Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2793–2799

TETRAHEDRON

Palladium-catalyzed carbonylative coupling of pyridine halides with aryl boronic acids

Samuel Couve-Bonnaire,[a] Jean-François Carpentier,[b] André Mortreux[a] and Yves Castanet[a,*]

[a]*Laboratoire de Catalyse de Lille, UMR 8010 CNRS-Université de Lille 1, Ecole Nationale Supérieure de Chimie de Lille, BP 108, 59652 Villeneuve d'Ascq Cedex, France*

[b]*Organométalliques et Catalyse, Institut de Chimie, UMR 6509 CNRS-Université de Rennes 1, 35042 Rennes Cedex, France*

Received 14 January 2003; revised 25 February 2003; accepted 5 March 2003

Abstract—The carbonylative Suzuki cross-coupling of a variety of mono-iodopyridines and bromopyridines (**1a**,**b**, **3a**–**c**, **5**) catalyzed by palladium-phosphane systems has been studied to prepare benzoylpyridine derivatives (**2**, **4**, **6**). The selectivity and the rate of the reaction are highly dependent on the reaction conditions, i.e. nature of the palladium catalyst precursor, solvent, temperature and CO pressure. The main side-products arise from direct, non-carbonylative cross-coupling. Under optimized conditions, benzoylpyridines are recovered in high yields (80–95%). The order of reactivity decreases from iodo- to bromopyridines and from 2-, 4- to 3-substituted halopyridines. The reactivity of dihalopyridines has been investigated; 2,6-dibromopyridine (**7**) and 3,5-dibromopyridine (**11**) are selectively transformed into either the corresponding benzoyl-phenylpyridine (**8**, **12**) or the corresponding dibenzoylpyridine (**9**, **13**). Dissymmetric 2,5-dihalopyridines (**15a**,**b**) are transformed into 2-benzoyl-5-bromopyridine (**16**) or 2,5-dibenzoylpyridine (**17**) in high yields.

1. Introduction

α-Pyridyl ketones are useful intermediates in the synthesis of various natural products and drugs.[1] Different methodologies have been proposed to access this important class of products. Many of them use the stoichiometric reaction of a pyridyl organometallic derivative with an electrophile; i.e. selective *ortho*-metallation of pyridine with lithiated reagents followed by reaction with amides,[2] addition of amides, anhydrides or aroyl chlorides to pyridyl Grignard reagents,[3] pyridyl-tellurides,[4] pyridyl-zinc[5] or pyridyl-trialkylstannyl derivatives.[6] Other routes involve oxidation of hydroxy-, imino- and benzyl-substituents on pyridyl rings,[7] or use multistep procedures.[8] As a matter of fact, the aforementioned methodologies used rather expensive and/or unfriendly reagents (oxidizers), had poor yields and/or were only effective with specific substrates. To develop a more attractive and general approach toward variously substituted pyridyl aryl ketones, we envisioned a palladium-catalyzed carbonylative coupling reaction.

Aryl halides with various coupling partners, including stannanes, silanes, Grignard, zinc reagents and boronic acids, have found much success in recent years.[9] The nature of boronic acids, which are generally nontoxic and thermally, air and moisture stable, is an obvious practical advantage compared to other cross-coupling processes that explains the emergence of the Suzuki reactions as an extremely powerful tool in organic synthesis.[10] However, the major limitation to the carbonylative approach of the Suzuki reactions often lies in the formation of significant amounts of biaryl products, which results from direct coupling without carbon monoxide insertion. The reaction conditions, that are the nature of the palladium catalyst precursor, ligand, base, additive as well as the nature of the substrates (aryl halide and boronic acid), have been found to have a dramatic effect on the amount of ketone formed versus that of simple biaryl. In this regard, to our knowledge, only three examples of Suzuki carbonylative cross-coupling of 2-pyridine halides and 3-bromoquinoline have been reported, which have given the expected benzoyl products up to 66% yields.[11] In this paper, we report that the proper choice of the reaction conditions enables the easy and selective transformation of a variety of mono- and dihalopyridines into phenyl pyridyl ketones.[12]

2. Results and discussion

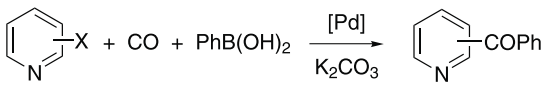
2.1. Carbonylative Suzuki cross-coupling of mono-iodopyridines

The reaction of 4-iodopyridine (**1a**) with phenyl boronic acid (1.1 equiv.) was examined as a model reaction to optimize the reaction conditions (Scheme 1, Table 1). Under atmospheric pressure of CO, at 80°C, using $PdCl_2(PPh_3)_2$ as

Keywords: carbonylation; cross-coupling; ketones; palladium; pyridines.

* Corresponding author. Tel.: +33-320-434-927; fax: +33-320-436-585; e-mail: yves.castanet@ensc-lille.fr

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00342-9



1a: X = 4-I; **1b**: X = 4-Br — **2**: X = 4-COPh
3a: X = 2-I; **3b**: X = 2-Br; **3c**: X = 2-Cl — **4**: X = 2-COPh
5: X = 3-Br — **6**: X = 3-COPh

Scheme 1. Carbonylative Suzuki cross-coupling of monohalopyridines.

catalyst precursor and anisole as solvent, direct non-carbonylative cross-coupling is the major process and 4-benzoylpyridine (**2**) was recovered with a poor final selectivity (entry 2); under the same reaction conditions, high selectivity (93%) into benzophenone was obtained starting from iodobenzene (entry 1). This result shows the detrimental electron-withdrawing effect of the nitrogen atom of the pyridine ring that disfavors CO insertion into the pyridyl-palladium intermediate to the benefit of the transmetallation step.[10a,11] As expected, increase in the CO pressure up to 5 bar resulted in a significant increase of the yield of the carbonylation product (75%), as well as the overall reaction rate (entry 3). Under those conditions, the substrate-to-catalyst ratio could be increased up to 200 without affecting noticeably the selectivity (entry 4). A further enhancement of the selectivity (91%) was obtained on using a catalyst precursor with the more bulky and basic tricyclohexylphosphine ligand, i.e. $PdCl_2(PCy_3)_2$ (entry 5).

