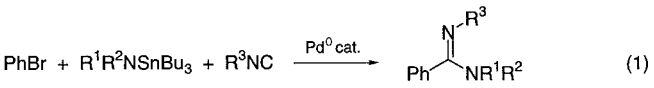
A Palladium-Catalyzed Synthesis of Amidines from Aryl Halides**

C. Gustaf Saluste, Richard J. Whitby,* and Mark Furber

The advent of high-throughput screening of compounds for biological activity has created a demand for synthetic methods that allow diverse arrays of organic compounds to be synthesized quickly. Palladium-catalyzed elaborations of aryl halides, for example by Suzuki couplings with arylboronates,[1] or Buchwald/Hartwig coupling with amines[2] are important tools. Extension of palladium-catalyzed reactions to three-component couplings by incorporation of a carbenoid fragment would be valuable. Such reactions incorporating carbon monoxide are well known,[3] but use of isoelectronic (and structurally variable) isocyanides is virtually unexplored.[4] One exception is the coupling between bromobenzene, *tert*-butyl isocyanide, and tributylstannyl(diethyl)amine **1a** (5 mol% $[Pd(PPh_3)_4]$, benzene, 120 °C, 20 h) to afford the amidine **2** in 22% yield (GC) [Eq. (1)], described by Kosugi et al. in 1986.[4a] We now report on the optimization of this



(1)

1a R^1,R^2 = Et
1b R^1,R^2 = -$(CH_2)_4$-

2 R^1,R^2 = Et, R^3 = *t*Bu
3 R^1,R^2 = -$(CH_2)_4$-, R^3 = *t*Bu
4 R^1,R^2 = -$(CH_2)_4$-, R^3 = *c*-C_6H_{11}
5 R^1,R^2 = -$(CH_2)_4$-, R^3 = CH_2Ph

reaction and development of a tin-free system to provide a useful convergent synthesis of aromatic and heteroaromatic amidines. Amidines are important constituents of many biologically active compounds.[5]

We initially optimized the coupling of bromobenzene with *N*-tributylstannylpyrrolidine (**1b**) (1.3 equiv) and *tert*-butyl isocyanide (1.5 equiv).[6, 7] High yields of the amidine **3** could be obtained by using (dibenzylideneacetone)dipalladium(**0**)–chloroform adduct ($[Pd_2dba_3]\cdot CHCl_3$; 2.5 mol%) as the palladium source and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf, 10 mol%) as the ligand in a variety of solvents (toluene, benzene, THF, DMF) at 109 °C for 20 h [Eq. (1)]. Under these conditions other isocyanides (*c*-$C_6H_{11}NC$, $PhCH_2NC$, BuNC, PhNC) gave minimal conversions. Moderate yields of the amidines **4** and **5** [Eq. (1)] could be obtained by slow addition (13 h) of cyclohexyl isocyanide (42%) or benzylisocyanide (36%), respectively.

[*] Prof. R. J. Whitby, C. G. Saluste
Department of Chemistry
Southampton University
Southampton, SO17 1BJ (UK)
Fax: (+44) 23-8059-3781
E-mail: rjw1@soton.ac.uk
Dr. M. Furber
AstraZeneca Charnwood,
Department of Medicinal Chemistry
Bakewell Road, Loughborough, LE11 5RH (UK)

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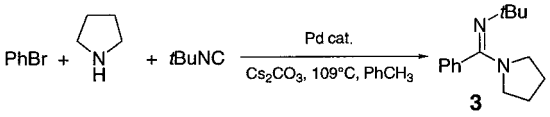
Tin is toxic and best avoided in preparations of compounds for biological application so we next investigated the development of a tin-free system. Using the $[Pd_2dba_3]\cdot CHCl_3$/dppf/toluene conditions developed above the coupling of bromobenzene, *tert*-butyl isocyanide, and pyrrolidine (5 equiv), failed. As found for the direct coupling of amines and aromatic halides[2] addition of the inorganic base Cs_2CO_3 (1.3 equiv) allowed the reaction to proceed to give amidine **3** in quantitative yield [Eq. (2), Table 1, entry 1]. Initial



(2)

Table 1. Optimization of tin-free conditions for amidine formation[a].

