Efficient Palladium-Catalyzed Alkoxycarbonylation of *N*-Heteroaryl Chlorides – A Practical Synthesis of Building Blocks for Pharmaceuticals and Herbicides

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Dedicated to Professor K. B. Sharpless on the occasion of his 60th birthday

Abstract: The alkoxycarbonylation of various *N*-heteroaryl chlorides was examined in detail. Studies of the butoxycarbonylation of 2- and 3-chloropyridine revealed the importance of selecting both the right phosphine ligand and ligand concentration in order to obtain efficient conversion and selectivity. Amongst the different ligands tested, 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) led to the most efficient palladium catalyst systems for the conversion of 2- and 4-chloropyridines and similar heteroaryl chlorides. The best catalytic systems for the alkoxycarbonylation of less activated substrates, such as 3-chloropyridines, were found to be those containing 1,4-bis(dicyclohexylphosphino)butane. Good to excellent yields of a number of *N*-heterocyclic carboxylic acid esters were realized by applying the appropriate ligand in the right concentration at low catalyst loadings (0.005–0.5 mol% Pd). For the first time catalyst turnover numbers (TON) of up to 13,000 were obtained for the carbonylation of a (hetero)aryl chloride.

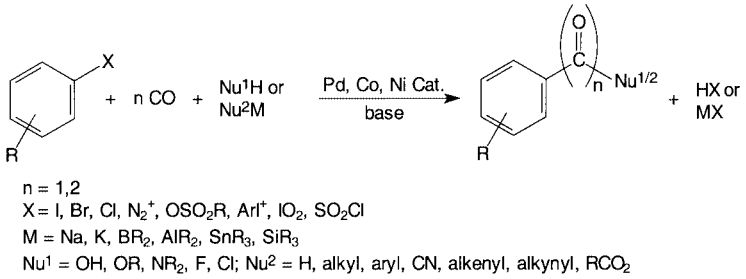
Key words: carbonylation, palladium, homogeneous catalysis, pyridines, coupling reactions

Introduction

Although it is well accepted that the palladium-catalyzed C–C coupling reaction of aryl halides[1] constitutes a powerful tool for functionalizing aromatic rings, the corresponding palladium-catalyzed carbonylation of aryl-X derivatives (X = Cl, Br, I, OTf, OMs) has so far found little application in synthetic organic chemistry and in industry. This is in part understandable since reactions with carbon monoxide generally require certain safety precautions, in addition to specific high-pressure equipment. On the other hand, these reactions offer numerous possibilities for the selective synthesis of various aromatic carboxylic acid derivatives. Acids, esters, amides, aldehydes, ketones and other carboxylic acid derivatives are easily accessible by reacting an aryl halide with carbon monoxide and ubiquitous nucleophiles (Scheme 1).[2]

Aryl halides are the most interesting class of starting materials for further palladium-catalyzed refinement, as they are commercially available in a range of substitution patterns at low cost. Unfortunately, chloroaromatics display a lower reactivity than the corresponding bromides and iodides. This difference in reactivity is generally ascribed to the reluctance of the sp^2-C–Cl bond to undergo oxidative addition (dissociation energy 402 kJmol^{-1}, 339 kJmol^{-1} and 272 kJmol^{-1} for PhCl, PhBr and PhI, respectively, at 298 K) to give the catalytically active Pd(II) species. Therefore, special catalyst systems, which facilitate the oxidative addition of the aryl chlorides, are required for efficient activation.[3]

While significant progress has recently been made in the palladium-catalyzed activation of aryl chlorides for coupling reactions such as the Heck olefination,[4] the Suzuki arylation,[5] and the Buchwald–Hartwig amination,[6] there has been little progress regarding the carbonylation of aryl chlorides.[7] This is demonstrated by comparing the best known catalyst productivity (turnover number, TON), e.g., for the Suzuki reaction of aryl chlorides (TON = 10,000–100,000)[5,k] and for the carbonylation of aryl chlorides (TON = 100–1,000).[8]



Scheme 1 Carbonylation of aryl–X derivatives

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The difficulty of activating aryl chlorides in the presence of a large excess of carbon monoxide ligand is a result of the π-accepting character of CO. The activity of the palladium(0) complex towards oxidative addition is reduced due to the binding of carbon monoxide to the metal center. Moreover, clustering and agglomeration of Pd atoms is facile in the presence of CO[9] leading to non-active palladium species. A solution to these problems was presented by Milstein and co-workers, who introduced palladium catalysts containing the highly basic 1,3-bis(di-*iso*-propylphosphino)propane ligand.[8] The drawbacks of this catalyst system are however, the difficult synthesis and the highly sensitive nature of this pyrophoric phosphine along with comparatively low catalyst turnover numbers (1 mol% of palladium). Very recently we were able to develop a more general solution to this problem by using air-stable basic chelating ferrocenyl phosphines.[10]

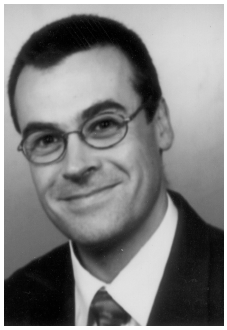
Biographical Sketches

Matthias Beller, born 1962 in Gudensberg, Germany, studied chemistry at the University of Göttingen from 1982–1987 and obtained his doctorate (Dr. rer. nat.) in 1989 under the guidance of Prof. L. F. Tietze. After postdoctoral studies (1990) with Prof. K. B. Sharpless at Massachussetts Institute of Technology (USA) funded with a Liebig scholarship of the Verband der Chemischen Industrie, he became research chemist in the Central Research of Hoechst AG in Frankfurt, Germany. In 1993 he became group leader of "Organometallic chemistry – catalysis" and in 1994 project leader of "Homogeneous catalysis" at Hoechst AG. From 1996 to 1998 he was Associate Professor for Inorganic Chemistry at the Technical University of Munich and since June 1998 he is Director of the "Institute for Organic Catalysis" (IfOK) at the University of Rostock aligned with a full professorship "Catalysis" at the University of Rostock.

In 1998 he was awarded the Otto-Roelen-Medaille for Homogeneous Catalysis of the Dechema and was elected to the board of the German Society of Catalysis.

His research topics cover the development of practical catalytic methodologies. Special attention is given to selective and environmentally benign transformations. More specific, he is interested in palladium-catalyzed coupling reactions, carbonylation reactions, catalytic amination of olefins, and oxidations of olefins using air or molecular oxygen as final oxidant. His scientific work has been published in more than 100 original publications and review articles. In addition ca. 50 patent applications have been filed in the last decade. Together with Prof. Cartsten Bolm he has edited a book on the use of "Transition Metals for Organic Synthesis".

Wolfgang Maegerlein was born near Nürnberg, Germany, in 1972. He studied chemistry at the Technical University of Munich, where he received his doctorate in 2000 under the supervision of Prof. M. Beller. He is currently pursuing postdoctoral research with Prof. K. C. Nicolaou at The Scripps Institute in La Jolla, California.



Adriano F. Indolese gained his PhD in transition-metal catalysis in 1992 from die ETH Zürich under the supervision of Prof. G. Consiglio. After postdoctoral studies with Prof. B. Trost at the University of Stanford, CA, he joined the Catalysis Research Group of Ciba-Geigy AG, Basel. He currently works at Solvias AG as a research scientist in the field of metal-catalyzed coupling reactions. His research interests focus on the palladium- and nickel-catalyzed coupling reaction such as Suzuki coupling, Heck reaction, and carbonylation reactions of aryl halides.

