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“On water” sp^3–sp^2 cross-couplings between benzylic and alkenyl halides†

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Abstract

Organic-solvent-free cross-couplings between benzylic and alkenyl halides have been developed. Various alkenyl halides can be effciently benzylated by combining the precursor halides in the presence of Zn dust and a Pd catalyst at room temperature, in water as the only medium.

Recently, we described a new process for effecting sp^2–sp^3 cross-coupling reactions that avoids prior preparation of organozinc reagents. Zinc-mediated, palladium-catalyzed cross-couplings between two organic halides were accomplished in water using micellar catalysis,[1] and on water[2] at room temperature.

Allylated aromatics (**I**) are important subunits in organic synthesis.[3] Classically, compounds of general formula **I** (Scheme 1) have been accessed *via* Friedel–Crafts allylation[4] of aromatic precursors. More recent strategies involve transition metal-catalyzed cross-couplings of sp^2-organometallics with activated halides, or allylic organometallics with sp^2-halides/triflates (Scheme 1).[5] The corresponding organometallic reagents, therefore, require preparation in a separate step.[6] Based on our previous work[2] it was anticipated that direct ‘on water’ cross-couplings of benzylic halides with alkenyl halides would provide a 1-step synthesis of functionalized allylated aromatics (Scheme 1). The important issue of olefin geometry would also need to be addressed.

Initially, 1-(chloromethyl)-4-methylbenzene (2 equiv) was coupled with (*E*)-1-iodooctene (**1**) to afford unsymmetrically substituted allylated toluene **2** (Table 1). Under optimized conditions, **1** coupled within six hours, on water at room temperature, using 2 mol % $PdCl_2(Amphos)_2$[7] along with Zn dust (3 equiv) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA; 1 equiv).[1,2] Modifications (entries 2–5), including use of a lesser excess of benzylic chloride (entry 2), less TMEDA (entry 3) or Pd catalyst (entry 4), Zn powder in place of Zn dust (entry 5), or alkenyl bromide (entry 6), suggested some flexibility in reagents and/or the standard stoichiometry. Use of a surfactant for purposes of generating nanomicelles[1] in this reaction type neither enhanced the rate of reaction, nor improved the overall yield of products.

As illustrated in Table 2, the substrates that participate in these cross-couplings leading to allylated aromatics are of broad scope. In all representative cases examined, >98% retention of olefin stereochemistry was observed, regardless of starting olefin geometry. Three equivalents of electron-poor benzylic chlorides were needed to achieve good isolated yields due to competitive Zn-insertion and subsequent protio-quenching by water[8] of the *in situ*-

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[†] Electronic supplementary information (ESI) available: Experimental section and spectroscopic data.

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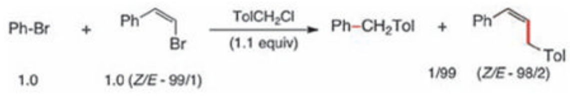
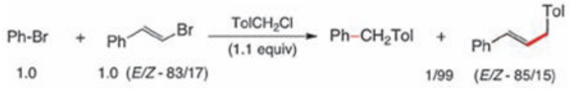
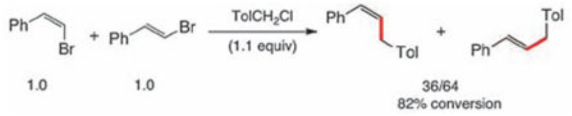
formed benzylic zinc halides. Unlike cross-couplings with aryl halides,[2] switching to zinc powder instead of zinc dust did not impact yields. Attempts to control the rate of Zn-insertion by employing only 0.25 equivalents of TMEDA with two equivalents of an electron-poor benzylic chloride led to full consumption of starting alkenyl halide; however, 10–30% of diene formation occurred, leading to poor isolated yields of final products. This coupling does tolerate *β*,*β*-disubstituted alkenyl iodides (entry 11), as well as secondary benzylic chlorides (entries 13 and 14). Nevertheless, sterically crowded 2-(chloromethyl)-1,3,5-tri-methylbenzene did not afford the desired product, and under a variety of conditions, no product was detected using benz-hydryl chloride. α-Benzylated styrene **15** could be efficiently prepared starting from commercially available α-bromostyrene (entry 14). A highly lipophilic, solanesol-derived alkenyl halide was successfully coupled on water with a functionalized benzyl chloride at room temperature (entry 15).