Entry	Pyrrolidine [equiv]	Ligand	Pd source	L:Pd	*t*[b] [h]	Yield[c] [%]
1	5	dppf	$[Pd_2(dba)_3]\cdot CHCl_3$	2:1	6	100
2	5	dppf	$PdCl_2$	2:1	3	100
3	5	dppf	$PdCl_2$	1:1	2	100
4	5	–	$PdCl_2$	–	20	54
5	5	dppf	$PdCl_2$	4:1	20	100
6	5	PPh_3	$PdCl_2$	4:1	20	28
7	5	$(2\text{-furyl})_3P$	$PdCl_2$	4:1	20	36
8	5	tBu_3P	$PdCl_2$	4:1	20	11
9	5	$(C_6F_5)_2PPh$	$PdCl_2$	4:1	20	0
10	5	BINAP	$PdCl_2$	2:1	6	77
11	5	dppe	$PdCl_2$	2:1	3	100
12	5	dppp	$PdCl_2$	2:1	3	100
13	1.5	dppf	$PdCl_2$	2:1	5	100
14	1.1	dppf	$PdCl_2$	2:1	8	86
15	0.9	dppf	$PdCl_2$	2:1	8	63[d]
16	1.5	dppf	$PdCl_2$	1:1	15	83
17	5	dppf	$Pd(OAc)_2$	2:1	2	100
18	5	dppf	$Pd(OAc)_2$	1:1	2	100
19	5	–	$Pd(OAc)_2$	–	20	56
20	1.5	dppf	$Pd(OAc)_2$	2:1	2	100
21	1.5	dppf	$Pd(OAc)_2$	1:1	5	100

[a] Conditions: Toluene, 109 °C, *t*BuNC (1.5 equiv), Pd (5 mol%), dry Cs_2CO_3 (1.3 equiv). [b] Time for complete or maximum conversion. [c] Yield of **3** based on PhBr by GC using an internal standard of *n*-tridecane. [d] Yield based on pyrrolidine.

variability in results was traced to the dryness of the commercial anhydrous Cs_2CO_3 used. Carefully dried material gave consistent and high-yielding results. A significant increase in rate was observed on changing the palladium source to the much cheaper, and more easily handled $PdCl_2$ (Table 1, entry 2). Lowering the ligand:palladium ratio to 1:1 gave almost equivalent results (Table 1, entry 3), and even in the absence of a phosphane ligand the reaction gave **3** in 54% yield (Table 1, entry 4). Using a ligand:palladium ratio of 4:1 slowed the reaction (Table 1, entry 5). Triphenylphosphane, tri(2-furyl)phosphane, tri(*tert*-butyl)phosphane, bis(pentafluorophenyl)phenylphosphane, *rac*-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP), 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,3-bis(diphenylphosphanyl)propane (dppp) were tried as ligands (Table 1, entries 6–12). Only the bidentate ligands were effective, dppe and dppp proving comparable to the more expensive but easily handled dppf.

