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Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature *Without* Prior Formation of Organozinc Reagents

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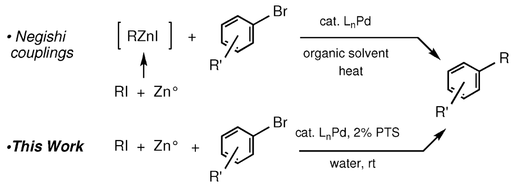
Palladium-catalyzed cross-couplings of organozinc reagents with aryl halides and pseudohalides (Ar−X) are considered fundamental transition metal mediated C−C bond forming reactions. Such couplings continue to offer a highly valued entry to alkylated aromatic rings (Scheme 1).[1] Without exception, preformation of an organozinc halide (e.g., RZnI) is required, frequently relying on insertion of zinc(0) into an alkyl iodide precursor (R−I).[2] Typically, a coupling partner Ar−X and a group 10 metal catalyst (e.g., ligated palladium, L_nPd) are subsequently introduced. Although alkylzinc halides as nucleophiles are commonly regarded as the most reactive of partners and yet especially functional group tolerant, the conditions of their use in Pd catalysis are rigorously aprotic and not forgiving.[3] Hence, prospects for effecting such reactions to any synthetically meaningful degree in the presence of moisture would typically be viewed as dim.[4−7]

Scheme 1. Zn-Mediated, Pd-Catalyzed Cross-Couplings with Aryl Bromides



Hints that such reactions might be possible come from a limited number of tangential literature reports describing the use of Zn metal in protic media. Early studies by Wolinsky[5a] and Luche[5b] demonstrated that allylic residues could be trapped by aldehydes in a Barbier-type sense.[5] An amalgam of Zn/Cu has been shown to lead to conjugate additions with enones and enals following insertion of Zn into a carbon−halogen bond.[6] Most recently, Fleming, likewise, has used a Zn/Cu couple (mainly on silica) to add alkyl residues to unsaturated nitriles in water.[6e] The closest literature analogy is the very recent method reported by von Wangelin and co-workers,[8] which uses Fe to catalyze cross-couplings with in situ generated Grignard reagents. Given the nature of the organometallic, however, there is very limited tolerance for functionality in either reaction partner, and these couplings must be conducted with cooling under strictly anhydrous conditions. We now describe new technology that allows Pd-catalyzed Zn-mediated cross-couplings to be conducted without organic solvents, i.e. in water and at room temperature. This discovery also obviates prior stoichiometric formation of RZnI; i.e., *there is no need to preform any organometallic*. Our approach utilizes homogeneous micellar catalysis within catalytic nanoreactors formed spontaneously upon dissolution in water of the commercially available amphiphile PTS.[9] Other nonionic surfactants (e.g., TPGS, Brij 30, and Solutol) can also be used with roughly comparable efficiencies.

The scope of this experimentally simple process has been studied with regard to the nature of both the alkyl halide (1°, 2°, 3°) and the aryl bromide. Initially, the combination of excess *n*-heptyl iodide and *m*-bromoanisole (as limiting reagent) in the presence of fresh Zn powder (or dust) and a Pd catalyst was examined as a model system, with 2 wt % PTS/H_2O as medium (entry 1, Table 1). Remarkably, the cross-coupling of an unactivated aryl bromide could be effected at rt in the presence of excess, albeit variable amounts of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; Table S1); no homocoupling of the bromide is observed. The crucial role of the diamine is likely to involve both activation of the Zn surface toward insertion into an alkyl halide and stabilization of the organozinc species. In its absence, there is no insertion and, hence, no subsequent coupling. Of several catalysts surveyed, only catalyst **1** was useful (Table S2). Even the parent ligand in this series (**2**) gave significantly inferior results, although the explanation to account for these unexpected variations remains unclear. Other species, including more active catalysts containing Pd(0) were surprisingly ineffective.

Table 1 illustrates a number of representative aryl bromides that have been alkylated. Both simple alkyl (entries 1−9) and several functionalized primary alkyl iodides (entries 10−15) led to good isolated yields, indicative of considerable generality. Noteworthy among these are aryl bromides bearing sensitive groups (e.g., ketone or aldehyde) that remain intact under these conditions (entries 5, 6, respectively). Also included are educts bearing ester residues (entries 11, 13), an amide (entry 14), and a highly adorned aromatic ring (entry 16). Prospects for alkyl bromides under related conditions look promising (entries 1, 11).

Secondary iodides, typified by iodocyclohexane, were found to be far more reactive toward insertion of Zn than that seen with primary systems. Attempts to apply our standard conditions (TMEDA, 2% PTS/H_2O, cat. L_nPd, rt) to the coupling of this halide with *m*-bromoanisole afforded low conversion (<20%) of the starting aryl bromide, albeit with complete consumption of the excess iodide present (path A, Scheme 2). The rate at which (cyclohexyl)ZnI•diamine is presumably formed on the zinc surface could be controlled by simply increasing the steric bulk of the alkyl groups on nitrogen in the ethylenediamine ligand. While both the unsymmetrical diamine homologue **22** and symmetrical version **23** gave results similar to those seen with TMEDA, the tetraethyl derivative (TEEDA, **24**) increased the overall conversion dramatically to 78%. Curiously, in the case of a *p*-bromobenzoate (path B), diamine **22** was found to give the highest levels of conversion (72%). Applications of these diamine-modified conditions to other secondary iodide-derived products **25** and **26** further demonstrate the potential for these cross-couplings in water. Notably, by contrast to recent studies using acyclic secondary zinc halides,[10] there was no observed rearrangement in the coupling of *s*-butyl iodide to give alkylated aromatic **26**.

