JOC Article

Carbonylation of Aryl Chlorides with Oxygen Nucleophiles at Atmospheric Pressure. Preparation of Phenyl Esters as Acyl Transfer Agents and the Direct Preparation of Alkyl Esters and Carboxylic Acids

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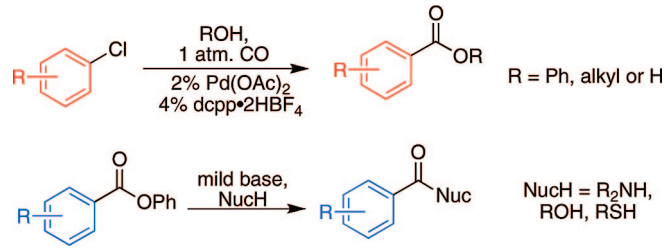

A mild, functional group tolerant method of the preparation of phenyl esters from aryl chlorides via palladium-catalyzed carbonylation is described using atmospheric pressure of carbon monoxide. Phenyl esters are shown to be useful acylating agents, delivering libraries of carbonyl derivatives, including alkyl, allyl and thioesters, under very mild conditions. Direct preparation of alkyl esters and carboxylic acids is also demonstrated, providing the first method for the preparation of methyl and ethyl esters from aryl chlorides without pressured reactors.

Introduction

Aromatic and heteroaromatic carboxylate derivatives are important building blocks in the synthesis of many high-value organic compounds, including pharmaceuticals and agrochemicals.[1] Of the various methods available for their synthesis, the palladium-catalyzed Heck carbonylation[2] is highly attractive due to its high atom economy, availability of starting materials, and functional group tolerant reaction conditions.[3] Although numerous protocols have been published for the carbonylation of aryl iodides, bromides, and triflates, aryl chlorides have seldom been used as starting materials as they are significantly more difficult to activate using palladium catalysts. Recent studies from our laboratory and others have demonstrated, however, that aryl chlorides can undergo numerous palladium-catalyzed processes, provided appropriate ligands are employed.[4] Aryl chlorides are highly attractive substrates for palladium catalysis due to their significantly lower cost and greater commercial availability, when compared to aryl iodides, bromides, and triflates.[5] Given these advantages, we wished to develop general carbonylation conditions for aryl and heteroaryl chlorides that would have both broad applicability and proceed under mild and laboratory-safe conditions.

Our initial entry into this area focused on the development of improved conditions for the aminocarbonylation of aryl chlorides to produce amides. Despite seminal contributions to aryl chloride carbonylation by Milstein,[6] and later by Beller,[7,8] aminocarbonylation had received only scant attention. The

(1) (a) *The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; John Wiley and Sons, Inc.: Hoboken, NJ, 2007. (b) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101. (c) Stetter, J.; Lieb, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 1724.

(2) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(3) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; de Meijere, A., Eds.; Wiley: New York, 2002; Vol *2*, p 2309. (b) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A* **1995**, *104*, 17. (d) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

(4) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(5) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Shultz, C. S.; Sun, Y. *Org. Lett.* **2006**, *8*, 5161.

(6) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742.

(7) (a) Mägerlein, W.; Insolese, A. F.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2856. (b) Mägerlein, W.; Insolese, A. F.; Beller, M. *J. Organomet. Chem.* **2002**, *641*, 30. (c) Beller, M.; Magerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, *7*, 1098.

(8) For additional studies of aryl chloride carbonylation, see: Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4.

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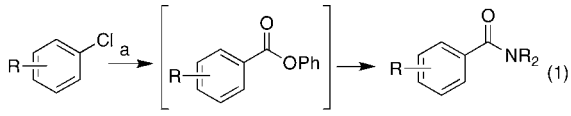
previously reported methods for this important reaction lacked substrate scope and required high pressures and/or temperatures. Recently, we have described a procedure for the aminocarbonylation of aryl chlorides that provides access to a wide variety of amides.[9] This new protocol operates at moderate temperatures and requires only atmospheric carbon monoxide pressures; thus, it can be readily applied under laboratory conditions.

Our development of these aminocarbonylation conditions hinged on the discovery that sodium phenoxide was a uniquely active basic additive. In situ IR spectroscopy studies revealed that phenyl esters, which arose from initial nucleophilic attack from phenoxide anion, were formed as intermediates and served as acyl transfer agents in the ultimate formation of the amide products (eq 1).



