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Carbonylative Coupling

Palladium-Catalyzed Carbonylative Reactions of 1-Bromo-2-fluorobenzenes with Various Nucleophiles: Effective Combination of Carbonylation and Nucleophilic Substitution

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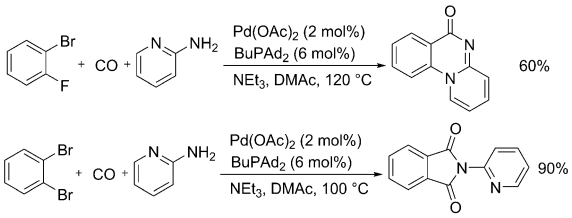
Abstract: A systematic study on the carbonylative transformation of 1-bromo-2-fluorobenzenes with various nucleophiles has been performed. Different types of double nucleophiles, such as N–N, N–C, O–C, and N–S, can be effectively applied as coupling partners. The corresponding six-membered heterocycles were isolated in moderate to good yields.



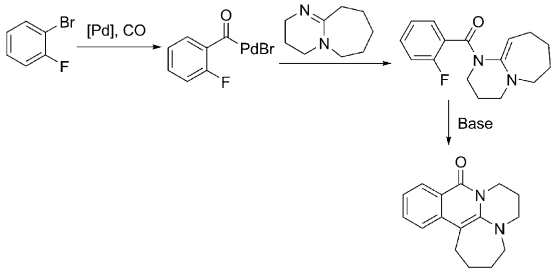
Scheme 1. Synthetic strategies.

The development of novel and improved palladium-catalyzed coupling reactions is a current topic in modern organic synthesis.[1] Many efforts have been devoted toward and impressive progress has been achieved in this area during the past decades, which has also been awarded with the Nobel Prize in 2010.[2] Among the known coupling reactions, palladium-catalyzed carbonylation reactions are an interesting topic with unique advantages.[3] Through carbonylation reactions, carbon monoxide, one of the cheapest C1 sources, can be installed into the parent molecules. In this way, synthetically important and valuable carbonyl-containing compounds are easily prepared, which can be submitted to further modifications. After 40 years of development, many named procedures have been established, such as the aminocarbonylation, the alkoxycarbonylation, the carbonylative Suzuki reaction, the carbonylative Heck reaction, the carbonylative Sonogashira reaction, etc. However, the merge of a carbonylation with a nucleophilic substitution reeation has been rarely studied, which provides new options for synthetic chemists, especially for the synthesis of heterocycles (Scheme 1).[4]

Heterocycles constitute an essential structural motif that is found in a variety of biologically active substances; this stimulates the development of new strategies and technologies for their synthesis.[5] Remarkably, seven out of the top ten pharmaceutical products according to worldwide sales in 2009 contain a heterocyclic motif as their core structure.[6] Herein, we wish to report our new results on the carbonylative transformation of 1-bromo-2-fluorobenzenes with various nucleophiles. The corresponding six-membered heterocyclic compounds were isolated in moderate to good yields.

Fused isoquinolinones have been reported with various biological and medicinal activities, such as antihypertensive activity, NK3 antagonists, melatonin MT_1 and MT_2 receptor agonists, Rho-kinase inhibitors, and JNK inhibitors.[7,8] In our previous study on the carbonylation of 1-bromo-2-fluorobenzenes with 2-aminopyridine, the formation of a fused isoquinolinone was observed in some cases.[4b] After careful analysis, we found that the fused isoquinolinone was produced from the carbonylative reaction between 1-bromo-2-fluorobenzene and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The best result of the unexpected isoquinolinone formation was achieved in the presence of $Pd(OAc)_2$ (5 mol%) and $BuPAd_2$ (10 mol%; Ad = adamantyl) in DMAc under 15 bar of carbon monoxide at 120 °C (68% isolated yield; Table 1, **a**).[2a,b,3,5,6]

In this case, DBU was applied as both the reagent and base. Regarding the reaction pathway, we believe that it involves a nucleophilic attack of the less hindered nitrogen atom of DBU to the acylpalladium complex and rearrangement of the C=N bond to a C=C and, at last, nucleophilic substitution of C–F with RHC=C to give the final product (Scheme 2). As



Scheme 2. Proposed reaction mechanism for the synthesis of isoquinolinones.

