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Efficient heterogeneous vinylation of aryl halides using potassium vinyltrifluoroborate

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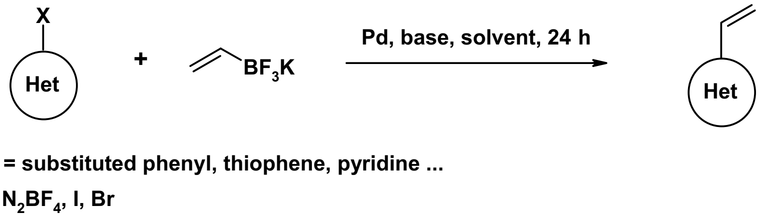
ABSTRACT

An efficient heterogeneously palladium catalysed procedure for the vinylation of aryl iodides and bromides is reported. Using common reaction conditions (Pd/C 2 mol %, $AcONa{\cdot}3H_2O$, NMP or NMP/H_2O), good to complete conversions (40–100%) with high selectivities (79–100%) towards the expected vinylaromatic were achieved.

Functional vinylaromatic compounds (i.e., substituted styrene derivatives) are valuable materials not only for the preparation of functional polymers and copolymers[1] but also as raw materials for the synthesis of biologically relevant molecules for pharmaceutical, agrochemical and medicinal speciality chemicals.[2,3]

Several methods have been reported for their synthesis, among them are Wittig or Horner–Wittig stoichiometric synthesis, Hoffmann elimination or dehydration. Recently, several catalysed procedures, mainly based on palladium catalysts, were reported which include, without being exhaustive, reaction between aryl magnesium compounds and vinyl halides,[4,5] some Stille coupling variants,[6,7] or Heck coupling reactions of ethylene with aryl halides, a method that requires usually high pressure of ethylene and relatively high reaction temperatures to lead to low selectivity due to the formation of stilbene derivatives.[8–10]

Recently, an elegant and efficient route for the synthesis of styrene derivatives from vinyl borane was described by several authors (Scheme 1).[11–13] Initially, this coupling reaction was reported by Genêt and co-workers starting from aryldiazonium salts and potassium vinyltrifluoroborate. Using palladium acetate as catalyst (5 mol %), the authors reported high conversions (75–100%) towards the expected compounds for a large range of aryl derivatives.[14–17] While interesting, this procedure remains limited due to the unavoidable synthesis of the aryl diazonium salts. This reaction known further developments through the work reported by Scalone and co-workers from Hoffmann-La Roche for the syntheses of vinyl pyrimidine starting from chloro, bromo or iodo derivatives.[18] Molander and co-workers extended Scalone conditions to various aryl bromides: after optimisation of the reaction conditions ($PdCl_2$ (2%)/PPh_3 (6%), Cs_2CO_3 (3 equiv), THF/H_2O,



Scheme 1. Pd-catalysed synthesis of styrene derivatives from potassium vinyltrifluoroborate.

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85 °C), they reported moderate to good yields in expected products.[19,20]

To our knowledge, the vinylation of aryl substrates, excepting a procedure using vinyltin reagents,[21] was carried out exclusively in the presence of homogeneous palladium catalysts that are often tedious to separate from the reaction mixture leading to relatively high Pd-contamination of the products that is not tolerated for biological applications. However, these problems can be solved by using easily separable heterogeneous palladium catalytic systems.

We describe in this contribution the first successful application of commercially available heterogeneous palladium catalyst for the selective vinylation of aryl halides.

Initially, the cross-coupling reaction between potassium vinyltrifluoroborate and 2-iodotolyl (Scheme 2) was carried out using 2 mol % Pd/C catalyst (Aldrich, 5 wt % Pd) under the reaction conditions reported by Molander and co-workers (Table 1, entry 1).[20] As expected good conversion was achieved (77%) but the reaction led to rather low selectivity (62%).