Christine Fischer, born 1955 in Rostock, Germany, studied chemistry at the University of Rostock from 1974–1979, and received her doctorate (Dr. rer. nat.) in 1986 under the guidance of Prof. G. Oehme. During a postdoctoral stay (1986) with Prof. V. Davankov (Moscow), she worked on enantiomeric resolutions in HPLC. Since 1987 she is in charge of the HPLC laboratory of the "Institut für Organische Katalyseforschung" at the University of Rostock, and since 2000 she is also in charge of the GC laboratory. Her research interests deal with chiral resolutions in chromatography.

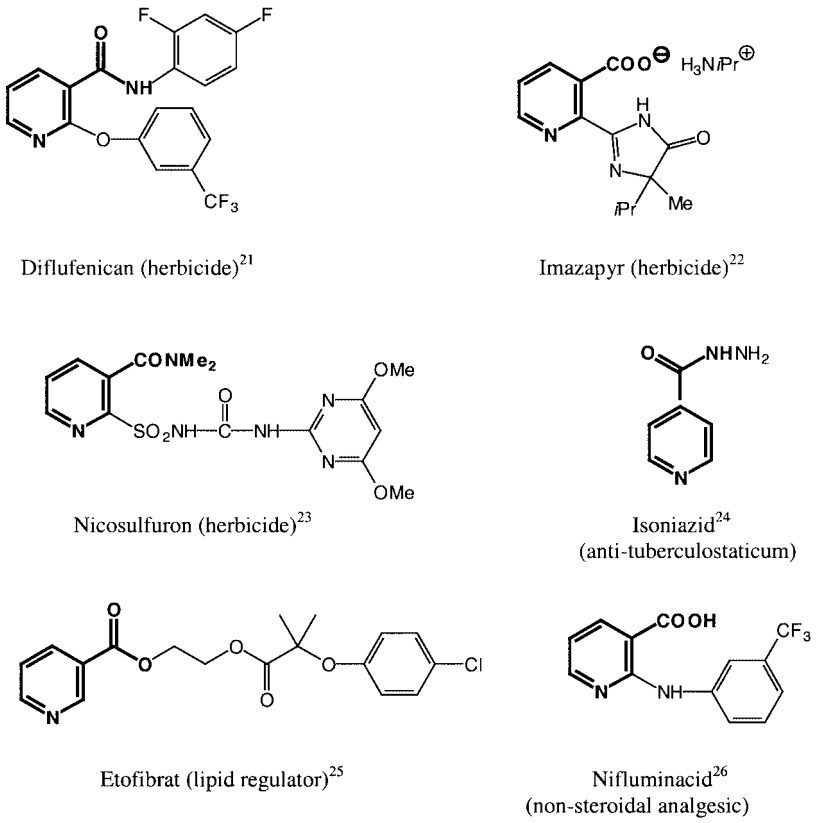


Figure Selected examples of pyridine carboxylic acid derivatives

In addition to the carbonylation of chlorobenzenes, we are also interested in the carbonylation of *N*-heteroaryl chlorides. *N*-Heterocyclic carboxylic acid derivatives are useful intermediates for the synthesis of a number of biologically active molecules, with pyridine derivatives being particularly important intermediates for pharmaceuticals and agrochemicals.[11]

Selected examples of biologically active pyridine carboxylic acid derivatives, which are produced by fine chemical companies, are shown in the Figure. It is interesting to note that even structurally simple nicotinic acid displays pharmacological effects as a lipid regulator.

Catalytic systems known in the literature for the carbonylation of *N*-heteroaryl chlorides include simple in situ catalysts consisting of a Pd(II) precursor and either PPh_3 or a chelating phosphine such as dppp or dppb. Table 1 gives an overview of the known catalytic systems for the carbonylation of chloropyridines and similar *N*-heteroaryl chlorides.

In general, the carbonylation of the most active 2- and 4-positions of the pyridine ring in the presence of standard palladium catalysts is described. Except for the aminocarbonylation of 2,5-dichloropyridine[28] and the alkoxycarbonylation of 5-methoxymethyl-2,3-dichloropyridine,[33] comparatively large amounts of palladium (> 2 mol%) were used. Interestingly, the former reaction has been developed into an efficient industrial process for the production of the monoaminoxidase B inhibitor Lazabemid by Hofmann-La Roche. This process, shown in Scheme 2, is a significant improvement on the former 8- and 4-step reaction sequences.

Herein, we report the application of simple, commercially available palladium catalyst systems that enable efficient carbonylation of 2- and 4-chloropyridines as well as the less activated 3-chloropyridines. The scope of these catalysts is demonstrated by the butoxycarbonylation of a variety of *N*-heteroaryl chlorides. A substantial improvement in catalyst efficiency compared to previously known carbonylations of *N*-heteroaryl chlorides has been observed.

Results and Discussion

It is obvious that the palladium-catalyzed carbonylation of 2- or 3-chloropyridine would not be the method of choice for the synthesis of 2-picolinic or 3-nicotinic acid.[12] Nevertheless, we chose these transformations as model reactions for catalyst development due to the availability of starting materials and as procedures for product analysis already exist. Initially, the influence of critical reaction parameters (temperature, CO pressure, ligand/Pd ratio) on the test system (butoxycarbonylation of 2-chloropyridine) was evaluated in order to establish optimum reaction conditions. Due to the strong activation of the C-Cl bond in 2-chloropyridine, we chose similar initial reaction condi-

Table 1 Known Pd-Catalyzed Carbonylation of Chloropyridines and Similar Derivatives

Reference	Heteroaryl chloride	Nucleophile	Catalyst	Reaction conditions	TON (Yield)
Head 1984[27]	3,5-Dichloro-pyridine	EtOH	2 mol% $PdCl_2(PPh_3)_2$	7 bar CO, 100 °C,8 h	Monoester: 18 (35%)
Scalone 1990[28]	2,5–Dichloro-pyridine	$H_2N(CH_2)_2NHRR$ = H, Bzl, COO-*t*-Bu; MeOH	0.03–0.1 mol% $PdCl_2$ or $PdCl_2(MeCN)_2$, 0.03–0.2 mol% dppp; alkoxycarbonylation: 2 mol% $PdCl_2(PPh_3)_2$	10 bar CO, 110 °C, 24 h	750–3100 (75–93%) Monoester: 25 (49%)
Takeuchi 1991[29]	2-Chloropyridine, 2-chloropyrazine, chloro-(methyl)pyrazines	MeOH, Et_2NH, *n*–$BuNH_2$	1–2 mol% $Pd(OAc)_2$, $Pd(dba)_2$ or $PdCl_2L_2$, 2 mol% PPh_3 or 1 mol% dppe or dppb	20–40 bar CO, 120–150 °C, 16 h	45–95 (45–95%)
Ciufolini 1996[30]	2–Chloro-quinolines	MeOH	2–4 mol% $Pd(OAc)_2$, 4 mol% dppp	100 bar CO, 100–140 °C, 48–96 h	18−49 (72–98%)
Ziessel 1998, 2000[31]	2,9–Dichloro-1,10-phenanthroline, 2,7-dichloro-1,8-naphthyridine	*n*–BuOH	2 mol% $PdCl_2(PPh_3)_2$	1 bar CO, 120 °C, 20 h	20–30 (40–60%)
Carpentier 1999[32]	4,7-Dichloro-quinoline, 2,3-, 2,5-, 2,6-dichloropyridine	MeOH, EtOH, Et_2NH	2 mol% $PdCl_2(PPh_3)_2$, 10 mol% PPh_3	50 bar CO, 130–155 °C, 1–16 h	34–45(68–90%)
Bessard 1999[33]	5–Methoxy-methyl-2,3-di-chloropyridine	MeOH, EtOH	0.2 mol% $PdCl_2(PPh_3)$ or $Pd(OAc)_2$, 3 mol% dppb or dppf	15 bar CO, 145–160 °C, 3–5 h	2-Monoester: 470 (94%) 2,3-Diester: 450 (90%)

