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Development of new palladium catalysts for the alkoxycarbonylation of aryl chlorides

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Abstract

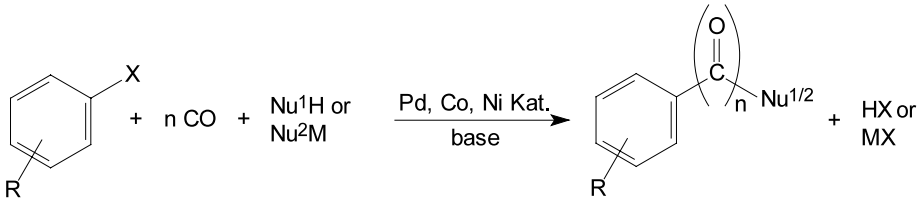
The alkoxycarbonylation of different aryl chlorides was studied. Studies of the butoxycarbonylation of 4-chlorobenzotrifluoride and chlorobenzene using chelating ferrocenylphosphines reveal the advantages of these ligands compared to the well-known tricyclohexylphosphine (PCy_3). (1-{2-(Dicyclohexylphosphino)ferrocenyl}ethyldicyclohexylphosphine (**4**) was shown to give the most active palladium catalyst system. The usefulness of this catalyst is demonstrated in the alkoxycarbonylation of various aryl chlorides. Optimized carbonylation conditions were realized by a statistical design of three critical reaction parameters.

Keywords: Carbonylation; Palladium; Ferrocenyl phosphines; Aryl chlorides; Homogeneous catalysis; Benzoic acids

1. Introduction

Palladium-catalyzed C–C and C–X (X = N, O, S) coupling reactions of aryl halides constitute powerful methods in synthetic organic chemistry [1]. The palladium-catalyzed carbonylation of aryl halides (or halide equivalents) is an especially valuable tool for the selective introduction of a carboxylic group into aromatic frameworks. By reacting the respective aryl substrate with carbon monoxide and ubiquitously available nucleophiles a variety of acids, esters, amides, aldehydes, ketones and other carboxylic acid derivatives are accessible [2] (Scheme 1).

An especially interesting class of starting materials for the refinement of aryl halides are aryl chlorides, owing to their low cost and commercial availability with a variety of substitution patterns. These substrates, however, usually display a lower reactivity compared to the corresponding bromides and iodides. Therefore, special catalyst systems, which facilitate the oxidative



n = 1,2
X = I, Br, Cl, N_2^+, OSO_2R, ArI^+, IO_2, SO_2Cl
M = Na, K, BR_2, AlR_2, SnR_3, SiR_3
Nu^1 = OH, OR, NR_2, F, Cl; Nu^2 = H, alkyl, aryl, CN, alkenyl, alkinyl, RCO_2

Scheme 1. Carbonylation of aryl-X derivatives.

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addition of the aryl chlorides are required for efficient activation [3].

Significant progress has been made very recently in the activation of aryl chlorides for coupling reactions such as the Heck olefination [4], and the Suzuki arylation [5], using palladium catalyst systems modified with sterically demanding, basic, monodentate phosphine or carbene ligands.

With regard to the importance of benzoic acid derivatives, it is surprising that the efficient carbonylation of aryl chlorides is still a challenging problem. Clearly, the carbonylation of aryl chlorides is more difficult compared to other C–C coupling reactions due to the presence of a large excess of π-accepting carbon monoxide ligand. Carbon monoxide bound to the metal center reduces the activity of the palladium complex towards oxidative addition. Moreover, clustering and agglomeration of Pd atoms is facile in the presence of CO [6], leading to non-active palladium species. Until recently, only the discovery by Milstein and coworkers [7], who introduced palladium complexes containing the highly basic 1,3-bis(di-*iso*-propylphosphino)propane ligand, provided a more general solution to the carbonylation of aryl chlorides. The drawbacks of this catalyst system, however, are the difficulty in synthesis and the high sensitivity of this pyrophoric phosphine along with the comparatively low turnover numbers of the catalyst (1 mol% of palladium). Other catalyst systems known in the literature for the carbonylation of aryl chlorides suffer from additional disadvantages. Tricyclohexylphosphine (PCy_3) has been most often employed as a ligand for the palladium-catalyzed hydroxy- or methoxycarbonylation of chloroarenes. Unfortunately, the reported yields of the carbonylation products were always below 30% [8]. In another approach, aryl chlorides were reacted using a heterogeneous Pd/C catalyst at high temperatures (200 °C) within 50 h. Again product yields were comparably low (20%) and the high temperature required for the reaction makes the incorporation of sensitive functional groups into the substrate impossible [9]. Aminocarbonylation employing a palladium catalyst based on 1,2-bis(diphenylphosphino)ethane in the presence of sodium iodide proceeds under mild conditions with high yields. In general, the scope of aryl chloride substrates was restricted to electron-deficient (i.e. activated) derivatives [10]. Lately, we demonstrated that palladium salts in the presence of dppb or dppf are efficient catalysts for the carbonylation of heteroaryl chlorides [11]. However, these catalysts only work efficiently with activated aryl chloride substrates.

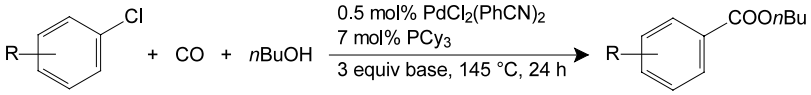
Very recently we discovered that a catalyst system consisting of palladium and a ferrocenylphosphine enables the carbonylation of electron-deficient, electronically neutral and electron-rich aryl chlorides in good to excellent yield [12]. This represents a substantial improvement in efficiency, utility and practicability of this interesting coupling reaction. Critical to the success of this method is the use of cyclohexyl-substituted, bidentate ferrocenyl phosphine ligands along with sodium carbonate as a base. After an initial communication [12], we describe here a full account of our work on the development of this new catalyst.

