the allylic palladium NHC complex **3** and explored its catalytic potential toward aminocarbonylation of (hetero)aryl iodides with various amines under atmospheric pressure.

Palladium complex **3** was readily accessible in a good yield from the corresponding acenaphthoimidazolium salt by stirring with $[Pd(allyl)Cl]_2$ and KO*t*-Bu in THF at room

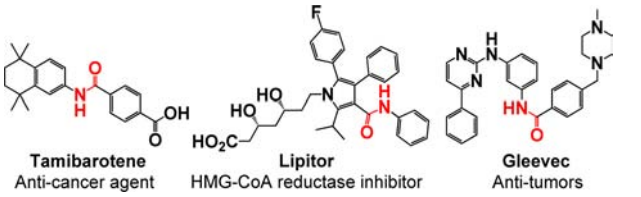


**Figure 1.** Selected pharmaceuticals containing the amide bonds.

temperature. Yellow needle-shaped crystals were obtained by slow diffusion of petroleum ether into a dichloromethane solution of complex **3**, which were suitable for single crystal diffraction analysis. As anticipated, the space around the Pd center is quite congested in contrast to its imidazol-2-ylidene analogues **1** (see the Supporting Information (SI)). The two phenyl rings are almost perpendicular to the plane of the acenaphtho-ring. The distance of Pd−$_N$C$_N$ is 2.048(4) Å, which is similar to what was observed in Pd-NHC **1** in the literature,[14] while the distances of Pd−$C_{allyl}$ are 2.096(5), 2.121(5), and 2.175(5) Å, respectively, which are shorter than what was reported for Pd-NHC **1** due to the trans-effect of the strong $\sigma$-donor property of the acenaphtho-ring.[15]

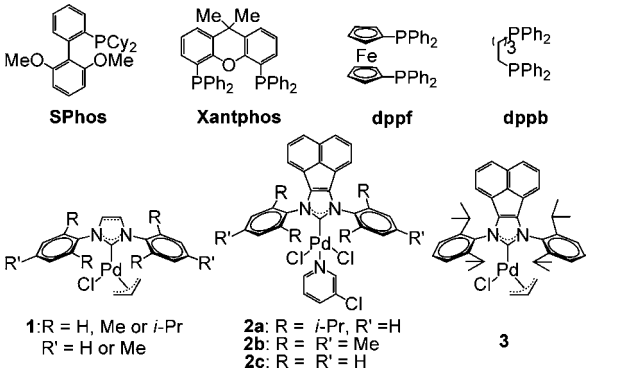


**Figure 2.** A selection of phosphine ligands and Pd−NHC complexes for the Pd-catalyzed aminocarbonylation reactions.

To evaluate the efficiency of Pd-NHC complex **3**, *p*-iodotoluene and morpholine were selected as model substrates to optimize the reaction conditions (Table 1). Delightedly, with 5 mol % catalyst, *N*-(4-methylbenzoyl) morpholine **4a** was formed in an 87% yield when the reaction was carried out with $K_3PO_4$ and toluene at 90 °C within 19 h under atmospheric CO pressure (balloon, entry 1, Table 1). However, both increasing the reaction temperature to 100 °C and decreasing it to 80 °C led to inferior yields (46% and 79% entries 2−3, Table 1).

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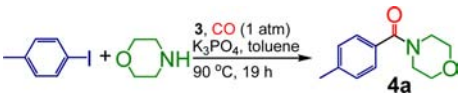
**Table 1.** Conditions Optimization with Pd−NHC Complex **3**[a]



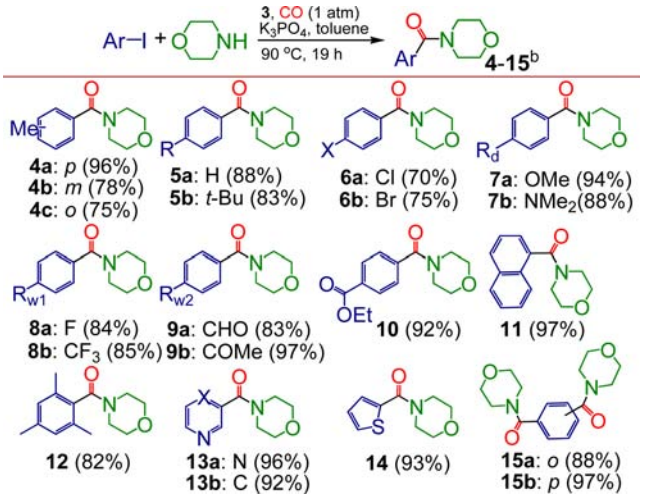

| entry | **3** (mol %) | temp (°C) | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | 5 | 90 | 19 | 87 |
| 2 | 5 | 100 | 19 | 46 |
| 3 | 5 | 80 | 19 | 79 |
| 4 | 0.5 | 90 | 19 | **96** |
| 5 | 0.5 | 90 | 12 | 83 |
| 6 | 0.5 | 80 | 19 | 82 |
| 7 | 0.3 | 90 | 19 | 77 |
| 8 | 0.1 | 90 | 19 | 71 |
| 9 | 0.05 | 90 | 19 | 67 |
| 10 | 0.01 | 90 | 19 | N.R. |

[a] 0.873 mmol scale for 19 h. [b] Isolated yield.