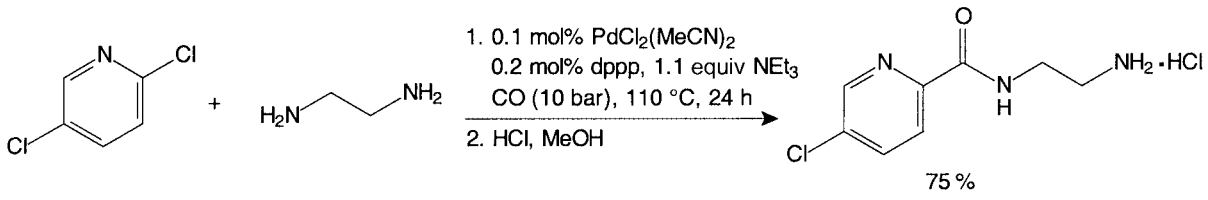
tions to those previously published for the butoxycarbonylation of 4-bromoacetophenone[13] (0.3 mol% Pd, 5 bar CO, 100 °C, Et_3N). However, under these conditions palladium black precipitation was observed and only very low conversions were obtained (Table 2, entry 1).

Increasing the temperature and decreasing the CO pressure, both of which should facilitate the oxidative addition step, did not significantly increase the yield of the desired product (Table 2, entry 2), but instead resulted in rapid palladium black precipitation. Hence, we attempted to stabilize the palladium catalyst by increasing the P/Pd ratio (Table 2, entries 3−5). Using palladium ratios of 8:1, 15:1, and 25:1 respectively, much improved yields of butyl pyridine-2-carboxylate (51−64%) were observed. Variation of the temperature and CO pressure at a high P/Pd ratio did not lead to better product yields (Table 2, entries 6−10). The utilization of a $PdCl_2(PCy_3)_2$/6 PCy_3 catalyst system under conditions similar to entry 3 only gave lower yields and not the expected improvement.

This observation suggested that the oxidative addition of the Pd catalyst into the C-Cl bond is **not** the critical reaction step under these conditions. Instead we postulate that CO insertion is difficult. As shown in Scheme 3, 2-chloropyridine reacts with $Pd(PPh_3)_n$ to give the corresponding pyridinepalladium(II) dimer.[14] This dimer does not undergo any stoichiometric reaction with CO even after several hours at 80 °C.

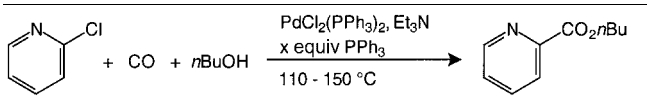
In order to prevent dimer formation, the performance of a series of chelating ligands was studied. While carbonylation at 1 bar CO gave only low product yields, performing the reaction at 25 bar of CO gave excellent yields of butyl pyridine-2-carboxylate, if the appropriate ligand was used (Table 3).

The reaction of 2-chloropyridine with CO and *n*-butanol in the presence of only 0.03 mol% $PdCl_2(PhCN)_2$, 0.6 mol% 1,3-bis(diphenylphosphino)propane (dppp) and 1.2 equivalents of triethylamine led to *n*-butyl pyridine-2-carboxylate in 61% yield after 14 h (Table 3, entry 3). Ligands which give either smaller or much larger chelate



Scheme 2 Monocarbonylation of 2,5-dichloropyridine to give Lazabemid

Table 2 Butoxycarbonylation of 2-Chloropyridine in the Presence of $PdCl_2(PPh_3)_2/PPh_3$[a]

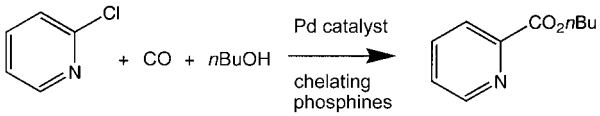


Entry	Temp (°C)	*P* (bar)	P/Pd	Yield of Ester (%)[b]
1	100	5	2	2
2	130	2.5	2	9
3	130	2.5	8	51
4	130	2.5	15	64
5	130	2.5	25	62
6	110	2.5	8	41
7	150	2.5	8	50
8	130	1	8	3
9	130	60	8	30
10	130	100	8	28

[a]7.0 mmol 2-chloropyridine, 14 mL *n*-BuOH, 8.4 mmol Et_3N, 0.3 mol% $PdCl_2(PPh_3)_2$.
[b]Determined by GC using diethyleneglycol di-*n*-butylether as the internal standard.

rings lead to lower yields. On the other hand 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) gave even better yields of 94% and 95% yield, respectively (Table 3, entries 4, 7). Applying the previously best known catalyst system (0.03 mol% $PdCl_2(PhCN)_2$, 0.45 mol% dppb, 300 mol% NaOAc) reported by Bessard,[33] a product yield of 85% was obtained. Decreasing the palladium concentration to 0.005 mol% still gave *n*-butylpyridine-2-carboxylate in 65% yield under our optimized conditions. This corresponds to a turnover number of 13,000 and a turnover frequency of more than 900 h^{-1} (Table 3, entry 10). To the best of our knowledge, this is the highest catalyst productivity known in the literature for any carbonylation of an aryl or heteroaryl chloride.[15]

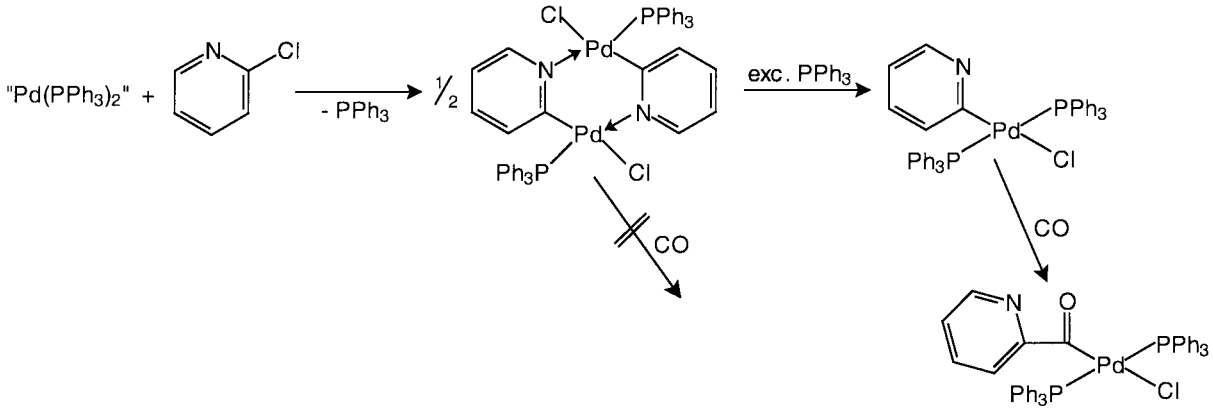
Table 3 Carbonylation of 2-Chloropyridine in the Presence of Chelating Ligands[a]



Entry	Ligand	$PdCl_2(PhCN)_2$ (mol%)	P/Pd	*P* (bar)	Yield (TON) (%)[b]
1	dppm	0.03	40	25	0
2	dppe	0.03	40	25	8 (266)
3	dppp	0.03	40	25	61 (2033)
4	**dppb**	**0.03**	**40**	**25**	**94 (3133)**
5	dpppe	0.03	40	25	46 (1533)
6	dpphe	0.03	40	25	7 (233)
7	**dppf**	**0.03**	**40**	**25**	**95 (3167)**
8	dppb	0.1	12	25	96 (96)
9	dppb	0.03	12	25	29 (967)
10	**dppb**	**0.005**	**240**	**25**	**65 (13000)**
11	dppb	0.3	4	1	17 (57)
12	dppb	0.3	14	1	9 (30)
13	dppf	0.03	40	3	76 (2533)

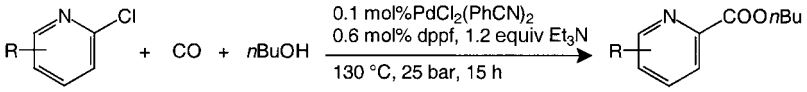
[a]7.0 mmol 2-chloropyridine, 14 mL *n*-BuOH, 8.4 mmol Et_3N, 130 °C, 14 h.
[b]Determined by GC using diethyleneglycol di-*n*-butylether as the internal standard.