Table 1
Cross-coupling optimization of 2-iodotolyl with potassium vinyltrifluoroborate[a]

Entry	Base	T (°C)	Solvent	Conversions (Sel.) (%)
1	Cs_2CO_3	85	THF/H_2O 9/1	77 (62)
2	AcONa·3H_2O	100	NMP	40
3			NMP/H_2O 1/1	90 (88)
4	Na_2CO_3	100	NMP	**55**
5			**NMP/H_2O 1/1**	**88 (84)**

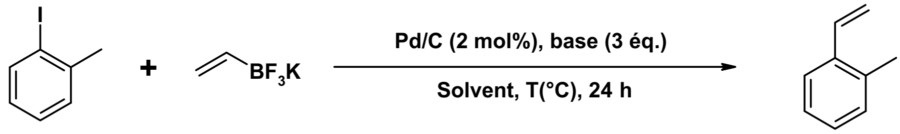
[a] Reaction conditions: 1 mmol aryl halide (i.e., 1 mol L^{-1}), 1.1 mmol potassium vinyltrifluoroborate, 2 mol % Pd/C, 3 equiv AcONa·3H_2O, 1 mL NMP.

[b] Conversions based on unreacted aryl halide. Selectivities are given in parentheses; when not reported full selectivity was achieved. Biphenyl was used as internal standard.

Encouraged by this result, but in order to propose benign procedures, we removed the expensive Cs_2CO_3, a compound generally considered as very hazardous, by bases commonly used in cross-coupling reaction like AcONa·3H_2O or Na_2CO_3. Additionally, as higher reaction temperatures are required to improve the reaction rates when lower reactive aryl substrates (i.e., mainly bromides) are engaged, we developed the use of NMP a solvent commonly used in the chemical industry. Associated to the use of heterogeneous easily removable and reusable Pd/C catalysts, these conditions can be regarded as an eco-friendly procedure.

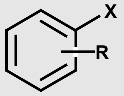
Under such conditions, Na_2CO_3 or AcONa·3H_2O, afforded lower conversions (Table 1, entries 2 and 4) than that previously obtained under the conditions issued from Molander's work. However, these conditions yielded the exclusive formation of the expected vinyl compound. Replacing NMP by a mixture NMP/H_2O (1/1) led almost to complete conversions whatever the base used (Table1, entries 3 and 5). These results are in good agreement with previous reports by Köhler and co-workers[22] and Sun and co-workers[23] on the application of Pd/C catalysts for the coupling reaction of phenyl boronic acids with aryl halides. However, under these conditions minor by-products were detected by GC analysis.

Having these conditions in hand, we explored the scopes and limitations of the reaction focusing on the tolerance towards various functional groups.[24] As shown in Table 2, high conversions (i.e., 58–97%) were achieved for a large range of aryl iodides (AcONa 3 equiv, NMP, 100 °C, 24 h, Table 2, entries 2–6). Interestingly, the electronic nature of the *ortho* substituents has low impact on the conversion (75% and 72% for electron-withdrawing and electron-donating group, respectively, Table 2, entries 2 and 4).



Scheme 2. Heterogeneous Pd-catalysed vinylation of *o*-iodotoluene.

Table 2
Vinylation of aryl halides with potassium vinyltrifluoroborate[a]

