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Halide effects on the Heck reaction in room temperature ionic liquids

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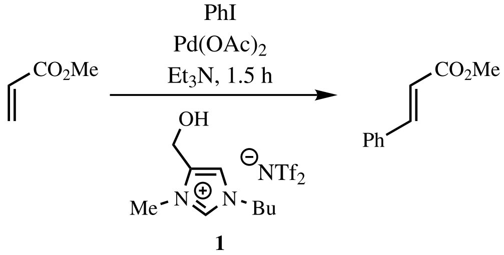
Abstract—An interesting accelerating effect of catalytic amounts of certain halide ions on the Heck reaction in room temperature ionic liquids has been observed.

Transition metal catalyzed reactions in room temperature ionic liquids (RTILs) are gaining increased importance and use in synthetic chemistry.[1] Among the features that render these systems so interesting is the ability to recycle both the transition metal catalyst and the reaction solvent. Further, it has been frequently observed that imidazolium derived RTILs form imidazolium carbene complexes with transition metals such as palladium and nickel, thereby generating more active and/or stable catalytic species.[2] At the same time, these new RTILs are not without their potential problems. As non-volatile salts, they cannot be purified by simple distillation and yet as liquids they cannot readily be recrystallized. These features, though useful in other regards, render the purification of RTILs a significant challenge.[3] One of the primary concerns to date has been the presence of halide ions, since the final RTILs are generally prepared by anion metathesis of the halide salts with other less coordinating anions (BF_4, PF_6, NTf_2). Usually, this concern is due to the deleterious effect that halides, such as chloride, can have on the activity of transition metal catalysts.[4]

In the course of studying the use of a new polar RTIL based on fructose (RTIL **1**), we made an unusual observation.[5] Initially we prepared triflimide salt **1** by ion exchange of the corresponding iodide salt with lithium triflimide. Following exchange, RTIL **1** was isolated by extraction with methylene chloride and then washed with water. The use of this solvent in the Heck reaction of methyl acrylate with iodobenzene afforded results (yield, reaction time, and reaction temperature) in keeping with those reported by Earle and co-workers in a simple RTIL such as 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM PF_6) (Scheme 1).[6] In a subsequent larger scale preparation, RTIL **1** separated out as a second layer during the exchange. The use of this solvent (after drying) resulted in a reaction that was much faster, even at lower temperatures. Interestingly, by dissolving this 'accelerated' RTIL **1** in methylene chloride and washing with water, a material was obtained that displayed identical reaction properties to the initial preparation of RTIL **1**.

Based upon these observations, we suspected that residual lithium iodide from the exchange step could be responsible for the observed acceleration. In order to test this hypothesis, a catalytic amount (1 equiv. relative to the catalyst) of tetrabutylammonium iodide was added to the purified RTIL. As can be seen in Table 1 (entry 1), results similar to that observed with the unwashed RTIL **1** were observed.[7]



first batch	100°C	94%
second batch, unwashed	60°C	97%
second batch, washed	60°C	72%

Scheme 1. Heck coupling in RTIL **1**.

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Table 1. Halide effects on RTIL **1**[a]

Entry	Additive[b]	Temperature (°C)/time (h)	Yield (%)[c]
1	Bu_4N I	60/1	98
2	Bu_4N Br	60/1	95
3	Bu_4N Cl	60/1	52
4	None	60/1	45
5	NaI	60/1	37

[a] Reaction of methyl acrylate (12.5 mmol) with iodobenzene (10 mmol) in RTIL **1** (4 mL) using palladium acetate (2 mol%) as the catalyst.

[b] 2 mol% (same amount as palladium catalyst).

[c] Isolated yield. Average of three runs.

Although surprising, these results are not unprecedented. Indeed, Jeffery has carefully studied the effect of tetrabutylammonium salts in conventional solvents over many years and noted that halide salts such as bromide and chloride afford both enhanced rates as well as improved catalyst stability in a variety of Heck reactions.[8] These observations made us explore other halide additives as well (Table 1, entries 2 and 3). The order that was observed in RTIL **1** was iodide>bromide>chloride=no addition. Interestingly, this order is different from that observed by Jeffery in polar aprotic solvents such as DMF and acetonitrile, in which tetrabutylammonium chloride was a more efficient additive than tetrabutylammonium bromide. It is worth noting, however, that Jeffery observed a difference in the relative effect of halide additives depending upon the type of base used, so the presence of a solvent effect is not entirely unexpected.[9]

An observation that was made during these halide studies is that the Heck reactions with added iodide or bromide gave a different appearance compared to those with no added halide or with chloride. Reactions were performed by first combining the palladium catalyst and additive in RTIL **1** and stirring for 10 min. During this time, the bromide and iodide reactions afforded a homogeneous reddish colored solution. The chloride and halide free reactions did not become red or completely homogeneous. Further, after addition of the iodobenzene and methyl acrylate, the halide free and chloride reactions fairly quickly (within 15 min) began to show the deposition of palladium black on the sides of the reaction vessel, whereas this was not observed in the bromide or iodide reactions.

