Solvent- and Ligand-Free Palladium-Catalyzed Amination of Aryl Halides

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Abstract: An environmentally friendly and economically favorable approach to the formation of C–N bonds is presented. The methodology is particularly interesting in that the reaction is realized under both solvent- and ligand-free conditions and involves the use of a low loading of a palladium catalyst dispersed with the reactants on a suitable solid support. The reaction proceeds rapidly under microwave irradiation.

Key words: arylation, amination, catalysis, solid-phase synthesis, green-chemistry, microwave

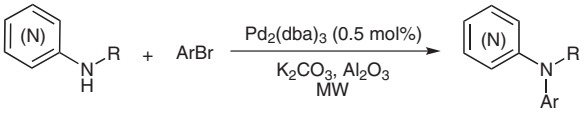
The formation of C–N bonds is an important operation in organic synthesis, and transition-metal-catalyzed reactions are useful tools for preparing a wide range of nitrogen-containing compounds.[1] Despite the considerable efforts that have been made to develop new procedures in this field, only a small percentage of fine chemicals are produced by using homogeneous catalysis, probably as a result of several critical factors, such as the availability, cost, activity, and stability of catalysts and compatibility matching of starting materials.

Arylamines are building blocks that are widely used in the synthesis of a variety of compounds, including pharmaceutical intermediates, agrochemicals, dyes, and polymers.[2] Among palladium-catalyzed amination processes, the Buchwald–Hartwig reaction represents a useful strategy for preparing substituted arylamines.[3] Since the initial reports on the reaction in 1995,[4] much attention has been directed to clarifying how the outcome of the Buchwald–Hartwig reaction is influenced by the choice of the palladium precatalyst, the base, and, above all, the ligands, which accelerate the oxidative addition and enhance the reductive elimination.[5] Also the ability of ligands to stabilize palladium(0)-species, to prevent palladium agglomeration, and to maintain catalytic properties ensures that they play a major role in the reaction. The literature reports the use of various combinations of a palladium compound, such as palladium(II) acetate, bis(dibenzylideneacetone)palladium, or tris(dibenzylideneacetone)dipalladium, with a range of phosphine ligands, such as 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine) (BINAP) or 1,1′-bis(diphenylphosphinyl)ferrocene (DPPF), tri-*tert*-butylphosphine, or biaryl(dialkyl)phosphines.[6] However, the use of ligands has some drawbacks resulting from their sensitivity to water or air. Moreover, ligands cannot normally be recovered after the reaction and their presence frequently hampers the isolation and purification of the desired product. Finally, ligands are often more expensive than catalysts and not easily available.

In attempts to overcome these drawbacks, several phosphine-free systems have been investigated; these show excellent activities in many typical palladium-catalyzed procedures, such as Heck reactions and arylation reactions[7,8] or carbonylation processes.[9] Recently, ligand-free palladium-catalyzed C–S bond-formation reactions have been reported in the literature,[10] and, very recently, studies on the Buchwald–Hartwig process have been reported.[11] Moreover, successful ligand-free approaches to copper-catalyzed amination reactions have also been described.[12]

Our recent attempts to develop synthetic procedures involving palladium-catalyzed amination reactions[13] led us to define conditions for palladium-catalyzed N-arylation of indolines by using 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (IAPU) as a phosphine ligand under solvent-free conditions with microwave activation.[14] Besides having the advantage of requiring no solvents, thereby eliminating any problems associated with their supply, purification, and disposal, this procedure provides significantly reduced reaction times and enhanced conversions.

In an attempt to develop a more ecofriendly and economically favorable approach to C–N bond formation, we investigated the palladium-catalyzed arylation of anilines under solvent-free and ligand-free conditions (Scheme 1).



Scheme 1 Solvent-free, ligand-free, palladium-catalyzed aniline arylation

To the best of our knowledge, this is the first example of solvent- and ligand-free palladium-catalyzed amination of aryl amines with aryl halides.