[a] 2 mol% $Pd(OAc)_2$, 4 mol% dcpp•$2HBF_4$, 3 equiv HNR_2, 2 equiv NaOPh, CO (1 atm), 4Å MS, DMSO, 100 - 120 °C, 15 h

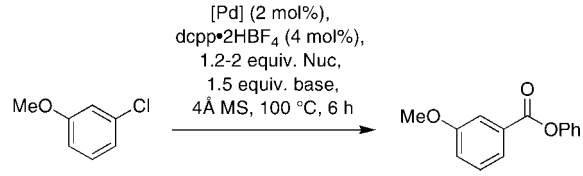
We recognized that phenyl esters could potentially serve as useful acylating reagents for the production of other carboxylate derivatives; a method for their direct production could be useful in providing a reactive, yet isolable, acylating agent via carbonylation. Such products would have utility both in the production of libraries of carbonyl derivatives from a single isolated carbonylation product and in the synthesis of carbonyl products that incorporate nucleophilic components that are not normally compatible with palladium-catalyzed conditions. Prior to this work, the preparative formation of phenyl esters from aryl chlorides was not known.[10]

Herein, we report optimized conditions for the production of numerous phenyl esters via carbonylation of aryl chlorides. These compounds can be readily isolated and subsequently reacted with numerous nucleophiles to produce amides, esters, and thioesters with varying substitution in good to excellent yields under mild conditions. In addition, these studies have also led us to explore the direct synthesis of carboxylic acids and alkyl esters via carbonylation of aryl halides. In this regard, we report improved conditions that allow the production of these important products under user-friendly conditions (moderate temperature and atmospheric pressure). Further, we report the first conditions for atmospheric-pressure aryl chloride carbonylation that are capable of preparing both methyl and ethyl esters.

Results and Discussion

We began our study of phenyl ester formation by examining the conversion of 3-chloroanisole to phenyl 3-methoxybenzoate. All reactions were conducted at atmospheric CO pressure in septum-sealed glass test tubes. Initially, we investigated conditions similar to those developed in our aminocarbonylation method. The ligand bis(dicyclohexylphosphino)propane (dcpp) was introduced as its commercially available, air-stable phosphonium salt dcpp•$2HBF_4$.[11] Under these conditions (NaOPh, 2 mol% $Pd(OAc)_2$, 4 mol% dcpp•$2HBF_4$, 4 Å MS, DMSO), only trace product and low conversion of the substrate were observed after 6 h at 100 °C (Table 1, entry 1). Based upon observations in our previous studies, we speculated that slow reduction of the $Pd(OAc)_2$ precatalyst was responsible for this result. Accordingly, we examined the use of dcppPd(Ph)Cl•tol (**1**) as the precatalyst.[9] This complex is structurally related to intermediates in the putative catalytic cycle and, therefore, does not require activation. With the use of **1** as the palladium source, high conversions and moderate yields of the desired phenyl ester were observed (entry 2). In contrast to our previous studies, the use of K_2CO_3/PhOH in place of NaOPh led to similarly good results (entry 3). More importantly, with PhOH as the source of phenoxide, the combination of $Pd(OAc)_2$ and dcpp•$2HBF_4$ proved to be an effective precatalyst, eliminating the need for the use of **1** (entry 4).[12] Examination of the solvent (entries 5−8) revealed the need for highly polar media, with DMF proving slightly better than DMSO. Even though molecular sieves were used in the reaction, addition of MeI to the reaction mixture prior to workup led to the formation of methyl 3-methyoxybenzoate, indicating that material was being lost as the carboxylic acid due to adventitious moisture. More rigorous exclusion of water[13] resulted in the optimal conditions and allowed isolation of phenyl 3-methoxybenzoate in 85% yield using silica gel chromatography.

