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Reductions of aryl bromides in water at room temperature

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Abstract

Micellar nanoreactors derived from commercially available 'Nok' (SPGS-550-M), in the presence of Fu's catalyst and a mild hydride source (NaBH₄), are useful for facile debromination of functionalized aromatic derivatives. This mild and environmentally responsible process is utilized in water at room temperature, and the reaction mixtures can be smoothly recycled.

Keywords

Micellar catalysis; Green chemistry; Recycling; Mild debromination; Functional group tolerance

Introduction

Current protocols for aromatic dehalogenation can be expensive at scale, as well as energy intensive, typically calling for relatively harsh reaction conditions in terms of the reducing agent and/or reaction temperatures. From the perspective of synthesis, halogen substituents can serve as excellent directing or blocking groups. Ideally, dehalogenation would proceed in a recyclable aqueous rather than organic medium, involve a recyclable catalyst, be highly functional group tolerant, and occur under mild conditions such that little-to-no investment of energy is required beyond that provided at ambient temperatures. Such a process would then subscribe to many of the *12 Principles of Green Chemistry* and thus, might be viewed not only as synthetically effective, but also as environmentally attractive.

The discovery of this novel method for aromatic dehalogenation in aqueous media was found serendipitously during prior comparisons between literature examples of Pd-catalyzed cross-couplings as performed by pharmaceutical companies in organic solvents versus identical couplings done in aqueous nanoparticles, as quantified by E Factors.¹ The intent was to perform a Heck coupling with allyl alcohol (Scheme 1), which was unsuccessful and led solely to dehalogenated starting material.²

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Dedicated to the memory of Professor Harry H. Wasserman

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Many of the current protocols of interest include room temperature hydrogenation with palladium-on-charcoal in methanol,³ Fe/*t*-BuMgCl as reductant in THF at 0 °C,⁴ (Ph₃P)₄Pd/HCHO at 80 °C in DMSO,⁵ Pd/NHC complexes with strong bases in isopropanol,⁶ polymer-supported Pd in ammonium formate in isopropanol,⁷ and *n*Bu₃SnH/AIBN in refluxing toluene.⁸ Various methods utilizing radical initiated silyl hydride dehalogenations include the use of indium acetate,⁹ chloride,¹⁰ and diazobiscarbononitrile-cyclohexyl.¹¹ Many of these protocols make use of H₂ gas, toxic reagents, harsh conditions, and in general, have limited substrate scope with little functional group tolerance.¹²

Results and Discussion

Using the conditions illustrated in Scheme 1, various sources of hydride that have been used previously for aromatic dehalogenations were screened (Table 1), with 4-bromobiphenyl (**1**) and 5-bromoindole (**2**) as model substrates. Sodium borohydride (entry 1) clearly afforded the best results. In the case of cinnamyl alcohol, cinnamaldehyde was detected by GCMS analysis (entry 3), confirming that hydride was being supplied from the alcohol precursor, in agreement with prior observations by Yoshida.¹³ Adjustments in both the amount of hydride, from 1.0 to 0.5 equivalents, and base (Et₃N), from two to one and a half equivalents, could be made as well without impacting yields (see SI). Reduction in the loading of Pd catalyst, from 3 to 2 mol %, was also possible, although mild heating of the reaction mixture to 40 °C was required.

From our previous work with micellar catalysis it was noted that the inclusion of salt (NaCl) can greatly affect the size of the micelle thus at times enhancing the rate of the reactions.¹⁴ Using the optimal reductant, NaBH₄ a salt affect screening was undertaken for the dehalogenation of **1**, an the results are shown in Table 2. The optimized concentration of NaCl in the aqueous medium was found to be 3 M.

A screening of alternative amphiphiles showed that our 3rd generation surfactant 'Nok',¹⁵ (Figure 1), enabled the highest levels of conversion of both bromides **3** and **4** (Table 3). While educt **3** led to high levels of conversion both in and on water, the *N*-Cbz-indole derivative **4** displayed a better indication of the anticipated differences between reaction inside a nanomicelle and the background reaction on water involving this water-insoluble bromide. Thus, commercially available surfactant Nok (SPGS-550-M), in water at the 2 weight percent level, was chosen for the remainder of this study.

It has been shown in earlier studies by us that the weight percent of surfactant can play a pivotal role in the success of certain reactions in micellar catalysis (e.g., Heck couplings).¹⁴ Results from varying the concentration of Nok from one to five weight percent for substrates **1** and **3** are shown in Table 4. Although 1, 2, and 5 weight percent all performed essentially equally, 2 wt. % was chosen for all remaining screening and substrate scope, as this concentration also corresponds to material that is commercially available (Aldrich catalog # 776033).

