Organic Process Research & Development **2002**, *6*, 220–224

Two Efficient Methods for the Preparation of 2-Chloro-6-methylbenzoic Acid

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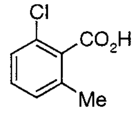
Abstract:

Two efficient methods for the preparation of 2-chloro-6-methylbenzoic acid were developed: one based on nucleophilic aromatic substitution and the other based on carbonylation. In the first approach, 2-chloro-6-fluorobenzaldehyde was converted to its *n*-butylimine, then treated with 2 equiv of methylmagnesium chloride in THF to give, after hydrolysis, 2-chloro-6-methylbenzaldehyde. Subsequent oxidation of this compound gave the title compound in 85% overall yield. In the second approach, 3-chloro-2-iodotoluene was efficiently carbonylated in methanol to give methyl 2-chloro-6-methylbenzoate, which after hydrolysis afforded the title compound in 94% yield (84% yield after recrystallization). The carbomethoxylation proceeded smoothly even at a high substrate-to-Pd ratio of 10 000. Both methods do not require isolation of intermediates and are suitable for the preparation of kilogram quantities of 2-chloro-6-methylbenzoic acid.

Introduction

2-Chloro-6-methylbenzoic acid (**1**) is a rather simple compound but is difficult to prepare in high purity on a large scale. A recent program at Roche required multikilogram quantities of this compound as a starting material to meet the ever increasing supply requirement of our molecules for toxicological evaluations. We had previously purchased **1** from commercial suppliers, but it was quite expensive (>$1000/kg) and of insufficient quality (<99% pure). The impurities contained in the commercial **1** (2-chlorobenzoic acid, 2-chloro-dimethylbenzoic acid, 2-chloro-6-ethylbenzoic acid, etc) were difficult to remove from **1** by recrystallization and, unfortunately, were incorporated into the final product.



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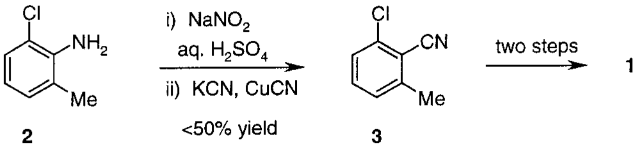
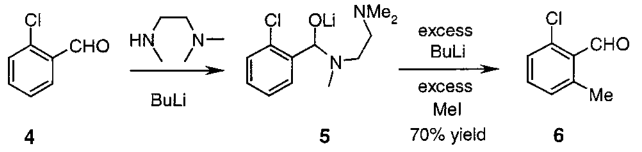
There are three known methods for the synthesis of **1**, which are based on: (1) the Sandmeyer reaction of 2-chloro-6-methylaniline (**2**) to form the corresponding nitrile, **3**, followed by two more steps to give **1** (Scheme 1),[1](2) ortho-metalation of 2-chlorobenzaldehyde (**4**) via in situ α-amino-alkoxide (**5**) formation with *N,N,N′*-trimethyl-ethylenediamine,[2] followed by oxidation of **6** to give **1** (Scheme 2), and (3) direct ortho-metalation of 2-chlorobenzoic acid, **7** (Scheme 3).[3]

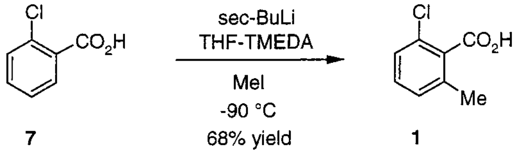
Scheme 1. **Sandmeyer reaction**



Scheme 2. **Ortho-metalation via α-amino-alkoxide**



Scheme 3. **Direct ortho-metalation**



The Sandmeyer reaction (Scheme 1) suffers from a low yield (<50%), high dilution, and tar formation—thus, it is not suitable for large-scale manufacturing. The second approach (Scheme 2) requires more than 3 equiv each of butyllithium and methyl iodide. It afforded **1** with an identical impurity profile as the commercial material, which was difficult to purify. The direct ortho-metalation of **7** (Scheme 3) requires a reaction temperature of −90 °C and was not reproducible in our hands.