We began our investigation by choosing the reaction of indoline with 1-bromo-4-nitrobenzene in the presence of tris(dibenzylideneacetone)dipalladium catalyst as a

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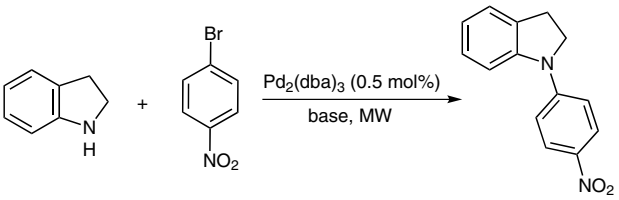
benchmark reaction (Table 1). Initially, we examined the reaction in which the reagents were supported on powdered potassium carbonate; this gave a good yield but an unsatisfactory conversion (Table 1, entry 1). Similar procedures with other solid bases (sodium and cesium carbonates) gave poor or no conversions (entries 2 and 3). The use of an inert material (alumina) as a support in the presence of various bases gave interesting outcomes (entries 4–6). The highest conversion and yield were achieved with potassium carbonate as base. Other transition metal salts, such as palladium(II) diacetate, platinum dichloride, or copper(II) acetate, failed to give any amination product.

Having identified the optimal conditions (entry 6), we applied this method to various substituted indolines, and we compared the results with those obtained under the previously reported solvent-free conditions in the presence of a ligand (Table 2). The absence of a ligand had some effect on the product conversions, but the yields were high and, after the reaction, only product and unreacted starting materials were recovered; no byproducts or side reactions were observed. The necessary conditions appear to be very mild and the improved economic and environmental aspects compensate for the lower conversion.

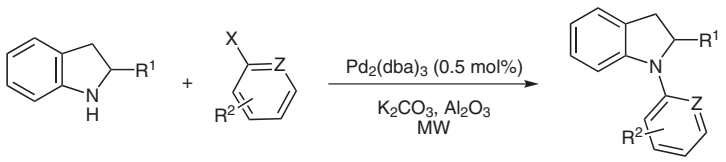
We then extended the procedure to various substituted anilines and hetaryl amines (Table 3). Among the aryl halides, aryl bromides were more efficient than iodides, and chlorides were found to be unsuitable for use in this method. Anilines reacted better than hetaryl amines, and N-substituted anilines gave better results than anilines. The use of a higher temperature improved the yield but, due to the absence of a solvent, heating to 160 °C was sometimes difficult to achieve and, consequently, the increase in yield was no more than 10%. Increasing the reaction time did not improve the yield and, in some cases, byproducts were formed. In our procedure, the critical step is fixing the catalyst on the support during the removal of the solvent in a manner that avoids aggregation of palladium particles and consequent inactivation of the catalyst (see the experimental details).

Table 1 Optimization of Ligand-Free Reaction Conditions



	Base	Solid support	Conversion (%)	Yield (%)
1	K_2CO_3	K_2CO_3	50	82
2	Na_2CO_3	Na_2CO_3	15	86
3	Ca_2CO_3	Ca_2CO_3	–	–
4	NaOH (4 equiv)	Al_2O_3	35	85
5	Et_3N (4 equiv)	Al_2O_3	26	80
6	K_2CO_3 (4 equiv)	Al_2O_3	68	91

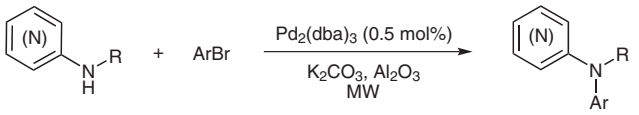
Table 2 N-Arylation of Indolines with Aryl Halides



Entry	R^1	Z	X	R^2	Product	Yield with ligand (%)	Ligand-free conversion[a] (%)	Ligand-free yield[b] (%)
1	H	N	Br	H	**1a**[15]	76	68	91
2	H	N	Br	3-Me	**1b**[16]	24	38	76
3	H	CH	Br	4-NO_2	**1c**[14]	75	68	87
4	H	CH	Br	H	**1d**[17]	59	47	85
5	H	CH	I	H	**1d**[17]	71	39	79
6	H	CH	Br	4-OMe	**1e**[18]	77	56	86
7	H	CH	I	4-OMe	**1e**[18]	84	51	86
8	Me	CH	Br	4-NO_2	**1f**[14]	65	50	88
9	CO_2H	CH	Br	4-NO_2	**1g**[14]	53	43	81
10	CO_2Me	CH	Br	4-NO_2	**1h**[14]	54	39	82

[a] Conversion determined by ^1H NMR spectroscopy of the crude reaction mixture.
[b] Yield of reacted material after chromatography.