TABLE 1. Optimization of Conditions for the Formation of Phenyl Esters



entry	[Pd]	nuc	base	solvent	yield (%)
1	$Pd(OAc)_2$	PhONa	none	DMSO	12[b,c]
2	dcppPdPhCl[a]	PhONa	none	DMSO	54[b]
3	dcppPdPhCl[a]	PhOH	K_2CO_3	DMSO	48[b]
4	$Pd(OAc)_2$	PhOH	K_2CO_3	DMSO	52[b]
5	$Pd(OAc)_2$	PhOH	K_2CO_3	DMSO	61[b,d]
6	$Pd(OAc)_2$	PhOH	K_2CO_3	Tol	0[b,d]
7	$Pd(OAc)_2$	PhOH	K_2CO_3	Bu_2O	4[b,d]
8	$Pd(OAc)_2$	PhOH	K_2CO_3	DMF	75[b,d]
9	$Pd(OAc)_2$	PhOH	K_2CO_3	DMF	85[d,e,f]

[a] 2 mol % of dcpp•$2HBF_4$ used. [b] GC yield using dodecane as internal standard. [c] 43% conversion. [d] K_2CO_3 flame dried. [e] PhOH introduced as a solution in DMF that was dried over activated 3 Å MS. [f] Isolated yield.

In order to examine the scope of this method, the transformation of a variety of aryl and heteroaryl chlorides was examined (Table 2). Electron-deficient substrates performed well under the optimized conditions. Both nitrile- and trifluoromethyl-substituted aryl chlorides reacted smoothly to provide the corresponding phenyl esters in high yields (entries 1−3).

(9) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.

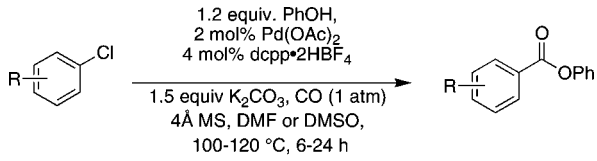
(10) A few studies have been published that report formation of aryl esters using aryl bromides and iodides. For examples, see: (a) Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* **2003**, 501. (b) Kubota, Y.; Nakada, S.; Sugi, Y. *Synlett* **1998**, 183. (c) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Mol. Catal. A* **1996**, *111*, 25.

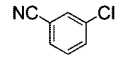
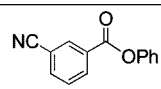
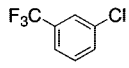
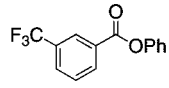
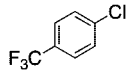
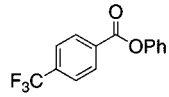
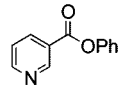
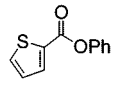
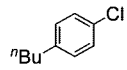
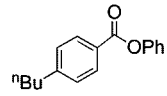
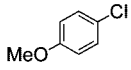
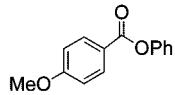
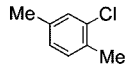
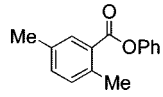
(11) Commercially available from Nippon Chemical Co. (103099−52−1). Also see ref 9 for a convenient synthesis.

(12) We speculate that the proton on PhOH is required for successful reduction of $Pd(OAc)_2$ to Pd(0) under these conditions. For general discussions regarding the reduction of $Pd(OAc)_2$ in the presence of phosphine ligands, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177. (b) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.

(13) Better exclusion of water was achieved by flame-drying of the K_2CO_3 prior to use and introduction the hydroscopic phenol as a solution in DMF that was predried over 3Å MS.

TABLE 2. Formation of Phenyl Esters



Entry	ArCl	Product	Yield[a]
1			78%[b]
2			82%[b]
3			91%[b]
4			74%[b]
5			84%[b]
6			83%[c]
7			78%[d]
8			57%[d]

[a] Average isolated yield from two runs. [b] 100 °C, DMF, 6 h. [c] 120 °C, DMF, 15 h. [d] 120 °C, DMSO, 6 h.

Heteroaromatic chlorides also proved to be viable substrates (entries 4 and 5), providing the products in good yields after 6 h at 100 °C. Not unexpectedly, more electron-rich substrates reacted more sluggishly. To achieve full conversion, *p*-alkyl-substituted substrates required higher temperatures and slightly longer reaction times to achieve full conversion (120 °C, 15 h). The more electron-rich 4-chloroanisole was even more recalcitrant and could not be fully converted in DMF. The use of DMSO as solvent provided much more rapid reactions for this substrate, with complete conversion being achieved within 6 h at 120 °C. Notably, for electron-poor substrates (such as those in entries 1−3), DMSO was far less effective than DMF as a solvent. Finally, we also examined the effects of ortho substituents on chloroarene carbonylations. While the reaction of 2-chloro-*m*-xylene did provide a moderate amount of the corresponding phenyl ester using DMSO as solvent, it did so only slowly and failed to proceed to completion (entry 8). Attempts to further optimize the conditions for this substrate were unsuccessful. These results stand in contrast to our results in the aminocarbonylation reaction, which was highly tolerant of ortho substitution.