The nature of the solvent affected also greatly both the activity of the catalyst and selectivity of the reaction (entries 3, 6–9). When the reaction was carried out in THF as solvent instead of anisole, with $PdCl_2(PPh_3)_2$ as the catalyst precursor, the selectivity reached 90% but concomitantly the time required for the reaction to go to completion increased from 5 to 24 h. Less polar solvents such as toluene or dichloromethane led to slightly higher activities than THF but the selectivity into ketone decreased and was even lower than in anisole. On the other hand, the reaction almost did not proceed when carried out in DMF; only small

Table 1. Palladium catalyzed carbonylative cross-coupling reaction of mono-iodopyridines

Entry	Substrate	Catalyst precursor	Solvent	Temperature (°C)	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[b] (%)
1	PhI	$PdCl_2(PPh_3)_2$	Anisole	80	1	8	100	93
2	**1a**	$PdCl_2(PPh_3)_2$	Anisole	80	1	10	100	25
3	**1a**	$PdCl_2(PPh_3)_2$	Anisole	80	5	5	100	75
4	**1a**	$PdCl_2(PPh_3)_2$[c]	Anisole	80	5	17	100	73
5	**1a**	$PdCl_2(PCy_3)_2$	Anisole	80	5	6	100	91 (80)
6	**1a**	$PdCl_2(PPh_3)_2$	Toluene	80	5	18	100	65
7	**1a**	$PdCl_2(PPh_3)_2$	CH_2Cl_2	80	5	18	100	58
8	**1a**	$PdCl_2(PPh_3)_2$	THF	80	5	24	100	90
9	**1a**	$PdCl_2(PPh_3)_2$	DMF	80	5	20	5	0
10	**3a**	$PdCl_2(PPh_3)_2$	THF	80	5	24	70	90
11	**3a**	$PdCl_2(PPh_3)_2$	THF	100	5	8	100	95 (82)
12	**3a**	$PdCl_2(PCy_3)_2$	THF	100	5	6	100	95

Substrate=1.0 mmol, $PhB(OH)_2$=1.1 mmol, [Pd]=0.03 mmol, K_2CO_3=3.0 mmol, solvent=20 mL.
[a] Conversion of the iodopyridine as determined by quantitative GLC.
[b] Selectivity for the pyridyl ketone as determined by quantitative GLC; direct non-carbonylative products (essentially Ph–Py) account for the balance (homocoupling products, i.e. bipyridyl and biphenyl, were only detected as trace amounts <0.5%); the values in parentheses refer to isolated yields of the corresponding, analytically pure pyridyl phenyl ketone.
[c] $PdCl_2(PPh_3)_2$=0.005 mmol.

Table 2. Palladium-catalyzed carbonylative cross-coupling reaction of mono-bromopyridines

Entry	Substrate	Catalyst precursor	Temperature (°C)	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[b] (%)
13	**3b**	$PdCl_2(PPh_3)_2$	100	5	20	70	86
14	**3b**	$PdCl_2(PPh_3)_2$	120	5	20	100	82 (70)
15	**5**	$PdCl_2(PPh_3)_2$	120	5	20	0	–
16	**5**	$PdCl_2(PPh_3)_2$	150	5	20	10	59
17	**1b**	$PdCl_2(PPh_3)_2$	120	5	20	100	35
18	**3b**	$PdCl_2(PCy_3)_2$	100	5	20	74	90
19	**3b**	$PdCl_2(PCy_3)_2$	120	5	20	100	88
20	**5**	$PdCl_2(PCy_3)_2$	120	5	20	100	91 (80)
21	**1b**	$PdCl_2(PCy_3)_2$	100	5	20	95	53
22	**1b**	$PdCl_2(PCy_3)_2$	120	5	20	100	62
23	**3b**	$Pd_2(dba)_3$/4 PCy_3	120	5	20	85	75
24	**5**	$Pd_2(dba)_3$/4 PCy_3	120	5	20	55	95
25	**3b**	$PdCl_2(PPh_3)_2$	120	50	10	100	94
26	**1b**	$PdCl_2(PCy_3)_2$	120	50	5	100	93 (81)
27	**3b**	$PdCl_2(PPh_3)_2$/KI	120	5	20	100	85
28	**3b**	$PdCl_2(PPh_3)_2$/PPh_3	120	5	20	72	25[c]

Substrate=1.0 mmol, $PhB(OH)_2$=1.1 mmol, [Pd]=0.03 mmol, K_2CO_3=3.0 mmol, THF=20 mL.
[a] Conversion of the bromopyridine as determined by quantitative GLC.
[b] Selectivity for the pyridyl ketone as determined by quantitative GLC; direct non-carbonylative products (essentially Ph–Py) account for the balance; the values in parentheses refer to isolated yields of the corresponding, analytically pure pyridyl phenyl ketone.
[c] 2,2′-Bipyridine was the major product (49%).

amounts of isonicotinic acid were observed. This result was rather unexpected since DMF proved to be a very useful solvent in direct Suzuki cross-coupling reactions.[10] However, Suzuki et al. have briefly reported similar detrimental role of DMF in the carbonylative cross-coupling of 4-iodoacetophenone with parallel formation of a carboxylic acid.[11]

The reactivity of 2-iodopyridine (**3a**) was investigated under the conditions optimized for 4-iodopyridine, i.e. using THF as the solvent, which is also more convenient in terms of final workup due to its volatility. With $PdCl_2(PPh_3)_2$ as the catalyst precursor, 2-iodopyridine was found to react more slowly than 4-iodopyridine; only 70% conversion was observed after 24 h (entry 10). This result is rather surprising since halogen in 2-position in halopyridines is normally more reactive than the one in 4-position toward nucleophilic substitution and hence oxidative addition of this substrate onto the palladium is expected to be facilitated. Increasing the reaction temperature to 100°C overcame this problem and led to a total conversion in 8 h with 95% selectivity for the desired ketone (entry 11). A similar good selectivity of 95% was observed with $PdCl_2(PCy_3)_2$ with a slightly higher reactivity since the reaction went to completion in only 6 h (entry 12).

