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Addition of halide to π-bond directly from aqueous NaX solution: a general strategy for installation of two different functional groups†

Palash Pandit, Krishnanka S. Gayen, Saikat Khamarui, Nirbhik Chatterjee and Dilip K. Maiti*

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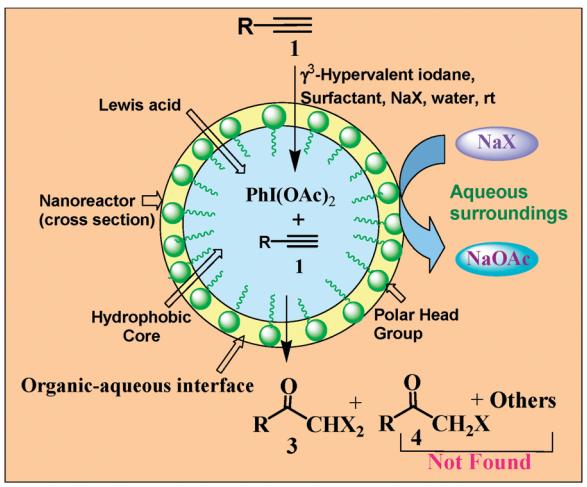
Activation of π-bond with organic Lewis acid and cationic surfactant mediated direct transfer of halides to alkyne and alkene are demonstrated to afford α,α-dihaloketones and other valuable synthons with outstanding selectivities.

Simultaneous installation of two different functional groups into the organic framework is a remarkable fundamental process in organic synthesis.[1] Vicinal difunctionalization offers ease of access to halogen containing attractive substrates, key intermediates, versatile building blocks[2] and valuable bioactive materials[3] with introduction of new bonds and stereocenters. However, production of these halogenated synthons utilizing volatile molecular halogens is unsafe for human health and the environment. Extensive research is devoted toward *in situ* generation of halogen or halogen-equivalents from halides. There are a few interesting reagents like NH_4Br–LDH–WO_4^{2-},[4a] HBr–H_2O_2,[4b,d,e] NaBr–$NaIO_4$,[4c] KBr–selectfluoro[4f] and NaBr–$NaBrO_3$[4g] which have been developed to afford halohydrins and their derivatives from olefins. Unfortunately, water–organic combo solvents, strong acid or alkali and also high temperature are usually employed to achieve the desired transformations. Br^+ is the active species for the difunctionalization of olefin involving a three-membered cyclic bromonium cation. However, the protocol is not successful with the triple bond because of large strain in the cationic species. For example, Floris *et al.* have studied the oxobromination of ethynylbenzene using H_2O_2–KBr–$HClO_4$ (pH ~1) in presence of molybdenum(VI) catalyst which has shown poor selectivities and formation of byproducts like two diastereomeric 1,2-dibromo alkene, α-bromoketone along with the desired α,α-dibromoketones.[5] There are only two other methods toward the synthesis of the significant synthons[5–7] with simultaneous formation of the monobromo compound. Aqueous HBr (48%)–O_2–*hν* to alkyne[7b] and molecular bromine–dioxane–silica to acetophenone under microwave[7a] are employed. Thus, a general method is required under homogeneous and mild reaction conditions especially to achieve a single regio- and stereochemical outcome typically being possible in the fascinating intermolecular approach. Currently, intensive research is devoted to metal catalyzed activation of C–C triple and double bonds and their transformation.[8] Organic Lewis acid[9]-like hypervalent iodane[10] can also be used to activate π-bond which opens up the opportunity for direct transfer of halide. We disclose herein the first ever breakthrough for simultaneous incorporation of halide and ketone/hydroxyl/acetoxy group to C≡C and C=C bonds with complete regio- and stereoselectivity.

$PhI(OAc)_2$ has displayed (Scheme 1) exceptional chemo- and regioselectivity in the difunctionalization of alkyne (**1a**) with sodium halides (NaX) at the interface between cetyltrimethylammonium bromide (CTAB)-assembled lipophilic nanoreactor[11] (ESI) and water to afford α,α-dibromoketone (**3a**, entry 1, Table 1). Herein, attempts are also made for the difunctionalization reaction utilizing anionic (SDS), neutral (Tween 80), acidic (DBSA) and basic (TPAOH) surfactant (entries 2–5), and also γ^3-hypervalent iodanes like PhIO[12] and $PhIF_2$[10] (entries 7,8) in vain. Presence of cationic surfactant is essential because the reaction does not proceed in absence of CTAB (entry 6). Gratifyingly, changeover of the surfactant CTAB to aliquat has efficiently transferred both bromide and



Scheme 1 Difunctionalization of alkyne inside the nanoreactor.