Our primary interest in the preparation of phenyl esters was that they are readily isolable but also sufficiently activated to be used as acyl transfer reagents.[14] Thus, we wanted to explore their reactivity with various nucleophiles. As expected from our previous observations in the aminocarbonylation chemistry, phenyl esters proved to be useful intermediates for the preparation of numerous carboxylate derivatives under mild reaction conditions.

Both simple alcohols and primary amines reacted rapidly to provide esters and amides in high yields (Table 3, entries 1−3). Weak bases accelerated the reactions, and the addition 0.5 equiv of K_2CO_3 (compared to the phenyl ester) proved effective in this regard. Reactions with alcohols could be conducted at room temperature, albeit at prolonged reaction times (ca. 24 h). At 70 °C, the reactions were rapid. With a moderate excess of nucleophile (3−10 equiv), formation of methyl esters and primary amides was complete within 1 h. Production of an ethyl ester required slightly longer reaction times, with full conversion being achieved in 2 h at 70 °C. Electron-rich phenyl esters could also be converted rapidly at 70 °C, with DMSO proving to be a more effective solvent in this case (entry 4). With regard to the alcohols, it is of note that this procedure can be used with low boiling alcohols such as methanol and ethanol. Although carbonylation conditions to provide *n*-butyl esters from aryl chlorides using atmospheric pressure of CO have been reported,[7] the temperatures required are not compatible with low-boiling alcohols without the use of sealed reaction vessels. Thus, the use of phenyl esters as intermediates provides a practical solution to the problem of preparing these useful light alcohol esters. Subsequently, we have developed conditions for the direct preparation of methyl and ethyl esters at atmospheric pressure (see below).

Phenyl esters also provide access to carboxylate derivatives not typically accessible by carbonylation techniques. For example, the use of allyl alcohol as nucleophile resulted in rapid formation of the corresponding allyl ester (entry 5). Likewise, thioesters could be readily prepared by reaction with as little as 1 equiv of thiol (entry 6). These products are notable as allyl esters are unstable to palladium catalysis[15] and thiols are often poisons for palladium catalysts,[16,17] making the direct preparation of these products via carbonylation highly challenging.

The utility of phenyl esters as acylating agents is also demonstrated by the fact that little excess alcohol was required for full conversion to alkyl esters.[18] For example, treatment of phenyl nicotinate with 1.2 equiv of benzyl alcohol resulted in the clean formation of the benzyl ester (entry 7). Similarly,

(14) (a) Bloom, M. S.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 152. (b) Hauser, C. R.; Ringler, B. I.; Swamer, F. W.; Thompson, D. F. *J. Am. Chem. Soc.* **1947**, *69*, 2649. (c) Field, G. F.; Zally, W. *Synthesis* **1979**, 295.

(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons, Inc.: New York, 1999; p 410.

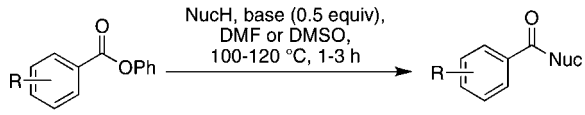
(16) For discussion and exceptions, see: Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205–3220.

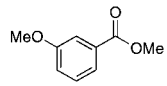
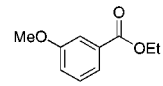
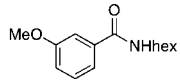
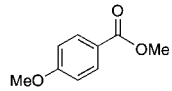
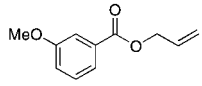
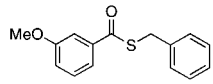
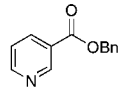
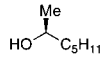
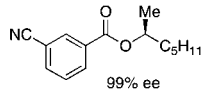
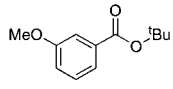
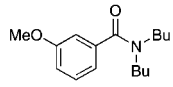
(17) Recently, a direct method for the preparation of thioesters from aryl iodides via carbonylation in ionic liquids has been published: Cao, H.; McNamee, L.; Alper, H. *J. Org. Chem.* **2008**, *73*, 3530.