2.2. Carbonylative Suzuki cross-coupling of monobromo- and chloropyridines

The good results obtained with iodopyridines prompted us to enlarge the scope of this reaction by investigating the reactivity of more commercially available and cheaper bromo- and chloropyridines (Scheme 1). Table 2 shows that the addition of KI or NaI, previously reported as a prerequisite to achieve selective carbonylative cross-coupling with simple aryl bromides,[11b] is unnecessary in the case of bromopyridines. Good yields for the desired pyridyl phenyl ketones are obtained under conditions similar to those employed for iodopyridines. Nevertheless, as expected, 2-bromopyridine (**3b**) and 4-bromopyridine (**1b**) are less reactive than their iodo counterparts and a higher temperature (120°C) was required to reach a total conversion in a reasonable reaction time, equally using PPh_3 or PCy_3 as ligand. As for iodopyridines, the position of the Br substituent on the pyridine ring and the reaction conditions have a major influence on the reactivity and the selectivity for pyridyl ketone. Thus, 4-bromopyridine is somewhat more reactive than 2-bromopyridine but leads to a much lower selectivity into the corresponding ketone (compare entries 18 and 21). The selectivity into 4-benzoylpyridine (**2**) did not exceed 35 and 62% under 5 bar of CO using $PdCl_2(PPh_3)_2$ and $PdCl_2(PCy_3)_2$, respectively (entries 17 and 22), whereas under the same conditions, 2-bromopyridine gave 82 and 88% selectivity, respectively (entries 14 and 19). Under the previous conditions, 3-bromopyridine (**5**) was completely inactive using $PdCl_2(PPh_3)_2$ as the catalyst precursor (entry 15). Even upon increasing the temperature up to 150°C, the reaction occurred with only 10% conversion and a modest selectivity of 59% for the pyridyl phenyl ketone (**6**) after 24 h (entry 16). High activity and selectivity (91%) into the corresponding ketone **6** were restored using $PdCl_2(PCy_3)_2$ in place of $PdCl_2(PPh_3)_2$ (entry 20), a catalyst precursor which obviously facilitates the oxidative addition step of this unactivated bromopyridine.

The influence of the CO pressure was also studied with the particular aim to improve the ketone selectivity in the case of 4-bromopyridine. Increasing the pressure up to 50 bar resulted not only into a significant enhancement of the selectivity for pyridyl phenyl ketone **4** (93, 81% isolated yield), but also into an higher reactivity since the reaction was completed after only 5 h (entry 26). The effect of CO pressure for 2-bromopyridine was less marked although the selectivity under 50 bar reached 94% and the time required for the reaction to go to completion was divided by a factor 2 (compare entries 14 and 25).

Addition of triphenylphosphine (2 equiv. vs $PdCl_2(PPh_3)_2$), which allows sometime to preserve the catalytic activity in carbonylation reactions by preventing deposit of 'Pd black', had a detrimental effect on the reaction (entry 28). Not only the activity was lowered but also higher amounts of non-carbonylative biaryl products were formed. Among the latter, 2,2′-bipyridine, which was generally observed only as trace amounts, was found surprisingly as the major product (49% selectivity). Addition of KI had almost no influence (compare entries 14 and 27). Finally, using $Pd_2(dba)_3$ as a preformed zerovalent catalyst precursor in conjunction with 2 equiv. vs Pd of tricyclohexylphosphine led to reduced activity as compared to its divalent analogue $PdCl_2(PCy_3)_2$, whereas the influence on the selectivity was more contrasted since that one slightly increased in the case of 3-bromopyridine and decreased for 2-bromopyridine (compare entries 19/23 and 20/24). Palladium systems based on tris(*tertio*-butyl)phosphine showed lower catalytic abilities.

Since our group and others have reported the efficient alkoxycarbonylation of chloropyridines,[10b,13,14] attempts were made to extend the carbonylative Suzuki cross-coupling reaction to chloropyridines. As illustrated in Table 3, 2-chloropyridine (**3c**), chosen as a representative model of this class of compounds, exhibited very low reactivity. When the reaction was carried out with

Table 3. Palladium-catalyzed carbonylative cross-coupling reaction of 2-chloropyridine (**3c**)

Entry	Catalyst precursor	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[a] (%)
29	$PdCl_2(PPh_3)_2$	5	24	0	–
30	$PdCl_2(PCy_3)_2$	5	70	36	53
31	$PdCl_2(PCy_3)_2$	50	24	11	88
32	$PdCl_2(Pcy_3)_2$/KI	5	45	10	65
33	$Pd_2(dba)_3$/4 P*t*-Bu_3	5	45	10	70

3c=1.0 mmol, $PhB(OH)_2$=1.1 mmol, [Pd]=0.03 mmol, K_2CO_3=3.0 mmol, THF=20 mL, temperature 150°C.

