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A Convenient Palladium-Catalyzed Carbonylative Synthesis of 2-Aminbenzoxazinones from 2-Bromoanilines and Isocyanates

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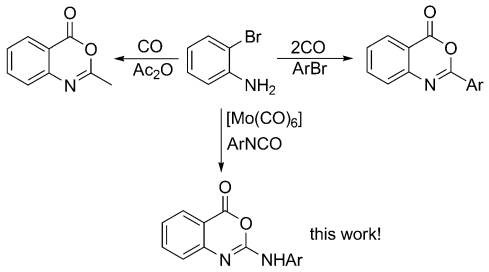
Benzoxazinones represent an important class of nitrogen heterocycles with various biological activities. Among all the substituted benzoxazinones, 2-amino substituted benzoxazinones can be considered as the most valuable as numerous biological activities have been reported for these compounds; however, methodologies for their preparation are still rare.[1,2]

Palladium-catalyzed carbonylation reactions allow for a general synthesis of all kinds of benzoic acid derivatives by starting from easily available (hetero)aryl halides and inexpensive carbon monoxide.[3] Combining such carbonylative processes with subsequent intramolecular cyclization reactions permits an efficient access to different heterocycles.[4] Palladium-catalyzed carbonylative syntheses of benzoxazinones have been developed for a long time, but the application of carbonylation in the preparation of biologically important 2-amino-substituted benzoxazinones is rarely reported.[5]

Even though carbon monoxide (CO) is known as one of the cheapest C1 sources, the necessity of special equipment (such as an autoclave) for its manipulation and its high toxicity have limited the synthetic applications of carbonylation reactions that require CO gas. With these problems in mind, over the last two decades, organic chemists have been looking for alternative CO sources.[6] Among all of them, $[Mo(CO)_6]$ is certainly an ideal candidate.[7]

Recently our group reported some interesting methodologies for the synthesis of 2-aryl and 2-alkyl-substituted benzoxazinones.[5h,i] However, we didn't succeed in the synthesis of the biologically more important 2-amino-substituted benzoxazinones (Scheme 1). As part of our continual interest in carbonylation reactions and also due to the importance of these compounds, we wish to report for the first time a convenient palladium-catalyzed carbonylative synthesis of 2-amino benzoxazinones. Notably, readily available 2-bromoaniline and isocyanates were applied as substrates and $[Mo(CO)_6]$ was used as a solid CO source.



Scheme 1. Synthetic strategies.

Based on our previous work and experience, the first reaction was carried out with 2-bromoaniline (1 mmol), phenylisocyanate (1 mmol), $[Mo(CO)_6]$ (1.5 mmol), $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%), and K_2CO_3 (2 mmol) in toluene (2 mL), at 140 °C for 16 h. To our delight, 42% of the desired product was formed. We then tested several organic and inorganic bases (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_3PO_4, NEt_3, *N*,*N*-diisopropylethylamine (DIPEA), Na_2CO_3) and K_3PO_4 was found to be the best base for this reaction and gave 84% of the desired product. The reaction temperature succeeded to be decreased to 120 °C, but the starting material could not be totally converted if we carried out the reaction at 100 °C. We then chose K_3PO_4 as the base to test the generality of this new procedure at 120 °C.

Regarding the reaction mechanism, the most possible one has been proposed and is shown in Scheme 2. The first step is the formation of the urea **1** from 2-bromoaniline and phenylisocyanate, followed by oxidative addition of in situ generated Pd^0 to the C–Br bond to form the complex **2**. After coordination and insertion of $[Mo(CO)_6]$ released CO, the key intermediate **3** is produced. Reductive elimination produces the final product, 2-amino benzoxazinone, and Pd^0 for

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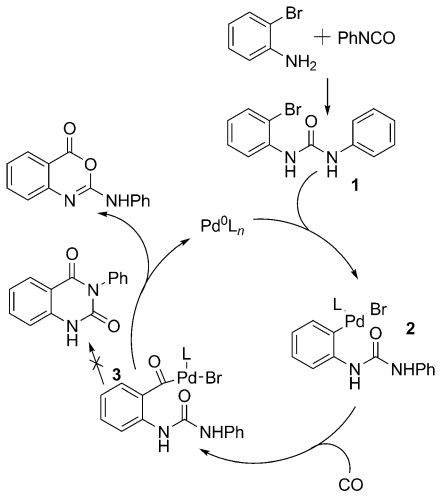


Scheme 2. Proposed reaction mechanism.