(18) These conditions contrast those of typical trans-acylation reactions, which require a large excess of alcohol in order to drive the reaction to completion. See: March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley and Sons, Inc.: New York, 1992; p 397.

(19) Longer reaction times and higher temperatures were required for this reaction due to the greater steric demand of the secondary alcohol and its use in only stoichiometic quantities, both of which slow the rate of reaction compared to primary alcohols.

TABLE 3. Reactions of Phenyl Esters



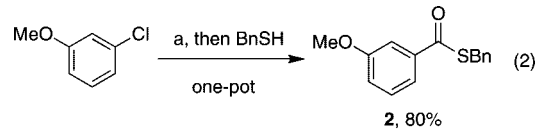
Entry	NucH	Product	Yield[a]
1	MeOH		89%[b,c]
2	EtOH		91%[b,d]
3	H_2N-*n*-hex		87%[b,c]
4	MeOH		82%[b,e]
5			82%[b,d]
6	BnSH		85%[b,d]
7	BnOH		91%[b,d]
8		 99% ee	86%[f]
9	^{t}BuOH		93%[g]
10	Bu_2NH		85%[g]

[a] Average isolated yield from two runs. [b] Base = K_2CO_3. [c] 70 °C, DMF, 1 h. [d] 70 °C, DMF, 2 h. [e] 70 °C, DMSO, 1 h. [f] 100 °C, DMF, 24 h. Starting material reported to be 99% ee (*S*). [g] Base = NaOPh, 120 °C, DMSO, 3 h.

treatment of phenyl 3-cyanobenzoate with 1.2 equiv of enantiopure (*S*)-2-heptanol, afforded the chiral ester in 85% yield (entry 8).[19] As direct ester formation via carbonylation often requires the use of a large excess of nucleophile for efficient catalysis, phenyl ester intermediates are highly advantageous in cases where the use of excess alcohol is not practical due to cost or purification concerns.

More sterically demanding nucleophiles could also be used with modification of the reaction conditions. The use of higher temperatures, longer reaction times, and slightly stronger bases proved necessary. For example, treatment of phenyl 3-methoxybenzoate with *tert*-butyl alcohol and 0.5 equiv of NaOPh at 120 °C for 3 h resulted in the formation of the *t*ert-butyl ester in high yield (entry 9). These conditions also proved effective for the formation of tertiary amide; the use of *N,N*-dibutylamine as the nucleophile provided the corresponding amide in 85% yield (entry 10).[20]

As the conditions (solvent, base and temperature) for phenyl ester formation are similar to those for the trans-acylation, isolation of the phenyl ester was not always required; simple addition of the nucleophile to the resulting crude reaction mixture, followed by gentle heating resulted in formation of the desired product in a single reaction pot. This sequence is demonstrated by the preparation of thioester **2** (80%) in the one-pot, two-step procedure (eq 2). Not surprisingly, attempts to prepare **2** in a single step by combining aryl chloride and benzyl thiol under palladium-catalyzed carbonylation conditions failed due to poisoning of the catalyst by the thiol,[16] demonstrating the utility of this one-pot, two-step protocol.



2, 80%

[a] 1.2 equiv. PhOH, 2 mol% $Pd(OAc)_2$, 4 mol% dcpp•2HBF$_4$, K_2CO_3, CO (1 atm), 4Å MS, DMF, 100 °C, 6 h,

With the successful development of conditions for the preparation of phenyl esters, we wondered whether this method could be extended to prepare other esters under direct carbonylation conditions without the use of phenyl esters. In particular, we were interested in developing methods compatible with the use of low boiling alcohols such as methanol and ethanol. As mentioned previously, Beller has reported conditions for the formation of alkyl esters from aryl chlorides using atmospheric pressure of CO and Solvias' Josiphos ligand. However, the reported system operates at high temperatures (140 °C) and has only been reported with high boiling alcohols (typically *n*-butanol) to form long-chain alkyl esters.[21,22] To our knowledge, no methods have been reported for the preparation of methyl or ethyl esters via carbonylation of aryl chlorides at atmospheric pressure. On the other hand, by using high pressure and temperatures, Milstein reported the formation of three methyl esters via aryl chloride carbonylation using di(isopropylphosphino)propane/$Pd(OAc)_2$ as the catalyst system.[23] Given the similarities between Milstein's and our catalyst system, we wondered if the high temperatures and pressures were required for alkyl ester formation.