To produce high-quality final products in an economical manner, we then envisioned two potential routes to **1**, which are based on nucleophilic aromatic substitution and carbonylation, respectively.

Results and Discussion

Nucleophilic Aromatic Substitution Approach. This route is based on chemistry described by Cahiez et al.,[4] in which they report a substitution reaction of the fluorine atom in compound **8** by butylmagnesium bromide to give **9** in 90% yield after hydrolysis (Scheme 4). If a methyl Grignard reagent would react with **8** as cleanly as butylmagnesium

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(1) Häring, M. *Helv. Chim. Acta* **1960**, *43*, 104.

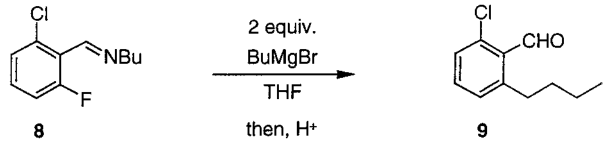
(2) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

(3) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265.

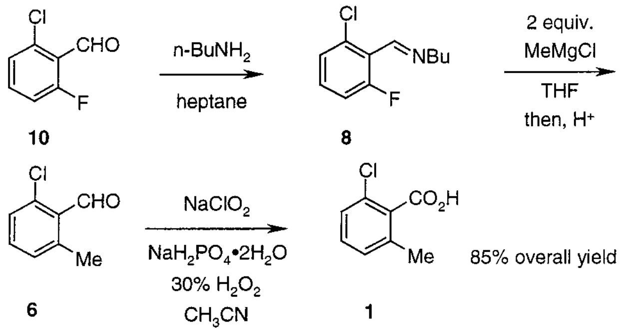
(4) Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138.

10.1021/op0102363 CCC: $22.00

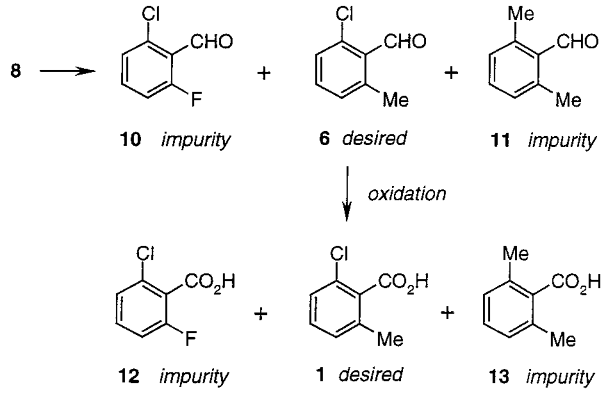
Scheme 4. **Reported nucleophilic aromatic substitution with BuMgBr**



Scheme 5. **Nucleophilic aromatic substitution approach**



Scheme 6. **Impurities and their fate**

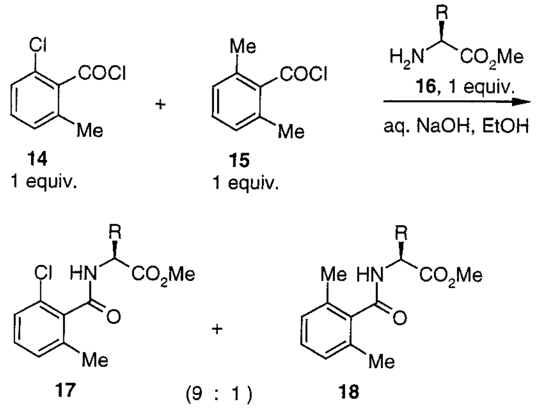


bromide, the requisite aldehyde **6** would be obtained in a good yield. More importantly, the starting material, 2-chloro-6-fluorobenzaldehyde (**10**), is quite inexpensive (<$40/kg for 200-kg quantities).