2. Results and discussion

2.1. Preliminary carbonylation experiments with tricyclohexylphosphine as the ligand

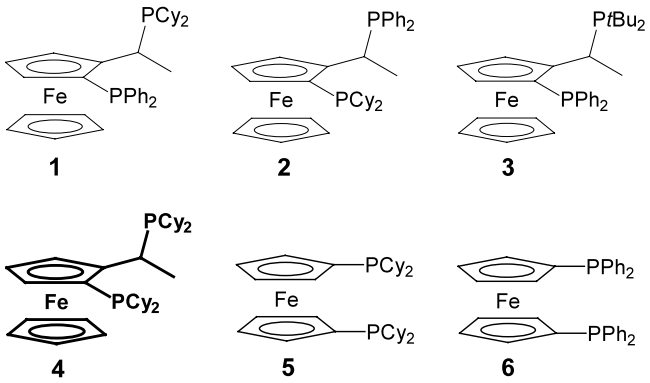
In initial studies to develop more efficient carbonylation catalysts we examined the butoxycarbonylation of aryl chlorides in the presence of the PCy_3 ligand (Table 1). Aryl chloride substrates 4-chloroacetophenone

Table 1
Carbonylation of aryl chlorides in the presence of PCy_3 as the ligand [a]



Entry	Aryl chloride (R)	Base	CO-pressure (bar)	Yield (%) [b]
1	4-$COCH_3$	NaOAc	15	80
2 [c]	4-$COCH_3$	NaOAc	15	25
3	4-$COCH_3$	NEt_3	15	14
4	4-CF_3	NaOAc	15	56
5	4-CF_3	NaOAc	25	24
6	4-CF_3	NaOAc	3	38
7 [d]	H	NaOAc	15	6
8	4-OCH_3	NaOAc	15	<5

[a] Aryl chloride (7 mmol), 14 ml *n*-butanol.
[b] Determined by GC using diethyleneglycol di-*n*-butylether as an internal standard.
[c] 130 °C.
[d] 15 h.



Scheme 2. Ferrocenyl phosphine ligands for aryl chloride carbonylation.

(highly activated aryl chloride), 4-chlorobenzotrifluoride (slightly activated aryl chloride), chlorobenzene (non-activated aryl chloride) and 4-chloroanisole (deactivated aryl chloride) were chosen. PCy_3 was employed because this is the most common ligand previously reported for aryl chloride carbonylations. We thought the results would give a good impression about the current status of aryl chloride alkoxycarbonylation in the presence of a standard ligand.

When employing the activated substrate (4-chloroacetophenone) we observed an 80% yield of *n*-butyl 4-acetylbenzoate in the presence of 0.5 mol% $PdCl_2(PhCN)_2$, PCy_3 and three equivalents of NaOAc (145 °C, 15 bar CO, 24 h, entry 1, Table 1). Based on our previous model studies of carbonylation reactions [13], we employed an excess of phosphine ligand (P/Pd = 14) in order to activate the palladium catalyst by displacing CO ligands from the metal center [14].

A temperature of about 145 °C seems to be a lower limit for the activity of the Pd/PCy_3-catalyst since the ester yield decreases to 25% when the temperature is lowered to 130 °C (entry 2, Table 1). The use of NEt_3 instead of NaOAc as the base leads to a dramatic drop in the catalyst efficiency (entry 3, Table 1). In general, we found that amines are inferior to inorganic bases for aryl chloride carbonylation [15].

With the less-activated substrate (4-chlorobenzotrifluoride) a yield of only 56% of the *n*-butyl ester was observed, which is significantly lower compared to 4-chloroacetophenone (cf. entries 1 and 4, Table 1). CO pressures above or below 15 bar (entries 5 and 6, Table 1) had a negative effect on the catalyst productivity. Electron-neutral/electron-rich substrates (chlorobenzene and 4-chloroanisole, entries 7 and 8, Table 1) essentially fail to react under the same conditions.

In addition to the desired products, considerable amounts of *n*-butyl acetate were formed in all experiments where NaOAc was used as the base (e.g. entry 2: 73%, entry 4: 41%). Interestingly, the yield of *n*-butyl acetate is directly proportional to the product yield. Furthermore, the respective benzoic acids were identified in small amount as by-products (< 10%).

Catalyst systems based on the PCy_3 ligand (at reasonable temperatures and Pd concentrations) are apparently restricted to the conversion of chloroarenes activated by electron-withdrawing groups.

In order to overcome this problem we sought ligands leading to more efficient palladium catalysts, thus permitting the reaction of aryl chlorides independent of their electronic nature under milder reaction conditions (temperature, CO pressure, Pd concentration). During the course of our ligand studies, Pd in the presence of bidentate phosphines with ferrocenyl moiety as the ligand backbone showed considerable carbonylation activity (Scheme 2).

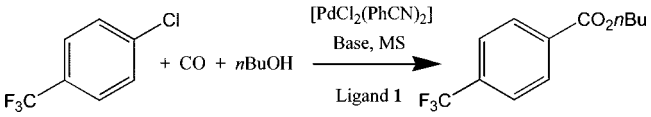
In the past enantiomerically pure ligands **1**–**4** of the Josiphos type [16] were employed very successfully in asymmetric catalytic processes, e.g. hydrogenations [17]. Contrary to most other electron-rich phosphines **1**–**5** are comparatively stable and can be handled under air in solid form.

2.2. Test system 4-chlorobenzotrifluoride/Josiphos: evaluation of critical reaction parameters

The reaction of 4-chlorobenzotrifluoride with CO and *n*-butanol in the presence of a $PdCl_2(PhCN)_2$/Josiphos (**1**) catalyst under similar conditions compared to the PCy_3 ligand (i.e. 0.5 mol% Pd, P/Pd = 14, 3 equivalents NaOAc, 145 °C, 14 bar CO) leads to *n*-butyl 4-trifluoromethylbenzoate in 67% yield after 15 h (cf. 56% yield after 24 h with PCy_3). This promising result encouraged us to establish optimal conditions for the reaction. Based on our results [13] as well as those of other groups [18], the most important reaction parameters (temperature: 130, 145, 160 °C; CO pressure: 3, 14, 25 bar; P/Pd-ratio: 2, 8, 14) were varied using a statistical approach. Clearly, these variables are not independent of each other, i.e. a change of one variable may be different at two different values of another variable. It is possible to reduce the necessary $3^3 = 27$ experiments to 15 by virtue of statistical calculations, without losing any essential information [19] (Table 2).