Table 3 N-Arylation of (Het)aryl Amines with Aryl Bromides



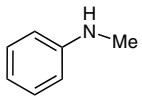
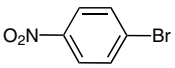
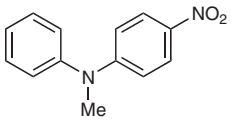
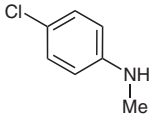
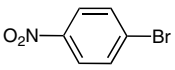
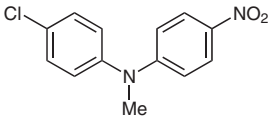
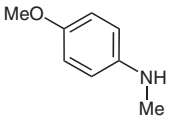
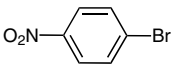
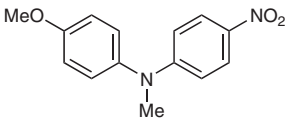
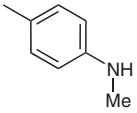
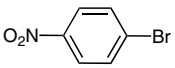
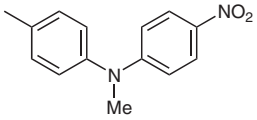
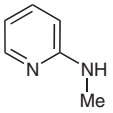
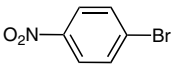
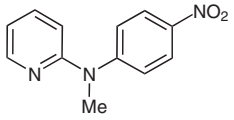
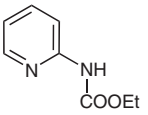
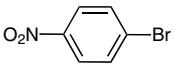
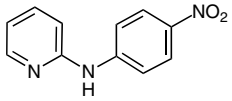
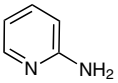
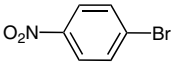
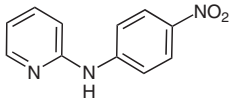
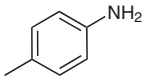
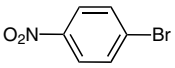
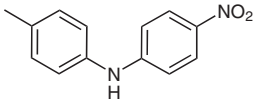
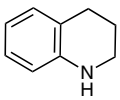
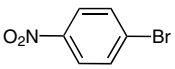
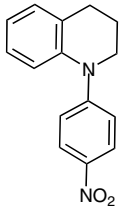
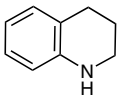
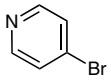
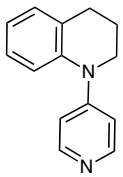
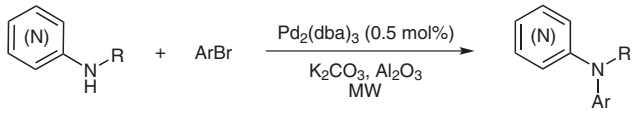
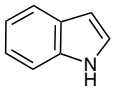
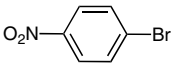
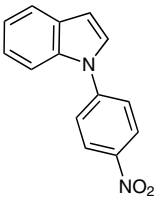
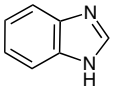
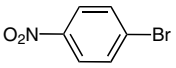
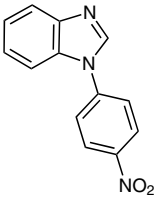
Entry	(Het)aryl amine	Aryl bromide	Product	Conversion (%)	Yield[a] (%)
1			**2** 	52	75[19]
2			**3** 	42	73
3			**4** 	67	88
4			**5** 	50	82
5			**6** 	55	89[20]
6			**7** 	35	74[21]
7			**8** 	–	–
8			**9** 	44	79[22]
9			**10** 	62	90[23]
10			**11** 	47	83

Table 3 N-Arylation of (Het)aryl Amines with Aryl Bromides (continued)



Entry	(Het)aryl amine	Aryl bromide	Product	Conversion (%)	Yield[a] (%)
11			**12** 	33	76[24]
12			**13** 	27	92[25]

[a] Yields based on reacted material after chromatography.

Some details of the experimental procedure are critical. The alumina and potassium carbonate must be finely powdered, because the total exposed area increases markedly on reducing the particle size. The potassium carbonate must be correctly hydrated; if it is absolutely dry, the reaction does not work, and if it is too hydrated, the yield is halved. It is necessary to pack the powder tightly into the reactor. The initial power of the microwave oven must be high to overcome the inertial barrier of the solid reaction mixture.

The electronic properties of dibenzylideneacetone had no effect on the catalytic activity of the palladium(0) in the Buchwald–Hartwig reaction.[26] In fact, the amination reaction could also be performed with palladium diacetate as a catalyst, although better results were obtained with tris(dibenzylideneacetone)dipalladium.