On addition of *n*-butylamine (1.13 equiv) to a slurry of **10** in heptane, the solids dissolved rapidly and water formed (Scheme 5). After washing the organic layer with brine, the residual water in the organic layer was removed azeotropically with heptane. Crude **8**, thus obtained as an oil, was used directly in the next step. The starting material, **10**, is sensitive to air oxidation and is usually contaminated with 2-chloro-6-fluorobenzoic acid (**12**). Although **12** is removed during the aqueous wash, monitoring by GC to ensure the complete removal of this impurity is advisable.

The substitution reaction was carried out at ca. 17 °C for 4 h (Scheme 5). Two equivalents of methylmagnesium chloride were required to achieve complete conversion (i.e., less than 0.05% of **10** after hydrolysis). The reaction was then quenched with acetone at a lower temperature to minimize over-reaction. Under these conditions, **6** of high purity is consistently obtained after hydrolysis—typically containing 0.01−0.05% of **10** and 0.03−0.15% of **11** (Scheme 6). Careful monitoring for complete conversion is important since **10** can be oxidized in the subsequent step to give 2-chloro-6-fluorobenzoic acid (**12**), which is difficult (although possible, as described later) to remove from **1**. If **12** is not removed at this stage, it will be incorporated into the final product. On the other hand, the formation of a small amount (<0.2%) of the double-substitution product, 2,6-dimethylbenzaldehyde (**11**), which gives **13** upon oxidation, was of less significance to us. In the preparation of the final drug substance, **1** is converted into acid chloride **14**, then coupled with an amino acid methyl ester, **16**, to give key intermediate **17** (see Scheme 7). When 1.03 equiv of **1** that contained ca. 0.2% of **13** was utilized in this coupling reaction (via the acid chloride), desired **17** was obtained in high yield, and the dimethylbenzoyl impurity, **18**, was undetected. Indeed, when a 1:1 mixture of **14** and **15** (the acid chloride of **13**) was allowed to react with 1 equiv of amino acid methyl ester **16** in the presence of sodium hydroxide (Scheme 7), a 9:1 mixture of **17** and **18** was formed. Clearly, dimethylbenzoyl chloride, **15**, is far less reactive than **14**. Thus, taking advantage of this difference in reactivity, the substitution reaction giving **6** was allowed to go to completion, while formation of **11** was minimized (<0.2%) by running the reaction at ca. 17 °C. At higher temperatures, the formation of **11** increased.

Scheme 7. **Relative reactivities of 14 and 15**



Oxidation of the aldehyde **6**, obtained after acidic workup, to afford the title compound, **1**, was performed with sodium chlorite−hydrogen peroxide (Scheme 5).[5] The reaction was carried out by the addition of 1.4 equiv of aqueous sodium chlorite to an aqueous acetonitrile solution of aldehyde **6** and 1.4 equiv of 30% hydrogen peroxide, at 15−19 °C, buffered with sodium dihydrogen phosphate. Although crude acid **1** can be obtained directly from the reaction mixture by removing the acetonitrile, the product thus obtained is colored and contaminated with inorganic salts. Thus, to remove inorganic materials, the product was first extracted into toluene and then into aqueous sodium hydroxide to remove nonacidic organic materials. Addition of concentrated hydrochloric acid to the basic phase precipitated the desired acid. Product **1**, obtained in this fashion, is quite pure, typically containing less than 0.1 and 0.2% of **12** and **13**, respectively. The overall yield of **1** from 2-chloro-6-fluorobenzaldehyde (**10**) is typically 85%.

During the early development work, when reliable analytical methods had not been established, impure acid **1**,

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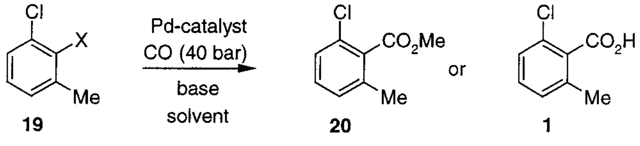
(5) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

Scheme 8. **Carbonylation approach**



X = I (**a**), Br (**b**), OTf (**c**), $N_2^+BF_4^-$ (**d**)

containing 0.4% of **12**, was produced. This necessitated the development of an efficient purification method of this compound. After several fruitless attempts, recrystallization from dilute aqueous acetic acid, buffered with a small amount of sodium acetate, was found to be quite effective to give **1** of a high purity with 81% recovery, containing only 0.07% of the impurity, **12**. Without addition of sodium acetate, recrystallization was less effective. Presumably, sodium acetate maintains 2-chloro-6-fluorobenzoic acid (**12**), the most acidic component in the mixture, ionized at least partially in the aqueous mixture, preventing crystallization of this impurity. Once appropriate in-process control methods had been established, **1** of a high quality has consistently been produced without resorting to this purification method.

