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A fast and selective decarboxylative difunctionalization and cyclization for easy access to *gem*-dihalo alcohol, ether, ester and bromo-1,4-dioxane†

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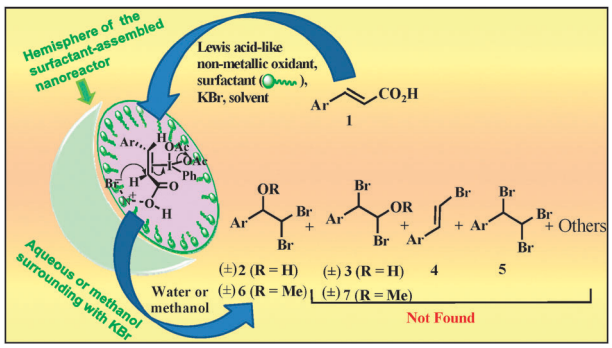
A general strategy for fast decarboxylative difunctionalization to *gem*-dihalohydrin, *gem*-dihaloether, *gem*-dibromoester and cyclized bromo-1,4-dioxane synthons with outstanding regio- and stereoselectivity is demonstrated.

Halogenated organic molecules are the precursors of Heck, Suzuki and other fundamental transformations and used as key intermediates, bioactive natural products, agrochemicals, pharmaceuticals and semiconductors.[1] Hunsdiecker reaction of α,β-unsaturated carboxylic acids with molecular bromine–metal catalysts[2] and *in situ* generation of bromine by metal halides and oxidants (KBr-H_2O_2-Na_2MoO_4 and LiCl/LiBr-CAN), NBS-$MnCl_2$ and HBr-O_2-$NaNO_2$ are utilized to access bromoalkenes.[3] However, utilization of functionalized *gem*-dihalogenated building blocks in organic synthesis suffers the lack of a robust process which can selectively install two halogen atoms.[1f,4] In particular, substituted α,α-dibromohydrins (**2**) andtheir ether analogues are available in natural products.[5] They are key intermediates for synthesis of terminal alkynes[6] and α-methoxy phenyl acetic acid which are used as chiral resolution agents for amines,[7] apoptosis inhibitors,[8c] plant growth regulators[8b] and calcium antagonists.[8a] In general, it is very difficult to obtain α,α-dibromohydrins (**2**) due to the formation of a number of possible products (Scheme 1). One short method has been pioneered by Chowdhury and Roy[3a] using $Mn(OAc)_2$ catalyst and expensive NBS (2 mol) in CH_3CN–water to provide **2** (yield: 37–98%) in 16 h. Two other methods require the use of a Grignard reagent at low temperature[9a] or hydride reduction of the dibromoketone precursor.[9b] To the best of our knowledge, till now, no efficient 1,2-difunctionalization[10] method has been devised for decarboxylative *gem*-dihalogenation of α,β-unsaturated carboxylic acids with simultaneous installation of a hydroxyl/alkoxy/carboxylate group and a cyclization process.

Being most abundant, cheap and environmentally safe, water[11] is the solvent of our choice for development of a cleaner and more benign dibromohydroxylation reaction using KBr as the direct source of Br. We have envisioned that upon activation, a π-bond bearing carboxylic acid (**1**) with a hypervalent iodane[12] inside a surfactant-assembled lipophilic nanoreactor[13] can regioselectively accept Br^- from an aqueous surrounding (Scheme 1). Subsequent decarboxylation, selective installation of Br^- and solvolysis will furnish the new synthons. Upon treatment of our model substrate *trans*-cinnamic acid (**1a**, entry 1, Table 1) with π-bond activator $PhI(OAc)_2$, cationic surfactant CTAB and KBr at room temperature in aqueous medium, Br^- is transferred very rapidly (25 min) to afford α,α-(dibromomethyl)phenylmethanol (**2a**, entry 1, Scheme 2). Anionic (SDS) and neutral Tween 80 could not transfer Br^- (entries 2 and 3). Polymeric PhIO[14] is inactive (entry 4) and the use of the "TEAB/IBD" protocol does not produce the desired product **4a** (entry 5).[15] Under the reaction conditions synthon **2a** is obtained in 63% yield. Gratifyingly, the *gem*-dibromination with addition of a methoxy group is observed simply by changing the solvent from water to methanol (entry 6, Table 1).



Scheme 1 Decarboxylative dibromohydroxylation in a nanoreactor.

Table 1 Development and optimization of the reaction

Entry	Reagent and reaction conditions[a,b]	*t*/min	Conversion (%)	Yield (%)
1	$PhI(OAc)_2$, CTAB, H_2O	25	100	**2a**, 88
2	$PhI(OAc)_2$, SDS, H_2O	300	0	**2a**, nd[c]
3	$PhI(OAc)_2$, Tween 80, H_2O	300	0	**2a**, nd
4	PhIO, CTAB, H_2O	300	0	**2a**, nd
5	$PhI(OAc)_2$, TBAB, H_2O	40	100	**4a**[d], nd
6	$PhI(OAc)_2$, CTAB, MeOH	25	100	**6a**, 90
7	$PhI(OAc)_2$, CTAB, DCM[e]	45	100	**5a**, 76

[a] γ^3-Hypervalent iodanes (2.0 mol). [b] Surfactant (10 mol%). [c] Not detected. [d] **2a** (63%). [e] Dichloromethane.