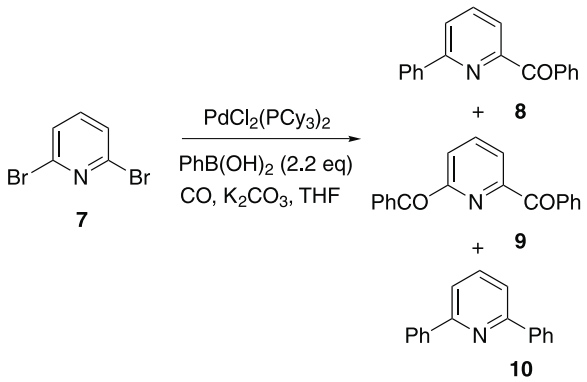
[a] Conversion of 2-chloropyridine and selectivity for 2-benzoylpyridine as determined by quantitative GLC; direct non-carbonylative products (essentially 2-Ph-Pyridine) account for the balance.

$PdCl_2(PPh_3)_2$ no conversion was observed after 24 h, even at 150°C. With $PdCl_2(PCy_3)_2$ the carbonylation proceeded but with poor conversion (36%) and modest selectivity (53%) and needed a long reaction time (70 h). Increasing the CO pressure to 50 bar improved the selectivity but, in contrast with the case of bromopyridines, had no effect on the activity, suggesting a different rate-determining-step (oxidative addition vs. CO insertion). In the same way, addition of KI or using $P(t\text{Bu})_3$ as ligand with $Pd_2(dba)_3$ were ineffective. Recent results in our group have shown that efficient carbonylative Suzuki cross-coupling of chloropyridines takes place in the presence of Pd–imidazolium carbene catalysts.[15]

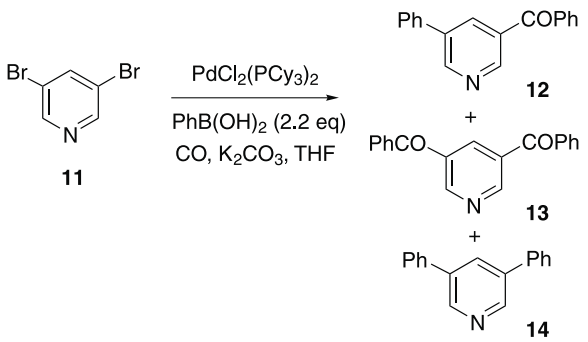
2.3. Carbonylative cross-coupling of dibromopyridines

For substrates that contain more than one halide, the ability to effect selective mono- or multi-functionalization can be a powerful tool. Considering the good results obtained with mono-bromopyridines, we examined the behavior of dibromopyridines with the purpose of studying the regioselectivity of the reaction.

Under moderate CO pressure (5 bar), 2,6-dibromopyridine (**7**) reacted at 120°C to give mainly compound **8** in 63% selectivity, which results from the combination of direct cross-coupling and carbonylative cross-coupling (Scheme 2, Table 4, entry 34). Total conversion was observed after 10 h whereas the reaction of 2-bromopyridines under the same conditions required 20 h to go to completion. This result clearly evidences the activating effect of the second halide that increases the rate of oxidative addition of the substrate onto $Pd^{(0)}$. As expected, higher CO pressure (50 bar) increased the activity and directed the reaction toward the formation of 2,6-dibenzoylpyridine (**9**) but with still rather modest selectivity (60%). This one markedly increased (82%) by lowering the temperature to 90°C, although in this case the activity was quite low (entry 37). Conversely, higher temperature led to higher amounts of **8** and **10** (entries 35 and 38). Various attempts to obtain selectively the monocoupling carbonylative product, i.e. 2-benzoyl-6-bromopyridine, failed even on using 1 equiv. of phenyl boronic acid vs **7**. Taking into account the high reactivity of 2,6-dibromopyridine, the carbonylative cross-coupling of 2,6-dichloropyridine was investigated. At 150°C, under 50 bar CO, the reaction proceeded with low activity to give only monocoupling products, mainly 2-benzoyl-6-chloro-pyridine (58%) (entry 39).



Scheme 2. Carbonylative Suzuki cross-coupling of 2,6-dibromopyridine.



Scheme 3. Carbonylative Suzuki cross-coupling of 3,5-dibromopyridine.

As illustrated in Scheme 3, 3,5-dibromopyridine (**11**) was efficiently coupled with phenyl boronic acid under the same conditions than those used for 2,6-dibromopyridine, but with a lower activity (Table 5). Since the two Br atoms should exhibit the same reactivity, as in the case of 2,6-dibromopyridine, it is not surprising to observe that only dicoupling products were obtained, that is mainly 3-benzoyl-5-phenylpyridine (**12**) under low CO pressure (entry 40) and more selectively 3,5-dibenzoylpyridine (**13**) under high pressure (entry 41).

In the case of 2,5-dibromopyridine (**15a**) (Scheme 4), experiments were first carried out with $PdCl_2(PPh_3)_2$ as the catalyst precursor with the aim to favor the formation of monocoupling products since the Br atom in *meta* position (5-Br) exhibited no reactivity with this catalytic system (vide supra). Unfortunately, various attempts involving 1 or

Table 4. Carbonylative cross-coupling reactions of 2,6-dibromopyridine (**7**)

Entry	Temperature (°C)	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[a] **8**	Selectivity[a] **9**	Selectivity[a] **10**
34	120	5	10	100	63 (54)	26	10
35	150	5	7	100	55	7	38
36	120	50	2	100	35	60	2
37	90	50	120	100	18	82 (71)	0
38	150	50	1.5	100	56	38	6
39[b]	150	50	70	25	58[c]	–	34[d]

2,6-Dibromopyridine=2.0 mmol, $PhB(OH)_2$=2.2 mmol, [$PdCl_2(PCy_3)_2$]=0.06 mmol, K_2CO_3=6.0 mmol, THF=40 mL.