Carbonylation Approach. Benzoic acid derivatives are generally accessible in good yield by carbonylation of aryl halides, -triflates, or -diazonium salts.[6] Surprisingly, however, there are only few reported examples employing carbonylation for the preparation of 2,6-disubstituted benzoic acids.[7] Carbonylation of 2,6-disubstituted substrates, such as **19a**−**d** (Scheme 8), may be impractical due to steric hindrance, requiring long reaction times, high catalyst loadings, and relatively high CO pressures. Moreover, the aryl chloride function in **19**, as well as in the product (e.g., **20**), could undergo carbonylation reaction to generate byproducts, particularly, if more forcing conditions are applied.

Four chlorotoluene derivatives, **19a**−**d**, were evaluated as starting materials for the methoxycarbonylation. Iodide **19a** smoothly converted to the desired methyl ester **20** under a variety of conditions. Using bromide **19b**, the carbonylation was quite sluggish even at a very high catalyst loading (S/C = 10) and elevated temperature (160 °C). Triflate **19c** only gave a mixture of 2-chloro-6-methylphenol and 2-chloro-6-methylanisole. Diazonium salt **19d** gave 3-chlorotoluene as a major product together with only 14% of **20**. As **19a** was found to be a good substrate for methoxycarbonylation, carbonylation in the presence of water to directly give **1** was attempted. Unfortunately, under the conditions examined, 3-chlorotoluene was obtained as the major product (50−80%), and the desired product, **1**, was formed only as a minor product (<30% yield). On the basis of these results, methoxycarbonylation of iodide **19a** was chosen for further investigation.[8]

Table 1. **Carbomethoxylation of 19a:**[a] **variation of ligands**

entry	catalyst[b]	conversion (GC area %) 2 h	16 h	product **20** (GC area %)
1	$Pd(OAc)_2[PPh(3,5\text{-di-}t\text{Bu-Ph})_2]_2$	97	99.8	98
2	$Pd(OAc)_2[P(3,5\text{-di-}t\text{Bu-Ph})_3]_2$	96	99.9	99
3	$Pd(OAc)_2[P(o\text{-Tol})_3]_2$	88	99.6	97
4	$Pd(OAc)_2(PPh_3)_2$	87	99.4	97
5	$Pd(OAc)_2(PPh_2Me)_2$	48	99.9	92
6	$Pd(OAc)_2$(DIOP)[c]	87	99.9	95
7	$Pd(OAc)_2$(BINAP)	64	99.8	92
8	$Pd(OAc)_2$(dppf)[d]	52	99.8	83
9	$Pd(OAc)_2$(dppp)[e]	6	33	31
10	$Pd(OAc)_2$(dppb)[f]	5	24	23
11	$PdCl_2(PPh_3)_2$	97	99.6	98
12	$PdCl_2[PPh(3,5\text{-di-}t\text{Bu-Ph})_2]_2$	92	99.4	98
13	$PdBr_2(PPh_3)_2$	86	99.3	98
14	$PdCl_2(NCMe)_2/2\ PPh_3$	65	90	87

[a] S/C 1000, 1.5 equiv of $NaHCO_3$, 40 bar initial CO pressure, 140 °C, 5 wt % of **19a** in methanol. [b] Isolated or in situ prepared catalysts. [c] DIOP: *O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [d] dppf: bis(diphenylphosphino)ferrocene. [e] dppp: bis(diphenyl-phosphino)propane. [f] dppb: bis(diphenylphosphino)butane.