It is likely that the rapid heating induced by microwave irradiation restricts the formation of oxidized byproducts, Ullmann-type biaryl byproducts, or dehalogenated substrates. Whereas most of the amination reactions described in the literature were conducted under inert conditions with exclusion of oxygen and moisture in a glove box, the stability and convenience of our catalytic system allowed the reactions to be run under less stringent conditions.

In summary, the combination of solvent- and ligand-free conditions under microwave heating provides a new methodology for performing palladium-catalyzed aryl amination reactions with short reaction times. In our opinion, if a low catalyst loading is used, the key point is optimization of the catalyst dispersion in a suitable solid support to increase the exposed surface area and to improve the conversion. The solvent- and ligand-free conditions will be helpful in the search for green laboratory-scale syntheses, and this method is a good starting point in providing a cost-effective and environmentally benign procedure for the preparation of substituted aromatic amines.

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 200 spectrometer. Chemical shifts are reported in ppm downfield from TMS. ^{13}C NMR spectra were ^{1}H-decoupled and the multiplicities were determined by using the APT pulse sequence. The reactions under microwave activation were performed with a CEM Discover SP instrument. K_2CO_3 (99%) was obtained from Sigma-Aldrich. Activated basic aluminum oxide 90 (0.063–0.200 mm) was obtained from Merck.

Amination Reaction; General Procedure

A round-bottomed flask was charged with the aryl halide (1 mmol), the indoline or (het)aryl amine (1 mmol), and $Pd_2(dba)_3$ (0.005 mmol, 5 mg). At this point, CH_2Cl_2 (10 mL) was used to dissolve the reactants and to suspend K_2CO_3 (4 mmol, 552 mg) and Al_2O_3 (2 g). The CH_2Cl_2 was then removed under reduced pressure and subsequently recovered. The residual powder was ground with a mortar and pestle for 5 min. A microwave oven reactor was charged with the reactant powder which was compacted as much as possible. The powder was heated at 140 °C for 20 min at medium power (350 W), then charged into a flash silica gel column which was eluted with hexane–EtOAc (4:1) to give the purified product. The solid products were further purified by crystallization from hexane–Et_2O.

(4-Chlorophenyl)methyl(4-nitrophenyl)amine (3)

Dark-yellow solid; conversion: 42%; yield: 80.5 mg (73%); mp 86–88 °C (hexane–Et_2O).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, *N*-Me), 6.68 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2), 7.17 (d, *J* = 8.6 Hz, 2 H, Ar *p*-Cl), 7.42 (d, *J* = 8.6 Hz, 2 H, Ar *p*-Cl), 8.07 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.7, 113.1, 126.0, 128.1, 130.6, 132.3, 138.9, 145.2, 153.7.

Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.21; H, 4.39; N, 10.44.

(4-Methoxyphenyl)methyl(4-nitrophenyl)amine (4)
Yellow solid; conversion: 67%; yield: 152.1 mg (88%); mp 122–123 °C (hexane–Et_2O).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, *N*-Me), 3.84 (s, 3 H, *O*-Me), 6.58 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2), 6.97 (d, *J* = 9.0 Hz, 2 H, Ar *p*-OMe), 7.13 (d, *J* = 9.0 Hz, 2 H, Ar *p*-OMe), 8.04 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.7, 55.3, 114.8, 127.3, 128.5, 132.3, 138.9, 145.2, 152.8, 154.4.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.01; H, 5.60; N, 10.72.

***N*,4-Dimethyl-*N*-(4-nitrophenyl)aniline (5)**
Yellow solid; conversion: 50%; yield: 99.2 mg (82%); mp 77–79 °C (hexane–Et_2O).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 3.37 (s, 3 H, *N*-Me), 6.63 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2), 7.10 (d, *J* = 8.4 Hz, 2 H, Ar *p*-Me), 7.26 (d, *J* = 8.4 Hz, 2 H, Ar *p*-Me), 8.04 (d, *J* = 9.4 Hz, 2 H, Ar *p*-NO_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3, 40.8, 112.4, 126.0, 126.8, 131.0, 137.0, 138.2, 144.0, 154.2.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.33; H, 5.94; N, 11.38.