A tertiary halide (e.g., *tert*-butyl iodide), on the other hand, reacted far too rapidly with zinc regardless of the diamine present. The trend, therefore, suggests involvement of an initial single electron transfer (SET) ultimately leading to an organozinc halide after a second, rapid SET event, as homocoupling was not a major competing process.

Additional control experiments confirmed the enabling role of PTS (Table S3), as cross-couplings in its absence (i.e., "on water")[11] led to highly variable levels of conversion based on the limiting aryl bromide and longer reaction times (entries 1 and 7 vs entries 2 and 8, Table S3). Use of dry THF as the only solvent (0.25 M) for this same reaction (i.e., no PTS/H_2O; entries 3 and 4, Table S3), run at ambient

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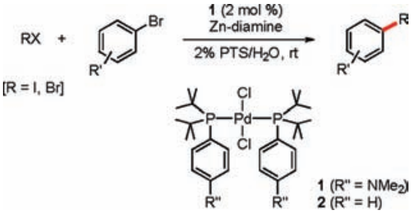
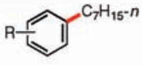
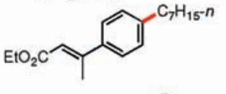
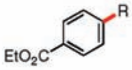
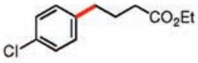
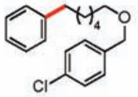
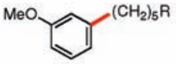
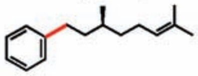
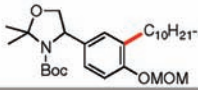
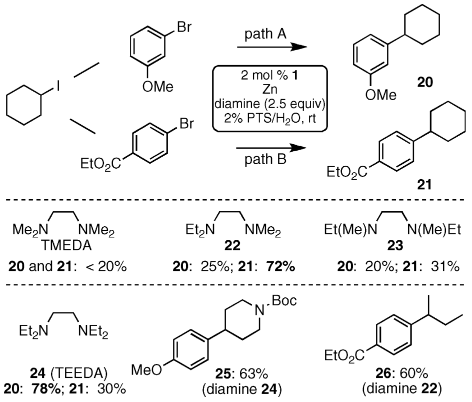
Table 1. Representative Zinc-Mediated Couplings Between Primary Alkyl Iodides and Aryl Bromides in Water at RT



entry	product		yield (%)[a,b]
			
1	R = *m*-OMe	**3**	90(92[c,d])
2	R = *o*-OMe	**4**	65
3	R = 3,4,5-trimethoxy	**5**	80
4	R = *p*-Cl	**6**	96
5	R = *p*-C(O)CH_3	**7**	70[d]
6	R = *p*-CHO	**8**	80[d]
7		**9**	82[d]
			
8	R = CH_2CH_2Ph	**10**	75
9	R = *i*-Bu	**11**	72[e]
10		**12**	83[f]
11		**13**	69[g](84[c,d])
12		**14**	65
			
13	R = $CH_2OC(O)$-*t*-Bu	**15**	88
14	R = C(O)NBn_2	**16**	79
15		**17**	93
16		**18**	74

[a] All reactions were run using 5 equiv of TMEDA for 24 h (except for entries 1 and 4, 12 h). [b] Isolated, chromatrographically purified. [c] Using the corresponding alkyl bromide. [d] Run over 48 h. [e] Using 1 equiv of *N*,*N*-diethyl-*N*′,*N*′-dimethylethylene-diamine. [f] Product was treated with TBAF in THF and isolated as alcohol. [g] Using 1 equiv of TMEDA.

Scheme 2. Cross-Couplings with Secondary Alkyl Iodides



temperature with or without preformed n-C_7H_{15}ZnI, did not lead to any significant amount of the desired product (<20%), further attesting to the virtues of high concentrations of reactants typically associated with micellar catalysis.[12] Given the lipophilicity of n-C_7H_{15}ZnI, quenching of this preformed organozinc reagent in either pure water or PTS/water does not occur as rapidly as might be anticipated. Thus, addition of n-C_7H_{15}ZnI (prepared in THF) to an aqueous solution containing PTS, a coupling partner, and catalyst led to a 30% level of conversion (entry 5, Table S3). Prior complexation of the preformed n-C_7H_{15}ZnI with TMEDA under aqueous micellar conditions increased the conversion to 60% (entry 6, Table S3). These observations alone represent the first such report in the literature of an organozinc reagent gaining sufficient lifetime in pure water to allow for a Pd-catalyzed cross-coupling, as is use of a complexing ligand to further enhance the extent of this C−C bond formation.

In summary, this work represents the first report of aqueous micellar catalysis using a designer surfactant applied to moisture-sensitive, zinc-mediated, Pd-catalyzed cross-couplings. This new methodology provides a remarkably straightforward means of effecting transition metal catalyzed $C_{sp^2}-C_{sp^3}$ bond constructions *in the absence of a stoichiometrically preformed organometallic coupling partner*. Alternative substrate combinations for related reactive metal chemistry *in water* will be reported in due course.

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Supporting Information Available: Additional results for control experiments, general procedures, and product spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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