First, the influence of phosphine ligands was investigated using palladium acetate as the metal source (Table 1, entries 1−10). In the monodentate ligand series (entries 1−5), catalysts containing bulky ligands (entries 1 and 2) were found to be more effective than those containing sterically less hindered phosphines; for example, triphenylphosphine (entry 4). Catalysts containing bidentate ligands (entries 6−10) were generally less effective; only DIOP was comparable with triphenylphosphine. Interestingly, dppp, which was found to be 500 times more effective than triphenylphosphine in the carbomethoxylation of aryl triflates,[7a,b] was one of the least effective ligands examined (entry 9).

Having identified triphenylphosphine analogues as the most effective ligands for this reaction, the influence of anionic ligands (i.e., OAc, Cl, and Br) was examined (Table 1, entries 11−14). $PdCl_2(PPh_3)_2$ was found to be the most active catalyst (entry 11), which was comparable with the more elaborate catalyst, $Pd(OAc)_2[PPh(3,5\text{-di-}t\text{Bu-Ph})_2]_2$ (entry 1). Interestingly, the corresponding chloride of the latter was found to be less active (entry 12). $PdBr_2(PPh_3)_2$ was similar to $Pd(OAc)_2(PPh_3)_2$ (entries 4 and 13). Since $PdCl_2(PPh_3)_2$ is commercially available and most active of those examined, this catalyst was chosen for further development.

With $PdCl_2(PPh_3)_2$ as the catalyst, other reaction parameters were then examined. Both the substrate, **19a**, and the product, **20**, were found to be thermally stable—no major decomposition products were detected when the reaction was performed even at 160 °C for 16 h. Lowering CO pressure from 40 to 10 bar resulted in a slight decrease in selectivity (99 to 97% GC area%). Of the bases evaluated ($NaHCO_3$, NaOAc, and Et_3N), sodium bicarbonate was found to be superior to the others in terms of reaction rate. From these and other experiments, a reaction temperature of 140 °C, initial CO pressure of 40 bar, and use of 1.5 equiv of sodium bicarbonate were chosen. Catalyst loading and substrate concentration were then examined (Table 2). Increasing the

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(6) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

(7) (a) Nicolau, K. C.; Ebata, T.; Stylianides, N. A.; Groneberg, R. D.; Carrol, P. J. *Angew. Chem.* **1988**, *100*, 1138. (b) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904. (c) Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1980**, *45*, 2365.

(8) Another plausible approach to prepare **1**, metalation of **19a** (Grignard or lithiation) followed by quenching with CO_2, was also examined but was found to be unsuccessful, presumably due to concomitant benzyne formation.

Table 2. **$PdCl_2(PPh_3)_2$-catalyzed carbomethoxylation of 19a:[a] variation of catalyst loading and substrate concentration**

entry	catalyst loading S/C	**19a** concentration (wt %) in methanol	conversion (GC area %) 2 h	16 h	product **20** (GC area %)
1	2000	5	93	99.5	98
2	5000	5	86	99.4	98
3	10000	5	80	98.7	98
4	10000	10	91	99.2	98
5	10000	20	94	>99.9	98

[a] 1.5 equiv of $NaHCO_3$, 40 bar initial CO pressure, 140 °C.

substrate concentration (entries 3−5) was found to be beneficial in terms of reaction rate. Even at a very low catalyst loading (S/C 10 000) the reaction proceeded smoothly with high selectivity (entry 5). In a preparative experiment on a 100-g scale, with a substrate concentration of 20 wt % and S/C 10 000, the reaction was complete within 8 h (see Experimental Section). The resulting reaction mixture was then directly subjected to hydrolysis with aqueous sodium hydroxide at reflux to give, after acidic workup, 99.5% pure **1** in 94% yield. This material should be suitable for subsequent transformations. If desired, 99.8% pure **1** with a palladium content of less than 5 ppm can be obtained after charcoal treatment and recrystallization from hexane.