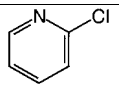
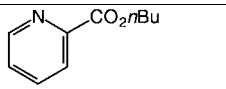
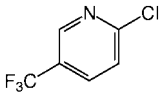
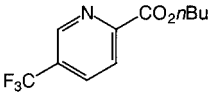
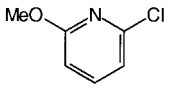
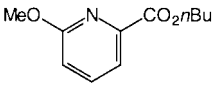
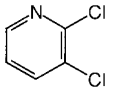
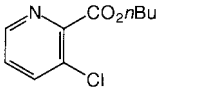
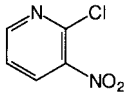
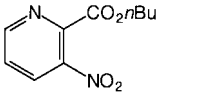
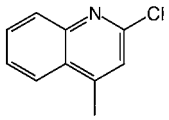
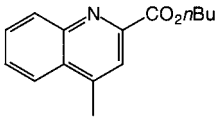
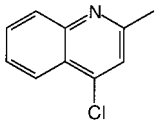
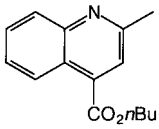
It is important to note that the "correct" ligand concentration required for a stabilization of palladium(0) and partial activation of the unreactive palladium(0)carbonyl complexes is the key factor in achieving an efficient reaction (compare entries 4, 8 and 9, Table 3). We believe that this



Scheme 3 Formation of dimeric oxidative addition products

able 4 Butoxycarbonylation of 2-Chloropyridines and 2- and 4-Chloroquinolines[a]



ntry	Substrate	Product	Yield (%)[b]
			95
			94
			83
			73
			25
			74
			70

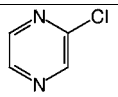
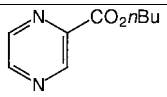
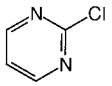
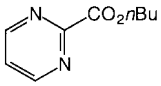
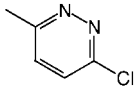
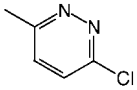
7.0 mmol *N*-heteroaryl chloride, 14 mL *n*-BuOH, 1.2 equiv Et_3N, 0.1 mol% $PdCl_2(PhCN)_2$, 0.6 mol% dppf, 130 °C, 25 bar CO, 15 h. Isolated yield.

observation is also true for similar types of palladium-catalyzed coupling reactions. In these reactions attention is often only paid to the metal to ligand ratio. *However, as shown above, the ligand concentration and not the metal to ligand ratio has to be studied in order to gain objective information about the productivity of the metal center.*

The promising results obtained with the dppf and dppb ligands encouraged us to study the general scope and limitations of this catalyst system for the alkoxycarbonylations of different *N*-heteroaryl chlorides (Tables 4 and 5).

A quantitative conversion of the heteroaryl chlorides was observed in all reactions examined except for 2-chloro-3-nitropyridine and 2-chloropyrimidine. 2-Chloro-5-trifluoromethylpyridine, 2-chloro-6-methoxypyridine, 2-chloropyrazine, and 3-chloro-6-methylpyridazine afforded the respectively substituted heterocyclic carboxylic acid esters in high yield (82–95%) (Table 4, entries 2, 3; Table 5, entries 1, 3). This catalyst is also active for chloroquinolines, as indicated by entries 6 and 7 (Table 4).[16] 2,3-Dichloropyridine was selectively converted to butyl 3-chloropyridine-2-carboxylate in 73% yield. With the more sensitive 2-chloro-3-nitropyridine, the desired product was formed in only approximately 25% yield, as butyl 3-aminopyridine-2-carboxylate (approx. 35%) and 3-amino-2-chloropyridine were observed as major side products (Table 4, entry 5).

Table 5 Butoxycarbonylation of other *N*-Heteroaryl Chlorides[a]

Entry	Substrate	Product	Yield (%)[b]
1			82
2			55
3			83

[a]7.0 mmol *N*-heteroaryl chloride, 14 mL *n*-BuOH, 1.2 equiv Et_3N, 0.1 mol% $PdCl_2(PhCN)_2$, 0.6 mol% dppf, 130 °C, 25 bar CO, 15 h.
[b]Isolated yield.

In the case of 2-chloropyrimidine, the yield of 55% is a result of the low solubility of this substrate in the reaction medium (Table 5, entry 2). As demonstrated by entry 4 (Table 4), catalyst systems based on dppf (at reasonable

Table 6 Butoxycarbonylation of 3-Chloropyridine[a]

Entry	Ligand	Temp (°C)	*P* (bar)	NaOAc (equiv)	Additive	Conversion (%)[b]	Yield (%)[b]
1	PCy_3	145	15	3	–	50	34
2	$Cy_2P(CH_2)_4PCy_2$	145	15	3	–	100	60
3[c]	$1,1'\text{-}(PCy_2)_2Fc$[34]	145	15	3	–	99	47
4	$Cy_2P(CH_2)_4PCy_2$	145	15	1	–	95	65
5	$Cy_2P(CH_2)_4PCy_2$	145	1	1	–	100	72
6	**$Cy_2P(CH_2)_4PCy_2$**	**145**	**1**	**1**	**MS 4 Å**	**100**	**80**
7[d]	$Cy_2P(CH_2)_4PCy_2$	130	1	1	–	80	60
8[e]	$Cy_2P(CH_2)_4PCy_2$	130	1	1	MS 4 Å	88	60
9	$Cy_2P(CH_2)_3PCy_2$	145	1	1	MS 4 Å	95	78

[a]7.0 mmol 3-chloropyridine, 14 mL *n*-BuOH, 0.5 mol% $PdCl_2(PhCN)_2$, P/Pd = 14, 18 h.
[b]Determined by GC using hexadecane as the internal standard.
[c] P/Pd = 6.
[d]16 h.
[e]22 h.

temperatures and Pd concentrations) are restricted to the conversion of chloropyridines, chloropyrazines, and chloroquinolines with the chloro substituent attached at the more activated 2- or 4-position. The less activated chlorine atom in 3- or 5-position does not react.