(20) Under conditions identical to entry 9, Table 3, treatment of methyl 3-methoxybenzoate with *N,N*-dibutylamine did not lead to detectable amide, even after 24 h. This contrast highlights the greater utility of phenyl esters as acylating agents compared to alkyl esters.

(21) A group working at Solvias has reported that this method is in fact limited to use with *n*-butanol. See: Blaser, H-B.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583.

(22) Kato has also reported a single example of the formation of a butyl ester using atmospheric CO pressure from an heteroaryl chloride. See: Kato, Y.; Niiyama, K.; Nemoto, T.; Jona, H.; Akao, A.; Okada, S.; Song, Z. J.; Zhao, M.; Tsuchiya, Y.; Tomimoto, K.; Mase, T. *Tetrahedron* **2002**, *58*, 3409.

(23) Various protocols have been published for heteroaryl chloride alkyoxycarbonylation, which are activated compared to aryl chlorides. In general, these reactions are all conducted at high CO pressures. For recent examples, see: (a) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097. (b) Blaser, H. U.; Diggelmann, M.; Meier, H.; Naud, F.; Scheppach, E.; Schnyder, A.; Studer, M. *J. Org. Chem.* **2003**, *68*, 3725.

In order to answer this question, we examined the reaction of 4-*n*-butylchlorobenzene and methanol using our reaction conditions (2 mol % of $Pd(OAc)_2$, 4 mol % of dcpp·$2HBF_4$, 4 Å MS, DMSO, 100 °C, 15 h, atmospheric CO). We were pleased to isolate the desired methyl ester in 80% yield, an isolated yield similar to those reported by Beller for the preparation of *n*-butyl esters under his conditions. It is evident that although the reaction temperature is above the boiling point of pure methanol, the use of a high boiling cosolvent allows the reaction to be conducted without the need to pressurize the reaction vessel, increasing both the ease and safety with which these reactions can be conducted.[24]

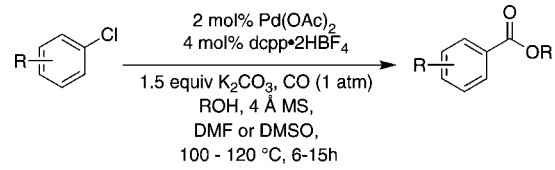
The conditions for the formation of alkyl esters proved to have substrate scope similar to that for the formation of phenyl esters. A variety of primary alkyl alcohols could be employed, including both methanol and ethanol. The reactions of electron-deficient chloroarenes and heteroaryl chlorides were best conducted in DMF at 100 °C (entries 1−4, Table 4). Electron-rich systems required the use of DMSO at 120 °C in order to achieve full conversion (entry 5). Even under these higher temperature conditions, the formation of methyl esters proceeded smoothly. As in the case of the phenyl esters, ortho-substituted chloroarenes proved to be challenging substrates, providing the desired ester in lower yield (entry 6). Likewise, more sterically demanding alcohols, such as 2-propanol, provided the products in lower yield (entry 9). For preparation of the esters of substituted alcohols, the phenyl ester methodology described above provides a better alternative (entries 8 and 10, Table 3).