***N*-Methyl-*N*-(4-nitrophenyl)pyridin-2-amine (6)**[20]
Dark-yellow solid; conversion: 55%; yield: 112.1 mg (89%); mp 107–109 °C (hexane–Et_2O).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.54 (s, 3 H, *N*-Me), 6.94 (dd, *J* = 7.3, 5.0 Hz, 1 H, py), 7.06 (d, *J* = 8.4 Hz, 1 H, py), 7.15 (d, *J* = 9.2 Hz, 2 H, Ar *p*-NO_2), 7.59 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1 H, py), 8.11 (d, *J* = 9.2 Hz, 2 H, Ar *p*-NO_2), 8.35 (dd, *J* = 5.0, 1.8 Hz, 1 H, py).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.3, 115.0, 118.5, 119.1, 125.5, 138.1, 141.5, 149.0, 152.7, 157.7.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 13.96. Found: C, 62.63; H, 4.95; N, 13.83.

1-Pyridin-4-yl-1,2,3,4-tetrahydroquinoline (11)
Yellow oil; conversion: 47%; yield: 81.8 mg (83%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2-Ar), 3.66 (t, *J* = 6.2 Hz, 2 H, CH_2-N), 7.00 (m, 2 H, Ar), 7.04 (m, 2 H, py), 7.29 (d, *J* = 7.3 Hz, 2 H, Ar), 8.31 (d, *J* = 5.5 Hz, 2 H, py).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.1, 27.2, 47.7, 111.8, 121.0, 123.2, 126.4, 129.1, 131.6, 139.9, 148.7, 154.0.

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.78; H, 6.90; N, 13.13.

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References

(1) (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (c) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166. (d) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (e) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (f) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (g) Hesp, K. D.; Stradiotto, M. *ChemCatChem* **2011**, *2*, 1346.

(2) (a) *The Chemistry and Application of Dyes*; Waring, D. R.; Hallas, G., Eds.; Plenum: New York, **1990**. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (c) D'Aprano, G.; Leclerc, M.; Zott, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33. (d) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

(3) (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (b) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; *Angew. Chem.* **2008**, *120*, 6438. (d) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825. (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (f) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; *Angew. Chem.* **1998**, *110*, 2154.

(4) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348; *Angew. Chem.* **1995**, *107*, 1456. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(5) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, **2010**.

(6) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (d) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481. (e) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (f) Tardiff, B. J.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *J. Org. Chem.* **2012**, *77*, 1056. (g) Tardiff, B. J.; Stradiotto, M. *Eur. J. Org. Chem.* **2012**, 3972. (h) Chen, L.; Yu, G.-A.; Li, F.; Zhu, X.; Zhang, B.; Guo, R.; Li, X.; Yang, Q.; Jin, S.; Liu, C.; Liu, S.-H. *J. Organomet. Chem.* **2010**, *695*, 1768.

(7) For ligand-free Heck reactions, see: (a) Dong, J. J.; Roger, J.; Pozgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 1832. (b) de Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van de Vondervoort, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; de Vries, J. G. *Adv. Synth. Catal.* **2002**, *344*, 996. (c) Beletskaya, I. P.; Kashin, A. N.; Karlstedt, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89. (d) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285. (e) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (f) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. (g) Beccalli, E. M.; Borsini, E.; Brenna, S.; Galli, S.; Rigamonti, M.; Broggini, G. *Chem. Eur. J.* **2010**, *16*, 1670. (h) Sun, P.; Qu, X.; Li, T.; Zhu, Y.; Yang, H. L.; Xing, Z. Y.; Mao, J. C. *Synlett* **2012**, *23*, 150.

(8) For ligand-free arylation reactions, see: (a) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G. *Tetrahedron* **2009**, *65*, 3486. (b) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (c) Wang, X.; Gribkov, D. V.; Sames, D. J. *J. Org. Chem.* **2007**, *72*, 1476. (d) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (e) Fu, H.; Chen, L.; Doucet,

H. *J. Org. Chem.* **2012**, *77*, 4473. (f) Wenig, F.; Wang, C.; Xu, B. *Tetrahedron Lett.* **2010**, *51*, 2593. (g) Bheeter, C. B.; Bera, J. K.; Doucet, H. *Adv. Synth. Catal.* **2012**, *354*, 3533.

(9) For ligand-free carbonylation reactions, see: (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (b) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951. (c) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2007**, *72*, 2008. (d) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, 1173.