With the optimal choices of reducing agent, surfactant, and its wt. %, we next screened various palladium sources (as shown in Table 5). Several other metal catalysts were also tested although none led to any appreciable dehalogenation (see SI).

Additional reaction parameters such as temperature and global substrate concentration were studied next (Table 6). Results obtained appear to be independent of both temperature (22–30 °C) and concentration (0.5 to 1.0 M). The resulting optimized conditions are summarized in Figure 2.

Direct comparisons between literature conditions and those outlined above for dehalogenations were made, as summarized in Table 7. Compound **1** was previously dehalogenated by MacArthur¹⁶ et al. in 77% isolated yield using CuI (20 mol %), NaI (2 equiv.), and racemic *N,N'*-dimethylcyclohexane-1,2-diamine (1.5 equiv) in CH₃CN under microwave irradiation. Brominated acetophenone **5** was dehalogenated in the ionic liquid 1-butyl-3-methyl-imidazolium bromide (bmim Br), and stoichiometric nanoindium, although only a 20% isolated yield was achieved.¹⁷ In work reported by Birman and co-workers, spirocyclic ligand precursor **6**, where bromine was used as a directing group, required its subsequent removal by *n*-BuLi in THF at –78 °C.¹⁸ Previously, brominated piperonal **7** was dehalogenated by Chen and co-workers using Pd(OAc)₂ with triphenylphosphine in *n*-butanol at 100 °C.¹⁹ By contrast, reactions utilizing this nanomicellar technology take place at ambient temperatures and afford high yields of products. It should be noted that while NaBH₄ is the inexpensive source of hydride, reagent formation takes place *in situ* and therefore, functional group compatibility, such as in the case of ketone **5**, is not a concern (and as shown for several other examples in Table 8; *vide infra*).

Additional substrates display the same responsiveness and functional group tolerance as suggested by ketone **5**. It is worth noting that aldehyde **7** was successfully debrominated in 87% yield, with <5% of the corresponding alcohol being observed. Ketone **12** (Table 8), as with educt **5**, was essentially untouched under these conditions. The benzyl protecting group in **13** remained intact, while the polyhalogenated amide **10** led solely to debromination. Dibromide **16** gave the doubly reduced aromatic product in a modest 66% yield, while monobromide **17** afforded the corresponding naphthol in 91% yield. With respect to observed limitations of this methodology, attempts to remove bromine from either an aromatic ring bearing a thioether residue or in a brominated pyridine led to no reaction.

Workup of these dehalogenation reactions involves addition of a minimal amount of a single (preferably “greener”) organic solvent, such as EtOAc, to the reaction vessel in order to extract the product. The total amount of water invested in the entire process is very modest, as reactions are run at 1.0 M and *no additional water need be added as part of the workup*. Hence, the eventual water waste stream drops to minimal levels. The aqueous layer retains the surfactant and hence, the reaction mixture can be recycled. The mode of further purification of crude product is totally dependent upon the product itself. Results from a recycling study for dehalogenation of **1** are shown in Table 9. For recycles 2–5 it was necessary to add 1.5 mol % additional catalyst, borohydride, and TEA in order to reach full conversion.

To further assess the “greenness” of this process, E Factors were calculated based on organic solvent usage, since most organic waste from organic reactions is attributable to this reaction variable.²⁰ Typical reactions performed by the pharmaceutical industry tend to have E Factors in the 25–100 range (not including water usage), while the fine chemicals arena is

usually in the 5–25 category.²¹ As shown in Figure 4, these dehalogenation reactions lead to E Factors that are quite low given the absence of any organic solvent in the reaction medium. An E Factor calculated inclusive of water raises this value to only 8.9, but upon recycling this value drops dramatically to 3.7.

In an effort to gain insight as to the source of the hydrogen in the product, a series of experiments was conducted as outlined in Figure 5. As expected, NaBH₄ promotes formation of a hydrido-palladium species that delivers hydrogen to the aromatic ring, rather than involvement by water. Likewise, use of NaBD₄ in H₂O led to 100% deuterium incorporation.

In conclusion, a mild, functional group tolerant, and environmentally friendly process for effecting aromatic debrominations has been described. This methodology relies on the use of a designer surfactant that forms nanoreactors in water within which the reductions take place. The reaction medium can be recycled, an important feature associated with this green technology.

