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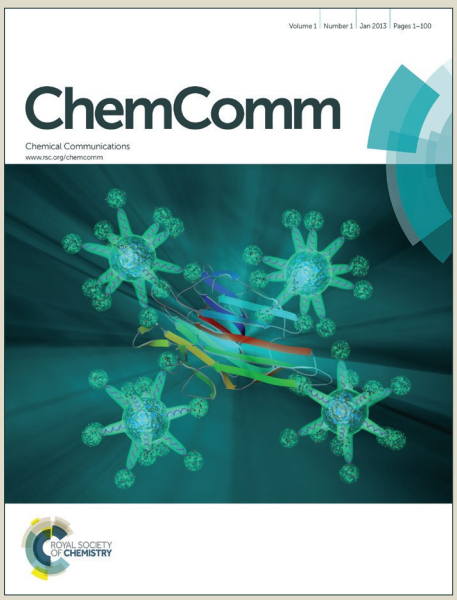

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Oxidant Controlled Regio- and Stereodivergent Azidohydroxylation of Alkenes via I_2 Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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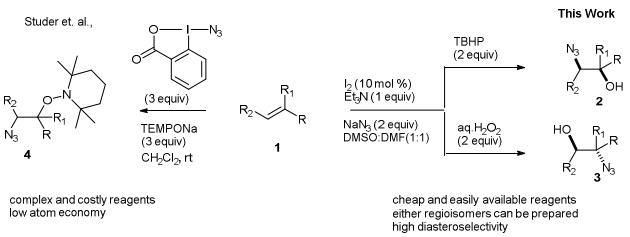
Abstract: A novel, I_2 catalyzed regio- and stereodivergent vicinal azidohydroxylation of alkenes leading to 1,2-azidoalcohols in high yields (up to 92%) and excellent dr (up to 98%) has been developed. This unprecedented transformation employs NaN_3 and DMF as N- and O- nucleophiles respectively. The role of DMF as O- source in the reaction has been unequivocally proven by ^{18}O labelling studies.

Vicinal difunctionalization of alkenes is an attractive strategy for the assembly of hetero-functionalized organic compounds. In this context, dioxygenation[1] dinitrogenation[2] and oxy-nitrogenation[3] across the alkenes are well studied. However, the direct vicinal azidohydroxylation across unsymmetrical alkenes in requisite regio- and diastereoselective fashion is rare.[3d,3e] The resulting structural units comprising vicinal azidohydroxy functional groups are recurrent in drugs, natural products and synthetic materials[4] and find tremendous utility in the synthesis of biologically active amino sugars,[5] nucleosides,[6] lactams,[7] triazoles,[8] oxazolines[9] and in the chemistry of peptidomimetics[10] and pseudopeptides[11]. Conventionally, 1,2-azidoalcohols are prepared from ring opening of epoxides[12] or displacement of halohydrin[13] with various azide sources under acidic/basic conditions as well as chemoselective reduction of α-azido ketones.[14] Nevertheless, these reports suffer from disadvantages such as use of prefunctionalized starting materials leading to reduced atom economy, harsh reaction conditions accompanied with low functional group tolerance and often poor regio- and diastereoselectivity. Thus, a mild synthetic procedure that employs readily available starting materials and overcomes the above difficulties is desirable for regio- and stereodivergent synthesis of 1,2-azidoalcohols.

I_2 catalysis has been increasingly explored for C-C, C-O and C-N bond formation as environmentally benign and inexpensive oxidation reagent in place of rare or toxic heavy metal oxidants.[15] However, olefin functionalization using catalytic electrophilic iodination with stoichiometric co-oxidants is rare. We reasoned that, 1,2-additions of two nucleophiles across -C=C- bond could be possible using electrophilic iodine source owing to its ability to form electrophilic iodonium ion. In this context, Komatsu and co-workers have first reported I_2-catalyzed aziridination of alkenes using chloramine-T as N-nucleophile.[16] Thereafter, Yoshimura et al. reported the I_2-mediated cyclopropanation of alkenes using malononitrile as *C*-nucleophile.[17] More recently, we have demonstrated the dihydroxylation of alkenes using benzoic acid and DMSO as *O*-nucleophiles.[18] In hetero-difunctionalization (*e.g.* azidohydroxylation), switching to one of the possible isomers with required regio- and diastereoselectivity is challenging due to little difference in the relative reactivity of *O*- and *N*-nucleophiles under different conditions.