(1)



(2)



(3)

To probe for potential differences in reactivity in these cross-couplings between sp^2-aryl and sp^2-alkenyl halides, several competition experiments were conducted (Scheme 2). The representative case of unfunctionalized bromobenzene and β-bromostyrene was chosen. Remarkably, both *Z*-and *E*-alkenyl bromides reacted far more rapidly, and with complete stereocontrol, than did bromobenzene with 1-(chloromethyl)-4-methylbenzene (equations 1, 2). Additionally, the *E*-isomer reacted faster than did *Z*-β-bromostyrene (equation 3), as expected.[9] These results suggested that selective, sequential cross-couplings on dibromide **17** should be possible. In the event, use of just 1.1 equivalents of 1-(chloromethyl)-4-methylbenzene led to cross-coupled product **18** with very good chemoselectivity and in good isolated yield. Hence, the corresponding 1-pot, stepwise dibenzylation of **17** could also be achieved to form the unsymmetrically derivatized product **19**, without introduction of additional Pd(II) catalyst in the second step.

In summary, new technology for preparing functionalized allylated benzenes has been developed. These reactions proceed in a green chemistry sense: in the absence of organic solvents, and without heating or cooling; *i.e.*, in water only, and at room temperature, to afford the targeted products without erosion of olefin geometries and in high chemical yields.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

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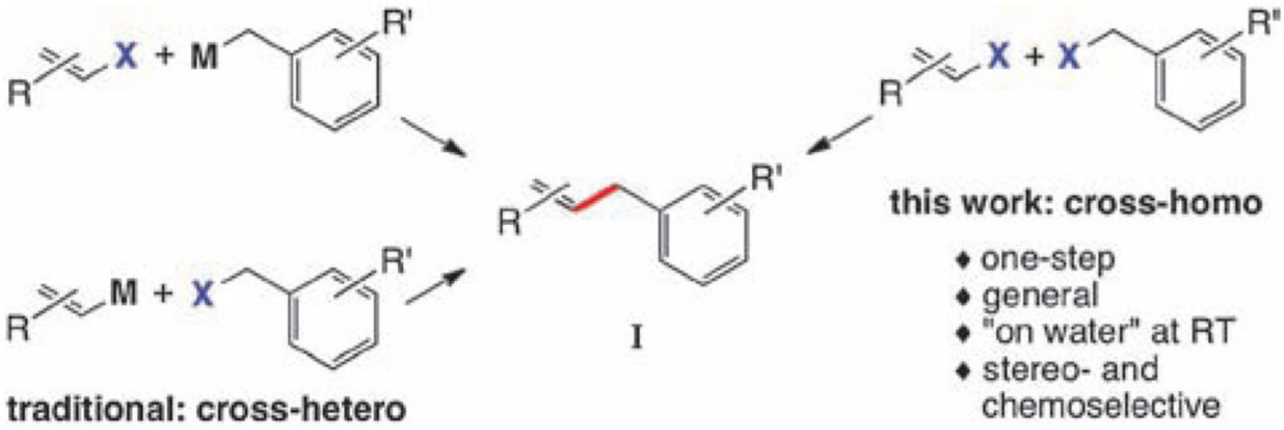
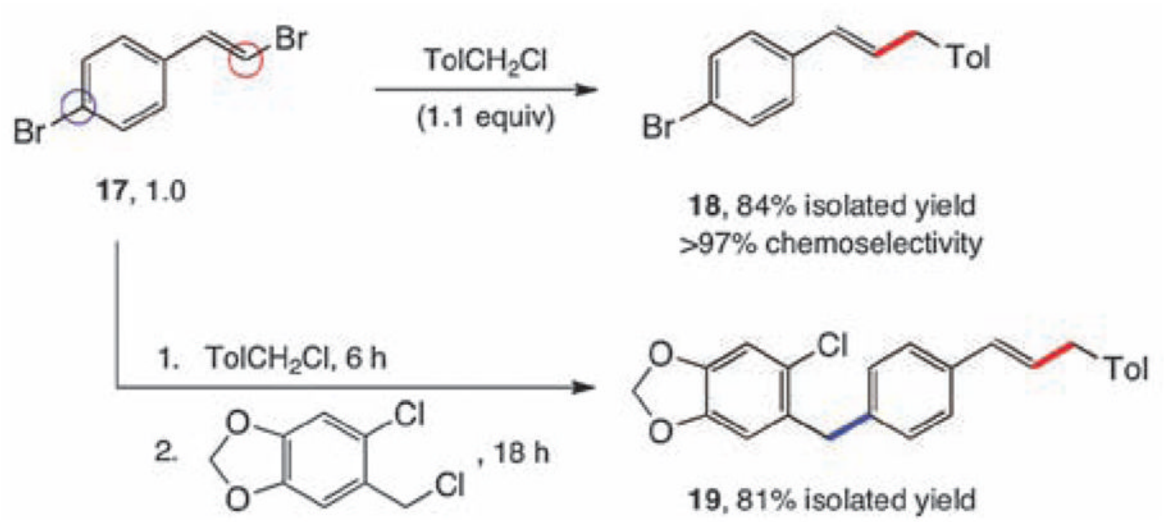