The results in Table 2 show that in all cases the yield of *n*-butyl 4-trifluoromethylbenzoate is lower than the conversion. This difference in yield is explained by the formation of 4-trifluoromethylbenzoic acid which is formed along with considerable amounts of *n*-butyl acetate (vide infra). Since no other side-products (e.g. through dehalogenation, aryl-aryl-coupling, etc.) were obtained, the conversion instead of the product yield is the measure for the carbonylation activity of the catalyst system. The time/conversion plot of the reaction and the fact that no palladium metal forms indicate that the catalyst is still active after 15 h.

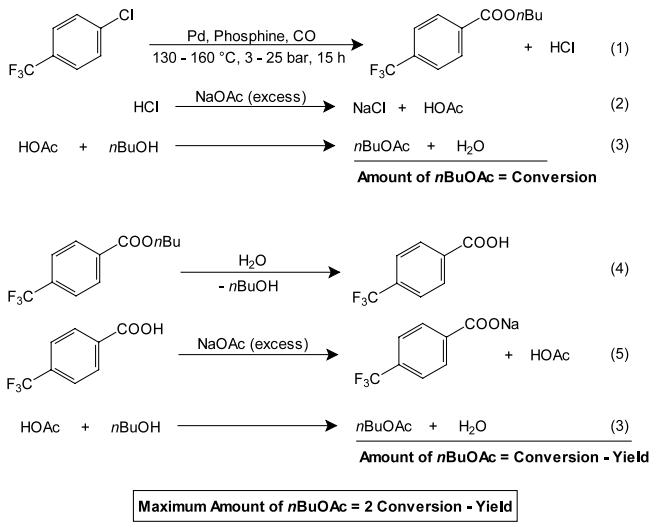
Table 2
Butoxycarbonylation of 4-chlorobenzotrifluoride in the presence of Josiphos (**1**) as the ligand; systematic variation of the reaction parameters temperature, pressure, P/Pd ratio



Entry	T (°C)	p (bar)	P/Pd	Conversion (%) [a]	Yield of ester (%) [a]	Selectivity (%) [b]
1	130	3	2	70	61	87
2	130	3	14	75	65	87
3	130	25	2	39	29	74
4	130	25	14	39	30	77
5	130	14	8	52	46	88
6	145	3	8	97	74	76
7 [c]	145	14	8	91 (89)	73 (72)	80 (81)
8	145	25	8	90	68	76
9	145	14	2	73	61	84
10	145	14	14	98	67	68
11	160	3	2	84	64	76
12	160	3	14	99	72	73
13	160	25	2	85	68	80
14	160	25	14	99	52	53
15	160	14	8	93	35	38
16	144.3	3	14	100	78	78

The difference in conversion and product yield is made up of 4-trifluoromethylbenzoic acid: 7 mmol 4-chlorobenzotrifluoride, 14 ml n-butanol.
[a] Determined by GC using diethyleneglycol di-n-butylether as an internal standard.
[b] Selectivity = ester yield/conversion.
[c] Results of a reproduction experiment in brackets.

The results indicate that 145 °C is a reasonable temperature for both activity and selectivity of the catalyst with the conversions essentially above 90% and yields of around 70% (entries 6–8, 10, Table 2). At 130 °C the change of CO pressure exerts a much stronger influence on the conversions and yields than the P/Pd ratio (cf. entries 1–4, Table 2). Thus, at 3 bar CO conversions and yields of about 70% are virtually not affected by the concentration of **1** (entries 1 and 2, Table 2). In contrast at 145 °C the decrease in catalyst efficiency upon raising the CO pressure is much less pronounced, as demonstrated by entries 6–8 (Table 2). Instead of which the P/Pd ratio influences the conversion much more (cf. entries 7, 9 and 10, Table 2). At 3 bar CO and with P/Pd = 8 (entry 6, Table 2) the conversion is essentially quantitative (76% selectivity). Repetition of the experiment in entry 7 underlines the very good reproducibility of the system (73 vs. 72% yield of n-butyl 4-trifluoromethylbenzoate). At 160 °C the general tendencies with regard to the influence of CO pressure and P/Pd ratio are the same as those at 145 °C. At this high temperature, the carbonylation activity (conversion) of the catalyst is generally higher, but the selectivity becomes worse (entries 11–15, Table 2). From these results an optimum set of values within the limits of the variables was calculated. Applying the calculated conditions (T = 144 °C, p = 3 bar, P/Pd = 14) lead to a further improved conversion of 100% and a product yield of 78% (entry 16, Table 2). This demonstrates clearly the feasibility of a statistical reaction design for palladium-catalyzed carbonylation reactions. This nice tool for optimizing catalytic reactions should be used more often, since a significant reduction of experiments and therefore time and consumables is possible.



Scheme 3. Proposed mechanism for the formation of 4-trifluoromethylbenzoic acid and n-butyl acetate under carbonylation conditions.

As mentioned above, in all experiments where NaOAc was used as the base the concomitant formation of the respective 4-trifluoromethylbenzoic acid and *n*-butyl acetate was observed. Interestingly, the yields of these by-products are related and increase with increasing temperature. The formation of 4-trifluoromethylbenzoic acid and *n*-butyl acetate is explained by the following reactions sequences (Scheme 3).

A successful carbonylation reaction of the aryl chloride formally gives an equimolar amount of HCl (Eq. (1), Scheme 3). The intermediate HPd(L)Cl-complexes react with NaOAc to give NaCl and HOAc and thus an amount of HOAc equivalent to the aryl chloride conversion is formed (Eq. (2), Scheme 3). In the presence of a large excess of alcohol, esterification with *n*-butanol takes place to give *n*-butyl acetate and H_2O (amount equal to the conversion).