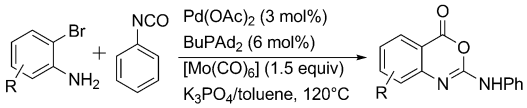
the next catalytic cycle. Notably, 3-phenylquinazoline-2,4-(1*H*,3*H*)dione, one of the most plausible possible products, was not detected in our system.[5j] We estimate that $[Mo(CO)_6]$ may also play a crucial role in this reaction system. Molybdenum salt might act as a Lewis acid and coordinate with **3** to assistant in the formation of 2-amino-benzoxazinones as our target product.

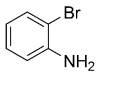
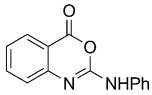
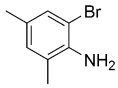
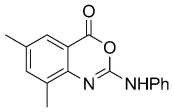
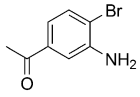
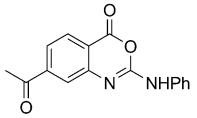
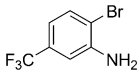
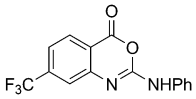
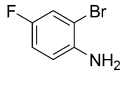
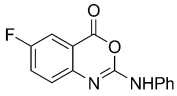
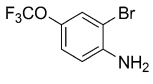
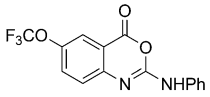
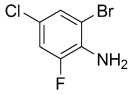
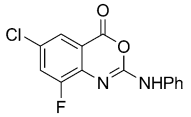
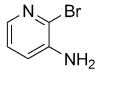
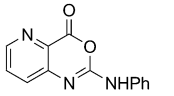
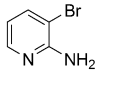
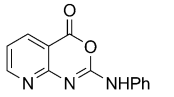
The generality and efficiency of this methodology has been proved by the 22 examples provided in Tables 1 and 2. For the first stage of discovering the reaction scope, we choose phenylisocyanate to test different 2-bromoanilines under our best reaction conditions ($[Mo(CO)_6]$ (1.5 mmol), $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%), K_3PO_4 (2 mmol), toluene (2 mL), 120 °C, 16 h). Both electron-donating and -withdrawing substituents are tolerable under our conditions (Table 1, entries 2–7). F–, CF_3–, and CF_3O– as important substituents can be tolerated in this system and give the corresponding products in 66–75% yields (entries 4–7).[8] Remarkably, 2-bromopyridin-3-amine and 3-bromopyridin-2-amine are two examples of heterocycles that can also be applied as substrates and resulted in the desired products in 63–68% yields (Table 1, entries 8, 9).

We then used 2-bromoaniline as a model substrate to check the generality of isocyanates (Table 2). Ethoxy, ethyl, methylthio, and halogen-substituted aromatic isocyanates were successfully applied and gave the desired products in good yields (Table 2, entries 1–7). CF_3–, CF_3O–, CN–, and EtOOC– as strong electron-withdrawing functional groups are all tolerable and the designed products were isolated in 40–84% yields (entries 8–11). Additionally, 60% of 2-(naphthalen-1-ylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one was prepared from the corresponding naphthylisocyanate under our conditions (entry 12). To our delight, even alkyl isocyanate succeeded to be applied and gave the desired product in a 90% yield (entry 13).

Additionally, we think it is also possible to generate the needed urea from 2-bromophenylisocyanate and aniline. As

Table 1. Palladium-catalyzed carbonylative coupling of phenylisocyanate with 2-bromoanilines.[a]



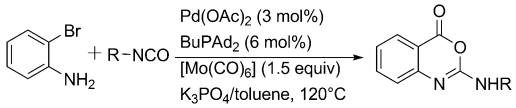
Entry	2-Bromoaniline	Product	Yield [%][b]
1			73
2			77
3			69
4			73
5			70
6			66
7			75
8			63
9			68