(10) (a) Velmathi, S.; Vijayaraghavan, R.; Amarendar, C.; Pal, R. P.; Vinu, A. *Synlett* **2010**, 2733. (b) Jiang, Z.; She, J.; Lin, X. *Adv. Synth. Catal.* **2009**, *351*, 2558.

(11) (a) Al-Amin, M.; Honma, T.; Hoshiya, N.; Shuto, S.; Arisawa, M. *Adv. Synth. Catal.* **2012**, *354*, 1061. (b) Guha, B. N. R.; Shil, A. K.; Sharma, D.; Das, P. *Tetrahedron Lett.* **2012**, *53*, 5318.

(12) For ligand-free copper-catalyzed amination reactions, see: (a) Correa, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2673. (b) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hu, Y. *Adv. Synth. Catal.* **2008**, *350*, 1253. (c) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2007**, 2147. (d) Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245. (e) Sperotto, E.; de Vries, J. G.; van Klink, G. P. M.; van Koten, G. *Tetrahedron Lett.* **2007**, *48*, 7366. (f) Yong, F. F.; Teo, Y. C. *Synlett* **2010**, 3068. (g) Teo, Y. C.; Yong, F. F. *Synlett* **2011**, 837. (h) Azzaro, S.; Desage-El Murr, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Synlett* **2011**, 849. (i) He, H.; Wu, Y. J. *Tetrahedron Lett.* **2003**, *44*, 3385. (j) Gavade, S.; Shingare, M.; Mane, D. *Bull. Korean Chem. Soc.* **2011**, *32*, 4167.

(13) (a) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Synlett* **2006**, 73. (b) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Khansaa, M.; Rigamonti, M. *Eur. J. Org. Chem.* **2010**, *9*, 1694. (c) Beccalli, E. M.; Bernasconi, A.; Borsini, E.; Broggini, G.; Rigamonti, M.; Zecchi, G. *J. Org. Chem.* **2010**, *75*, 6923. (d) Borsini, E.; Broggini, G.; Fasana, A.; Galli, S.; Khansaa, M.; Piarulli, U.; Rigamonti, M. *Adv. Synth. Catal.* **2011**, *353*, 985. (e) Broggini, G.; Barbera, V.; Beccalli, E. M.; Borsini, E.; Galli, S.; Lanza, G.; Zecchi, G. *Adv. Synth. Catal.* **2012**, *354*, 159. (f) Broggini, G.; Borsini, E.; Fasana, A.; Poli, G.; Liron, F. *Eur. J. Org. Chem.* **2012**, 3617. (g) Broggini, G.; Barbera, V.; Beccalli, E. M.; Cacchio, U.; Fasana, A.; Galli, S.; Gazzola, S. *Adv. Synth. Catal.* **2013**, *355*, 1640.

(14) Basolo, L.; Bernasconi, A.; Borsini, E.; Broggini, G.; Beccalli, E. M. *ChemSusChem* **2011**, *4*, 1637.

(15) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935.

(16) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557.

(17) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 3389.

(18) Omar-Amrani, R.; Schneider, R.; Fort, Y. *Synthesis* **2004**, 2527.

(19) (a) Urgaonkar, S.; Xu, J. H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416. (b) Urgaonka, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 9135.

(20) Shiraishi, M.; Kitayoshi, T.; Aramaki, Y.; Honda, S.; Oda, T. WO 9932468, **1999**.

(21) During the reaction of ethyl pyridin-2-ylcarbamate, hydrolysis of the ester group occurred and compound **12** was isolated; see: Fang, Y.; Larock, R. C. *Tetrahedron* **2012**, *68*, 2819.

(22) Xu, Z. L.; Li, H. X.; Ren, Z. G.; Du, W. Y.; Xu, W. C.; Lang, J. P. *Tetrahedron* **2011**, *67*, 5282.

(23) Meneyrol, J.; Helissey, P.; Tratrat, C.; Giorgi-Renault, S.; Husson, H.-P. *Synth. Commun.* **2001**, *31*, 987.

(24) Yang, K.; Qiu, Y.; Jiang, S.; Wang, Z.; Li, Z. *J. Org. Chem.* **2011**, *76*, 3151.

(25) Shan, Y.; Wang, Y.; Jia, X.; Cai, W.; Xiang, J. *Synth. Commun.* **2012**, *42*, 1192.

(26) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; McGlacken, G. P.; Weissburger, F.; de Vries, A. H. M.; Schmieder-van de Vondervoort, L. *Chem. Eur. J.* **2006**, *12*, 8750.