Varying the volume of toluene also resulted in unsatisfactory yields (see the SI). Except for hydrated potassium phosphates, no desired reactions occurred with other selected inorganic and organic bases. Furthermore, various solvents were screened for the optimization, yet all resulted in much worse results (see the SI). To our surprise, a nearly quantitative yield of product **4a** was obtained when the catalyst loading was reduced to 0.5 mol % (96%, entry 4, Table 1). A further decrease in the catalyst loading resulted in slightly lower yields (entries 7−9, Table 1). No product was detected with a 0.01 mol % catalyst (entry 10, Table 1). A 70% isolated yield was observed with the catalyst dimer (see the SI), which may indicate that the dimer formation at high catalyst concentration resulted in unsatisfactory yields. Further, reducing the reaction time or temperature resulted in lower yields (entries 5 and 6, Table 1). In order to compare the catalytic activity with other catalysts, catalysts **1** and **2** as well as XPhos were involved, and all exhibited less effective activities (see the SI).

With a defined protocol in hand, the substrate scope with various (hetero)aryl iodides was then explored. As shown in Scheme 1, the protocol well tolerated diverse electronic and steric substituents of the aryl iodides, as well as heterocyclic substrates, all resulting in good to excellent isolated yields. The relative position of substituents slightly impacted the coupling efficiency: *p*-iodotoluene resulted in a higher yield than its *m*- or *o*-analogues (**4a** vs **4b** and **4c**). Similar yields were obtained with iodobenzene and *p*-*tert*-butyl-iodobenzene (**5a** and **5b**). The aminocarbonylation only selectively occurred at the iodo-terminal for aryl hailides containing I and Cl/Br simultaneously (**6a** and **6b**). Furthermore, *p*-iodoanisole and *p*-iodo-*N*,*N*-dimethylbenzenamine gave 94% (**7a**) and 88% (**7b**) yields, respecively, indicating that a strong electron-donating group hardly affected the coupling process. To our delight, electron-deficient iodoarenes also provided good yields (**8**−**10**). As expected, heterocyclic and bulky iodoarenes all afforded excellent yields (**11**−**14**). Additionally, dicoupling in a one pot manner also worked well with 1,2- and 1,4-diiodobenzene resulting in excellent yields of products **15a** and **15b**.

**Scheme 1.** Aminocarbonylation of (Hetero-)aryl Iodides with Morpholine[a]

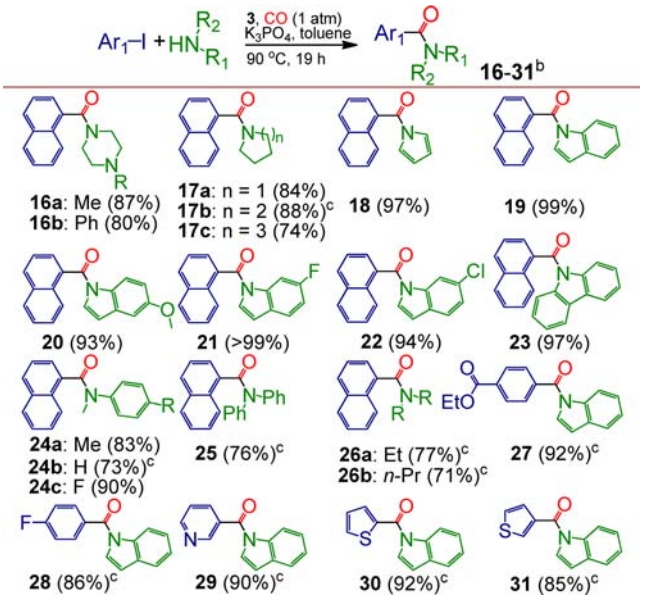



[a] 0.873 mmol scale for 19 h. [b] Isolated yield.

Encouraged by these results, a number of secondary amines were tested. As shown in Scheme 2, the aminocarbonylation of sterically hindered 1-iodo-naphthalene with *N*-methyl and *N*-phenyl-piperazine both led to good yields (**16a** and **16b**). The ring size of cyclic amines exhibited a noticeable effect: pyrrolidine gave a higher yield than that of azepane (**17a** vs **17c**); however, piperidine gave an 88% yield of **17b** even with 1.0 mol % catalyst. When other five-membered rings, such as pyrrole, indole, and its derivatives, were involved, all resulted in excellent yields (**18**−**22**, 93%−99%). To our surprise, the sterically more demanding carbazole was also successfully coupled to provide **23** in nearly quantitative yield. When *N*-methylanilines were screened, the electronic properties of the substituents in the phenyl ring slightly influenced the results, affording the products **24a**−**c** in 73−90% yields. Other bulky or heterocyclic secondary amines also resulted in moderate yields of carbonylative amination products (**25**−**26**) indicating broad substrate applicability. In addition, when indole was utilized as a nucleophile, a number of (hetero)aryl iodides were also involved, which all resulted in good to excellent isolated yields (**27**−**31**), further confirming the general applicability of the protocol.