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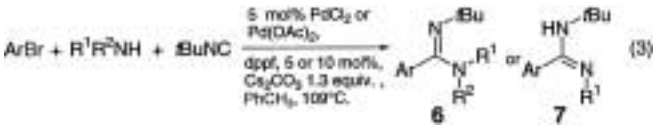
With the $PdCl_2$/dppf conditions we examined the effect of reducing the amount of pyrrolidine. With a ligand:palladium ratio of 2:1 the reaction reached 100% conversion after 5 h with 1.5 equivalents of pyrrolidine, and respectable yields were obtained with 1.1 or even 0.9 equivalents (Table 1, entries 13–15). The latter results are useful if the amine component is expensive. With only one equivalent of dppf per palladium and 1.5 equivalents pyrrolidine the reaction took 15 h to reach 83% yield (Table 1, entry 16, only 20% after 5 h). Reactions using $PdCl_2$ had a significant initiation period so we examined the use of $Pd(OAc)_2$ which is soluble in toluene. Using five equivalents of pyrrolidine the reactions quickly reached full conversion when using either two or one equivalents of dppf per palladium (Table 1, entries 17 and 18), and as with $PdCl_2$, even in the absence of a phosphane ligand gave a reasonable yield of **3** (Table 1, entry 19). Lowering the amount of amine to 1.5 equivalents still gave high-yielding and fast conversions with only one equivalent of ligand per palladium (Table 1, entry 21) providing our most cost effective conditions to date.

Extension to isocyanides other than *tert*-butyl isocyanide has had limited success. Our best result is a 39% yield of **4** obtained by slow addition (8 h) of cyclohexyl isocyanide (1.5 equiv) to bromobenzene, pyrrolidine (5 equiv), Cs_2CO_3 (1.3 equiv), $PdCl_2$ (5 mol%), dppf (10 mol%), in toluene at 109 °C.

With high-yielding conditions in hand we undertook the synthesis and isolation of a range of aryl amidines **6** [Eq. (3), Table 2]. In all cases the conversions were clean by GC, but there were losses on isolation of pure materials. In general we found the best work-up procedure to be extraction of the strongly basic amidine into dilute aqueous acetic acid. After washing with diethyl ether addition of concentrated KOH solution allowed extraction of the amidine. Removal of solvent and Kugelrohr distillation gave analytically pure amidines in good overall yield. The results show that electron-rich, electron-poor, and heteroaromatic halides work well. The amine may be primary or secondary, alkyl- or aryl-substituted, and cyclic or acyclic. Calculations, and ^{13}C NMR shifts of the *tert*-butyl groups indicate that the amidines derived from primary amines exist in the tautomeric form **7**.



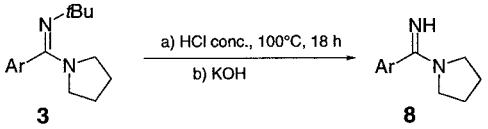
(3)

Table 2. Palladium-catalyzed synthesis of amidines.

ArBr	Amine		**6**/**7**	Yield (**6**/**7**)[a]	M.p. (**6**/**7**)	B.p. (**6**/**7**)[d]
	R^1	R^2		[%]	[°C]	[°C]
C_6H_5Br		$-(CH_2)_4-$	**6a**	78, 58[b]	49–50	
C_6H_5Br	Bu	H	**7b**	55, 29[b]		90–100
C_6H_5Br	Ph	H	**7c**	45, 40[c]	115–117	
C_6H_5Br	Et	Et	**6d**	61		80–90
p-$Me_2NC_6H_4Br$		$-(CH_2)_4-$	**6e**	74	91–92	
p-$Me_2NC_6H_4Br$		$-(CH_2)_2O(CH_2)_2-$	**6f**	76	125–127	
p-$MeOC_6H_4Br$		$-(CH_2)_4-$	**6g**	83, 79[c]	56–57	
p-$MeOC_6H_4Br$		$-(CH_2)_2O(CH_2)_2-$	**6h**	76	79–80	
p-$MeCOC_6H_4Br$		$-(CH_2)_4-$	**6i**	61	76–78	
p-$MeCOC_6H_4Br$	Bu	H	**7j**	49	74–76	
p-$MeCOC_6H_4Br$		$-(CH_2)_2O(CH_2)_2-$	**6k**	62	102–104	
3-brompyridine		$-(CH_2)_4-$	**6l**	71	28–29	
3-brompyridine		$-(CH_2)_2O(CH_2)_2-$	**6m**	57		110–115

[a] Conditions: Amine (5 equiv), *t*BuNC (1.5 equiv), Cs_2CO_3 (1.3 equiv), $PdCl_2$ (5 mol%), dppf (10 mol%), toluene, 109 °C, 3–24 h. [b] Conditions: As [a] but amine (1 equiv), $Pd(OAc)_2$ (5 mol%), dppf (5 mol%). [c] Conditions: As [b] but amine (1.5 equiv). [d] At 1 Torr.