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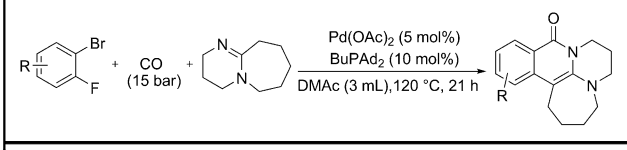
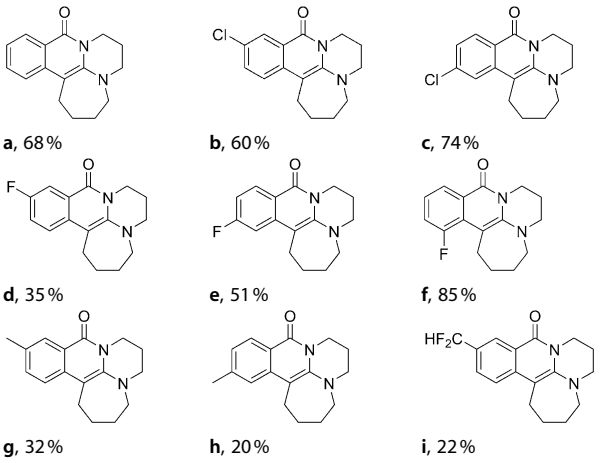
Table 1. Palladium-catalyzed carbonylative synthesis of isoquinolinones.[a]





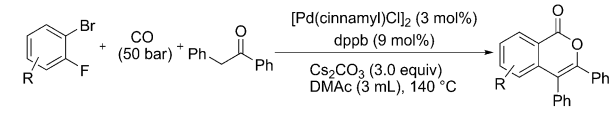
[a] Reaction conditions: 1-bromo-2-fluorobenzene (0.5 mmol), DBU (4.0 equiv), $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%), DMAc (3 mL), CO (15 bar), 120 °C, 21 h. Yield of the isolated product.

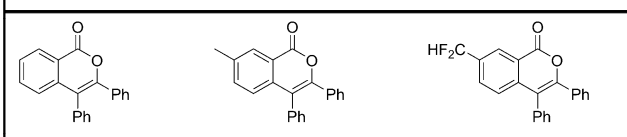
shown in Table 1, various 1-bromo-2-fluorobenzenes were successfully applied and the desired fused isoquinolinones were obtained in low to good yields. Both electron-donating and electron-withdrawing substitutions were tolerated, also at various positions.

To our delight, in addition to nitrogen–carbon nucleophiles, oxygen–carbon nucleophiles were applicable as well. In the reactions of 1-bromo-2-fluorobenzenes with 2-phenylacetophenone, the corresponding isochromenones were isolated in 34–40% yield (Table 2). In this transformation, the in situ formation of enolates was involved (Scheme 3).

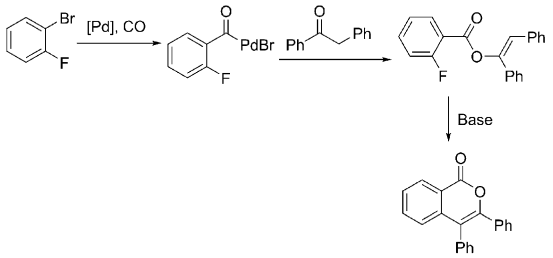
Meanwhile, we were wondering if this concept could be extended to the synthesis of quinazolinones, which represent important analogues of heterocyclic compounds.[9] By combining

Table 2. Palladium-catalyzed carbonylative synthesis of isochromenones.[a]





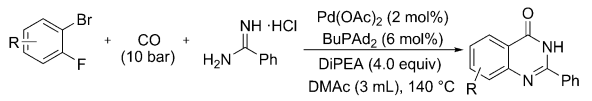
[a] Reaction conditions: 1-bromo-2-fluorobenzene (0.5 mmol), 2-phenylacetophenone (1.0 equiv), $[Pd(cinnamyl)Cl]_2$ (3 mol%), DPPB (9 mol%), Cs_2CO_3 (3.0 equiv), DMAc (3 mL), CO (50 bar), 140 °C, 40 h. Yield of the isolated product.