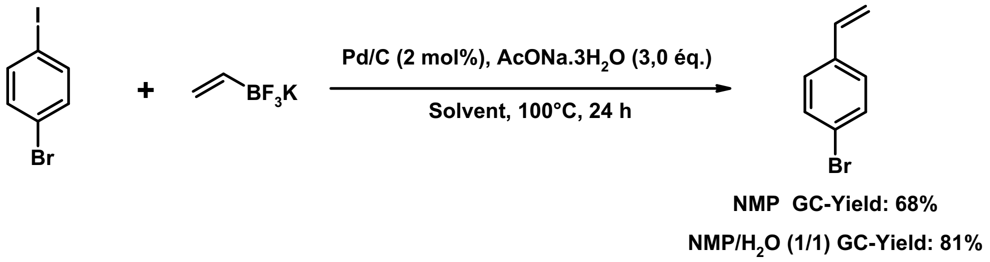
Entry	 X	R	T (°C)	Conversions[b] (%)		GC-yield[c] (%)	
	X	R		NMP	NMP/H_2O (1/1)	NMP	NMP/H_2O (1/1)
1	I	*o*-Me	100	**40**	90	**40**	79
2		*o*-NO_2	100	**75**	**100**	**75**	**100 [73]**
3		*o*-OH	100	**85**	–	**85 [67]**	–
4		*o*-OBn	100	**72**	–	**72 [60]**	–
5		*p*-NO_2	80	**97**	–	**90**	–
6		*p*-OMe	100	**58**	**95**	**58**	**75 [69]**
7	**Br**	*o*-NO_2	100	**53**	**18**	**53**	**18**
8		*m*-NO_2	100	**88**	–	**88**	–
9		*p*-NO_2	100	**100**	–	**100 [78]**	–
10		*p*-CN	100	**46**	**9**	**46**	**9**
11		*p*-$COCH_3$	100	**44**	–	**44**	–
12		*p*-OBn	100	**4**	–	**4**	–
13		*p*-OBn	140	**35**	**29**	**28**	**26**
14		*p*-OBn	140	–	**4**[d]	–	**39**[d]

[a] Reaction conditions: 1 mmol aryl halide (i.e., 1 mol L^{-1}), 1.1 mmol potassium vinyltrifluoroborate, 2 mol % Pd/C, 3 equiv AcONa·3H_2O, 1 mL NMP.

[b] Conversion based on unreacted aryl halides.

[c] GC-yields and when available [isolated yields] are given (Δ_{rel} = ±5%). Biphenyl was used as internal standard.

[d] Substrate concentration was 0.2 mol L^{-1}.



Scheme 3. Selective heterogeneously Pd-catalysed vinylation of 4-bromoiodobenzene.

Unexpectedly when referring to previous reports,[19,20] we observed that the free *o*-iodophenol (Table 2, entry 3) showed higher reactivity than the corresponding alkylated compound (Table 2, entry 4). Therefore, this result opens the route to green processes (i.e., atom economy procedure) for the synthesis of vinylphenol derivatives as it avoids the protective steps.

As predictable, aryl iodides bearing electron withdrawing group at *para* position show enhanced reactivity as complete conversion was achieved even at 80 °C (Table 2, entry 5).

Similarly, several aryl bromides were studied. Under such reaction conditions (Pd/C 2 mol %, AcONa·3H$_2$O, NMP) moderate to good conversions were achieved (Table 2, entries 7–12). Noticeably, the 3- and 4-bromonitrobenzene derivatives gave high conversions within 24 h (Table 2, entries 8 and 9), whereas lower reactivity was observed for the *ortho* derivative (Table 2, entry 7) that was attributed to steric hindrance. Aryl bromides bearing weakly electron withdrawing groups such as a nitrile (Table 2, entry 10) or a ketone (Table 2, entry 11) at *para* position gave, unexpectedly, low conversions (i.e., ~45%). Similarly, electron donating group at *para* position gave poor conversions even at 140 °C (Table 2, entries 12–14). In those cases dehalogenation was observed in relatively high rate (6–19%).

The role played by the solvent is not clear. While for the aryl bromides the use of NMP/H$_2$O (1/1) instead of NMP as solvent has no or negative influence on the reaction rate (Table 2, entries 7, 10, 13), it improves noticeably the conversion of 4-iodoanisole (58% and 95% conversion, respectively, Table 2, entry 6).

Accounting the lower reactivity of aryl bromides versus iodides, we investigated the iodo/bromo selectivity starting from 4-bromoiodobenzene. As expected a full selectivity towards the corresponding 4-bromovinylbenzene was achieved at 100 °C (Scheme 3). The reaction gave 68% GC-yield when carried out in NMP and 81% GC-yield in NMP/H$_2$O (1/1) leading in that case to 58% isolated yield due to its high volatility. Such syntheses of halovinylderivatives were to date only possible using the procedure reported by Genêt and co-workers[16,17] as aryliodides and arylbromides react equally under the procedure reported by Molander and co-workers.[19,20]