[a] Conversion of **7** and selectivity for pyridyl ketones **8** and **9** and 2,6-diphenylpyridine**10** as determined by quantitative GLC; the values in parentheses refer to isolated yields of the corresponding, analytically pure pyridyl ketone.

[b] 2,6-Dichloropyridine was used as the substrate.

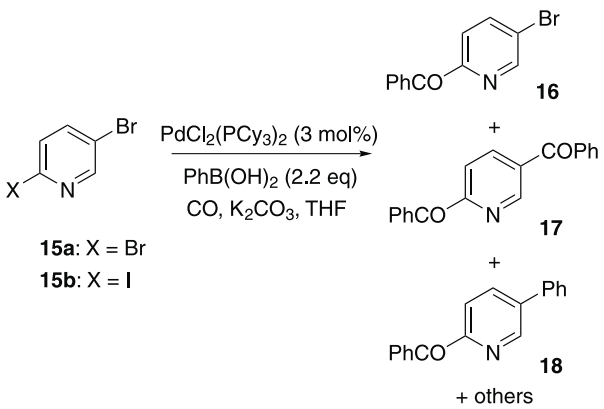
[c] 2-Benzoyl-6-chloropyridine selectivity.

[d] 2-Phenyl-6-chloropyridine selectivity; the homocoupling product, i.e. 2,2′-bis(6-chloropyridine), was also obtained in 8% selectivity.

Table 5. Carbonylative cross-coupling reactions of 3,5-dibromopyridine (**11**)

Entry	Temperature (°C)	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[a] **12**	Selectivity[a] **13**	Selectivity[a] **14**
40	120	5	75	100	61 (43)	27	12
41	120	50	24	100	27	72 (55)	1

See Table 4 for reaction conditions.
[a] Conversion of **11** and selectivity for coupling products **12**–**14** as determined by quantitative GLC; the values in parentheses refer to isolated yields of the corresponding, analytically pure products.



Scheme 4. Carbonylative Suzuki cross-coupling of 2,5-dihalopyridines.

2 equiv. of boronic acid vs **15a** carried out under different reaction conditions (temperature, CO pressure, solvent) led invariably to mixtures of mono- and di-coupling products at total conversion. GLC analyses of aliquot samples taken at different reaction times showed that the Br atom in 2-position reacts indeed first, as expected; however, the resulting monocoupling intermediates, mainly 2-benzoyl-5-bromopyridine (**16**), then react quickly before total consumption of 2,5-dibromopyridine to give the dicoupling products, i.e. mainly 2,5-dibenzoyl-pyridine (**17**) and 2-benzoyl-5-phenylpyridine (**18**). Best results in terms of selectivity were obtained in the presence of $PdCl_2(PCy_3)_2$ as the catalyst precursor (Table 6). Under relatively high pressure and high temperature, **15a** was selectively transformed into **17** and recovered in valuable yield (entry 42). Synthesis of monoketone **16** was achieved in high yield starting from 2-iodo-5-bromopyridine (**15b**), a substrate readily prepared from **15a** by bromide-iodide exchange,[16] and by carrying out the coupling reaction under mild conditions (entry 43).

3. Conclusion

In conclusion, we have shown that the carbonylative Suzuki cross-coupling of pyridyl iodides and bromides provides an efficient, and quite general alternative to access a variety of pyridyl aryl ketones. Most reactions are readily performed under smooth conditions, in particular under rather moderate CO pressure, starting from commercially available pyridyl bromides, phenyl boronic acid and palladium catalyst precursors. In some cases, the reactivity can be advantageously tuned using mixed iodo-bromo pyridine derivatives. Further developments of this chemistry using more attractive chloropyridine substrates will be reported in due course.[15]

4. Experimental

4.1. General

All experiments were carried out under nitrogen using standard Schlenk techniques. Solvents were freshly distilled with an appropriate drying agent (THF, anisole and toluene: Na or Na/K amalgam; CH_2Cl_2:CaH_2; DMF: BaO and $CuSO_4$) and degassed before use. Palladium complexes, phosphines, phenyl boronic acid were purchased from Strem, Aldrich or Acros and used as received. Bromo-, dibromo- and chloropyridines were purchased from Acros or Aldrich and purified by distillation under KOH or column chromatography. Iodopyridines **1a**[17] and **3a**[16] and 2-iodo-5-bromopyridine (**15b**)[16] were synthesized following the reported procedures and purified by column chromatography.

GLC analyses were performed on a Chrompack CP 9001 apparatus equipped with a flame ionization detector and a CPSil 5CB (25 m×0.32 mm, Chrompack) column. ^1H and ^{13}C NMR spectra were recorded on a AC-300 Bruker spectrometer at 23°C in $CDCl_3$; chemical shifts are reported in ppm downfield from TMS and were determined by reference to the residual ^1H (δ=7.25) and ^{13}C (δ=77.0) solvent peaks. All coupling constants are reported in Hz. MS and HRMS were performed on a JMS-700m Station mass spectrometer (JEOL) with either electron impact (70 eV) or chemical (CH_4) ionization mode. Melting points are uncorrected. All the carbonylative cross-coupling products described hereafter gave similar IR spectra (KBr pellets) with ν(C=O) in the range 1690–1640 cm^{-1} and ν(CN) in the range 1590–1550 cm^{-1}.

Table 6. Carbonylative cross-coupling reactions of 2,5-dihalopyridines (**15a**,**b**)

Entry	Substrate	Temperature (°C)	*P*(CO) (bar)	Reaction time (h)	Conversion[a] (%)	Selectivity[a] **16**	Selectivity[a] **17**	Selectivity[a] **18**
42	**15a**	120	50	42	100	0	84 (68)	11
43	**15b**	80	5	24	100	90 (78)	0	0

See Table 4 for reaction conditions.
[a] Conversion of **15a**,**b** and selectivity for coupling products **16**–**18** as determined by quantitative GLC; the values in parentheses refer to isolated yields of the corresponding, analytically pure products.