Due to the better leaving group ability of benzoate compared to acetate, partial hydrolysis of *n*-butyl 4-trifluoromethylbenzoate is observed under the reaction conditions (Eq. (4), Scheme 3). The resulting 4-trifluoromethylbenzoic acid and NaOAc yield HOAc since the pK_a of the substituted benzoic acid is lower than that of acetic acid (Eq. (5), Scheme 3). Esterification of butanol analogous to Eq. (3) (Scheme 3) leads to the formation of an additional amount of *n*-butyl acetate. Thus, the maximum amount of *n*-butyl acetate produced equals two times the conversion of aryl chloride minus the yield of benzoic acid ester.

The experimental results obtained are in good agreement with the proposed mechanism for the formation of the by-products. The observed yields of *n*-butyl acetate at 160 °C correlate well with the calculated maximum yields [Table 2, entry 13: 105% (observed) vs. 102% (calculated) or entry 15: 153% (observed) vs. 151% (calculated)]. At lower temperatures (130 °C) the esterification of acetic acid (and the formation of water) occurs to a lower extent compared to at 160 °C. Therefore, the yields of *n*-butyl 4-trifluoromethylbenzoate are higher and the observed yields of *n*-butyl acetate (13–43%) are below the respective maximum values (49–87%; entries 1–5, Table 2). In a control-carbonylation experiment in the absence of the aryl chloride (14 ml *n*-butanol, 21 mmol NaOAc, 0.5 mol% $PdCl_2(PhCN)_2$ and 7 mol% PCy_3 at 130 °C and 15 bar CO), but in the presence of HOAc (7 mmol) the formation of *n*-butyl acetate (79% after 24 h) was observed. This indicates that the esterification shown in Eq. (3) (Scheme 3) indeed takes place under the conditions of carbonylation catalysis.

According to Scheme 3, a water-removing agent should lead to an increased selectivity for the product (*n*-butyl 4-trifluoromethylbenzoate). Therefore, the experiment with the worst selectivity (entry 15, Table 2) was performed in the presence of molecular sieves (4 Å, ca. 3 g). As expected the yield of the product increased dramatically (77 vs. 35%):

Additive	Conversion (%)	Yield of ester (%)	Selectivity (%)
–	93	35	38
Molecular sieves (4 Å)	96	77	80

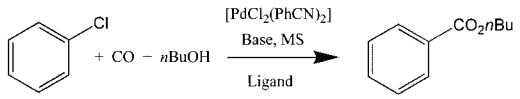
It has to be pointed out, that the formation of the by-products is also conceivable via nucleophilic attack of the acetate ion on the acyl palladium intermediate with concomitant formation of the mixed 4-trifluoromethylbenzoic acid–acetic acid anhydride and subsequent alcoholysis. However, this mechanism alone cannot account for the observed amounts of *n*-butyl acetate above 100%.

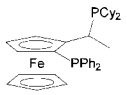
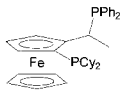
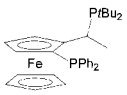
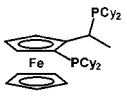
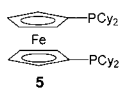
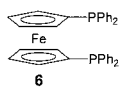
2.3. Butoxycarbonylation of non-activated aryl chlorides in the presence of ferrocenyl ligands

Since both high conversion and yield was achieved for the carbonylation of 4-chlorobenzotrifluoride in the presence of the $PdCl_2(PhCN)_2$/Josiphos (**1**) catalyst (Table 2), we were interested in the performance of this type of catalyst with non-activated aryl chlorides. First, the palladium-catalyzed carbonylation of chlorobenzene was studied in the presence of **1**. Next, other 1,2-disubstituted ferrocenyl ligands (**2**–**4**) and 1,1′-disubstituted ferrocenyl phosphines **5** and **6** were employed in this reaction. For all the experiments the previously optimized conditions of temperature (145 °C), CO pressure (3 bar) and P/Pd ratio (8) were applied. In addition molecular sieves (4 Å) were added in order to restrict the formation of benzoic acid.

Table 3 gives a summary of the results obtained. When chlorobenzene is reacted in the presence of the Josiphos ligand **1**, 59% conversion is seen and *n*-butyl benzoate is formed in 49% yield (entry 1, Table 3). Although conversion and product yield are significantly lower compared to the reaction with 4-chlorobenzotrifluoride, the catalyst turnover number (TON = 98) and turnover frequency (TOF = 6.5 h^{-1}) are similar to the best results reported for the alkoxycarbonylation of chlorobenzene [7]. A catalyst based on ligand **2**, which possesses an 'inverse' structure compared to Josiphos **1** and no strongly basic trialkylphosphine subunit, leads to a significantly lower conversion/yield (cf. entries 1 and 2, Table 3). Ligand **3** with a di-*tert*-butylphosphino moiety gives a similar conversion to **2**, with a much lower selectivity of only 27%, despite molecular sieves being employed (entry 3, Table 3). If both phosphorus atoms are substituted with cyclohexyl groups in the ligand (1-{2-(dicyclohexylphosphino)ferrocenyl}ethyl-dicyclohexylphosphine) (**4**), an efficient conversion of chlorobenzene (78%) with a yield of almost 70% of

Table 3
Butoxycarbonylation of chlorobenzene at 145 °C in the presence of 0.5 mol% $PdCl_2(PhCN)_2$ and bidentate ferrocenyl phosphine ligands[a]



Entry	Ligand	Conversion [%] [b]	Yield of Ester [%] [b]	Selectivity [%] [c]
1	 **1**	59	49	83
2	 **2**	52	39	75
3	 **3**	51	14	27
4	 **4**	**78**	**67**	**86**
5	 **5**	62	31	50
6	 **6**	35	22	63

[a] 7 mmol chlorobenzene, 14 mL *n*-butanol, molecular sieves 4 Å. [b] Determined by GC using diethyleneglycol di-*n*-butylether as internal standard. [c] Selectivity = ester yield / conversion.