Scheme 1.
Synthetic approaches to benzylic-alkenyl cross-couplings.

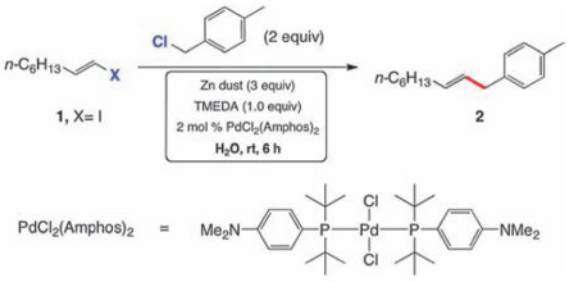


Scheme 2.

Competition experiments (rt, 6 h), and a 1-pot, double benzylation (1st step 6 h, 2nd step 18 h at rt).

Table 1

Optimization of the reaction between 1-(chloromethyl)-4-methylbenzene (**1**) and (*E*)-1-iodooct-1-ene[a]



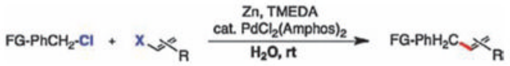
Entry	**Modification of original conditions**	**Conversion, %**[b]
1	None	100
2	1.5 equiv of benzylic chloride	98
3	TMEDA (0.5)	77
4	1 mol% $PdCl_2(Amphos)_2$	88
5	Zn powder	96
6	X = Br	90

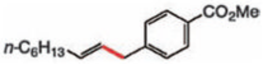
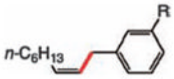
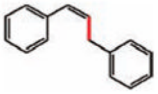
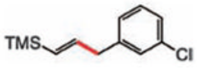
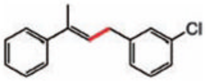
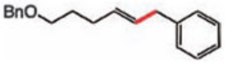
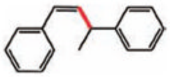
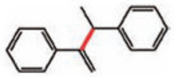
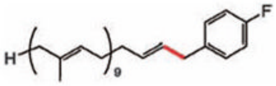
[a] Conditions: benzyl chloride (2 mmol), (*E*)-1-iodooct-1-ene (1 mmol), zinc dust (3 mmol), $PdCl_2(Amphos)_2$ (0.02 mmol), degassed water (3 mL).

[b] By GC.

Table 2

Representative benzylic-alkenyl cross-couplings[a]



Entry	Product (Yield)[b]	Entry	Product (Yield)[b]
1	 **2** (82%)	2	 **3** (91%)
			
3	**4** R = CF$_3$ (84%)	5	**6** R = H (95%)
4	**5** R = Cl (89%)	6	**7** R = OMe (81%)
7	 **8** (90%)	8	 **9** (85%) *E/Z* 83/17[c]
9	 **10** (77%) *E/Z* 92/8[d]	10	 **11** (95%)
11	 **12** (92%)	12	 **13** (96%)
13	 **14** (83%)	14	 **15** (79%)[e]
15	 **16** (82%)		

[a] Conditions: benzylic chloride (2–3 mmol), alkenyl halide (X = I, for entries 1–6, 10, 12, 15, and X = Br for entries 7–9, 11, 13–14; 1 mmol), zinc dust (3–4 mmol), PdCl$_2$(Amphos)$_2$ (0.02 mmol), degassed water (3 mL), rt, 6 h.

[b] Isolated yield.

[c] From commercially available β-bromo-styrene, *E/Z* = 87/13.

[d] From commercially available (2-bromovinyl)trimethylsilane, *E/Z* = 93/7.

[e] From commercially available 90% technical grade α-bromostyrene.