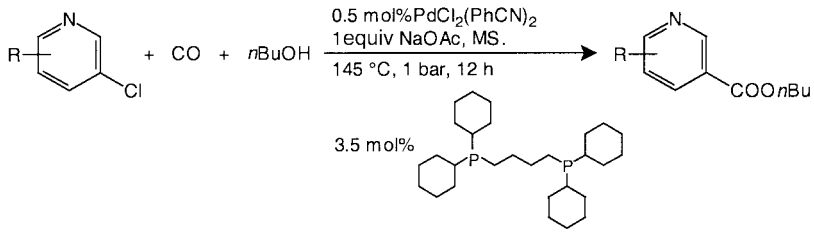
In order to overcome this problem, we sought ligands which would lead to more active palladium catalysts. Up to reaction temperatures of 145 °C, various monodentate ligands such as triphenylphosphine, tricyclohexylphosphine, tri-(*tert*-butyl)phosphine, dicyclohexyl-2-tolylphosphine and bidentate ligands, e.g., dppb, dppf, 1,5-bis(diphenylphosphino)pentane (dpppe), 2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthyl (NAPHOS) gave only minor yields of the desired product in the carbonylation of 3-chloropyridine. Some improvement was made by changing the base from triethylamine to NaOAc, although even with NaOAc a best conversion of 50% and yield of 34% was observed for butyl pyridine-3-carboxylate (Table 6, entry 1).

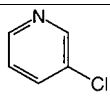
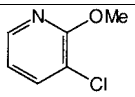
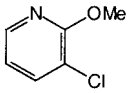
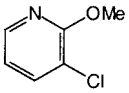
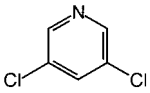
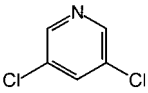
In order to facilitate the oxidative addition, the more basic dppb- and dppf-like ligands [1,4-bis(dicyclohexylphosphino)butane and 1,1′-bis(dicyclohexylphosphino)ferrocene] were tested. Based on previous screening results, the butoxycarbonylation of 3-chloropyridine was studied in the presence of NaOAc as base (Table 6). When 3-chloropyridine was reacted in presence of 1,4-bis(dicyclohexylphosphino)butane, total conversion was seen, however, *n*-butyl pyridine-3-carboxylate was formed in only 60% yield (entry 2, Table 6). A catalyst based on 1,1′-bis(dicyclohexylphosphino)ferrocene leads to both a slightly lower conversion and yield (Table 6, entry 3). The difference between the conversion of 3-chloropyridine and the yield of *n*-butyl pyridine-3-carboxylate is explained by the formation of 3-nicotinic acid which is produced together with small amounts of *n*-butyl acetate (*vide infra*). Interestingly, the yields of the byproducts are related and increase with increasing temperature. We propose the following mechanism for the formation of these byproducts: the carbonylation reaction of 3-chloropyridine formally gives an equimolar amount of HCl, which reacts with NaOAc to give NaCl and HOAc. Thus, an amount of HOAc equivalent to the heteroaryl chloride conversion is formed. In the presence of a large excess of *n*-butanol, esterification takes place to give *n*-butyl acetate and H_2O. H_2O is responsible for the partial hydrolysis of *n*-butyl pyridine-3-carboxylate.

The experimental results obtained are in good agreement with the proposed mechanism for the formation of the byproducts. Both the addition of a water-removing agent and the use of less NaOAc should lead to an increased selectivity for the product (*n*-butyl pyridine-3-carboxylate). This was shown by conducting the reaction in the presence of 1 equivalent NaOAc and molecular sieves (4 Å), which led to a significantly improved yield of product (80% versus 60%). Additionally, excellent product formation was observed even at 1 bar of carbon monoxide (Table 6, entries 4–6). Even at a lower temperature (130 °C), a satisfactory conversion and selectivity was obtained (Table 6, entries 7, 8). Kinetic studies in the presence of $Cy_2P(CH_2)_4PCy_2$ showed that the carbonylation of 3-chloropyridine is complete after 12 hours. $Cy_2P(CH_2)_3PCy_2$ also displays essentially the same catalytic performance.

Since both a high conversion and yield were achieved for the carbonylation of 3-chloropyridine in the presence of the $PdCl_2(PhCN)_2/Cy_2P(CH_2)_4PCy_2$ catalyst (Table 6),

Table 7 Butoxycarbonylation of Various 3-Chloropyridines[a]



Entry	Substrate	Product	Yield [%][b]
1			80[c]
2			83
3			70

[a]7.0 mmol *N*-heteroaryl chloride, 14 mL *n*-BuOH, 1 equiv NaOAc, 0.5 mol% $PdCl_2(PhCN)_2$, 3.5 mol% $Cy_2P(CH_2)_4PCy_2$, 145 °C, 1 bar CO, 12 h.
[b]Isolated yield.
[c]Yield determined by GC with hexadecane as the internal standard.

we were interested in examining the performance of this catalyst with two other commercially available 3-chloropyridines. In both cases the previously optimized conditions of temperature (145 °C), CO pressure (1 bar), phosphine and base were applied. In addition, molecular sieves (4 Å) were added in order to restrict the formation of the corresponding free acid (Table 7).

Butyl 2-methoxypyridine-3-carboxylate was obtained in 83% yield. In addition, double alkoxycarbonylation in the 3- and 5-positions proceeded smoothly to yield di-*n*-butyl pyridine-3,5-dicarboxylate in 70% yield.

Conclusions

In conclusion the palladium-catalyzed alkoxycarbonylation reaction of various chloropyridines and similar derivatives can be carried out with unprecedented efficiency using commercially available catalyst systems. Although for certain reactions the turnover frequencies still need to be improved, the productivity of the catalyst systems in most of the reactions shown makes their use in fine chemical synthesis viable.

Clearly most synthetic organic chemists are traditionally reluctant to use carbon monoxide for building block synthesis or natural product synthesis, however, one should be aware that these reactions are in general simple to perform, easy to scale-up and make use of cheap starting materials. Having these advantages in mind, the authors are optimistic that carbonylation chemistry[17] will see more use in organic synthesis and fine chemical production.

All reactions were carried out under an Ar atmosphere A 100 mL stainless steel autoclave (no. 4593 from Parr Co.) equipped with a magnetically driven 'propeller stirrer' was used in all of the carbonylation experiments. Experiments with CO pressures above 1 bar were conducted under non-isobaric conditions. Experiments with a CO pressure at 1 bar were conducted under isobaric conditions and with the pressure being kept constant by means of a pressure regulator and a CO reservoir. The course of the reaction was followed by measuring the decrease of the CO pressure in the reservoir. The CO gas (purity 99.97%) used was purchased from Aga Gas GmbH, Berlin (Germany).

Commercially obtained materials were used as received without further purification. Anhyd *n*-BuOH was purchased from the Aldrich Chemical Co. All solvents were saturated with Ar. Heteroaryl chlorides were purchased from the Aldrich Chemical Co. Et_3N and anhyd NaOAc were purchased from the Fluka Chemical Co. Tricyclohexylphosphine and 1,1′-bis(diphenylphosphino)ferrocene were purchased from the Strem Chemical Co. 1,1′-Bis(dicyclohexylphosphino)ferrocene was prepared according to a literature procedure.[18] Bis(benzonitrile)dichloropalladium(II) was prepared according to a literature procedure.[19] Diethyleneglycol di-*n*-butylether (internal GC standard) was purchased from the Fluka Chemical Co.

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer. Chemical shifts (δ) are given in ppm and were referenced to residual solvent as an internal standard. IR spectra were recorded on a Nicolet Magna 550 spectrometer. GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column. Mass spectra were recorded on a AMD 402/3-spectrometer (AMD Intectra GmbH). Elemental analyses were performed at the microanalytical laboratory of IfOK, Rostock.