The difference in conversion and product yield is due to the formation of benzoic acid.

n-butyl benzoate is achieved in the presence of only 0.5 mol% Pd catalyst (entry 4, Table 3).

If the structure of the cyclohexylphosphino ferrocenyl ligand is changed from a 1,2- to a 1,1′-disubstitution (ligand **5**), a lower catalyst activity is observed (cf. entries 4 and 5, Table 3). In this case the conversion drops to 62% with only 31% of the product being formed. The catalyst based on the phenylphosphine ligand **6** is much less efficient than the other systems $PdCl_2(PhCN)_2$/**1**–**5**, presumably due to the reduced nucleophilicity of the catalytically active palladium species.

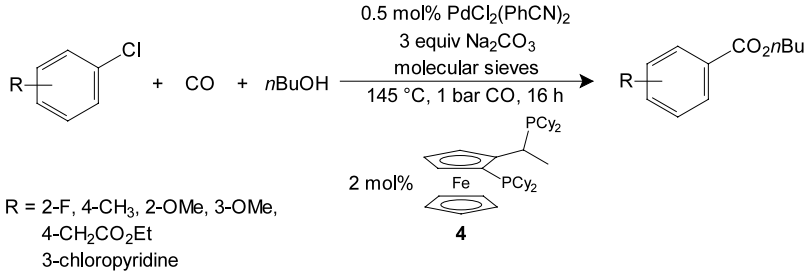
Further improvement of the carbonylation of chlorobenzene is possible by using Na_2CO_3 as base at low CO pressures of 1 or 3 bar. Here, the carbonylation of chlorobenzene in the presence of ligand **4** proceeds quantitatively (100%) with extremely high selectivities ($> 99\%$). Although the reaction time for the carbonylation experiments was in general 16 h, an examination of the time/conversion behavior of the reaction at 1 bar CO revealed that the reaction had essentially proceeded to completion after 5–6 h, indicating the much higher carbonylation activity of the catalyst in the presence of Na_2CO_3. At lower catalyst loadings, i.e. only 0.05 mol% of $PdCl_2(PhCN)_2$ [20], the conversion of the substrate is still 100%, however, the selectivity is somewhat lower (yield 78%; TON = 1560). This is the highest turnover number that we are aware of for the carbonylation of chlorobenzene [21]. The new carbonylation protocol is also useful for aryl chlorides other than chlorobenzene, especially electron rich, i.e. deactivated substrates. The results are depicted in Table 4.

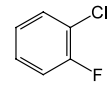
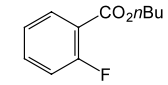
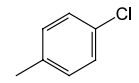
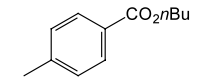
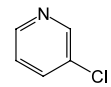
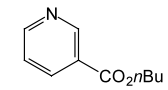
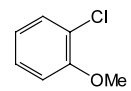
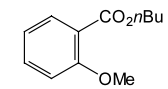
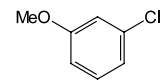
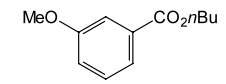
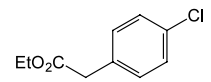
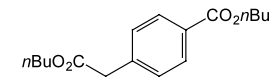
A quantitative conversion of the aryl chloride was observed in all the reactions examined [22]. 2-Chlorofluorobenzene and 4-chlorotoluene, which with respect to their π-electron density and steric bulk resemble chlorobenzene, reacted to afford the respective substituted benzoic acid esters in high yield (98–100%) (entries 1, 2, Table 4). The catalyst is also active for heterocyclic chloride substrates, as indicated by entry 3 (Table 4). 3-Chloropyridine is converted to the nicotinic ester in 72% yield (GC). With the electron rich and bulkier 2-chloroanisole, the desired product is formed in almost quantitative yield (95%) (entry 4, Table 4). The respective *o*-methoxybenzoic acid is not observed. In contrast, the butoxycarbonylation of the isomeric 3-chloroanisole proceeds with a significantly lower product selectivity of 80%. Here, *m*-methoxybenzoic acid is formed in 15% isolated yield (entry 5, Table 4). In addition ethyl (4-chlorophenyl)acetate was employed as a substrate. No side reactions occurred at the benzylic methylene group, although transesterification of the ethyl ester takes place and *n*-butyl (4-butoxycarbonylphenyl)acetate is formed in 80% yield (entry 6, Table 4). Additionally, a mixture of the diacid and (4-butoxycarbonylphenyl)acetic acid were isolated as by-products in 13% total yield.

3. Conclusions

In conclusions, we have examined the palladium-catalyzed alkoxycarbonylation reaction of activated and deactivated aryl chlorides with regard to the influence of critical reaction parameters, product selectivity, and the performance of various catalyst ligands. Our investigations resulted in the development of a new efficient catalyst system based on cyclohexyl-substituted ferrocenylphosphine ligands for the carbonylation of aryl chlorides. A considerable advantage is that these ligands are air stable and commercially available. With the $PdCl_2(PhCN)_2$/**4** catalyst (0.5 mol% Pd) in the presence of sodium carbonate as a base, chlorobenzene was converted to *n*-butyl benzoate in an essentially

Table 4
Butoxycarbonylation of various aryl chlorides[a]



Entry	Aryl Chloride	Conversion [%]	Product	Yield [%][b]	Chemo-selectivity [%][c]
1		100		100 (76)	95
2		100		98 (80)	92
3		100		>72 (67)	>72
4		100		95 (91)	100
5		100		95 (68)	84
6		>99		93 (68)	86 [d]

[a] 7 mmol aryl chloride, 14 ml *n*-butanol. [b] Yield (GC) of all carbonylation products (ester + acid). GC-Yield of product was determined by using diethyleneglycol di-*n*-butylether as internal standard. Isolated yield of product in brackets. [c] Chemoselectivity = GC-yield of product / yield of carbonylation products. [d] Mixture of 80 % (4-carboxyphenyl)acetic acid and 20 % (4-butoxycarbonylphenyl)acetic acid

quantitative yield within 16 h (130–145 °C). The CO pressure can be as low as 1 bar. A turnover number of almost 1600 was observed at catalyst loading of only 0.05 mol%, underlining the high productivity of the catalyst system. The observed catalyst productivity for the carbonylation of chlorobenzene is more than one order of magnitude higher compared to other known palladium catalysts. This result is noteworthy if one considers that catalyst costs are of special importance for aryl chloride activation, otherwise the use of these starting materials is not advantageous. The applicability of the carbonylation protocol to other aryl chloride substrates is demonstrated. Furthermore, it is shown that statistical reaction design is a useful tool for the optimization of carbonylation catalysts.