When using heterogeneous palladium catalysts, the questions regarding the reuse and the leaching of active Pd-species in solution should be addressed. The recycling was examined for the coupling reaction of 4-bromonitrobenzene under optimised reaction conditions (Pd/C 2 mol %, AcONa·3H$_2$O, NMP) over 16 h. The following procedure was performed: after the first run of the catalyst, the reaction mixture was allowed to cool to room temperature and the catalyst was separated by centrifugation, washed with NMP/H$_2$O (1:1), twice with NMP and allowed to dry at room temperature for 24 h. The recycled palladium catalyst was then used without any regeneration under the same reaction conditions as the fresh catalyst. The procedure was repeated up to 5 runs without any loss of activity.

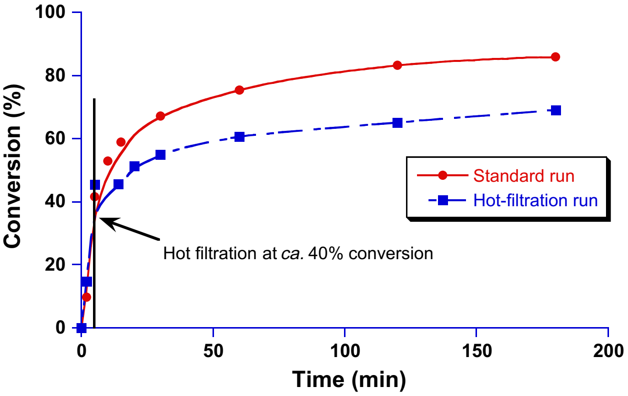


Figure 1. Leaching of active Pd-species in solution using the Pd:C catalyst. Residual catalytic activity after hot filtration -■- at ca. 40% conversion versus standard catalytic run -●-.

Leaching was examined for the coupling reaction of 4-bromonitrobenzene under optimised reaction conditions using the hot-filtration method: a catalytic run was started as for a standard reaction, and at ca. 40% conversion, the reaction mixture was filtered through a warmed Celite pad to afford a clear filtrate. The clear filtrate was then treated as the usual catalytic test, and its composition was followed by GC and compared to that of a standard catalytic run. Figure 1 shows clearly that the catalytic activity observed is mainly due to dissolved active Pd-species since after removal of the heterogeneous catalyst by hot filtration the conversion raised from 40% to 70% over 3 h.[25]

In conclusion, we reported for the first time an efficient heterogeneously palladium catalysed vinylation of aryl iodides and bromides. Using common reaction conditions (Pd/C 2 mol %, AcONa·3H$_2$O, NMP or NMP/H$_2$O), the vinylation gave good to full conversions with high selectivities towards the expected vinylaromatic.

From an environmental point of view, the most interesting outcome came from the full iodo/bromo selectivity leading to direct and selective formation of bromovinyl compounds and the applicability to OH-free phenols avoiding protection/deprotection steps for the synthesis of vinylphenol derivatives.

Some results suggest that the reaction rate depends not only on electronic factors but also on steric hindrance. Chelating effects of palladium centre by *ortho* substitutents after oxidative addition accounting for some of the reactivities observed could not be discarded (e.g., Table 2, entries 2–4 and 7).

Current investigations are in progress to optimise further the heterogeneous catalytic systems for lower reactive aryl bromides.

Acknowledgements

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24. *Typical procedure:* 1 mmol aryl halide, 1.1 mmol potassium vinyltrifluoroborate, 2 mol % Pd/C (43 mg), 3 mmol $AcONa\cdot 3H_2O$ (408 mg) were introduced in a sealed tube together with 1 mL NMP or NMP/H_2O (1:1). The reactor was placed under vigorous stirring in a preheated oil bath at 100 °C for 24 h. After cooling at room temperature the reaction mixture was poured in 20 mL water and extracted with 3 × 20 mL CH_2Cl_2. The combined organic layer was dried over sodium sulfate and concentrated under vacuum. The crude material was purified by flash chromatography over silica eluting with petroleum ether/ethyl acetate to give the expected compound.
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