4.2. Representative procedure for the carbonylative cross-coupling reaction of pyridine halides with phenyl boronic acid

In a typical experiment (Table 1, entry 8), all of the solid reagents, i.e. 4-iodopyridine (**1a**) (0.205 g, 1.0 mmol), $PhB(OH)_2$ (0.134 g, 1.1 mmol), K_2CO_3 (0.414 g, 3.0 mmol) and $PdCl_2(PCy_3)_2$ (0.021 g, 0.03 mmol) were charged into a 60 mL-stainless steel autoclave equipped with a magnetic stirrer bar. After sealing, the reactor was degassed and flushed with carbon monoxide and then THF (20 mL), previously degassed and kept under N_2, was added. The autoclave was pressurized to 5 bar with carbon monoxide and heated at 80°C under stirring for 24 h. After cooling to room temperature, the solution was analyzed by GLC using dodecane as an internal standard, which showed that 4-benzoylpyridine (**2**) has been formed in 90% selectivity along with 4-phenylpyridine in 10% selectivity. The solution was then filtered, the precipitate was washed with ether, the ether phases were joined to the filtrate and the mixture concentrated under vacuum. The crude product was then purified by column chromatography on silica gel using AcOEt/heptane (1:1) as eluent to give analytically pure 4-benzoylpyridine (**2**) (0.147 g, 80% yield).

4.2.1. 4-Benzoylpyridine (2). White solid, mp=70°C, ^{1}H NMR: δ 8.77 (d, 2H, J=5.8 Hz, H-2/H-6), 7.78 (d, 2H, J=7.4 Hz, H-9), 7.60 (t, 1H, J=7.4 Hz, H-11), 7.54 (d, 2H, J=5.8 Hz, H-3/H-5), 7.47 (t, 2H, J=7.4 Hz, H-10); ^{13}C NMR: δ 195.1 (CO), 150.3 (C-2), 144.3 (C-4), 135.8 (C-8), 133.5 (C-11), 128.6 (C-10), 122.9 (C-3); MS (EI, relative intensity %): m/z 183 (M^+, 34), 106 (M^+-Ph, 10), 105 (M^+-Py, 100), 78 (Py^+, 12), 77 (Ph^+, 52), 51 (C_4H_3, 38); HRMS: calcd for $C_{12}H_{10}NO$ $[M+H]^+$: 184.0762, found: 184.0767.

Reaction with other pyridine halides were performed in a similar manner except that in the case of liquid pyridine halides, the substrate was dissolved in the solvent before introduction in the reactor.

4.2.2. 2-Benzoylpyridine (4). Yield: 0.15 g, 82%; white solid, mp=42°C, ^{1}H NMR: δ 8.69 (d, 1H, J=4.8 Hz, H-6), 8.04 (d, 1H, J=7.6 Hz, H-3), 8.01 (d, 2H, J=7.5 Hz, H-9), 7.86 (td, 1H, J=7.6, 1.7 Hz, H-4), 7.56 (t, 1H, J=7.4 Hz, H-11), 7.48–7.43 (m, 3H, H-5/H-10); ^{13}C NMR: δ 193.9 (CO), 155.03 (C-2), 148.6 (C-6), 137.1 (C-4), 136.2 (C-8), 132.9 (C-11), 131.0 (C-9), 128.2 (C-10), 126.2 (C-5), 124.6 (C-3); MS (EI): m/z 183 (M^+, 38), 182 (62), 155 (M^+-CO, 92), 154 (42), 127 (6), 106 (M^+-Ph, 10), 105 (M^+-Py, 90), 78 (Py^+, 28), 77 (Ph^+, 100), 52 (18), 51 (C_4H_3, 76), 50 (28); HRMS: calcd for $C_{12}H_{10}NO$ $[M+H]^+$: 184.0762, found: 184.0768.

4.2.3. 3-Benzoylpyridine (6). Yield: 0.147 g, 80%; white solid, mp=40°C, ^{1}H NMR: δ 9.01 (d, 1H, J=2.0 Hz, H-2), 8.85 (dd, 1H, J=5.0, 2.0 Hz, H-6), 8.15 (dt, 1H, J=8.0, 2.0 Hz, H-4), 7.84 (d, 2H, J=7.5 Hz, H-9), 7.75 (dd, 1H, J=8.0, 2.0 Hz, H-5), 7.75–7.35 (m, 3H, H-10/H-11); ^{13}C NMR: δ 194.8 (CO), 152.8 (C-2), 151.0 (C-6), 137.1 (C-4), 136.6 (C-8), 133.1 (C-11), 129.9 (C-9), 128.5 (C-10), 128.4 (C-3), 123.3 (C-5); MS (EI): m/z 183 (M^+, 96), 182 (48), 155 (M+-CO, 8), 154 (10), 127 (5), 106 (M^+-Ph, 40), 105 (M^+-Py, 100), 78 (Py^+, 56), 77 (Ph^+, 84), 63 (2), 51 (C_4H_3, 78), 50 (28); HRMS: calcd For $C_{12}H_{10}NO$ $[M+H]^+$: 184.0762, found: 184.0766.