In an effort to study less expensive halide sources, a reaction using sodium iodide as the additive was performed (Table 1, entry 5). Unfortunately, reaction rates comparable to those in the uncatalyzed reaction were observed. This result may be partially due to the poor solubility of sodium iodide in RTIL **1**. Undissolved sodium iodide was observed during the catalyst formation stage, although the reaction medium did become largely homogeneous and reddish in color, as was the case in the other bromide and iodide accelerated reactions (entries 1 and 2).

As can be seen in Table 2, the amount of halide additive also plays a role in the rate acceleration of the Heck reaction in RTIL **1**. Thus, with small amounts (2–4 mol%, relative to iodobenzene) of tetrabutylammonium iodide, the reaction is accelerated relative to the background level, but is not complete within 30 min at 60°C. By employing larger amounts of the iodide salt, however, the reaction can be run to completion within 30 min.

In an effort to see if this effect was unique to protic RTIL **1**, the same series of experiments were performed in BMIM BF_4 (Table 3). Again, a significant rate acceleration was observed upon the addition of a catalytic amount of the ammonium halide salt. In contrast to RTIL **1**, however, a nearly equivalent degree of acceleration was observed for all three halide salts. Upon going to a less reactive substrate, though, a difference was noted. Thus, the Heck reaction of bromobenzene was conducted under identical conditions (entries 5–8). While none of these reactions went to completion within 16 h, it is readily apparent that the bromide salt is providing a much greater degree of acceleration compared to either the chloride or iodide salt.

The results of the effect of additional halide in RTIL **1** are not the first reports that have noticed a halide effect

Table 2. Effect of amount of halide additive in RTIL **1**[a]

Entry	Bu_4N I (mol%)	Temperature (°C)/time (h)	Yield (%)[b]
1	2	60/0.5	22
2	4	60/0.5	26
3	10	60/0.5	95
4	20	60/0.5	98

[a] Reaction of methyl acrylate (12.5 mmol) with iodobenzene (10 mmol) in RTIL **1** (4 mL) using palladium acetate (2 mol%) as the catalyst.

[b] Isolated yield of product (remainder unreacted starting material).

Table 3. Halide effects on BMIM BF_4[a]

Entry	Additive	Temperature (°C)/time (h)	Yield (%)[b]
1	None	60/1.5	53
2	Bu_4N Cl	60/1.5	90
3	Bu_4N Br	60/1.5	96
4	Bu_4N I	60/1.5	89
5	None[c]	100/16	<1
6	Bu_4N Cl[c]	100/16	8
7	Bu_4N Br[c]	100/16	28
8	Bu_4N I[c]	100/16	3

[a] Reaction of methyl acrylate (2 mmol) with iodobenzene (1 mmol) in BMIM BF_4 (1 mL) using palladium acetate (2 mol%) as the catalyst.

[b] Isolated yield (remainder unreacted starting material). Average of three runs.

[c] Reaction of methyl acrylate (2 mmol) with bromobenzene (1 mmol) in BMIM BF_4 (1 mL) using palladium acetate (2 mol%) as the catalyst.

in transition metal-catalyzed reactions in RTILs. Welton and co-workers first reported the effect of added halide on the in situ formation of imidazolylidene palladium complexes in BMIM BF_4.[10] Starting from tetrakis(triphenylphosphine)palladium, the addition of sodium chloride or sodium bromide under typical Suzuki coupling conditions resulted in the formation of a stable imidazolylidene palladium complex that was effective in catalyzing the Suzuki coupling and could be recycled several times. It is unclear at this point whether the results in RTIL **1** are forming the same type of complex, since Welton reports these complexes only for phosphine-containing palladium species and the present Heck reaction conditions are phosphine-free. Efforts are underway to determine what palladium catalyst species is being formed under the present Heck reaction conditions.

In conclusion, we have observed an interesting acceleration of the Heck coupling in RTILs by halide ions. These results demonstrate that halides can be both advantageous as well as deleterious in transition metal catalyzed reactions in RTILs. Further, they highlight the importance in carefully determining the purity of RTILs before reporting 'unusual' results. Efforts are underway to expand the halide acceleration to other coupling reactions and to determine the type of palladium catalyst that is being generated in situ.

Acknowledgements

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