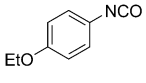
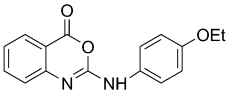
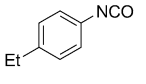
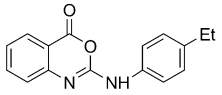
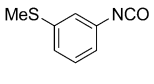
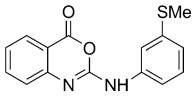
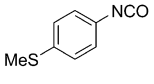
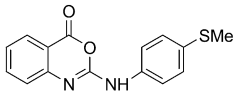
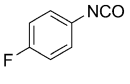
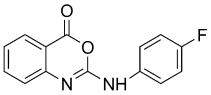
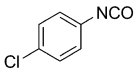
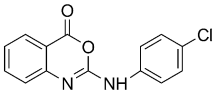
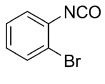
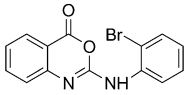
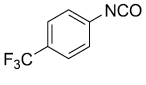
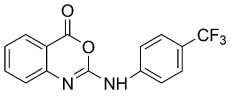
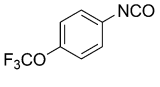
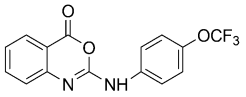
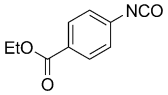
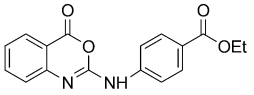
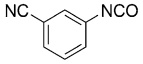
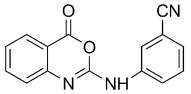
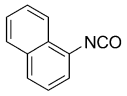
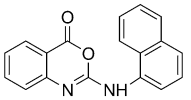
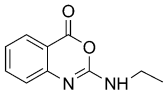
[a] $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%), toluene (2 mL), K_3PO_4 (2 mmol), 2-bromoanilines (1.0 mmol), phenylisocyanate (1 mmol), $[Mo(CO)_6]$ (1.5 mmol), 120 °C, 16 h. [b] Isolated yield.

we expected, 70% of 2-(phenylamino)-4*H*-benzo[*d*]-[1,3]oxazin-4-one was isolated from the reaction of 2-bromophenylisocyanate and aniline (Scheme 3). As anilines are ready available and abundant chemicals, this can dramatically extend the scope of our methodology and increase the application potential of our procedure.

In conclusion, a general and convenient methodology for 2-amino benzoxazinone synthesis has been developed. Ready available 2-bromoanilines and isocyanates were used as substrates and various products have been prepared in good yields. Notably, $[Mo(CO)_6]$ as a solid CO source was applied instead of gas, which increased the application potential of this methodology. Additionally, we could also extend our methodology to 2-bromophenylisocyanate and anilines, which will definitely increase the substrates scope

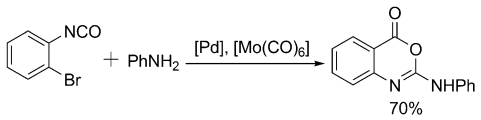
Table 2. Palladium-catalyzed carbonylative coupling of 2-bromoaniline with phenylisocyanates.[a]



Entry	Isocyanate	Product	Yield [%][b]
1			47
2			80
3			82
4			80
5			75
6			71
7			64
8			61
9			84
10			78
11			40
12			60
13			90

[a] $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%), toluene (2 mL), K_3PO_4 (2 mmol), 2-bromoaniline (1.0 mmol), isocyanates (1 mmol), $[Mo(CO)_6]$ (1.5 mmol), 120°C, 16 h. [b] Isolated yield.

of our procedure as anilines are abundant and readily available.



Scheme 3. Synthesis of 2-(phenylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one from 1-bromo-2-isocyanatobenzene and aniline.

Experimental Section

General procedure for the carbonylative synthesis of 2-amino-benzoxazinones: After the pressure tube was purged three times with argon, phenylisocyanate (1.0 mmol), 2-bromoaniline (1.0 mmol), and toluene (3 mL) were added and the mixture was stirred for 1 h at room temperature under argon. $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%), K_3PO_4 (2.0 mmol), and $[Mo(CO)_6]$ (1.5 mmol) were transferred into the pressure tube under an argon flow and the reaction was performed for 16 h at 120°C. The mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. After removal of the solvent in vacuum, the products were isolated by column chromatography in hexane/ethyl acetate 9:1 as the eluent.