4. Experimental

4.1. General

All reactions were carried out under an Ar atmosphere. A 100 ml stainless steel autoclave (no. 4593 from Parr Co.) equipped with a magnet-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. In this case the pressure was kept constant by using 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. Anhydrous *n*-butanol was purchased from Aldrich Chemical Co. Anhydrous DMF and anhydrous dioxane were purchased from Fluka Chemical Co. 2-Pentanol (Aldrich Chemical Co.) was dried over molecular sieves (4 Å). All of these solvents, as well as distilled water (if used as a reagent), were additionally saturated with Ar. Aryl chlorides were purchased from Aldrich Chemical Co. except for chlorobenzene which was purchased from Fluka Chemical Co., and ethyl(4-chlorophenyl)acetate which was prepared according to a literature procedure [23]. Et_3N (Fluka Chemical Co.) and di-*n*-propylamine (Aldrich Chemical Co.) were dried over molecular sieves (4 Å) and saturated with Ar. Anhydrous AcONa and Na_2CO_3 were purchased from Fluka Chemical Co. PCy_3 and 1,1′-bis(diphenylphosphino)ferrocene (**6**) were purchased from Strem Chemical Co. 1,1′-Bis(dicyclohexylphosphino)ferrocene (**5**) [24] was prepared according to the literature procedure. Bis(benzonitrile)-dichloropalladium(II) was prepared according to the literature procedure [25]. 1-{2-(Diphenylphosphino)-ferrocenyl}ethyl-dicyclohexylphosphine (**1**), 1-{2-(dicyclohexyl-phosphino)ferrocenyl}ethyl-diphenylphosphine (**2**), 1-{2-(diphenylphosphino)ferrocenyl}-ethyl-di-*tert*-butylphosphine (**3**), and 1-{2-(dicyclohexylphosphino)-ferrocenyl}ethyl-dicyclohexylphosphine (**4**) (all as racemates) were prepared by Solvias AG, Basel (Switzerland) and used as received. Diethyleneglycol di-*n*-butylether (internal GC standard) was purchased from Fluka Chemical Co.

^{1}H- and ^{13}C{^{1}H}-NMR spectra were recorded in a Bruker ARX 400 spectrometer. Chemical shifts (δ) are given in parts per million and refer to residual solvent as the internal standard. IR spectra were recorded in a Nicolet Magna 550 spectrometer. Gas chromatography was performed in a Hewlett–Packard HP 6890 chromatograph with a HP5 column.

4.2. General procedure for the carbonylation of aryl chlorides [26]

An oven-dried Schlenk flask was evacuated and filled with Ar (three cycles), then charged with the aryl chloride (7 mmol), *n*-butanol (14 ml) or another nucleophile/solvent, $PdCl_2(PhCN)_2$ (13.4 mg, 0.035 mmol, 0.5 mol%), and ligand **4** (84.9 mg, 0.140 mmol, 2 mol%) to give an orange solution. Sodium carbonate (2.226 g, 21 mmol, three equivalents) and molecular sieves (4 Å, ca. 3 g) were added to the autoclave. After evacuating and filling the autoclave with Ar (three cycles), the reaction mixture was transferred from the Schlenk flask into the autoclave by means of a PVC-tube ($\varnothing \approx 2$ mm) under a positive pressure of Ar. The autoclave was closed, heated to temperature of 145 °C and pressurized with 1 bar CO from a CO reservoir which was connected to the autoclave with a pressure regulator providing a constant pressure during the reaction. For experiments at higher CO pressures the autoclave was not connected to the CO reservoir (non-isobaric conditions). After 16 h and subsequent cooling to room temperature, the yellow–orange reaction mixture was diluted with CH_2Cl_2 (70 ml) and poured into a separating funnel. The mixture was washed with water (70 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×20 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, mixtures of EtOAc–hexanes as eluent).

In order to isolate benzoic acids, formed either as by-products or as the main product (in the case of water as nucleophile), the pH of the aqueous layer was adjusted to a pH of 0 by dropwise addition of concentrated HCl. The mixture was then extracted with Et_2O (3×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford the acids as white solids.

4.2.1. n-Butyl benzoate

The reaction of chlorobenzene (788 mg, 7 mmol) was effected using the general procedure to afford 1.060 g (5.95 mmol, 85%) of the title compound as a colorless oil. $R_f = 0.69$ (EtOAc–hexane 1:5); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 8.04 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 4.33 (t, 2H, ^3J(H,H) = 6.6 Hz), 1.76 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.48 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.98 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 166.7, 132.7, 130.5, 129.5, 128.3, 64.8, 30.7, 19.2, 13.7; IR (KBr, cm^{-1}): 2960, 1719, 1452, 1315, 1275, 1111, 710. Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 73.95; H, 7.90%.