Carbonylation of *N*-Heteroaryl Chlorides;[20] General Procedure
An oven-dried Schlenk flask was evacuated and filled with Ar (3 cycles), then charged with the *N*-heteroaryl chloride (7.0 mmol), *n*-butanol (14 mL), $PdCl_2(PhCN)_2$ (13.4 mg, 0.035 mmol, 0.5 mol%), and the appropriate amount of ligand (see Tables 1–7) to give an or-

ange solution. Et_3N (8.4 mmol, 1.2 equiv) or NaOAc (7.0 mmol, 1.0 equiv) and molecular sieves (4 Å, approx. 3 g) were added to the autoclave. After evacuating and filling the autoclave with Ar (3 cycles), the reaction mixture was transferred from the Schlenk flask into the autoclave by means of a PVC-tube (Ø ≈ 2 mm) under a positive pressure of Ar. The autoclave was closed, heated to 145 °C and pressurized with 1 bar CO from a CO reservoir which was connected to the autoclave through a pressure regulator, thus providing a constant CO pressure during the reaction. For experiments at higher CO pressures the autoclave was not connected to the CO reservoir (non-isobaric conditions). The reaction mixture was cooled to r.t. after 16 h and the resultant yellow-orange mixture was diluted with CH_2Cl_2 (70 mL). The mixture was washed with H_2O (70 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, mixtures of EtOAc–hexanes).

n-Butyl Pyridine-2-carboxylate

The carbonylation of 2-chloropyridine (795 mg, 7.0 mmol) was carried out according to the general procedure and afforded *n*-butyl pyridine-2-carboxylate in 95% yield (Table 4, entry 1).

R_f = 0.56 (hexane–EtOAc, 1:2).

IR (KBr): ν = 3058 (w, Aryl–H), 2961 (s), 2935 (m), 2874 (m, sp^3 CH), 1740 (vs), 1718 (vs, C=O), 1585 (m), 1467 (m), 1438 (m), 1382 (m), 1307 (vs), 1246 (s, C–O), 1131 (vs), 748 (m, Aryl–H), 708 (m) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.65 (dd, 1H, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.8 Hz, H-6), 8.01 (dd, 1H, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.2 Hz, H-3), 7.75 (td, 1H, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.8 Hz, H-4), 7.36 (ddd, 1H, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 4.8 Hz, $^4J_{H,H}$ = 1.2 Hz, H-5), 4.31 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 1.69 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.36 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.87 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 165.0 (C=O), 149.6 (C-6), 148.0 (C-2), 136.7 (C-4), 126.5, 124.8 (C-3, C-5), 65.5 (OCH_2), 30.4 (OCH_2CH_2), 18.9 (CH_2CH_3), 13.5 (CH_3).

MS (EI, 70 eV): *m/z* = 178 $[M-H]^+$, 151, 135 $[M-H-C_3H_7]^+$, 124 $[M+H-C_4H_8]^+$, 106 (10%) $[M-OC_4H_9]^+$, 79 $[M+H-OC_4H_9-CO]^+$.

Anal. Calcd for $C_{10}H_{13}NO_2$ (179.22): C, 67.0; H, 7.3; N, 7.8. Found: C, 66.6; H, 7.3; N, 7.8.

n-Butyl 5-Trifluoromethylpyridine-2-carboxylate

The carbonylation of 2-chloro-5-trifluoromethylpyridine (1.271 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.627 g (94%) of *n*-butyl 5-trifluoromethylpyridine-2-carboxylate (Table 4, entry 2).

R_f = 0.28 (hexane–EtOAc, 5:1).

IR (KBr): ν = 3046 (m, Aryl–H), 2963 (s), 2938 (m), 2876 (m, sp^3 C–H), 1736 (vs, C=O), 1601 (s), 1576 (s), 1468 (m), 1392 (s), 1331 (vs), 1315 (vs, C–F), 1285 (s, C–O), 1247 (s), 1164 (vs), 1130 (vs), 1078 (s), 1015 (s), 710 (s) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.95 (m, 1H, H-6), 8.19 (m, 1H, H-4), 8.04 (m, 1H, H-3), 4.39 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 1.75 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.41 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.91 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 163.9 (C=O), 151.1 (C-2), 146.6 (q, $^3J_{C,F}$ = 3.8 Hz, C-6), 134.3 (q, $^3J_{C,F}$ = 3.8 Hz, C-4), 129.0 (q, $^2J_{C,F}$ = 33.4 Hz, C-5), 124.6 (C-3), 122.8 (q, $^1J_{C,F}$ = 272.8 Hz, CF_3), 66.2 (OCH_2), 30.5 (OCH_2CH_2), 19.0 (CH_2CH_3); 13.5 (CH_3).

MS (EI, 70 eV): *m/z* = 248 $[M+H]^+$, 228 $[M-F]^+$, 203 $[M-H-C_3H_7]^+$, 192 $[M+H-C_4H_8]^+$, 174 (10 %) $[M-OC_4H_9]^+$, 146 $[M-OC_4H_9-CO]^+$, 126.

Anal. Calcd for $C_{11}H_{12}F_3NO_2$ (247.22): C, 53.4; H, 4.9; N, 5.7. Found: C, 53.5; H, 4.9; N, 5.6.

n-Butyl 6-Methoxypyridine-2-carboxylate

The carbonylation of 2-chloro-6-methoxypyridine (1.005 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.216 g (83%) of *n*-butyl 6-methoxypyridine-2-carboxylate (Table 4, entry 3).

R_f = 0.29 (hexane–EtOAc, 5:1).

IR (KBr): ν = 2959 (vs), 2874 (s, sp^3 C–H), 1740 (vs), 1719 (vs, C=O), 1594 (vs), 1575 (s), 1470 (vs), 1438 (s), 1414 (s), 1330 (vs), 1272 (vs, C–O), 1140 (vs), 1074 (s), 1029 (s), 771 (s, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 7.64 (m, ABX, 1H, H-3), 7.64 (m, ABX, 1H, H-4), 6.88 (m, ABX, 1H, H-5), 4.33 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 3.98 (s, 3H, OCH_3), 1.75 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.41 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.95 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 165.1, 163.8 (C=O, C-6), 145.6 (C-2), 138.8 (C-4), 118.3, 115.0 (C-3, C-5), 65.3 (OCH_2), 53.5 (OCH_3), 30.6 (OCH_2CH_2), 19.1 (CH_2CH_3), 13.8 (CH_2CH_3).

MS (EI, 70 eV): *m/z* = 209 M^+, 194 $[M-CH_3]^+$, 152 $[M-H-C_4H_8]^+$, 136 $[M-OC_4H_9]^+$, 109 (10 %) $[M+H-OC_4H_9-CO]^+$, 93.

Anal. Calcd for $C_{11}H_{15}NO_3$ (209.25): C, 63.1; H, 7.2; N, 6.7. Found: C, 63.2; H, 7.4; N, 6.5.

n-Butyl 3-Chloropyridine-2-carboxylate

The carbonylation of 2,3-dichloropyridine (1.036 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.216 g (73%) of *n*-butyl 3-chloropyridine-2-carboxylate (Table 4, entry 4).

R_f = 0.18 (hexane–EtOAc, 5:1).

IR (KBr): ν = 3058 (w, Aryl–H), 2961 (s), 2935 (m), 2874 (m, sp^3 C–H), 1739 (vs, C=O), 1573 (m), 1465 (m), 1427 (s), 1383 (m), 1298 (vs, C–O), 1206 (s), 1147 (vs), 1062 (s), 1040 (s), 799 (s, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.51 (dd, 1H, $^3J_{H,H}$ = 4.6 Hz, $^4J_{H,H}$ = 1.4 Hz, H-6), 7.74 (dd, 1H, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.4 Hz, H-4), 7.32 (dd, 1H, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 4.6 Hz, H-5), 4.37 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 1.73 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.41 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.91 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 164.5 (C=O), 148.1 (C-2), 147.2 (C-6), 138.4 (C-4), 130.5 (C-3), 126.0 (C-5), 66.0 (OCH_2), 30.4 (OCH_2CH_2), 19.0 (CH_2CH_3), 13.5 (CH_3).