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22. Representative procedure: To a dry 5 mL microwave vial equipped with a PTFE stir bar (1×5 mm) under Ar with a septum was added Pd[P(t-Bu)₃]₂ (0.03 mmol, 15.3 mg, 3 mol %), NaCl (3 mmol, 175 mg, [3.0]), NaBH₄ (0.50 mmol, 18.9 mg, 0.5 equiv), substrate (1.00 mmol), Methylamine

(1.50 mmol, 209 μ L, 1.5 equiv), and then 2 wt % Nok ([1.0], 1.0 mL). The mixture was allowed to stir at rt (~ 23 $^{\circ}$ C) until complete as judged by TLC or GCMS. The mixture was extracted with EtOAc (2 $\times$ 2 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with EtOAc:hexanes provided the desired debrominated analog. Note: Highly crystalline solids must be ground to a fine powder (mortar and pestle), thereby forming a uniform suspension in the aqueous medium.

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Figure 2.
Optimized reaction conditions

Figure 4.
E Factors associated with debrominations

Figure 5.
Source of hydrogen from reductions

Scheme 1.
Discovery conditions for aromatic dehalogenation

Table 1Hydride source screening^a

entry	reductant	conv (%) ^b	
		1	2
1	NaBH ₄	98	>99
2	allyl alcohol	69	50
3	cinnamyl alcohol	45	63
4	H ₂	23	59
5	formic acid	3	11
6	ammonium formate	<1	<1
7	isopropanol	<1	<1

^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), reductant (1.0 equiv), 5 wt % PTS with 3 M NaCl, 40 °C, 18 h.

^b Conversion determined via GCMS.

Table 2Salt effect on the conversion of **1**^a

entry	[NaCl]	conv(%) ^b
1	0	61
2	1	76
3	2	87
4	3	>99

^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), NaBH₄ (0.5 equiv), 5 wt % PTS with 3 M NaCl, 40 °C, 18 h.^b Conversion determined by GC

Table 3

Impact of the surfactant on debromination of **1**, **3** and **4**^a

entry	surfactant	conv (%) ^b			
		1	3	4	
1	SPGS-550-M (Nok)	>99	97	98	3 4
2	PTS-600	>99	95	–	
3	TPGS-750-M	59	72	–	
4	cremophor	70	64	–	
5	none (water)	97	93	72	

^a Conditions: Pd[P(*i*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv.), NaBH₄ (0.5 equiv.), surfactant (2 wt %) with 3 M NaCl, 30 °C, 4 h.^b Conversion determined by GCMS.

Table 4Impact of surfactant strength on debromination of **1** and **3**^a

entry	weight %	conv (%) ^b	
		1	3
1	1	96	98
2	2	95	98
3	5	96	94

^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), NaBH₄ (0.5 equiv), Nok (X wt %) with 3 M NaCl, 30 °C, 4 h.^b Conversion determined via GCMS.

Table 5Catalyst screening for the debromination of **1** and **3**^a

entry	catalyst	conv (%) ^b	
		1	3
1	Pd[P(<i>t</i> -Bu) ₃] ₂	>99	>99
2	PdCl ₂ (TMEDA)	65	>99
3	PdCl ₂ [P(Cy) ₃] ₂	12	25
4	Pd[P(Cy) ₃] ₂	96	46
5	Pd(dtbpf)Cl ₂	>99	>99
6	Pd[PPh ₃] ₄	39	20

^a Conditions: Pd catalyst (3 mol %), Et₃N (1.5 equiv), NaBH₄ (0.5 equiv), Nok (2 wt %) with 3 M NaCl, 30 °C, 18 h.^b Conversion determined via GC.

Table 6Concentration and temperature dependence on debromination of **1**

conv (%) ^a			
time (h)	A	B	C
3	45	48	59
5	58	57	62
7	64	61	64
17	100	100	98

conditions

A = 30 °C, 0.5 M

B = rt, 0.5 M

C = rt, 1.0 M

^a Conversion determined via GC; rt = 23 °C.

Table 7

Direct comparisons with literature methodology.

entry	compound	this work	literature
		yield (%) ^a	yield (%)
1	1	97	77 ^[16]
2	5	92	20 ^[17]
3	6	91	93 ^[18]
4	7	87	98 ^[19]

^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), NaBH₄ (0.5 equiv), surfactant (2 wt %) with 3 M NaCl, rt.

Table 8

Representative examples of debrominations^a ^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), NaBH₄, (0.5 equiv), surfactant (2 wt %) with 3 M NaCl, rt.

Table 9Recycling the aqueous medium for debromination of **1**^a

entry	cycle ^b	yield (%)
1	1	99
2	2 ^c	96
3	3 ^c	98
4	4 ^c	98
5	5 ^c	96

^a Conditions: Pd[P(*t*-Bu)₃]₂ (3 mol %), Et₃N (1.5 equiv), NaBH₄, (0.5 equiv), surfactant (2 wt %) with 3 M NaCl, rt, 1 M, 24 h.^b Extracted with EtOAc; aqueous medium used for next reaction.^c For cycle 2–5 1.5 mol % catalyst was used.