4.2.2. n-Butyl 4-trifluoromethylbenzoate

The reaction of 4-chlorobenzotrifluoride (1.264 g, 7 mmol) was effected using the general procedure, however, with NaOAc (1.723 g, 21 mmol) as the base and Josiphos **1** (83.2 mg, 0.140 mmol) as the ligand at 14 bar CO and 160 °C (15 h) to afford 1.051 g (4.27 mmol, 61%) of the title compound as a colorless oil along with 4-trifluoromethylbenzoic acid (199.6 mg, 1.05 mmol, 15%; analytical data, vide infra) as a by-product. $R_f = 0.67$ (EtOAc–hexane 1:10); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 8.07 (m, 2H), 7.61 (m, 2H), 4.28 (t, 2H, ^3J(H,H) = 6.6 Hz), 1.69 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.40 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.90 (t, 3H, ^3J(H,H) = 7.4 Hz, 3H, CH_3); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 165.4, 134.3 (q, ^2J(C,F) = 32.4 Hz), 133.7, 129.9, 125.3 (q, ^3J(C,F) =

3.8 Hz), 123.6 (q, ^1J(C,F) = 272.8 Hz), 65.4, 30.7, 19.2, 13.7; IR (KBr, cm^{-1}): 2964, 1727, 1327, 1279, 1169, 1132, 1067, 864, 776, 705. Anal. Calc. for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32. Found: C, 58.79; H, 5.15%.

4.2.3. 4-Trifluoromethylbenzoic acid

White solid, m.p. 220 °C. ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 8.10 (m, 2H), 7.69 (m, 2H); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 167.3, 134.0 (q, ^2J(C,F) = 32.4 Hz), 133.7, 129.9, 125.0 (q, ^3J(C,F) = 3.8 Hz), 123.5 (q, ^1J(C,F) = 272.8 Hz), 65.4, 30.7, 19.2, 13.7; IR (KBr, cm^{-1}): 2995, 1700, 1316, 1289, 1172, 1144, 1063, 863, 780. Anal. Calc. for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 51.16; H, 2.82%.

4.2.4. n-Butyl 2-fluorobenzoate

The reaction of 2-chlorofluorobenzene (914 mg, 7 mmol) was effected using the general procedure to afford 1.044 g (5.32 mmol, 76%) of the title compound as a light-yellow oil along with 2-fluorobenzoic acid (49 mg, 0.35 mmol, 5%; analytical data, vide infra) as a by-product. R_f = 0.51 (EtOAc–hexane 1:15); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.92 (td, 1H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.7 Hz), 7.49 (m, 1H), 7.18 (t, 1H, ^3J(H,H) = 8.0 Hz), 7.11 (dd, 1H, ^3J(H,F) = 10.8 Hz, ^3J(H,H) = 8.0 Hz), 4.32 (t, 2H, ^3J(H,H) = 6.6 Hz), 1.73 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.46 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.96 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 164.4 (d, ^3J(C,F) = 3.7 Hz), 161.8 (d, ^1J(C,F) = 259.6 Hz), 134.2 (d, ^3J(C,F) = 9.0 Hz), 131.9, 123.8 (d, ^4J(C,F) = 3.8 Hz), 119.0 (d, ^2J(C,F) = 9.6 Hz), 116.8 (d, ^2J(C,F) = 22.6 Hz), 65.1, 30.6, 19.1, 13.6. Anal. Calc. for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.68. Found: C, 67.59; H, 6.59%.

4.2.5. 2-Fluorobenzoic acid

White solid, m.p. 122–123 °C. ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.97 (td, 1H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.8 Hz), 7.62 (m, 1H), 7.29 (td, 1H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz), 7.23 (ddd, 1H, ^3J(H,F) = 11.1 Hz, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 167.8 (d, ^3J(C,F) = 2.8 Hz), 163.7 (d, ^1J(C,F) = 257.8 Hz), 136.1 (d, ^3J(C,F) = 8.9 Hz), 133.6, 125.5, (d, ^4J(C,F) = 4.0 Hz), 120.7 (d, ^2J(C,F) = 10.0 Hz), 118.1 (d, ^2J(C,F) = 22.3 Hz); IR (KBr, cm^{-1}): 3016, 2879, 1697, 1615, 1466, 1308, 753. Anal. Calc. for $C_7H_5FO_2$: C, 60.01; H, 3.60. Found: C, 60.37; H, 3.73%.

4.2.6. n-Butyl nicotinate

The reaction of 3-chloropyridine (795 mg, 7 mmol) was effected using the general procedure to afford 841 mg (4.69 mmol, 67%) of the title compound as a colorless oil. R_f = 0.23 (EtOAc–hexane 1:5); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 9.11 (s, 1H), 8.65 (m, 1H), 8.17 (m, 1H), 7.27 (m, 1H), 4.24 (m, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 0.86 (m, 3H); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 164.9, 153.0, 150.6, 136.7, 126.1, 123.0, 65.0, 30.4, 18.9, 13.4); IR (KBr, cm^{-1}): 3423, 2961, 1724, 1591, 1466, 1284, 741, 703. Anal. Calc. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.81; H, 7.38; N, 7.89%.

4.2.7. n-Butyl 2-methoxybenzoate

The reaction of 2-chloroanisole (998 mg, 7 mmol) was effected using the general procedure to afford 1.327 g (6.37 mmol, 91%) of the title compound as a colorless oil. R_f = 0.17 (EtOAc–hexane 1:20); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.77 (dd, 1H, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.8 Hz), 7.43 (ddd, 1H, ^3J(H,H) = 8.4, 7.4 Hz, ^4J(H,H) = 1.8 Hz), 6.95 (m, 2H), 4.28 (t, 2H, ^3J(H,H) = 6.6 Hz), 3.87 (s, 3H), 1.72 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.46 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.95 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 166.2, 159.0, 133.2, 131.4, 120.4, 120.0, 111.9, 64.5, 55.8, 30.6, 19.1, 13.6; IR (KBr, cm^{-1}): 2959, 1727, 1465, 1301, 1253, 1082, 757. Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.33; H, 7.58%.