4.2.4. 2-Benzoyl-6-phenylpyridine (8). Yield: 0.280 g, 54%; pale brown solid, mp=75°C; ^{1}H NMR: δ 8.22 (dd, 2H, J=7.0, 1.5 Hz, H-3), 8.06–7.94 (m, 4H, H-4, H-5 and H-9), 7.60 (d, 2H, J=7.6 Hz, H-13), 7.54–7.44 (m, 6H, H-10, H-11, H-14 and H-15); ^{13}C NMR: δ 193.7 (CO), 155.9 (C-6), 154.8 (C-2), 138.4 (C-12), 137.9 (C-4), 136.4 (C-8), 132.8 (C-11), 131.3 (C-9), 129.4 (C-15), 128.9 (C-14), 128.8 (C-10), 127 (C-13), 122.9–122.5 (C-5 and C-3); MS (EI): m/z 259 (M^+, 61), 258 (42), 231 (M^+-CO, 67), 230 (72), 154 ($Py-Ph^+$, 8), 127 (17), 106 (6), 105 ($PhCO^+$, 83), 78 (8), 77 (Ph^+, 100), 51 ($C_4H_3^+$, 22); HRMS: calcd for $C_{18}H_{14}NO$ $[M+H]^+$: 260.1075, found: 260.1075.

4.2.5. 2,6-Dibenzoylpyridine (9). Yield: 0.407 g, 71%; white solid, mp=105°C, ^{1}H NMR: δ 8.28 (d, 2H, J=7.5 Hz, H-3/H-5), 8.12 (m, 5H, H-4, H-9/H-14), 7.56 (t, 2H, J=7.4 Hz, H-11/H-16), 7.40 (t, 4H, J=7.4 Hz, H-10/H-15); ^{13}C NMR: δ 192.6 (CO), 153.8 (C-2/C-6), 138.3 (C-4), 135.9 (C-8/C-13), 133.0 (C-11/C-16), 131.1 (C-9/C-14), 128.0 (C-10/C-15), 126.9 (C-3/C-5); MS (EI): m/z 287 (M^+, 40), 259 (M+-CO, 10), 230 (12), 182 (11), 106 (7), 105 ($PhCO^+$, 98), 77 (Ph^+, 100), 51 ($C_4H_3^+$, 18), 50 (36); HRMS: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$: 288.1025, found: 288.1034.

4.2.6. 3-Benzoyl-5-phenylpyridine (12). Yield: 0.223 g, 43%; yellow oil, ^{1}H NMR: δ 9.03 (s, 1H, H-2), 8.94 (s, 1H, H-6), 8.29 (s, 1H, H-4), 7.83 (d, 2H, J=7.6 Hz, H-9), 7.62 (d, 2H, J=7.2 Hz, H-13), 7.56–7.44 (m, 6H, H-10, H-11, H-14, H-15); ^{13}C NMR: δ 193.5 (CO), 151.9 (C-2), 150.4 (C-6), 138.5 (C-12), 136.9 (C-4), 135.2–134.5 (C-5, C-8), 131.7–131.2 (C-11 and C-15), 130.6 (C-3), 127.6–127.1–126.6–126.3 (C-9, C-10, C-13 and C-14), 124.8 (C-3); HRMS: calcd for $C_{18}H_{14}NO$ $[M+H]^+$: 260.1075, found: 260.1085.

4.2.7. 3,5-Dibenzoylpyridine (13). Yield: 0.316 g, 55%, pale yellow solid, mp=100°C; ^{1}H NMR: δ 9.15 (d, 2H, J=1.5 Hz, H-2/H-6), 8.47 (t, 1H, J=1.5 Hz, H-4), 7.81 (d, 4H, J=7.8 Hz, H-9/H-14), 7.64 (t, 2H, J=7.8 Hz, H-11/H-16), 7.49 (t, 4H, J=7.8 Hz, H-10/H-15); ^{13}C NMR: δ 192.7 (CO), 152.3 (C-2/C-6), 136.8 (C-4), 134.9 (C-8/C-13), 132.4 (C-11/C-16), 131.8 (C-3/C-5), 129.0 (C-9/C-14), 127.4 (C-10/C-15); HRMS: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$: 288.1025, found: 288.1029.

4.2.8. 2-Benzoyl-5-bromopyridine (16). Yield: 0.409 g, 78%; pale brown solid, mp=53°C; ^{1}H NMR: δ 8.76 (d, 1H, J=2.2 Hz, H-6), 8.04 (m, 3H, H-3 and H-9), 7.94 (d, 1H, J=7.7 Hz, H-4), 7.63–7.45 (m, 3H, H-10/H-11); ^{13}C NMR: δ 192.9 (CO), 153.2 (C-2), 149.7 (C-6), 139.8 (C-4), 136.3 (C-8), 133.2 (C-11), 130.9 (C-9), 128.3 (C-10), 126.0 (C-3), 124.3 (C-5); MS (EI): m/z 263 ($M^+(^{81}Br)$, 19), 262 (28), 261 ($M^+(^{79}Br)$, 20), 260 (26), 235 (M^+-CO (^{81}Br), 64), 233 (M^+-CO (^{79}Br), 66), 154 ($M^+-CO-Br$, 50), 105 (M^+-Py, 98), 77 (Ph^+, 100), 76 (Py+,28), 51 ($C_4H_3^+$, 67), 50 (36); HRMS: calcd for $C_{12}H_9BrNO$ $[M+H]^+$ ^{79}Br (^{81}Br): 261.9868 (263.9848), found: 261.9872 (263.9834).

