On the scope of radical reactions in aqueous media utilizing quaternary ammonium salts of phosphinic acids as chiral and achiral hydrogen donors

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ABSTRACT

A broad range of fundamental free radical reactions such as hydrogen atom transfer, radical deoxygenations, and radical cyclizations utilizing quaternary ammonium salts of phosphinic acids as chiral and achiral hydrogen donors at room temperature are investigated. The reactions proceed in good to excellent yields with some degree of enantioselectivity.

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Radical hydrogen atom transfer reactions have become a versatile and powerful tool for forming new bonds due to the mild and neutral nature of this transformation as well as its broad functional group tolerance.[1,2] Considerable effort has been devoted to developing free radical reactions in aqueous media as well as introducing a degree of stereochemical outcome into a desired transformation.[3–7]

Phosphinic acid has been used as a radical chain carrier and radical hydrogen donor,[8] for processes including hydrogen atom transfer,[9] addition to carbon–carbon,[10] and carbon–nitrogen double bonds.[11] It is proposed that quaternary ammonium hypophosphites can generate radicals readily from alkyl halides as well as playing the role of efficient surfactants thereby increasing the solubility of organic molecules.[8] Recently, Jang et al. reported the use of quinine and quinidine-based chiral quaternary ammonium hypophosphates for enantioselective radical additions to C=N bonds in aqueous media (1:1 CH_2Cl_2–H_2O).[12] More recently, triethylborane (Et_3B/O_2) has been applied successfully in free radical reactions in aqueous and organic media as a radical chain initiator as well as chain propagator.[13–17]

In this Letter, we report the extension of the use of various hypophosphites for a diverse range of synthetic transformations with certain mechanistic aspects being addressed. The advantages of the quaternary ammonium hypophosphites (QAHPs) lie in their tolerance, availability, and their ease of preparation. The quaternary ammonium hypophosphites are prepared by reaction of the corresponding tetrabutylammonium salt or tertiary amine with an equimolar amount of phosphinic acid at room temperature in water. The chiral and achiral hypophosphites were prepared in quantitative yields and did not require any additional purification.

We chose to investigate the radical hydrogen transfer reaction of 1-bromoadamantane (1-BrAd) in the presence of tetrabutylammonium hypophosphite based ionic liquids at either elevated temperatures (80 °C, 10 wt % AIBN, H_2O) or at room temperature (0.5 equiv of Et_3B/air, H_2O) (Scheme 1). Reductions were carried out with 0.1 M substrate partially solubilized in H_2O and initiated with AIBN (10 wt %) at 80 °C or at ambient temperature with Et_3B/air as a suitable radical initiator. The reduced product (adamantane (Ad)) was obtained in good to excellent yields and characterized by ^1H NMR spectroscopy and GC/MS analysis.

Table 1 lists data obtained for the hydrogen atom transfer of 1-bromoadamantane as a model compound in water in the presence of radical initiators such as AIBN (entry 1) as well as in the absence
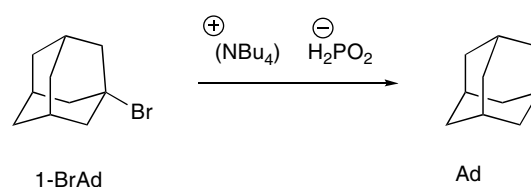
Scheme 1. Reduction of 1-bromoadamantane (1-BrAd) under various free radical conditions.

Table 1
Reduction of 1-bromoadamantane under various free radical conditions in the presence of tetrabutylammonium hypophosphite $(NBu_4)^+H_2PO_2^-$ as an efficient hydrogen donor in water as the solvent

Entry	Additive	Temperature (°C)	Product	Yield[a] (%)
1	AIBN	80	Ad	90
2	Et_3B/air	22	Ad	85
3	None	80	Ad	0
4	Phenol	80	Ad	0

[a] Yields are determined via ^1H NMR spectroscopy.

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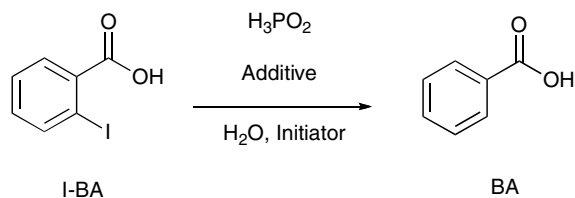
Scheme 2. Reduction of 2-iodobenzoic acid (I-BA) under free radical conditions in aqueous media. (To confirm the radical nature of the transformation and to avoid any ambiguity of the dual role of Et_3B/air as a hydrogen donor and radical initiator, additional control experiments were performed with 2-iodobenzoic acid as a radical precursor. Control experiments in the presence of Et_3B/N_2 or Et_3B/O_2 and in the absence of H_3PO_2/additive yielded no reduced product. Repeated control experiments in the presence of Et_3B/N_2 or Et_3B/O_2 and in the absence of H_3PO_2/no additive yielded a small amount (<10%) of reduced product. The experimental outcomes are in line with currently reported rates of background hydrogen atom transfer from triethylborane in comparison to the published rates[20] of H_3PO_2 as a hydrogen donor.[3c])

Table 2
Reduction of 2-iodobenzoic acid (I-BA) in the presence of tetrasubstituted ammonium hypophosphites (QAHPs) using 0.5 equiv of Et_3B/air as a radical initiator in water at 22 °C