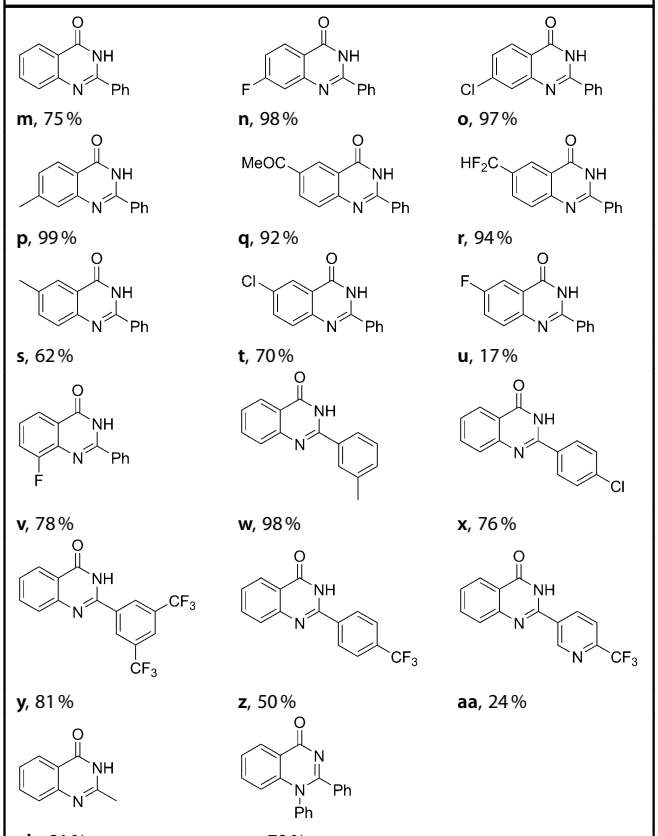


Scheme 3. Proposed reaction mechanism for the synthesis of isochromenones.

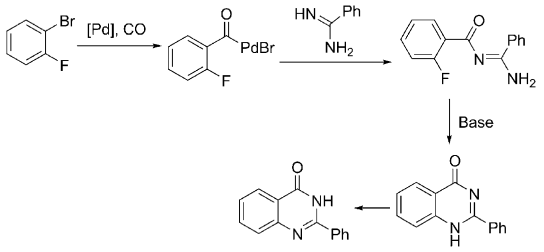
1-bromo-2-fluorobenzenes and amidines under the catalytic palladium system, the corresponding quinazolinones were formed in moderate to excellent yields (Table 3). Various functional groups were tolerated and the target quinazolinones were obtained in excellent yields with high selectivity. According to the proposed reaction mechanism, the acylpalladium species reacted with the in situ released NH and a nucleophilic substitution reaction between C–F and NH_2 occurred. The rear-

Table 3. Palladium-catalyzed carbonylative synthesis of quinazolinones.[a]





[a] Reaction conditions: 1-bromo-2-fluorobenzene (0.5 mmol), amidine (1.0 equiv), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), DiPEA (4.0 equiv), DMAc (3 mL), CO (10 bar), 140 °C, 22 h. Yield of the isolated product.

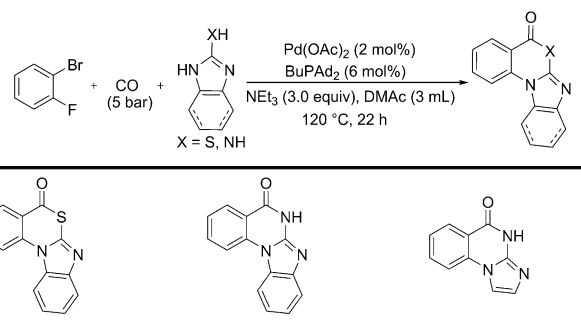


Scheme 4. Proposed reaction mechanism for the synthesis of quinazolinones.

rangement of the C=N bond was indirectly proven by the formation of 1,2-diphenylquinazolin-4(1*H*)-one **ac** (Scheme 4).