MS (EI, 70 eV): *m/z* = 214 M^+, 169, 158 $[M-C_4H_8]^+$, 140 (10 %) $[M-H-OC_4H_9]^+$, 113 $[M-OC_4H_9-CO]^+$, 76.

Anal. Calcd for $C_{10}H_{12}ClNO_2$ (213.66): C, 56.2; H, 5.7; N, 6.6. Found: C, 56.7; H, 5.8; N, 6.5.

n-Butyl 2-Methylquinoline-4-carboxylate

The carbonylation of 4-chloro-2-methylquinoline (1.243 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.192 g (70%) of *n*-butyl 2-methylquinoline-4-carboxylate (Table 4, entry 7).

R_f = 0.65 (hexane–EtOAc, 1:2).

IR (KBr): ν = 3064 (w, Aryl–H), 2960 (s), 2933 (m), 2873 (m, sp^3 C–H), 1724 (vs, C=O), 1595 (s), 1509 (m), 1387 (m), 1331 (s), 1269 (s, C–O), 1243 (v), 1203 (vs), 1187 (s), 1147 (s), 1020 (m), 797 (s), 774 (s, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.65 (ddd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.4 Hz, $^5J_{H,H}$ = 0.7 Hz, H-8), 8.04 (ddd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.4 Hz, $^5J_{H,H}$ = 0.7 Hz, H-5), 7.74 (s, 1H, H-3), 7.68, 7.54 (2 × ddd, 2H, $^3J_{H,H}$ = 8.3 Hz, $^3J_{H,H}$ = 6.9 Hz, $^4J_{H,H}$ = 1.4 Hz, H-6, H-7), 4.41 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 2.76 (s, 3H, Aryl-CH_3), 1.79 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.50 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.98 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 166.3 (C=O), 158.3 (C-2), 148.7 (C-8a), 135.4 (C-4), 129.5, 129.1 (C-7, C-8), 127.0 (C-6), 125.3 (C-5), 123.2 (C-4a), 123.0 (C-3), 65.5 (OCH_2), 30.6 (OCH_2CH_2), 25.2 (Aryl-CH_3), 19.2 (CH_2CH_3), 13.6 (CH_2CH_3).

MS (EI, 70 eV): *m/z* = 243 M^+, 200 $[M-C_3H_7]^+$, 187 $[M-C_4H_8]^+$, 177, 170 $[M-OC_4H_9]^+$, 142 $[M-OC_4H_9-CO]^+$, 115, 101, 57 (10 %).

Anal. Calcd for $C_{15}H_{17}NO_2$ (243.31): C, 74.0; H, 7.0; N, 5.8. Found: C, 73.5; H, 7.0; N, 5.7.

n-Butyl 4-Methylquinoline-2-carboxylate

The carbonylation of 2-chloro-4-methylquinoline (1.243 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.260 g (74 %) of *n*-butyl 4-methylquinoline-2-carboxylate (Table 4, entry 6).

R_f = 0.16 (hexane–EtOAc, 5:1).

IR (KBr): ν = 3060 (w), 3040 (w, Aryl–H), 2966 (m), 2953 (s), 2933 (m), 2873 (m, sp^3 C–H), 1735 (vs, C=O), 1592 (m), 1456 (m), 1411 (m), 1273 (s, C–O), 1242 (s), 1219 (vs), 1160 (s), 1114 (s), 1068 (m), 799 (s), 776 (m), 766 (Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.28 (ddd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.4 Hz, $^5J_{H,H}$ = 0.7 Hz, H-8), 7.98 (ddd, 1H, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.4 Hz, $^5J_{H,H}$ = 0.7 Hz, H-5), 7.97 (s, 1H, H-3), 7.73, 7.61 (2 × ddd, 2H, $^3J_{H,H}$ = 8.3 Hz, $^3J_{H,H}$ = 6.9 Hz, $^4J_{H,H}$ = 1.4 Hz, H-6, H-7), 4.46 (t, 2H, $^3J_{H,H}$ = 6.9 Hz, OCH_2), 2.73 (s, 3H, Aryl-CH_3), 1.83 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.9 Hz, OCH_2CH_2), 1.48 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.97 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 165.6 (C=O), 147.8, 147.4, 145.7 (C-2, C-4, C-8a), 131.3, 129.7, 128.1 (C-6, C-7, C-8), 129.1 (C-4a), 123.5, 121.5 (C-3, C-5), 65.9 (OCH_2), 30.7 (OCH_2CH_2), 19.1 (CH_2CH_3), 18.8 (Aryl-CH_3), 13.7 (CH_2CH_3).

MS (EI, 70 eV): *m/z* = 243 M^+, 199 $[M-H-C_3H_7]^+$, 188 $[M+H-C_4H_8]^+$, 171 $[M+H-OC_4H_9]^+$, 143 (10 %) $[M+H-OC_4H_9-CO]^+$, 115.

Anal. Calcd for $C_{15}H_{17}NO_2$ (243.31): C, 74.0; H, 7.0; N, 5.8. Found: C, 73.9; H, 7.2; N, 5.8.

n-Butyl Pyrazinecarboxylate

The carbonylation of chloropyrazine (802 mg, 7.0 mmol) was carried out according to the general procedure and afforded 1.034 g (82%) of *n*-butyl pyrazinecarboxylate (Table 5, entry 1).

R_f = 0.55 (hexane–EtOAc, 2:1).

IR (KBr): ν = 3051 (w, Aryl–H), 2961 (s), 2936 (m), 2875 (m, sp^3 C–H), 1746 (s), 1723 (vs, C=O), 1467 (m), 1412 (m), 1387 (m), 1304 (vs), 1281 (s, C–O), 1136 (vs), 1049 (m), 1018 (s), 775 (m, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 9.27 (d, 1H, $^4J_{H,H}$ = 1.4 Hz, H-3), 8.73 (d, 1H, $^3J_{H,H}$ = 2.4 Hz, H-6), 8.69 (dd, 1H, $^3J_{H,H}$ = 2.4 Hz, $^4J_{H,H}$ = 1.4 Hz, H-5), 4.42 (t, 2H, $^3J_{H,H}$ = 6.8 Hz, OCH_2), 1.78 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.8 Hz, OCH_2CH_2), 1.44 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.94 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 163.9 (C=O), 147.5, 146.2, 144.4 (C-3, C-5, C-6), 143.5 (C-2), 66.1 (OCH_2), 30.5 (OCH_2CH_2), 19.0 (CH_2CH_3), 13.6 (CH_3).

MS (EI, 70 eV): *m/z* = 181 $[M+H]^+$, 136 $[M-H-C_3H_7]^+$, 125 $[M+H-C_4H_8]^+$, 107 $[M-OC_4H_9]^+$, 80 (10 %) $[M+H-OC_4H_9-CO]^+$.

Anal. Calcd for $C_9H_{12}N_2O_2$ (180.21): C, 60.0; H, 6.7; N, 15.6. Found: C, 59.8; H, 6.8; N, 15.4.

n-Butyl Pyrimidine-2-carboxylate

The carbonylation of 2-chloropyrimidine (802 mg, 7.0 mmol) was carried out according to the general procedure and afforded 694 mg (55%) of *n*-butyl pyrimidine-2-carboxylate (Table 5, entry 2).

R_f = 0.32 (hexane–EtOAc, 1:5).