Department of Chemistry, University of Calcutta, University College of Science, 92, A. P. C. Road, Kolkata-700009, India. E-mail: maitidk@yahoo.com; Fax: +91-33-2351-9755; Tel: +91-33-2350-9937

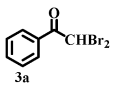
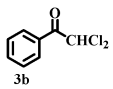
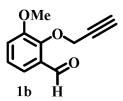
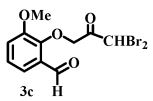
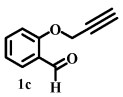
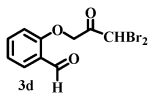
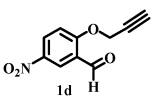
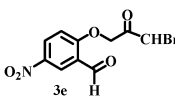
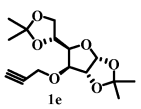
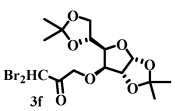
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra, and CIF file. CCDC 799249. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11685a

Table 1 Development and optimization of the reaction

Entry	Reagent[b]	Time (h)	Conversion (%)	Yield[a] (%)
1	$PhI(OAc)_2$, CTAB, NaBr	3.5	100	**3a**, 83
2	$PhI(OAc)_2$, SDS, NaBr	24	no reaction	**3a**, —
3	$PhI(OAc)_2$, Tween-80, NaBr	24	no reaction	**3a**, —
4	$PhI(OAc)_2$, DBSA, NaBr	25	no reaction	**3a**, —
5	$PhI(OAc)_2$, n-Pr_4NOH, NaBr	20	no reaction	**3a**, —
6	$PhI(OAc)_2$, NaBr	24	no reaction	**3a**, —
7	PhIO, CTAB, NaBr	24	no reaction	**3a**, —
8	$PhIF_2$, CTAB, NaBr	22	no reaction	**3a**, —
9	$PhI(OAc)_2$, aliquat, NaBr	4.5	100	**3a**, 82
10	$PhI(OAc)_2$, aliquat, NaCl	4.0	100	**3b**, 65
11	$PhICl_2$, CTAB, NaBr	5.0	100	**3a**, 61

[a] Isolated yield. [b] Surfactant (10 mol%), γ^3-hypervalent iodanes (two mole).

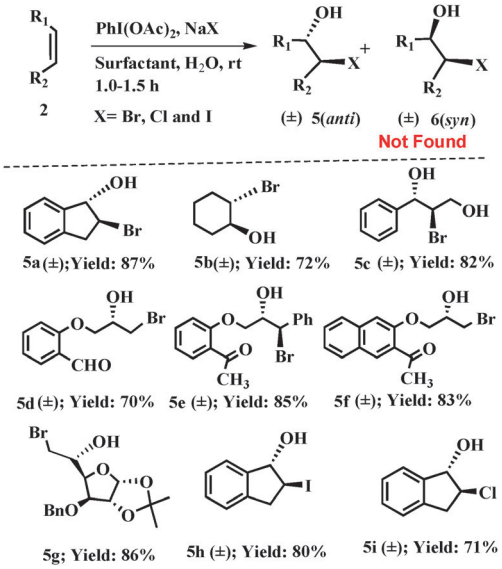
Table 2 Substrate scope toward synthesis of α,α-dihaloketone

Entry	Starting material	Product	Time (h)	Yield (%)
1			3.5	83
2	**1a**		4.5	65
3			3.0	80
4			2.5	82
5			4.0	78
6			3.5	75

chloride (entries 9,10) to furnish corresponding α,α-dibromo- and α,α-dichloroketone (**3a**,**b**, Table 2, entries 1,2). $PhICl_2$ is also active for the reaction to produce **3a** with lower yield (entry 11).

With this optimization study, the substrate scope for synthesis of α,α-dibromoketone is illustrated utilizing various unactivated and functionalized alkynes possessing electron donating and electron withdrawing substituents (**1b–e**, Table 2) toward rapidly (2.5–4.5 h) accessed valuable synthons (**3c–f**). Only one product is found in each reaction with two bromine atoms at the terminal position. The synthetic process often necessitates sugar-based chiral synthons[13] for construction of chiral heterocycles. It led us to examine the synthesis of a new chiral synthon **3f** (entry 6).

Recent studies on palladium-catalyzed difunctionalization of olefin with similar groups like diarylation, diamination *etc.*[14] have prompted us to examine the scope of the metal-free mild heterofunctionalization approach toward synthesis of halohydrins and also evaluate the capability of the reagent to afford a possible single stereochemical outcome (**5**, **6**, Scheme 2).

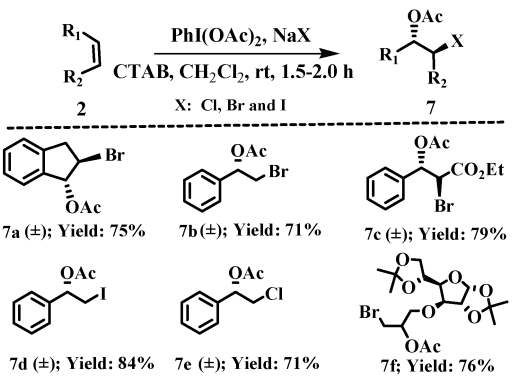


Scheme 2 Diastereoselective vicinal difunctionalization of olefin.

