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Efficient Carbonylation Reactions in Phosphonium Salt Ionic Liquids: Anionic Effects

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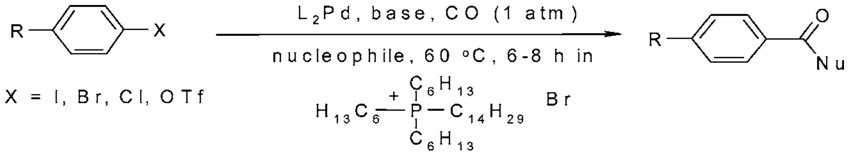
ABSTRACT



Application of phosphonium salt ionic liquids in the carbonylation of aryl and vinyl halides is presented. Anionic effects were uncovered with the bromide ionic liquid emerging as the superior media. Acid bromide intermediates were detected in control experiments providing an extended view on the overall catalytic cycle involved. Solvent-free product isolation and recycling of the ionic liquid containing active Pd-catalyst are also demonstrated.

The palladium-catalyzed carbonylation of aryl, vinyl, and aliphatic halides (or halide equivalents) is established as a useful, atom-economical method for the selective introduction of carbonyl groups into an organic molecule.[1] These reactions, originally established in the mid-70s by the pioneering work of Heck et al.,[2] have since found a number of synthetic applications,[3] and have been applied industrially, for example, in the preparation of ibuprofen on a metric ton scale and in a two-stage route to methyl methacrylate.[4,5] In terms of atom economy, highly efficient catalytic addition reactions are actively sought after since they can occur without formation of byproducts.[6] Room temperature ionic liquids (ILs) have recently attracted much attention as versatile reaction media. Often, they are thermally stable, nonvolatile, nonflammable, and recyclable liquids and as such have emerged as promising green-substitutes for conventional organic solvents.[7] The combination of developing atom-economical catalytic addition reactions in potentially recyclable ILs is thus a desirable goal in synthetic chemistry.

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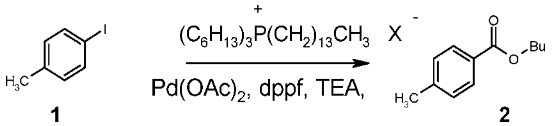
Over the past few years we have been actively involved in the development of cross-coupling reactions in phosphonium salt ionic liquids (PSILs) in general and specifically palladium-catalyzed processes. Both Suzuki and Heck cross-coupling reactions were demonstrated by us to occur efficiently in PSILs allowing recovery and reuse of both active Pd-catalyst and IL.[8] In addition to the potential advantages offered by ionic liquids described above, we have observed mechanistically significant anionic and cationic effects operable in esterification, general alkylation, and palladium-catalyzed amination reactions carried out in PSILs.[8e,f] Thus, in addition to the "green" credentials of these liquids, they have proven to be valuable reaction media in which to probe anionic and cationic effects and uncover fundamentally valuable information about these reactions. Herein we disclose the first examples of carbonylation reactions conducted in a PSIL, highlight a bromide effect, and establish acyl halides as viable intermediates in the catalytic cycle.

A few reports[9] on the use of imidazolium- and ammonium-based ILs in the carbonylation process have appeared. Of note, Nacci and co-workers[9d] reported tetrabutylammonium bromide (TBAB) to be a superior media to a range of other quaternary nitrogen-based systems. This was attributed to the involvement of a reactive anionic palladium species of type L_2PdBr^-, in accord with previous studies of Amatore and Jutand.[10] The use of a soluble bromide ion source now appears to be a tacit ploy in carbonylation reactions.[10c] In the present study, we investigated carbonylative cross coupling as a further probe of ionic effects exhibited in PSILs. In the initial screening, a range of PSILs consisting of the trihexyl(tetradecyl)phosphonium cation with a range of common ions were screened in the reaction of 4-iodotoluene and 1-butanol with a $Pd(OAc)_2$/dppf catalyst system,[11] and the results of the study are reported in Table 1. The reactions were conducted at atmospheric pressure of CO for 6 h. In contrast, most literature carbonylations[9] are conducted under pressure (10−30 atm).[12] The results reveal most of these PSIL media to be effective; however, the superiority of the bromide-containing media is readily apparent (Table 1, entry 5). This reaction proceeded to completion in the bromide PSIL under mild conditions (1 atm of CO at 60 °C containing 2 equiv of 1-butanol), giving the product in 93% isolated yield. While other anions were not as effective, the significant difference observed between bromide and chloride counteranions with all other parameters unchanged also draws attention, given that anionic complexes $LPdX^-$ or L_2PdX^- are the assumed reactive catalyst. That chloride-doped Pd-catalysts have proven to be very effective in a range of cross-coupling reactions[10a] raises the possibility that bromide anion plays a more specific role in the present and other[9d] carbonylation reactions. Overall, the anionic effects (Table 1) demonstrate that a viable catalytic cycle is operative with coordinating chloride as well as noncoordinating anions such as dicyanamide and bistriflimide, with an accelerating effect being observed only with bromide. These results are therefore not consistent simply with the involvement of an anionic L_2PdX^- species and led us to suspect that the bromide-anionic effect may be exerted through a completely different pathway.