IR (KBr): ν = 3178 (m, Aryl–H), 2959,(s), 2933 (m), 2874 (m, sp^3 C–H), 1758 (vs, C=O), 1577 (vs), 1531 (vs), 1448 (vs), 1425 (s), 1275 (s, C–O), 1209 (vs), 1172 (s), 1088 (s), 1067 (s), 809 (s), 770 (s, Aryl–H), 641 (m) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.90 (d, 2H, $^3J_{H,H}$ = 4.8 Hz, H-4, H-6), 7.45 (t, 1H, $^3J_{H,H}$ = 4.8 Hz, H-5), 4.43 (t, 2H, $^3J_{H,H}$ = 6.9 Hz, OCH_2), 1.79 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.9 Hz, OCH_2CH_2), 1.42 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.92 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 163.4 (C=O), 157.8 (C-4, C-6), 156.7 (C-2), 122.9 (C-5), 66.6 (OCH_2), 30.5 (OCH_2CH_2), 18.9 (CH_2CH_3), 13.6 (CH_3).

MS (EI, 70 eV): *m/z* = 181 $[M+H]^+$, 136 $[M-H-C_3H_7]^+$, 125 $[M+H-C_4H_8]^+$, 107 (10%) $[M-OC_4H_9]^+$, 80 $[M+H-OC_4H_9-CO]^+$.

Anal. Calcd for $C_9H_{12}N_2O_2$ (180.21): C, 60.0; H, 6.7; N, 15.6. Found: C, 59.6; H, 6.9; N, 15.5.

n-Butyl 6-Methylpyridazine-3-carboxylate

The carbonylation of 3-chloro-6-methylpyridazine (900 mg, 7.0 mmol) was carried out according to the general procedure and afforded 1.128 g (83%) of *n*-butyl 6-methylpyridazine-3-carboxylate (Table 5, entry 3).

R_f = 0.48 (hexane–EtOAc. 1:10).

IR (KBr): ν = 3060 (w, Aryl–H), 2969 (m), 2954 (m), 2932 (w), 2875 (w, sp^3 C–H), 1735 (vs, C=O), 1579 (s), 1552 (w), 1477 (w), 1458 (w), 1289 (vs, C–O), 1265 (m), 1232 (m), 1158 (s), 1081 (s), 968 (w), 808 (w), 787 (m, Aryl–H), 725 (w) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.03 (d, 1H, $^3J_{H,H}$ = 8.5 Hz, H-4), 7.44 (d, 1H, $^3J_{H,H}$ = 8.5 Hz, H-5), 4.43 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 2.78 (s, 3H, Aryl-CH_3), 1.79 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.45 (qt, 2H, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.94 (t, 3H, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 164.3, 162.4 (C=O, C-6), 149.9 (C-3), 127.3, 127.0 (C-4, C-5), 66.1 (OCH_2), 30.5 (OCH_2CH_2), 22.4 (Aryl-CH_3), 19.0 (CH_2CH_3), 13.6 (CH_2CH_3).

MS (EI, 70 eV): *m/z* = 194 M^+, 179 $[M-CH_3]^+$, 150 $[M-H-C_3H_7]^+$, 139 $[M+H-C_4H_8]^+$, 121 $[M-OC_4H_9]^+$, 94 (10 %) $[M+H-OC_4H_9-CO]^+$.

Anal. Calcd for $C_{10}H_{14}N_2O_2$ (194.23): C, 61.8; H, 7.3; N, 14.4. Found: C, 61.9; H, 7.3; N, 14.4.

Di-*n*-butyl Pyridine-3,5-dicarboxylate

The carbonylation of 3,5-dichloropyridine (1.036 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.369 g (70%) of di-*n*-butyl pyridine-3,5-dicarboxylate (Table 7, entry 3).

R_f = 0.64 (hexane–EtOAc, 2:1).

IR (KBr): ν = 2961 (s), 2930 (m), 2875 (m, *sp*^{3} C–H), 1730 (vs, C=O), 1601 (m), 1458 (m), 1427 (w), 1386 (w), 1311 (s), 1241 (vs, C–O), 1177 (w), 1102 (s), 1028 (m), 966 (w), 747 (s, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 9.32 (d, 2H, $^4J_{H,H}$ = 1.5 Hz, H-2, H-6), 8.81 (t, 1H, $^4J_{H,H}$ = 1.5 Hz, H-4), 4.36 (t, 4H, $^3J_{H,H}$ = 6.7 Hz, OCH_2), 1.76 (tt, 4H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.7 Hz, OCH_2CH_2), 1.45 (qt, 4H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.96 (t, 6H, $^3J_{H,H}$ = 7.4 Hz, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 164.5 (C=O), 154.0 (C-2, C-6), 137.8 (C-4), 126.2 (C-3, C-5), 65.6 (OCH_2), 30.6 (OCH_2CH_2), 19.1 (CH_2CH_3), 13.6 (CH_3).

MS (EI, 70 eV): *m/z* = 278 $[M-H]^+$, 237 $[M+H-C_3H_7]^+$, 224 (10 %) $[M+H-C_4H_8]^+$, 206 $[M-OC_4H_9]^+$, 168 $[M+H-C_4H_8-C_4H_8]^+$, 150 $[M-C_4H_8-OC_4H_9]^+$, 122 $[M-C_4H_8-OC_4H_9\text{-}CO]^+$, 105, 94, 77.

Anal. Calcd for $C_{15}H_{21}NO_4$ (279.34): C, 64.5; H, 7.6; N, 5.0. Found: C, 64.6; H, 7.5; N, 5.2.

n-Butyl 2-Methoxypyridine-3-carboxylate

The carbonylation of 3-chloro-2-methoxypyridine (1.005 g, 7.0 mmol) was carried out according to the general procedure and afforded 1.216 g (83%) of *n*-butyl 2-methoxypyridine-3-carboxylate (Table 7, entry 2).

R_f = 0.39 (hexane–EtOAc, 5:1).

IR (KBr): ν = 2958 (s), 2873 (s, *sp*^{3} C–H), 1734 (vs), 1708 (s, C=O), 1591 (s), 1579 (s), 1469 (vs), 1408 (vs), 1384 (m), 1316 (s), 1262 (s, C–O), 1129 (s), 1084 (s), 1016 (s), 780 (s, Aryl–H) cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$, 297 K): δ = 8.26 (dd, 1H, $^3J_{H,H}$ = 4.9 Hz, $^4J_{H,H}$ = 2.0 Hz, H-6), 8.09 (dd, 1H, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 2.0 Hz, H-4), 6.89 (dd, 1H, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 4.9 Hz, H-5), 4.26 (t, 2H, $^3J_{H,H}$ = 6.6 Hz, OCH_2), 3.99 (s, 3H, OCH_3), 1.69 (tt, 2H, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 6.6 Hz, OCH_2CH_2), 1.43 (qt, 2H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 0.93 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$, 297 K): δ = 164.9, 162.3 (C=O, C-2), 150.4 (C-6), 140.8 (C-4), 116.1 (C-5), 114.3 (C-3), 64.9 (OCH_2), 53.9 (OCH_3), 30.6 (OCH_2CH_2), 19.1 (CH_2CH_3), 13.6 (CH_2CH_3).

MS (EI, 70 eV): *m/z* = 209 M^+, 167 $[M+H-C_3H_7]^+$, 154 $[M+H-C_4H_8]^+$, 136 (10 %) $[M-OC_4H_9]^+$, 107 $[M-H-OC_4H_9-CO]^+$.

Anal. Calcd for $C_{11}H_{15}NO_3$ (209.25): C, 63.1; H, 7.2; N, 6.7. Found: C, 63.1; H, 7.6; N, 6.2.

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