In addition to amidines, 2-aminoimidazoles and 2-thiolbenzoimidazole were tested as coupling partners under our optimized conditions. As expected, 5*H*-benzo[*d*]benzo[4,5]imidazo-[2,1-*b*][1,3]thiazin-5-one was isolated in a high yield (85%) in the presence of $Pd(OAc)_2$/$BuPAd_2$ (Table 4, **ad**). Under the same conditions, benzo[4,5]imidazo[1,2-*a*]quinazolin-5(6*H*)-one was produced in 62% yield from 1*H*-benzo[*d*]imidazol-2-amine and 1-bromo-2-fluorobenzene (Table 4, **ae**).

Table 4. Palladium-catalyzed carbonylative synthesis of other heterocycles.[a]



ad, 85% **ae**, 62% **af**, 16%[b]

[a] Reaction conditions: 1-bromo-2-fluorobenzene (0.5 mmol), 2-aminoimidazole (1.0 equiv), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%) NEt_3 (3.0 equiv), DMAc (3 mL), CO (5 bar), 120 °C, 22 h. Yield of the isolated product. [b] $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%) NEt_3 (3.0 equiv), DMAc (3 mL), CO (15 bar), 140 °C, 41 h.[9]

In summary, a systematic study on the palladium-catalyzed carbonylative transformation of 1-bromo-2-fluorobenzenes with various nucleophiles has been performed. By the merge of a carbonylative coupling and nucleophilic substitution, the desired six-membered isoquinolinones, isochromenones, and quinazolinones were formed in low to excellent yields. It is worth noting that the combination of carbonylative coupling and nucleophilic substitution offers an ideal route for the preparation of heterocycles that are usually difficult to prepare by other methodologies.

Experimental Section

Representative procedure for the synthesis of isoquinolinones

A vial (12 or 6 mL) was charged with $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%), and a stirring bar. Then, 1-bromo-2-fluorobenzene (0.5 mmol), DBU (4.0 equiv), and DMAc (3 mL) were injected under argon by using a syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 15 bar of CO was adjusted at ambient temperature. Then, the reaction was performed for 21 h at 120 °C. After the reaction was complete, the autoclave was cooled down with ice water to room temperature and the pressure was released carefully. The solution was extracted with ethyl acetate (EA) or CH_2Cl_2, then with saturated brine (3×5 times) and dried with $MgSO_4$. After evaporation of the organic solvent, the residue was adsorbed on silica gel and the crude product was purified by column chromatography using EA/pentane as eluent.

Representative procedure for the synthesis of isochromenones

A vial (12 or 6 mL) was charged with $(Pd(cinnamyl)Cl)_2$ (3 mol%), DPPB (9 mol%), 2-phenylacetophenone, Cs_2CO_3, and a stirring bar. Then, 1-bromo-2-fluorobenzene (0.5 mmol) and DMAc (3 mL) were injected under argon by using a syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 50 bar of CO was adjusted at ambient temperature. Then, the reaction was performed for 40 h at 140 °C. After the reaction was complete, the autoclave was cooled down with ice water to room temperature and the pressure was released carefully. The solution was extracted with ethyl acetate or CH_2Cl_2, then with saturated brine (3×5 times) and dried with $MgSO_4$. After evaporation of the organic solvent, the residue was adsorbed on silica gel and the crude product was purified by column chromatography using EA/pentane as eluent.

Representative procedure for the synthesis of quinazolinones

A vial (12 or 6 mL) was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), amidine and a stirring bar. Then, 1-bromo-2-fluorobenzene (0.5 mmol), DiPEA (4.0 equiv) and DMAc (3 mL) were injected under argon by using a syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar of CO was adjusted at ambient temperature. Then, the reaction was performed for 22 h at 140 °C. After the reaction was complete, the autoclave was cooled down with ice water to room temperature and the pressure was released carefully. The solution was extracted with ethyl acetate or CH_2Cl_2, then with saturated brine (3×5 times) and dried with $MgSO_4$. After evaporation of the organic solvent, the residue was adsorbed on silica gel and the crude product was purified by column chromatography using EA/pentane as eluent.

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