4.2.8. n-Butyl 3-methoxybenzoate

The reaction of 3-chloroanisole (998 mg, 7 mmol) was effected using the general procedure to afford 991 mg (4.76 mmol, 68%) of the title compound as a light-yellow oil along with 3-methoxybenzoic acid (160 mg, 1.05 mmol, 15%; analytical data, vide infra) as a by-product. R_f = 0.65 (EtOAc–hexane 1:5); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.77 (dd, 1H, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.8 Hz), 7.43 (ddd, 1H, ^3J(H,H) = 8.4, 7.4 Hz, ^4J(H,H) = 1.8 Hz), 6.95 (m, 2H), 4.28 (t, 2H, ^3J(H,H) = 6.6 Hz), 3.87 (s, 3H), 1.72 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.46 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.95 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 166.2, 159.0, 133.2, 131.4, 120.4, 120.0, 111.9, 64.5, 55.8, 30.6, 19.1, 13.6; IR (KBr, cm^{-1}): 2959, 1727, 1465, 1301, 1253, 1082, 757. Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.96; H, 7.88%.

4.2.9. 3-Methoxybenzoic acid

White solid, m.p. 104–105 °C. ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.72 (dt, 1H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.1 Hz), 7.63 (dd, 1H, ^4J(H,H) = 2.6, 1.1 Hz), 7.39 (t, 1H, ^3J(H,H) = 8.0 Hz), 7.16 (ddd, 1H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 2.6, 1.1 Hz), 3.87 (s, 3H); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 171.4, 159.6, 130.5, 129.5, 122.7, 120.5, 114.4, 55.5; IR (KBr, cm^{-1}): 2961, 1694, 1466, 1311, 1291, 1044, 755. Anal. Calc. for $C_8H_8O_3$: C, 63.14; H, 5.30. Found: C, 63.57; H, 5.45%.

4.2.10. n-Butyl 4-methylbenzoate

The reaction of 4-chlorotoluene (886 mg, 7 mmol) was effected using the general procedure to afford 1.077 g (5.6 mmol, 80%) of the title compound as a light-yellow oil along with 4-methylbenzoic acid (76 mg, 0.56 mmol, 8%; analytical data, vide infra) as a by-product. $R_f = 0.59$ (EtOAc–hexane 1:15); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.93 (m, 2H), 7.22 (m, 2H), 4.31 (t, 2H, ^3J(H,H) = 6.6 Hz), 2.40 (s, 3H), 1.75 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.47 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.98 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 166.7, 143.3, 129.5, 128.9, 127.7, 64.6, 30.7, 21.5, 19.2, 13.7; IR (KBr, cm^{-1}): 2960, 1719, 1458, 1310, 1275, 1107, 754. Anal. Calc. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.79; H, 8.40%.

4.2.11. 4-Methylbenzoic acid

White solid, m.p. 179–180 °C. ^{1}H-NMR (400.1 MHz, CD_3OD, 297 K): δ 7.93 (d, 2H, ^3J(H,H) = 8.2 Hz), 7.28 (d, 2H, ^3J(H,H) = 8.2 Hz), 2.41 (s, 3H); ^{13}C{^{1}H}-NMR (100.6 MHz, CD_3OD, 297 K): δ 170.3, 145.2, 131.1, 130.4, 129.3, 21.9; IR (KBr, cm^{-1}): 2977, 2549, 1677, 1419, 1286, 1184, 756. Anal. Calc. for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.68. Found: C, 67.59; H, 6.59%.

4.2.12. n-Butyl (4-butoxycarbonylphenyl)acetate

The reaction of ethyl (4-chlorophenyl)acetate (1.391 g, 7 mmol) was effected using the general procedure to afford 1.392 g (4.76 mmol, 68%) of the title compound as a light-yellow oil along with a mixture of (4-carboxyphenyl)acetic acid and (4-butoxycarbonylphenyl)acetic acid (4:1 ratio according to NMR, not separated; NMR data, vide infra) as by-products. $R_f = 0.52$ (EtOAc–hexane 1:5); ^{1}H-NMR (400.1 MHz, $CDCl_3$, 297 K): δ 7.99 (d, 2H, ^3J(H,H) = 8.3 Hz), 7.34 (d, 2H, ^3J(H,H) = 8.3 Hz), 4.31 (t, 2H, ^3J(H,H) = 6.6 Hz), 4.09 (t, 2H, ^3J(H,H) = 6.7 Hz), 3.66 (s, 2H), 1.74 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.59 (tt, 2H, ^3J(H,H) = 7.1, 6.7 Hz), 1.47 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 1.33 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 0.97 (t, 3H, ^3J(H,H) = 7.4 Hz), 0.90 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 297 K): δ 170.9, 166.4, 139.1, 129.7, 129.3, 129.2, 64.9, 64.7, 41.3, 30.7, 30.5, 19.2, 19.0, 13.7, 13.6; IR (KBr, cm^{-1}): 2960, 1736, 1720, 1613, 1466, 1418, 1277, 1106, 740. Anal. Calc. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.85; H, 8.33%.

4.2.13. (4-Carboxyphenyl)acetic acid

[27] ^{1}H-NMR (400.1 MHz, CD_3OD, 297 K): δ 8.00 (m, 2H), 7.42 (m, 2H), 5.10 (s, br., 2H), 3.72 (s, 2H); ^{13}C{^{1}H}-NMR (100.6 MHz, CD_3OD, 297 K): δ 175.1, 170.0, 141.9, 131.2, 130.9, 130.8, 42.0.

4.2.14. (4-Butoxycarbonylphenyl)acetic acid

^{1}H-NMR (400.1 MHz, CD_3OD, 297 K): δ 8.00 (m, 2H), 7.42 (m, 2H), 5.10 (s, br., 2H), 4.34 (t, 2H, ^3J(H,H) = 6.6 Hz), 3.72 (s, 2H), 1.78 (tt, 2H, ^3J(H,H) = 7.1, 6.6 Hz), 1.51 (qt, 2H, ^3J(H,H) = 7.4, 7.1 Hz), 1.02 (t, 3H, ^3J(H,H) = 7.4 Hz); ^{13}C{^{1}H}-NMR (100.6 MHz, CD_3OD, 297 K): δ 175.0, 168.3, 141.7, 131.2, 130.9, 130.5, 66.2, 42.0, 32.2, 20.6, 14.4.

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