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Keywords: benzoxazinones · carbonylation · catalysis · nitrogen heterocycles · palladium

[1] For selected reports on bioactive amino-substituted benzoxazinones, see: a) E. Colson, J. Wallach, M. Hauteville, *Biochimie* **2005**, *87*, 223–230; b) M. Pietsch, M. Gütschow, *J. Biol. Chem.* **2002**, *277*, 24006–24013; c) A. Krantz, R. W. Spencer, T. F. Tam, E. Thomas, L. J. Copp, *J. Med. Chem.* **1987**, *30*, 589–591; d) M. Gütschow, M. Schlenk, J. Gäb, M. Paskaleva, M. W. Alnouri, S. Scolari, J. Iqbal, C. E. Müller, *J. Med. Chem.* **2012**, *55*, 3331–3341; e) M. Pietsch, M. Gütschow, *J. Med. Chem.* **2005**, *48*, 8270–8288; f) S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang, J. C. Jaen, *J. Med. Chem.* **1998**, *41*, 1060–1067; g) M. Gütschow, L. Kuerschner, U. Neumann, M. Pietsch, R. Löser, N. Koglin, K. Eger, *J. Med. Chem.* **1999**, *42*, 5437–5447; h) H. G. Häcker, F. Grundmann, F. Lohr, P. A. Ottersbach, J. Zhou, G. Schnakenburg, M. Gütschow, *Molecules* **2009**, *14*, 378–402; i) M. Gütschow, L. Kuerschner, M. Pietsch, A. Ambrozak, U. Neumann, R. Günther, H. J. Hofmann, *Arch. Biochem. Biophys.* **2002**, *402*, 180–191; j) U. Neumann, N. M. Schechter, M. Gütschow, *Bioorg. Med. Chem.* **2001**, *9*, 947–954.

[2] For reviews on benzoxazinone syntheses, see: a) G. M. Coppola, *J. Heterocycl. Chem.* **1999**, *36*, 563–588; b) G. M. Coppola, *J. Heterocycl. Chem.* **2000**, *37*, 1369–1388.

[3] For reviews on palladium-catalyzed carbonylations, see: a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; b) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; c) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; d) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402–5422; e) Q. Liu, H. Zhang, A. Lei, *Angew. Chem.* **2011**, *123*, 10978–10989; *Angew. Chem. Int. Ed.*

2011, *50*, 10788–10799; f) X. F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229–241.

[4] a) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; b) B. Willy, T. J. J. Müller, *Curr. Org. Chem.* **2009**, *13*, 1777–1790; c) E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Eur. J.* **2009**, *15*, 5006–5011; d) B. Willy, T. J. J. Müller, *Synthesis* **2008**, 293–303; e) A. V. Rotaru, I. D. Druta, T. Oeser, T. J. J. Müller, *Helv. Chim. Acta* **2005**, *88*, 1798–1812; f) B. Willy, T. J. J. Müller, *Eur. J. Org. Chem.* **2008**, *24*, 4157–4168; g) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581–2583; h) E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817–4819; i) A. S. Karpov, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2004**, 1502–1503.

[5] a) R. C. Larock, C. A. Fellows, *J. Org. Chem.* **1980**, *45*, 363–365; b) S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett* **1996**, 997–998; c) C. Larksarp, H. Alper, *Org. Lett.* **1999**, *1*, 1619–1622; d) J. Salvadori, E. Balducci, S. Zaza, E. Petricci, M. Taddei, *J. Org. Chem.* **2010**, *75*, 1841–1847; e) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. g. Tyler, M. R. Gagne, G. C. Loyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862–1865; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830–1833; f) R. Giri, J. K. Lam, J. Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686–693; g) P. Ács, E. Mueller, G. Rangits, T. Lorand, L. Kollar, *Tetrahedron* **2006**, *62*, 12051–12056; h) X. F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 12246–12249; i) X. F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 12599–12602; j) C. Larksarp, H. Alper, *J. Org. Chem.* **2000**, *65*, 2773–2777.

[6] T. Morimoto, K. Kakiuchi, *Angew. Chem.* **2004**, *116*, 5698–5706; *Angew. Chem. Int. Ed.* **2004**, *43*, 5580–5588.

[7] For an excellent account on using $[Mo(CO)_6]$ as a CO source, see: L. R. Odell, F. Russo, M. Larhed, *Synlett* **2012**, 685–698.

[8] For selected reviews on these topics, see: a) X. F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) V. V. Grushin, *Acc. Chem. Res.* **2010**, *43*, 160–171; d) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521.

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