Table 1. Alkoxycarbonylation of 4-iodotoluene in Various PSILs



1 2

entry	anion (X^-)	**2** isolated yield (%)
1	tosylate	0
2	chloride	60
3	dicyanamide	65
4	bis(triflimide)	75
5	bromide	93
6	PF_6	73
7	decanoate	70
8	BF_4	55
9	phosphate	33
10	sulfate	28

In considering the generally accepted catalytic cycle invoved (Figure 1, path a), one possible hypothesis that might explain the bromide effect would be the intervention of the intermediate acyl-palladium species A with the nucleophilic bromide anion yielding a reactive acid bromide intermediate. Acid halides were postulated by both Heck[2a] and Moser,[2e] but discounted as significant contributors on kinetic grounds.[13] Under typical carbonylation reaction conditions (nucleophile, base) rapid ester or amide formation would be expected from any acid bromide formed, and excess bromide would simply

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(11) Choice of Pd-source [$Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$] and ligand [BINAP, Ph_3P, DPPE, DPPP, DPPB, DPPF] was not critical; however, the 1:2 ratio of $Pd(OAc)_2$:DPPF proved to be a general and optimal choice.

(12) Attempts to measure the saturation solubility of CO in the IL media by mass transfer indicated only low solubility.

(13) The reductive elimination of acyl halide intermediates is a key step in the Rh- or Ir-mediated carbonylation of alcohols, see: Haynes, A.; Maitilis, P. M.; Morris, G. E.; Sunley, G. J.; Adams, H.; Badger, P. W.; Bowers, C. M.; Cook, D. B.; Elliot, P. I. P.; Ghaffar, T.; Green, H.; Griffin, T. R.; Payne, M.; Pearson, J. M.; Taylor, M. J.; Vickers, P. W.; Watt, R. J. *J. Am. Chem. Soc.* **2004**, *126*, 2847−2861.

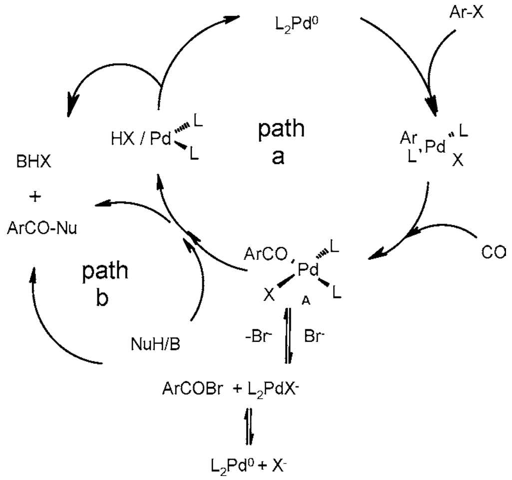


Figure 1. General catalytic cycle (path a) and bromide-mediated exit opening path b via the acylbromide intermediate. Details of the ligand exchange step in path a are removed for clarity.

provide an exit from the catalytic cycle opening an alternative path (path b) to the product and catalyst regeneration as shown.

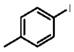
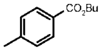
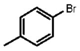
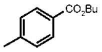
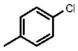
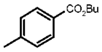
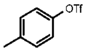
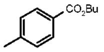
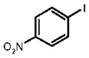
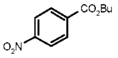
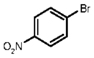
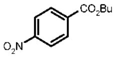
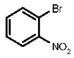
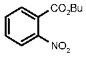
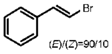
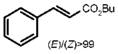
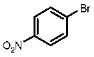
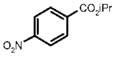
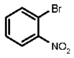
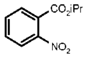
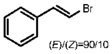
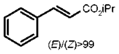
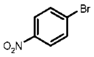
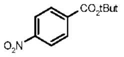
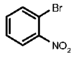
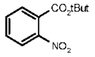
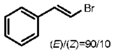
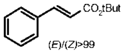
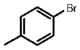
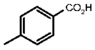
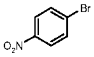
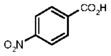
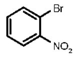
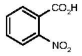
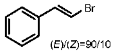
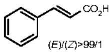
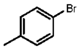
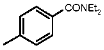
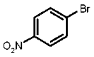
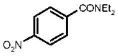
The oxidative addition of Pd complexes to acyl halides is well documented providing acyl-palladium intermediates.[1a] The present hypothesis simply implies that this latter reaction is reversible and given the PSIL conditions (i.e., high concentration of soluble bromide) the acid halide intermediate may previously have been overlooked.