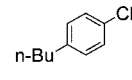
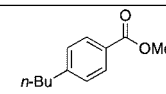
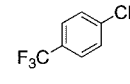
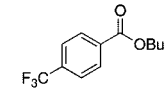
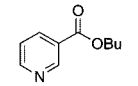
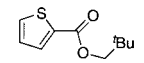
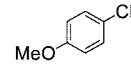
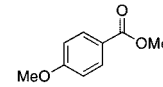
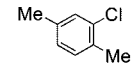
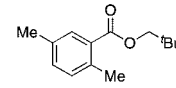
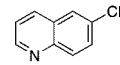
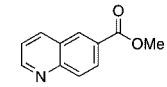
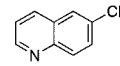
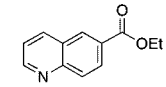
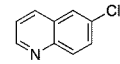
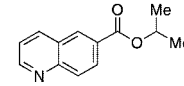
The direct formation of carboxylic acids from chloroarenes using carbonylation techniques has rarely been examined. Beller has published a single example of the process conducted at atmospheric pressure.[7] Milstein has reported only two examples, which were at high pressure and temperature.[25] Given both the lack of study in this area and the success of our conditions for the preparation of alkyl esters, we decided to examine the direct preparation of carboxylic acids using water as the nucleophile. Replacement of the phenol for water in our standard conditions led to the facile formation of the carboxylic acids (Table 5). Numerous functional groups proved compatible with these conditions (including a nitrile). While DMSO was a suitable solvent for all reactions, the choice of temperature depended upon the nature of the substrate, with electron-rich substrates requiring higher temperatures (120 °C). Notably, ortho substituents were better tolerated in the formation of carboxylic acids than in the previous cases described above and provided yields similar to those of other electron-rich substrates. The smaller size of water compared to phenol or the alcohols is presumably responsible for the increased production of the carboxylic acid product.

Conclusion

Our recent studies into the aminocarbonylation of aryl chlorides identified sodium phenoxide as a uniquely effective base for the preparation of a broad range of amides at moderate temperatures and atmospheric pressure of CO. In situ IR spectroscopy revealed phenyl esters as a key intermediate in this process. In this paper, we have described general conditions for the preparation of phenyl esters from aryl and hetereoaryl chlorides. These conditions proceed under atmospheric pressure of CO, using commercially available, air-stable precatalysts. Under these conditions, a variety of phenyl esters can be prepared in high yield. Capitalizing on the property of being both isolable yet reactive, phenyl esters have been demonstrated to be useful acylating agents. These compounds have been used to prepare numerous amide and ester derivatives under mild conditions. Not only did this method prove useful for the preparation of libraries of carboxylate derivatives from single carbonylation products, but it has also been demonstrated to allow access to carboxylate derivatives not normally accessible by palladium-catalyzed methods such as thio and allyl esters. This method can also be used to prepare esters of highly substituted alcohols, which are esters that cannot be prepared in high yield from aryl chlorides via carbonylation. Finally, we have re-examined the need for high pressure and temperature

TABLE 4. Synthesis of Alkyl Ester



Entry	ArCl	Product	Yield[a]
1			80%[b]
2			85%[c]
3			73%[c]
4			75%[c]
5			81%[d]
6			59%[d]
7			73%[d]
8			74%[d]
9			60%[d]

[a] Average isolated yield from two runs. [b] 100 °C, DMSO, 15 h. [c] 100 °C, DMF, 6 h. [d] 120 °C, DMSO, 15 h.

(24) Carbon monoxide is a highly toxic gas and should only be used in a well-ventilated fume hood and with proper leak detection equipment.

(25) Alper has also published an aryl chloride hydroxycarbonylation method using atmospheric CO pressure; however, a maximum of 29% isolated yield is reported: Grushin, V. V.; Alper, H. *J. Chem. Soc., Chem. Commun.* **1992**, 611.

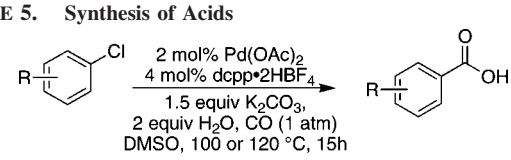
in the formation of alkyl esters via carbonylation of chloroarenes. For the first time, we report atmospheric pressure carbonylation conditions capable of producing a wide variety of esters, including those derived from low boiling alcohols such as methanol. These conditions have also been extended to the direct preparation of carboxylic acids. The studies described herein greatly expand the scope of carbonylation using aryl chlorides as substrates under convenient and practical laboratory conditions.