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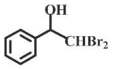
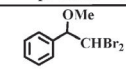
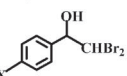
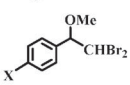
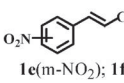
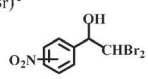
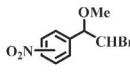
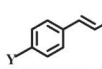
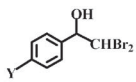
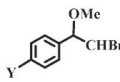
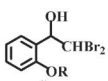
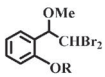
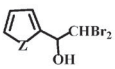
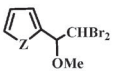
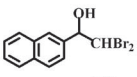
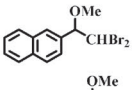
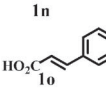
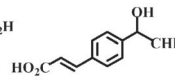
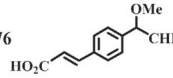
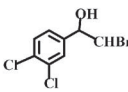
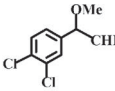
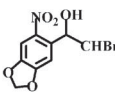
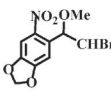
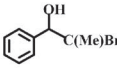
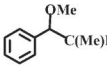
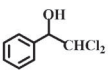
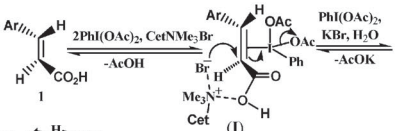
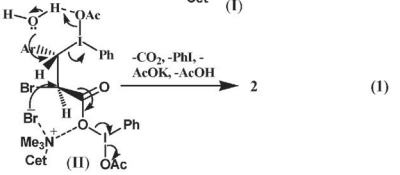
α,α-(Dibromomethyl)phenylmethylmethyl ether (**6a**, entry 1, Scheme 2) is obtained in excellent yield (90%). Other possible regioisomer **7a** is not found in the post-reaction mixture. In contrast to the commonly used Hunsdiecker reaction of **1a** to form α-bromostyrene (**4a**), it has furnished only the tribromo-product **5a** upon the use of a polar aprotic solvent (entry 7).

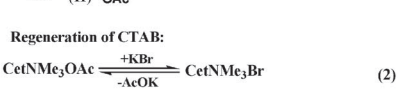
The scope for synthesis of functionalized vicinal dibromohydrins is demonstrated using various α,β-unsaturated carboxylic acids (**1b–r**, Scheme 2, entries 2–18) toward rapidly (20–60 min) accessed synthons (**2b–r**) with moderate to excellent yield (61–92%). Aromatic precursors possessing electron donating substituents (**1g–k**, entries 7–11) undergo the reaction at a faster rate and give better yields (85–92%) compared to the precursors with electron withdrawing substituents (72–83%, **1b–f**,**p**,**q** entries 2–6, 16, 17). α,β-Unsaturated carboxylic acids bearing hetero-cyclic rings (**1l**,**m** entries 12 and 13), naphthyl (**1n**, entry 14) and α-methyl substituents (entry 18) are tolerated in this innovative protocol. Other than water, methanol is utilized as a solvent for direct addition of new bonds toward rapidly (15–60 min) accessed α,α-dibromomethylmethylmethylether (**6b–r**, entries 2–18) with high yield (60–92%) and complete regioselectivity. It is applicable to the substrates having unactivated, activated and heterocyclic aromatic rings and many sensitive functionalities like 3°-amine, methoxy, allyl, propargyl *etc*. and also α-methyl substituent. However, the reaction is unsuccessful with aliphatic α,β-unsaturated acids. Surprisingly, in the case of precursor 3-[4-(2-carboxyvinyl)-phenyl] acrylic acid (entry 15) one unsaturated moiety with a carboxylic acid group remains intact with the reagent. This approach is also compatible for synthesis of *gem*-dichloro-hydrin (**8a**) and *gem*-dichloroether (**8b**) in the presence of CPC (entry 19). The metal-free reaction has great synthetic value since treatment of easily available α,β-unsaturated carboxylic acids[16] and nonhazardous KBr leads to synthesis of rare types of halogenated building blocks with very fast reaction convergence, outstanding selectivities and excellent yield.