The useful building blocks are normally accessed by stepwise processes involving metal catalysts. For example, 1,2-halohydrins are obtained with moderate to good selectivities *via* ring opening of epoxides by $Ce(OTf)_4$,[15] followed by nucleophilic addition. The direct addition approach is equally effective for activation of double bonds and their vicinal difunctionalization to afford synthon **5**. Versatility of the reaction is examined utilizing functionalized unactivated, activated and sugar-based olefins toward rapidly (1.0–2.0 h) accessed valuable building blocks (**5a–g**) with good yield (70–87%). Surprisingly, complete regio- and *trans*-diastereoselective addition is accomplished. The cationic surfactant can also transfer iodine with desired selectivities (**5h**). The structure is confirmed by means of single crystal X-ray diffraction data (**5a**) and spectroscopic analyses (ESI). Recently, γ^3-hypervalent iodanes mediated diamination[14a] and diacetoxylation[16] have been reported where metal catalysts are essential.

We have found a pronounced effect on changing the reaction from water to organic media where OAc group is transferred along with the halogen (**7**, Scheme 3). The reaction is also successfully extended with NaI, NaCl and sugar substrates toward synthesis of valuable 1,2-difunctionalized synthons **7d–f**.

A probable reaction path is depicted in eqn (1). Organic substrate (**1a**) and reagent remain inside the CTAB-assembled



Scheme 3 Solvent dependent 1,2-heterofunctionalization of olefin.

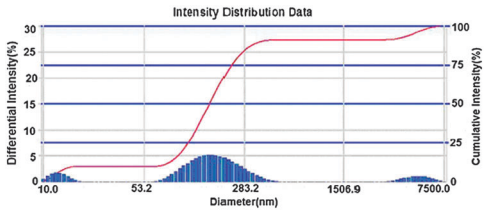
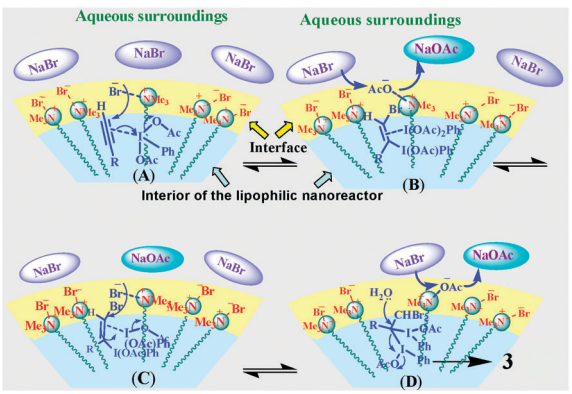
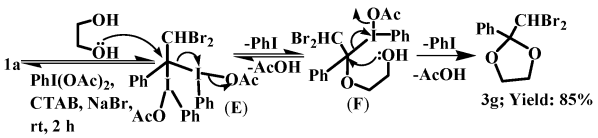


Fig. 1 Size and intensity data of the nanoreactor in DLS.

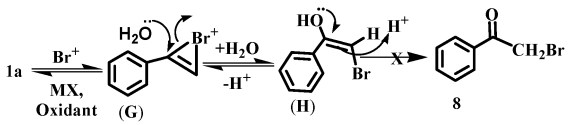
lipophilic nanoreactor and sodium bromide in the aqueous surroundings. Addition of cationic surfactant bearing bromide anion to $PhI(OAc)_2$-polarized alkyne takes place at the interface involving a six-membered transition state (**A**). The AcO^- group of the modified surfactant CTAA is immediately exchanged with the more polarizable halide anion (**B**). A second bromide anion is transferred to the putative intermediate through coordination of the cationic nitrogen of CTAB to form **C**. Its solvolysis with water (**D**) and simultaneous reductive elimination of hypervalent iodane afford **3a**. Complete regioselectivity of the reaction can be explained due to placement of the relatively smaller and larger organic part of the substrate directed toward the interface and strongly lipophilic micellar core respectively. To understand the reaction path, we have studied the reaction in ethylene glycol media (eqn (2)) which probably progresses through formation of intermediate **E** and subsequent solvolysis (**F**) to afford keto-protected **3g**. Indeed, α-bromoketone (**8**) is not found in our experiments but is obtained in the commonly used Br^+ addition method involving formation of bromonium species[4] (**G**, eqn (3)).



(1)



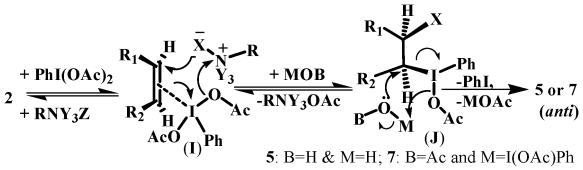
(2)



(3)

Similarly, difunctionalization of olefin involves *syn*-addition of $PhI(OAc)_2$ and halide ion (X^-, **I**, eqn (4)) and subsequent reductive elimination (**J**) in a stereoelectronically *anti* fashion.

Interestingly, dynamic light scattering data of the aqueous CTAB solution (Fig. 1) have supported the formation of spherical nanoreactors (polarized optical microscope image, ESI) with maximum population at 183 nm. However, there is an equilibration between the spherical and small amount (~10%) of ultralong cylindrical nanoreactor (~7500 nm).[17]



(4)

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