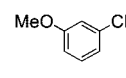
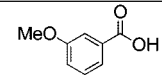
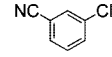
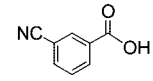
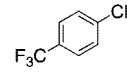
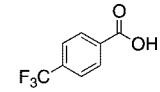
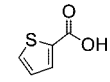
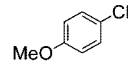
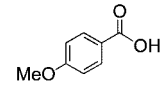
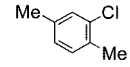
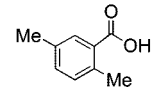
Experimental Section

The following is an example of the synthesis of a phenyl ester from an aryl chloride using atmospheric carbon monoxide pressure and is representative of the carbonylation procedures described herein. A complete description of all experimental details can be found in the Supporting Information. Note: carbon monoxide is a highly toxic gas and should be used only in a well-ventilated fume hood and with proper leak detection equipment.

General Procedure A, Preparation of Phenyl Esters. Potassium carbonate (208 mg, 1.50 mmol) and molecular sieves (4 Å, 150 mg, powdered) were added to a 18 × 150 mm test tube containing a stir bar. The tube was sealed with an inverted septum, the tube was evacuated (<0.5 mmHg), and the contents were heated using a Bunsen burner for 1−2 min. The tube was cooled to room temperature under vacuum and then refilled with nitrogen. The septum was briefly removed, and palladium acetate (4.5 mg, 0.02 mmol) and dcpp•$2HBF_4$ (24.4 mg, 0.04 mmol) were added to the tube. In cases where the substrate was a solid, it was also added (1.0 mmol) to the tube at this point. The septum was attached to the tube and secured using electrical tape. The tube was evacuated and refilled with nitrogen. Liquid substrates (1.0 mmol) were added using a syringe. A standard solution of phenol (in DMF or DMSO, 1.0 mL, 1.2 mmol, 1.2 M) was added using a syringe. Meanwhile, two nested helium-grade balloons were attached to a short section of vacuum tubing using rubber bands. The tube was fitted with a luer-adapter and a nylon three-way valve (Kontes part no. 420163-4503). The balloon apparatus was attached to a carbon monoxide source via the three-way valve, flushed three times with CO (to remove air), filled with CO, sealed using the valve, and removed from the CO source. With the valve still closed to the balloon, the balloon apparatus was attached to a vacuum line using the sidearm of the three-way valve. A needle (20 gauge) was attached to the remaining port using the luer attachment, and the needle was then immediately inserted into the reaction tube through the septum. (In this way, the operator avoids contact with a needle pressurized with CO.) The tube was evacuated and refilled with CO (the sequence was repeated a total of three times). After third backfill, the balloon was left attached and open to the tube. The tube was then placed in a heated oil bath (100 or 120 °C) for the specified time, while the contents were rapidly stirred. The tube was then removed from the oil bath, the balloon apparatus was removed, and the tube was allowed to cool to room temperature. The septum was carefully removed, and the residual CO was allowed to dissipate in the fume hood. For reactions involving DMF, the contents of the tube were filtered through a plug of Celite, and the filter cake was washed with ethyl acetate. The filtrate was then concentrated on ca. 5 g of Celite with the aid of a rotory evaporator. The resulting solid was then dry-loaded onto a chromatography column, and the product was purified using automated chromatography (ethyl acetate/hexanes, silica gel). For reactions involving DMSO, the contents of the test tube were filtered through Celite, and the filter cake was washed with ethyl acetate. The filtrate was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated on ca. 5 g of Celite. The product was then purified in an identical fashion to that described above.

TABLE 5. Synthesis of Acids



Entry	ArCl	Product	Yield[a]
1			90%[b]
2			97%[b]
3			91%[b]
4			84%[c]
5			70%[c]
6			71%[c]

[a] Average isolated yield from two runs. [b] 100 °C. [c] 120 °C.

Phenyl Nicotinate (Table 2, Entry 4). According to general procedure A, 3-chloropyridine (114 mg, 1.0 mmol, 95 μL) was heated in DMF for 6 h at 100 °C to provide the title compound (152 mg) in 76% isolated yield as a colorless solid: mp 75−77 °C; IR (KBr, cm^{-1}) 2360, 2341, 1734, 1272, 1192; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.86 (d, J = 5.5 Hz, 1H), 8.52−8.54 (m, 1H), 7.52−7.54 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 153.7, 151.1, 150.4, 137.7, 129.5, 126.2, 125.6, 123.5, 121.5. Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55. Found: C, 72.34; H, 4.52.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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