In order to provide access to *N*-unsubstituted amidines we investigated methods for removal of the *tert*-butyl group in **3** and found that refluxing concentrated hydrochloric acid was effective [Eq. (4)].[8] The deprotection could be carried out on the crude product from the palladium-catalyzed coupling providing **8** in 60% yield from bromobenzene.



(4)

Overall we have developed a simple and efficient intermolecular three-component synthesis of aromatic and heteroaromatic *N*-*tert*-butyl amidines from aryl and heteroaryl halides which should find use in pharmaceutical discovery.

Experimental Section

6g: Dry Cs_2CO_3 (0.85 g, 2.6 mmol), dppf (0.111 g, 0.20 mmol), 4-bromoanisole (0.375 g, 2.0 mmol), and pyrrolidine (0.71 g, 10 mmol) were added to a 20 mL Schlenk tube under argon. Dry, degassed toluene (10 mL) was added, followed by *t*BuNC (0.34 mL, 3.0 mmol), and finally $PdCl_2$ (17.7 mg, 0.10 mmol) was added against a flow of argon. The tube was stoppered and heated with stirring at 109 °C for 20 h. After the mixture had been cooled to room temperature, diethyl ether (20 mL) was added and the resulting mixture filtered to give a dark brown solution which was extracted with dilute acetic acid (2.5% in water, 6×5 mL). The combined aqueous extracts were washed with diethyl ether (2×10 mL), then treated with a concentrated KOH solution (30 mL) in the presence of diethyl ether (20 mL). The ethereal layer was collected and the aqueous layer extracted with diethyl ether (3×30 mL). The combined diethyl ether phases were dried over $MgSO_4$ before evaporation. Kugelrohr distillation (100–110 °C/1 Torr) gave the amidine **6g** as a pale yellow oil which crystallized to a white solid (0.43 g, 83%). M.p. 56–57 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.12 (2H, d, $J = 8.8$ Hz), 6.87 (2H, d, $J = 8.8$ Hz), 3.83 (3H, s), 3.11 (4H, br s), 1.78 (4H, m), 1.02 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.19$ (s), 156.70 (s), 131.65 (s), 129.67 (d), 113.35 (d), 55.32 (q) 52.82 (s), 47.61 (t), 33.09 (q), 25.46 (t); MS (APCI): *m*/*z* (%): 261 (100) [$M+H^+$]; IR (neat): $\tilde{\nu} = 2958$ (s), 2921 (m), 1597 (s), 1509 (m), 1375 (s), 1354 (s), 1245 (s), 1186 (m), 1221 (s), 1025 (m) cm^{-1}; elemental analysis (%) calcd for $C_{16}H_{24}N_2O$: C 73.81, H 9.29, N 10.76; found: C 73.83, H 9.50, N 10.95.

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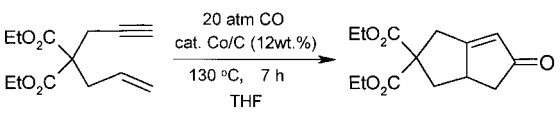
Cobalt on Charcoal: A Convenient and Inexpensive Heterogeneous Pauson – Khand Catalyst**