4.2.9. 2,5-Dibenzoylpyridine (17). Yield: 0.390 g, 68%,

yellow solid, mp=106°C; ^{1}H NMR: δ 9.07 (d, 1H, J=2.1 Hz, H-6), 8.28 (dd, 1H, J=8.1, 2.1 Hz, H-4), 8.14 (d, 1H, J=8.1 Hz, H-9), 7.85 (d, 2H, J=7.1 Hz, H-14), 7.69–7.48 (m, 6H, H-10, H-11, H-15, H-16); ^{13}C NMR: δ 192.6 and 193.0 (CO), 157.2 (C-2), 149.5 (C-6), 138.2 (C-4), 136.3–135.7–134.8 (C-5, C-8, C-13), 133.6–133.4 (C-11, C-16), 131.0–130.1 (C-9, C-14), 128.8–128.3 (C-10, C-15), 124.1 (C-3); MS (EI): *m/z* 287 (M^+, 11), 286 (10), 259 (M^+-CO, 15), 258 (17), 231 (M^+-2CO, 4), 230 (12), 105 ($PhCO^+$, 82), 77 (Ph^+, 100), 51 ($C_4H_3^+$, 21); HRMS: calcd for $C_{19}H_{14}NO_2$ $[M+H]^+$: 288.1025, found: 288.1034.

4.2.10. 2-Benzoyl-5-phenylpyridine (18). Yield: 0.026 g, 5%; yellow oil; ^{1}H NMR: δ 8.95 (d, 1H, J=1.6 Hz, H-6), 8.18–8.07 (m, 4H, H-3, H-4 and H-9), 7.68–7.44 (m, 8H, H-10, H-11, H-13, H-14 and H-15); ^{13}C NMR: δ 193.6 (CO), 153.6 (C-2), 147 (C-6), 138.7 (C-8), 136.9–136.5 (C-5 and C-12), 135.2 (C-4), 132.9 (C-11), 131.0–129.3 (C-9 and C-13), 128.9 (C-15), 128.2–127.3 (C-10 and C-14), 124.8 (C-3); MS (EI): *m/z* 259 (M^+, 24), 258 (27), 231 (M^+-CO, 59), 230 (51), 127 (16), 105 ($PhCO^+$, 57), 77 (Ph^+, 100), 51 ($C_4H_3^+$, 25); HRMS: calcd for $C_{18}H_{14}NO$ $[M+H]^+$: 260.1075, found: 260.1068.

4.2.11. 5-Benzoyl-2-phenylpyridine. This compound was not isolated and characterized by GC-MS. MS (EI): *m/z* 259 (M^+, 73), 258 (43), 231 (M^+-CO, 6), 230 (8), 154 (Py–Ph^+, 18), 127 (44), 105 ($PhCO^+$, 55), 77 (Ph^+, 100), 51 ($C_4H_3^+$, 30).

Acknowledgements

This work was supported by the Ministère de la Recherche et de l'Enseignement Supérieur (PhD grant to SCB) and by the CNRS.

References

1. (a) Yates, F. S. *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., Mckillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2. Chapter 2.08. (b) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Mckillop, A., Ed.; Pergamon: Oxford, 1995; Vol. 5. Chapter 5.06.
2. (a) Hlasta, D. J.; Court, J. J. *Tetrahedron Lett.* **1989**, *30*, 1773–1776. (b) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3597–3600.
3. (a) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H. *Tetrahedron Lett.* **1986**, *27*, 3899–3902. (b) Trécourt, F.; Breton, G.; Bonnett, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339–4342.
4. Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1781–1782.
5. (a) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 5373–5374. (b) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713–9720.
6. (a) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003–2010. (b) Yamamoto, Y.; Ouchi, H.; Tanaka, T. *Chem. Pharm. Bull.* **1995**, *43*, 1028–1030.
7. (a) Choudary, B. M.; Bhuma, V.; Narender, N. *Ind. J. Chem., Sect. B* **1996**, *35B*, 281–282. (b) Mohammadpoor-Baltork, I.; Sadeghi, M. M.; Mahmoodi, N.; Kharamesh, B. *Ind. J. Chem., Sect. B* **1997**, *36B*, 438–441. (c) Mohammad-Baltork, I.; Hajipour, A. R.; Mohammadi, H. *Bull. Chem. Soc. Jpn* **1998**, *71*, 1649–1653. (d) Hajipour, A. R.; Mahboobkhak, N. *Ind. J. Chem., Sect. B* **1998**, *37B*, 285–287. (e) Hajipour, A. R.; Mohammadpoor-Baltork, I.; Kianfar, G. *Bull. Chem. Soc. Jpn* **1998**, *71*, 2655–2659. (f) Hajipour, A. R.; Mahboobkhak, N. *Synth. Commun.* **1998**, *28*, 3143–3150.
8. (a) Herrmann, C. K. F.; Sachdeva, Y. P.; Wolfe, J. F. *J. Heterocycl. Chem.* **1987**, *24*, 1061–1065. (b) De Kimpe, R.; Keppens, M.; Fonck, G. *Chem. Commun.* **1996**, 635–636.
9. (a) In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley/VCH: New York, 1998. (b) For a recent review on palladium-catalyzed coupling reactions of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
10. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (c) Miyaura, N. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, pp 187–243. (d) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley/VCH: New York, 1998; Chapter 2.
11. (a) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595–7598. (b) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726–4731.
12. Preliminary communication: Couve-Bonnaire, S.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* **2001**, *42*, 3689–3691.
13. Najiba, D.; Carpentier, J.-F.; Castanet, Y.; Biot, C.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3719–3722.
14. (a) Takeuchi, R.; Suzuki, K.; Sato, N. *Synthesis* **1990**, 923–924. (b) Bessard, Y.; Roduit, J.-P. *Tetrahedron* **1999**, *55*, 393–404. (c) El-ghayoury, A.; Ziessel, R. *Tetrahedron Lett.* **1998**, *39*, 4473–4476.
15. Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. Manuscript in preparation.
16. Corcoran, R. C.; Bang, S. H. *Tetrahedron Lett.* **1990**, *31*, 6757–6758.
17. Coudret, C. *Synth. Commun.* **1996**, *26*, 3543–3547.