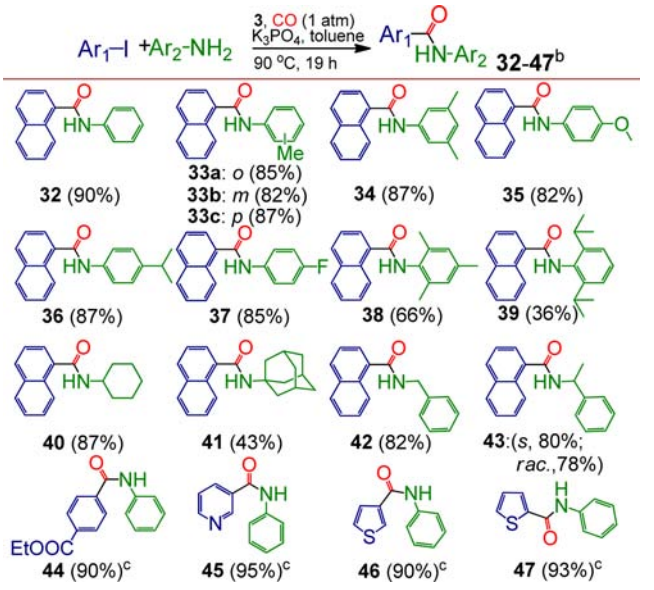
Primary amines were regarded as rather poor partners in the previously reported Pd-catalyzed aminations.[12a] Therefore, various primary amines were involved (Scheme 3). Delightedly, the aminocarbonylation of 1-iodo-naphthalene with various anilines all revealed excellent yields (**32**−**39**). The relative position and electronic properties of substituents did not affect the coupling efficiency (**32**−**37**). To our surprise, sterically more hindered substrates, such as 2,4,6-trimethylaniline and 2,6-diisopropylaniline, still resulted in acceptable yields (66% and 36% for **38** and **39**, respectively).

**Scheme 2.** Aminocarbonylation of (Hetero-)aryl Iodides with Secondary Amines[a]




[a] 0.873 mmol scale for 19 h. [b] Isolated yield. [c] With 1 mol % **3**.

**Scheme 3.** Aminocarbonylation of (Hetero-)aryl Iodides with Primary Amines[a]




[a] 0.873 mmol scale for 19 h. [b] Isolated yield. [c] With 1 mol % **3**.

In the case of aliphatic primary amines, moderate to good yields of products were achieved (**40** and **41**). When benzyl amines were applied, good yields were observed (**42** and **43**), even in the case of a chiral amine (80%). Furthermore, when aniline was utilized as a nucleophile, a variety of (hetero)aryl iodides were also well accommodated (**44**–**47**).

To further explore the potential application of our protocol in pharmaceutical targets, a concise synthesis of tamibarotene was performed (Figure 3). Unlike the expensive and complicated synthetic procedures in the literature,[16] we want to present a new straightforward methodology to access tamibarotene by using our new developed protocol from inexpensive commercial available starting materials. Amine **48** was readily prepared from aniline by using the literature method.[16c] With 1.0 mol % catalyst, the aminocarbonylation of ethyl 4-iodobenzoate with amine **48** afforded compound **49** in a 99% yield. In general, large scale carbonylation is difficult to realize.[6d] However, our protocol can be readily scaled up to a 5 mmol scale (1.75 g, 92%). After hydration, tamibarotene **50** was obtained in a 90% yield. Therefore, our synthetic procedure clearly illustrated the merits and applicability of complex **3** toward synthetic methodology for drugs in a complex setting.

In summary, a robust Pd–NHC **3** was developed and revealed high activity toward aminocarbonylation of a wide variety of (hetero)aryl iodides. The reactions were performed at low catalyst loadings with carbon monoxide at atmospheric pressure, which tolerated a broad range of functional groups, electronic properties, and bulkiness on both sides of the substrates, and afforded the products in good to excellent yields, even in the heterocyclic and multiple coupling cases. The protocol herein presented a novel straightforward, efficient, and practical means to access diverse aryl amides. In addition, a concise synthesis of an anticancer drug tamibarotene was also accomplished, which can be readily scaled up to 5 mmol scale and highlight the potential applicability in the industrial manufacturing process.

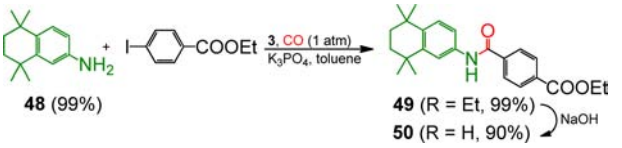



**Figure 3.** Syntheses of tamibarotene.

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**Supporting Information Available.** Experimental details and data for important compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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