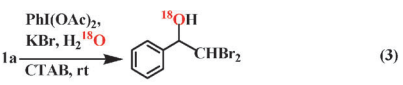
Transfer of bromide from the homogeneous aqueous solution is expected at the interface (Stern layer) between the surface of the cationic surfactant-assembled nanoreactor[1f] and water (eqn (1), Scheme 2). Activation of the double bond by

entry	starting material	water: product	water: time(min.)	water: yield(%)	methanol: product	methanol: time(min.)	methanol: yield(%)
1			25	2a, 88		25	6a, 90
2			30	2b, 83		35	6b, 89
3			30	2c, 80		35	6c, 83
4	1b(X=F); 1c(X=Cl); 1d(X=Br)		25	2d, 82		35	6d, 84
5			50	2e, 72		55	6e, 73
6	1e(m-NO_2); 1f(p-NO_2)		60	2f, 75		55	6f, 72
7			20	2g, 92		20	6g, 92
8			20	2h, 85		25	6h, 85
	1g(Y= OMe; 1h(Y=NMe_2)						
9			20	2i, 90		15	6i, 90
10			20	2j, 91		15	6j, 92
11	1i(R=Me); 1j(R=allyl); 1k(R=Propargyl)		20	2k, 91		15	6k, 91
12			35	2l, 79		40	6l, 79
13	1l(Z= S); 1m(Z=O)		45	2m,73		45	6m, 76
14			40	2n, 80		45	6n, 76
15			50	2o, 76		55	6o, 75
16			30	2p, 69		25	6p, 70
17			45	2q, 62		60	6q, 66
18			30	2r, 61		30	6r, 60
19			30	8a, 60		25	8b, 74
	1a						





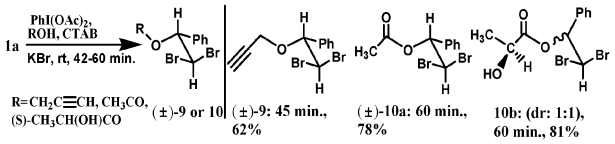




Possible reaction path

EI-MS spectra of ^{16}O-**2a**(**a**) and ^{18}O-**2a**(**b**)

Scheme 2 Substrate scope toward α,α-dihalohydrin and α,α-dihaloether, possible reaction path (eqn (1)–(3)) and ESI-MS spectra.

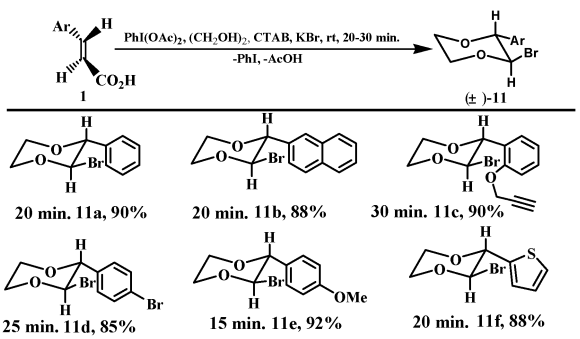


Scheme 3 Reaction with activated hydroxyl group (R–OH).

$PhI(OAc)_2$ and subsequent transfer of Br^- is expected to involve a five membered cyclic transition state (**I**) with a carboxylic acid bound ammonium head group. Simultaneous addition of another Br^- (**II**), reductive elimination of γ^3-hypervalent iodine, decarboxylation and removal of the I (**III**) moiety at the most bulky center by water lead to formation of **2**. Replacement of AcO^- with surrounding Br^- regenerates CTAB (eqn (2), Scheme 2). Involvement of water is established by using $H_2{}^{18}O$ (eqn (3), Scheme 2) and subsequent analysis of both the products. For clarity, only the characteristic peaks of the EI-MS spectra (^{16}O-**2a** and ^{18}O-**2a**) are displayed in Scheme 2.

Surprisingly, the valuable ether-forming reaction in ethanol and other higher alcohols remains unsuccessful. However, activated hydroxyl group containing propargyl alcohol, acetic acid and L-lactic acid are successfully converted to corresponding *gem*-dibromopropargyl ether (**9**, Scheme 3), *gem*-dibromoacetate (**10a**) and chiral *gem*-dibromolactate (**10b**).

We are curious to determine whether this approach could be extended to construct a novel 1,4-dioxane framework in one step. In fact, ethylene glycol responds well to react rapidly (15–30 min) with an α,β-unsaturated carboxylic acid (**1**) and KBr at room temperature to provide 1,2-bromoaryl-1,4-dioxane (**11a–f**, Scheme 4) in excellent yield (85–92%). We are surprised to see the complete diastereoselectivity during the cyclization process. To our knowledge, this decarboxylative halogenation with cyclization is unprecedented and the first report toward synthesis of the new synthons. Phenyl, activated aryl, naphthyl, heterocyclic aromatic rings, halogen and triple bonds are tolerated in this approach. Unfortunately, the reaction of **1f** possessing NO_2 remains unsuccessful. It is expected that two hypervalent residues in the intermediate **II** (Scheme 2) are simultaneously removed by ethylene glycol. Formation of a surfactant-assembled nanoreactor during the chemical process



Scheme 4 Decarboxylative cyclization with ethylene glycol.

is confirmed by means of a DLS experiment (ESI†) of the reaction mixture in water (R = 333.5 nm), methanol (R = 383.5 nm) and ethylene glycol (R = 666.6 nm).

In summary, the present study reveals an efficient decarboxylative vicinal heterodifunctionalization of α,β-unsaturated carboxylic acids to afford a series of functionalized halogenated synthons. It is simple in execution, rapid, high yielding and completely regio- and diastereoselective. The metal-free mild reaction conditions with no environmental hazard highlight the importance of our strategy which puts into another frontier to the Hunsdiecker halo-decarboxylation reaction.

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