Seung Uk Son, Sang Ick Lee, and Young Keun Chung*

Although much success has been achieved in the field of transition metal mediated (or catalyzed) synthesis of cyclopentenones from readily available substrates,[1] industrial applications are surprisingly still undeveloped. In order to develop large-scale processes, it is extremely important and prerequisite to heterogenize homogeneous systems. Recently we published[2] the first heterogeneous catalyst system for the Pauson – Khand reaction based on cobalt on mesoporous silica. Polymer-supported cobalt carbonyl complexes have been reported[3] as catalysts of the intramolecular Pauson – Khand reaction, but the catalytic activity was low. The cobalt on a mesoporous material system is a quite effective catalyst for the intramolecular Pauson – Khand reaction, but displays low activity in the intermolecular Pauson – Khand reaction. Furthermore, mesoporous silica is not freely available. In view of the drawbacks of cobalt on mesoporous materials, much work has focused on finding more suitable supports. Herein we report on a new catalyst system based on cobalt on charcoal (Co/C). This heterogeneous catalyst system exhibits an excellent catalytic performance for intra- and intermolecular Pauson – Khand reactions [Eq. (1)]. The catalyst system is quite stable and can be reused. Recently, catalyst systems based on transition metals on charcoal have attracted much attention.[4]



(1)

The catalyst system was prepared by thermal decomposition of $[Co_2(CO)_8]$ in the presence of commercially available charcoal bone in THF under reflux.[5] The catalytic activity of Co/C strongly depends on the amount of cobalt on charcoal (wt %). When the cobalt loading on charcoal was less than 7.5 wt %, no catalytic reaction was observed. The optimum cobalt loading on charcoal was about 12 wt %. The IR spectra of the supported catalysts show no carbonyl absorptions, confirming a complete decomposition of the metal carbonyl. X-ray powder diffraction (XRD) patterns of the supported catalysts revealed peaks of hexagonal close packed (hcp) metallic cobalt, as in the bulk phase.[6] A transmission electron microscopic (TEM) study (Figure 1) shows that cobalt atoms are not distributed homogeneously in the charcoal surface, but form metallic cobalt particles (100 – 1000 nm). The black Co/C shows ferromagnetism and is easily recovered by filtration or by using a magnet.

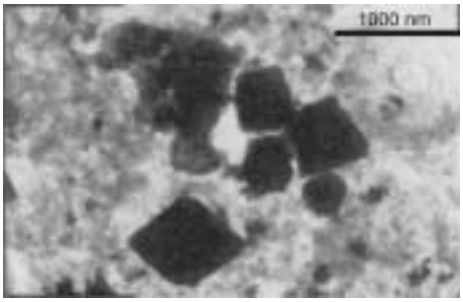


Figure 1. Transmission electron micrograph of Co/C.

The scope of application of this catalyst was examined with a number of substrates both in inter- and intramolecular variants of the Pauson – Khand reaction. Several representative results obtained under standard conditions are given in Table 1. The intramolecular cycloaddition proceeded smoothly with monosubstituted olefins regardless of the substitution pattern of alkynes (Table 1, entries 1 – 4), although the internal olefin substrate (Table 1, entry 5) needs a relatively long reaction time. Heteroatom-bridged enynes produced aza- (Table 1, entry 4) and oxobicyclic compounds (Table 1, entries 3 and 5) from the corresponding substrates. In most cases, the yields of the intramolecular reactions are almost quantitative. For intermolecular cycloadditions with the Co/C system the substrate structure has little influence on the results. Satisfactory results are obtained with simple terminal alkynes (Table 1, entries 6 and 7), a conjugated alkyne (Table 1, entry 8), and a diyne (Table 1, entry 10). In contrast, an *n*-alkyl halide substituted alkyne (Table 1, entry 9)[7] was not a suitable substrate for the Co/C system. In the case of the diyne substrate (entry 10), a double intermolecular Pauson – Khand reaction[8] occurred and no [2+2+2] cycloaddition product was observed.

The most important advantage of heterogenous catalysis over its homogeneous counterpart is the possibility of recovering the catalyst after reaction by simple filtration. For the intramolecular Pauson – Khand reaction according to

[*] Prof. Y. K. Chung, S. U. Son, S. I. Lee
School of Chemistry and Center for Molecular Catalysis
Seoul National University, Seoul 151-747 (Korea)
Fax: (+82) 2-889-1568

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