Summary

We have developed two efficient methods for the preparation of 2-chloro-6-methylbenzoic acid (**1**). The first method based on nucleophilic aromatic substitution gave the desired acid in three chemical steps and 85% yield from 2-chloro-6-fluorobenzaldehyde (**10**). The second method, which is based on a catalytic carbonylation, gave **1** in two chemical steps and 94% yield (84% yield after recrystallization) from 3-chloro-2-iodotoluene (**19a**). Both methods do not require isolation of intermediates and are suitable for the preparation of kilogram quantities of 2-chloro-6-methylbenzoic acid.

Experimental Section

General. Melting points are uncorrected. All reagents and solvents were obtained from commercial suppliers and used without further purification. The GC analysis data is reported in area % and is not adjusted to weight %.

GC conditions.

column	Restek Rtx-35, 15 m × 0.32 mm, 0.25 μm thick coating
carrier gas	He, 65 kPa
injection	250 °C, split ratio of 1:50
temperature	50−150 °C at 10 °C/min
detection	300 °C, FID

Nucleophilic Aromatic Substitution Approach. *2-Chloro-6-methylbenzaldehyde (6).*[9] To a slurry of 2-chloro-6-fluorobenzaldehyde (**10**, 85.4 g, 539 mmol) in 255 mL of heptane was added *n*-butylamine (60 mL, 607 mmol). After stirring at room temperature for 1 h, the resulting water layer was separated, and the organic layer was washed with saturated sodium chloride solution (2 × 50 mL) and concentrated (40 °C/8 mmHg) to give 117 g (overweight) of crude **8** as a pale-yellow oil.[4]

To a solution of **8** (67.3 g, 315 mmol) in THF (100 mL) at 5 °C was added a 3 M methylmagnesium chloride solution in THF (210 mL, 630 mmol) over 30 min, while maintaining the temperature of the reaction mixture at 5−15 °C. The mixture was then stirred at room temperature (ca. 17 °C) for 4 h to achieve complete reaction (i.e., less than 0.05% of **10** after hydrolysis). After cooling to 5 °C with an ice−water bath, the reaction was quenched by the addition of acetone (30 mL, 409 mmol), while maintaining the temperature of the mixture at 0−10 °C. Then, 3 N HCl (360 mL) was added. An exotherm ensued that raised the temperature of the mixture from 10 to 40 °C. The mixture was allowed to cool to 25 °C over 1 h and then extracted with hexane (2 × 170 mL). The combined organic layers were washed with 1% sodium chloride solution (2 × 150 mL) and concentrated to dryness (40 °C/14 mmHg) to give 49.1 g (overweight) of crude **6** as a light-yellow, low-melting solid.

GC retention times: **10**, 4.50 min; **11**, 4.61 min; **6**, 4.96 min.

2-Chloro-6-methylbenzoic Acid (1).[3] To a mixture of **6** (63.0 g, 408 mmol), sodium dihydrogen phosphate dihydrate (16 g, 116 mmol), water (100 mL), 30% hydrogen peroxide (64 mL, 564 mmol), and acetonitrile (190 mL) at 10 °C was added a solution of 80% sodium chlorite (64 g, 566 mmol) in water (190 mL) over 1 h, while maintaining the temperature at 15−19 °C with an ice−water bath. After stirring at room temperature for 1 h, TLC analysis of the organic layer indicated complete reaction. After cooling with an ice−water bath, sodium metabisulfite (54 g, 284 mmol) was added in portions. An exotherm ensued that raised the temperature of the mixture from 10 to 50 °C. After stirring for 0.5 h, the mixture was concentrated (40 °C/14 mmHg) to remove most of the acetonitrile and then acidified by the addition of concentrated HCl (20 mL) and again concentrated. Toluene (200 mL) was added to the resulting aqueous slurry, and the aqueous layer was separated. The organic layer was then extracted with a solution of sodium hydroxide (31 g, 775 mmol) in water (300 mL) and then with water (30 mL). The combined aqueous layers were concentrated (40 °C/14 mmHg) to remove residual solvents. The resulting clear solution was then acidified by the addition of concentrated HCl (96 mL). After cooling to 10 °C, the resulting solid was collected by filtration, washed with cold water (2 × 50 mL), and dried by suction overnight to give 58.1 g (85.5% overall yield from **10**) of **1** as a white solid; 99.7% pure by GC analysis, containing 0.06% of 2-chloro-6-fluorobenzoic acid (**12**) and 0.12% of 2,6-dimethylbenzoic acid (**13**). For GC analysis, samples (1 mg of **1**) were treated with a 1:2 mixture of bis(trimethylsilyl)trifluoroacetamide and pyridine (350 μL) at 70 °C for 30 min.