Entry	QAHP	Yield[a] (%)
1	$(Bu_4N)^+H_2PO_2^-$	75
2	$(Me_4N)^+H_2PO_2^-$	78
3	$(Et_4N)^+H_2PO_2^-$	85
4	$(isoPr_4N)^+H_2PO_2^-$	83
5	$(Oct_4N)^+H_2PO_2^-$	85
6	$(Hex_4N)^+H_2PO_2^-$	90
7	$HDABCO^+H_2PO_2^-$	90

[a] Yields were determined via ^1H NMR spectroscopy.

of AIBN (entry 3) and in the presence of a radical inhibitor such as phenol (entry 4). In parallel, 1-bromoadamantane underwent hydrogen atom transfer using Et_3B/air in water (entry 2) in the

Table 3
Various free radical reactions at room temperature in the presence of chiral and achiral tetrasubstituted-ammonium hypophosphites in water using 0.5 equiv of Et_3B/air as a radical initiator

Entry	QAHP	Radical precursor	Product	Yield[a] (%)
1	$(Bu_4N)^+H_2PO_2^-$			65
2	$(Bu_4N)^+H_2PO_2^-$			64
3	$(Bu_4N)^+H_2PO_2^-$			73
4	$(Bu_4N)^+H_2PO_2^-$			87
5	$(Bu_4N)^+H_2PO_2^-$			47
6	$(Bu_4N)^+H_2PO_2^-$			86
7	$(Bu_4N)^+H_2PO_2^-$			77
8	(S,S)-$HMe_2NCHMePh^+H_2PO_2^-$			82[b]
9	(S,S)-$HMe_2NCHMePh^+H_2PO_2^-$			76[c]

[a] Yields reported for materials obtained without need for purification.
[b] The absolute configuration of the final product was assigned to the (S)-enantiomer with 15% ee based on comparison of the optical rotation with the literature value.[18]
[c] The absolute configuration of the final product was assigned as the (S)-enantiomer with 22% ee based on comparison of the optical rotation with the literature value.[18]

presence of tetrabutylammonium hypophosphite, as an aqueous ionic liquid. As expected, reaction of 1-bromoadamantane in the absence of 'aqueous ionic liquid' yielded only unreacted starting material (entry 3). Reaction in the presence of phenol, a well-known free radical inhibitor, gave no formation of the reduced product (entry 4), thereby confirming the free radical nature of the transformation in question.

2-Iodobenzoic acid (I-BA) as a test case alkyl halide was reduced under radical reduction conditions at room temperature in the presence of Et_3B/air (0.5 equiv) as a radical initiator (Scheme 2) in the presence of a range of hypophosphite hydrogen donors, a series of which were prepared from the corresponding achiral tetrasubstituted ammonium salts and H_3PO_2 (Table 2, entries 1–7). The reduced product was obtained in good to excellent yields. This transformation highlights the immense potential of the tetrasubstituted hypoposphites in green free radical chemistry.

To test the scope and limitations of this novel method, 'aqueous ionic liquids/hydrogen donors' were subjected to a broad range of typical radical precursors (1°, 2°) halides (Table 3, entries 1, 5, and 6), benzyl bromide (Table 3, entry 4) as well as the xanthate of cholesterol (entry 7). Free radical cyclization of 1-(allyloxy)-2-bromobenzene (Table 3, entry 3)[19] proceeded smoothly under the specified conditions at room temperature and the results are summarized in Table 3. The same reactions were repeated at 80 °C under predetermined reaction conditions using either AIBN (10 wt %) (organic soluble radical initiator) or V-501 (10 wt %) (a water soluble radical initiator) and comparable results were obtained.

The results exceeded expectations as not only did the reactions proceed with good to excellent yields but they also showed a degree of stereoselectivity and enantioselectivity (Table 3, entry 8, 15% enantiomeric excess obtained). Table 3, entry 9, 22% enantiomeric excess obtained). The results represent the first examples of enantioselectivity being observed in free radical hydrogen transfer reactions in aqueous media and work is currently in progress to explore this novel aspect of enantioselectivity in an aqueous environment.

In conclusion, we have expanded the utility of novel and green aqueous chiral and achiral hypophosphites and have applied them to a broad range of organic halides as radical precursors in hydrogen transfer reactions, radical deoxygenation reactions as well as in cyclizations. The performance of novel aqueous ionic liquids are currently being assessed in a broad range of synthetically useful transformations including stereospecific additions to C=C and C=N bonds. The advantages of these reagents (chiral and achiral hypophosphinates) lie in their affordability, low toxicity, avoidance of the use of highly toxic 'tin based hydrogen donors', and green reaction conditions.

Acknowledgments

General experimental procedure at ambient temperature: To a solution of H_3PO_2 (20% solution in water, 5 equiv) and $Bu_4N^+Cl^-$ (5 equiv) in water (5 ml) was added radical precursor (0.1 mmol) followed by Et_3B/air (0.5 equiv, 1 M solution in hexane). The solution was stirred at room temperature for 3 h. The reaction mixture was then extracted with EtOAc (2 × 10 ml) and the organic phase dried with $MgSO_4$. The crude mixture did not require further purification and was analyzed by ^1H, gCOSY NMR spectroscopy, and GC–MS to confirm formation of the reduced product.

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