Control experiments were run to test this acid bromide hypothesis. Under standard carbonylation conditions in the bromide PSIL but absence of alcohol or other nucleophile, 4-bromotoluene (4 mol % of Pd(OAc)$_2$, 8 mol % of dppf, 60 °C) remained essentially unchanged; however, GC and GCMS analysis from this reaction *readily showed the formation of 4-methylbenzoyl bromide*. A more detailed GCMS analysis of a similar blank control run with bromobenzene in the bromide-containing PSIL also showed low conversion after 8 h, but confirmed the presence of benzoyl bromide as well as traces of benzene and benzaldehyde as minor hydride elimination products and a trace of the homocoupled product biphenyl. This result confirms the existence of the acid bromide exit from the catalytic cycle: the low yield of acid bromide is attributable to the reversibility of this reaction via the well-known acyl-bromide Pd insertion pathway. Consumption of the acid bromide in the presence of a nucleophile (e.g., alcohol, water, or amine) under typical conditions would make the acid bromide path a more productive pathway, in addition to product emanating from the standard catalytic cycle (path a), thus explaining the observed effects. Attempts to prepare bromobenzene through reaction of benzoyl bromide under the same control conditions (parging with argon) failed, indicating the irreversibility of the CO insertion step under these conditions in accord with previous reports.[2e]

The scope of the carbonylative cross-coupling reaction in the bromide PSIL was extended by screening a series of aryl and vinyl halides reacting with a range of alcohols (primary, secondary, tertiary) providing the ester products in good to excellent yields, Table 2. In general, aryl bromides and iodides are effective partners with considerably lower reactivity being observed with aryl chlorides and triflates under these conditions. Electron-withdrawing groups enhance the reactivity as expected and yields drop as the steric bulk of the alcohol increases, and slightly with the introduction of an ortho-substituent on the ring. 2-Arylbromoethylene

Table 2. Generality of the Carbonylation Reaction in Trihexyl(tetradecyl)phosphonium Bromide PSIL

$$\underset{\mathbf{1}}{\text{R-X}} \xrightarrow[\text{Nu, 60 °C, 6-8 h in bromide PSIL}]{\text{Pd(dppf), TEA, CO (1 atm)}} \underset{\mathbf{2}}{\text{R-CO-Nu}}$$

entry	R-X	Nu	product **2**	isolated yield of **2** (%)
1		BuOH		93%
2		BuOH		81%
3		BuOH		25%
4		BuOH		20%
5		BuOH		95%
6		BuOH		89%
7		BuOH		75%
8		BuOH		82%
9		*i*-PrOH		70%
10		*i*-PrOH		62%
11		*i*-PrOH		63%
12		*t*-BuOH		40%
13		*t*-BuOH		36%
14		*t*-BuOH		38%
15		H$_2$O		75%
16		H$_2$O		82%
17		H$_2$O		77%
18		H$_2$O		73%
19		NHEt$_2$		81%
20		NHEt$_2$		85%

gave good yields (entries 8, 11, 14, and 18) of cinnamic ester derivatives with essentially complete (*E*)-geometry, similar to results recently described by Alper et al.[9c] A range of carboxylic acids and amides could be similarly obtained through the introduction of water or a secondary amine as the nucleophile.

In addition to replacing volatile organic solvents, the recyclability of IL's is perhaps one of their greatest potentials, in particular where this can be linked to recycling an active IL-soluble catalyst.[7,8] While the chemical yields reported in Table 2 involve solvent-mediated product extraction, solvent-free product isolation and recyclability of active catalyst in the carbonylation reaction of 4-iodotoluene (Table 2, entry 1) with *n*-butanol were also investigated. The ester could be directly distilled (90% isolated yield, see experimental details in the Supporting Information) from the PSIL at this point without the use of any volatile organic solvent. Catalyst reuse was also investigated with this system. After the reaction, the ionic liquid was partitioned with methanol/water (3/2) and the ester product extracted into hexane. The initial run gave complete conversion and buty(4-methyl)benzoate was isolated in 93% yield from the hexane phase by using this workup process. The IL phase containing active Pd-catalyst was dried under vacuum and recharged with starting materials with the exception of fresh Pd(OAc)$_2$ and ligand. High conversion of the aryl iodide was again observed and the ester was isolated in 85% yield proving that a viable, recyclable catalyst is present in the PSIL. The full scope of catalyst reprocessing remains to be investigated.

In conclusion, the phosphonium salt ionic liquid trihexyl(tetradecyl)phosphonium bromide has proven to be a particularly effective general reaction media for carbonylation reactions under mild conditions, including atmospheric pressure of CO. An interesting bromide effect was uncovered through screening a range of ionic liquids with differing counteranions. Control experiments showed that carboxylic acid bromides are reaction intermediates providing a mechanistic rationale for this effect and allowing an expanded view of the overall reaction mechanism that implies a slow ligand exchange step with the incoming nucleophile. Recyclability of the IL and active Pd-catalyst was demonstrated. Finally, the use of ILs as valuable reaction media in which to probe anionic effects[8f] is again highlighted as a fundamental rationale for their continued development.[7]

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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