GC retention times: **13**, 6.66 min; **12**, 6.79 min; **1**, 7.79 min.

Removal of 2-Chloro-6-fluorobenzoic Acid (12) from Impure 1. Ten grams of **1** containing 0.4% of **12** was dissolved in a mixture of acetic acid (14 mL) and water (100

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(9) Bedard, T. C.; Corey, J. Y.; Lange, L. D.; Rath, N. P. *J. Organomet. Chem.* **1991**, *401*, 261.

mL) by heating to 84 °C. After cooling to 50 °C, sodium acetate (50 mg) was added, and at 45 °C, seed crystals of **1** were added. The resulting suspension was slowly cooled to 4 °C. The solid was then collected by filtration, washed with water, and dried to give 8.13 g of **1** (81% recovery), containing 0.07% of **12**.

*2-Chloro-6-methylbenzoyl Chloride (**14**).*[1] To a mixture of **1** (20.0 g, 117 mmol), DMF (50 μL), and toluene (70 mL) was added oxalyl chloride (16 mL, 180 mmol). The resulting solution was stirred at room temperature for 1 h, and then ca. 50 mL of toluene was removed by distillation at atmospheric pressure to give a concentrated toluene solution of **14**, which was used in the subsequent acylation reactions without purification. GC analysis indicated this material to be 98.4% pure, containing three impurities, <0.1% of 2-chloro-6-fluorobenzoyl chloride, ca. 0.1−0.2% of 2,6-dimethylbenzoyl chloride (**15**), and ca. 1.4% of 2-chloro-6-methylbenzoic anhydride.

Carbonylation Approach. *2-Chloro-6-methylbenzoic Acid (**1**).*[3] 3-Chloro-2-iodotoluene (**19a**, 100 g, 396 mmol), sodium bicarbonate (49.9 g, 594 mmol), bis(triphenylphosphine)-palladium(II) chloride (27.8 mg, 0.0396 mmol), and methanol (500 mL) were charged into an autoclave. After purging with argon [three cycles of vacuum (0.2 bar)/argon (8 bar)], the autoclave was pressurized with carbon monoxide (40 bar). The mixture was heated to 140 °C with stirring (750 rpm) for 8 h. After cooling, the autoclave was vented and purged with argon. GC analysis confirmed complete conversion. The reaction mixture containing methyl ester **20** was transferred to a flask with the aid of methanol (500 mL), and a solution of sodium hydroxide (47.53 g, 1.19 mol) in 400 mL of water was added. After heating to reflux for 21 h, the mixture was concentrated to a volume of ca. 600 mL. The aqueous solution was washed with *tert*-butyl methyl ether (4 × 300 mL), diluted with water (300 mL), and cooled to 5 °C with an ice−water bath. After dropwise addition of concentrated HCl (105 mL, 1.24 mol) over 90 min, a white suspension formed, which was extracted with dichloromethane (3 × 500 mL). The combined organic layers were dried over magnesium sulfate, concentrated to dryness, and further dried at room temperature under vacuum (0.1 mbar) for 16 h to give 64.5 g (94% yield) of **1** as a pale yellow solid; 99.5% pure by GC analysis. This material was further purified by treatment with charcoal (3.14 g) in hexane at 50 °C for 1 h. The charcoal was then removed by filtration, and the product, **1**, was crystallized from the hexane by cooling to −23 °C (not optimized) to give 57.0 g (84% overall yield) of **1** as white crystals; mp 98−99 °C (lit. mp 100−102 °C),[3] 99.8% pure by GC analysis.

Received for review November 7, 2001.

OP0102363