Scheme 1: Azidohydroxylation of alkenes

In 2013, Studer et al. have reported the direct azidooxygenation of alkenes giving azidohydroxy derivative **4** using excess amount of N_3-I(III) reagent and TEMPONa as *N*- and *O*-nucleophiles respectively, thus requiring additional steps to achieve 1,2-azidoalcohols.[19] *N,N*-Dimethylformamide is a popular formylating agent;[20] however, its role in nucleophilic substitution reactions is quite rare[21] and opens up a new area of research yet to be established. For the first time, we report, a controlled synthesis of either regioisomers of 1,2-azidoalcohols with high diastereomeric ratios using DMF as *O*-nucleophile and NaN_3 as *N*-nucleophile (**Scheme 1**).

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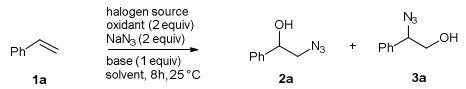
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1: I_2-catalyzed regiodivergent azidohydroxylation of styrene: optimization studies[a]



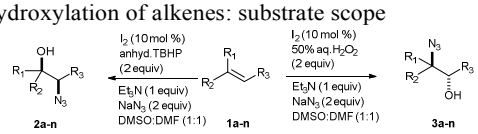
no.	halogen (10 mol %)	oxidant	base	solvent	yield of **2a**[b]
1	I_2	TBHP	Et_3N	DMF	53
2	I_2	TBHP	Et_3N	THF+DMF	10
3	I_2	TBHP	Et_3N	CH_3CN+DMF	48
4	I_2	TBHP	Et_3N	CH_2Cl_2+DMF	18
5	I_2	TBHP	Et_3N	DMSO+ DMF	90,38[c]
6	I_2	TBHP	K_2CO_3	DMSO+ DMF	18
7	I_2	TBHP	K^{t}OBu	DMSO+ DMF	44
8	I_2	TBHP	NaH	DMSO+ DMF	32
9	I_2	TBHP	DBU	DMSO+ DMF	65
10	^{n}Bu$_4$NI	TBHP	Et_3N	DMSO+ DMF	5
11	NaI	TBHP	Et_3N	DMSO+ DMF	11
12	KI	TBHP	Et_3N	DMSO+ DMF	14
13[d]	I_2	50% aq.H_2O_2	Et_3N	DMSO+ DMF	82,78[e]

[a]Reaction conditions: styrene (1 mmol), NaN_3 (2 mmol), halogen source (10 mol %), base (1 mmol), oxidant (2 mmol); 8 mL of solvent (1:1), 25 °C, 8 h. [b]Isolated yields after column chromatographic purification. [c] 5 mol % of I_2 was used. [d] **3a** was formed as major product. [e] 30% aq. H_2O_2 was used.

Initially, when styrene (**1a**) (1 mmol) was treated with a mixture of I_2 (10 mol %) and TBHP (5-6 M solution in decane contains <4 % water, 2 mmol) followed by addition of Et_3N (1 mmol) and sodium azide (2 mmol) at 0 °C in DMF, to our delight we obtained 2-azido-1-phenylethan-1-ol (**2a**) as exclusive regioisomer *albeit* in moderate yield 53% (**Table 1**). Encouraged by this result, it was of interest to optimize the reaction conditions in order to obtain improved yield without affecting its regioselectivity. Thus, other solvents like THF, CH_3CN and CH_2Cl_2 were screened and found to be unsuitable for this reaction. Hence, we found DMF was crucial in obtaining desired azidoalcohol **2a**. Surprisingly, out of solvent combinations screened (entries 2-5), DMSO+DMF (v/v = 1/1) mixture resulted in excellent yield (90%) of the desired product **2a**. Decrease in I_2 catalyst loading to 5 mol % however had a deleterious effect on yield (38%) (entry 5). Further modification, either in iodine source or base did not show any significant improvement in the product yield (entries 6-12). On the contrary, when 50% aq. H_2O_2 was used as oxidant instead of TBHP, a complete reversal in product regioselectivity was observed affording 2-azido-2-phenylethan-1-ol (**3a**) in 82% yield (entry 13). Even, 30% aq. H_2O_2 can be employed that afforded **3a** in good yield (78%). Furthermore, with 70% aq. TBHP, it gave a 3:1 mixture of **2a** and **3a** in 78% combined yield. Other oxidants such as cumene hydroperoxide and oxone afforded **2a** in 26 and 14% yields respectively. Thus, the preliminary studies established an oxidant-directed switch to either regioisomers **2a** or **3a** in excellent yields directly from styrene in a single step.

In order to determine its scope, a variety of olefins were evaluated under the optimized reaction conditions and the results are summarized in **Table 2**. When styrenes, with $–CH_3$ (**1b**), -OH (**1c**), -Br (**1d**), $-NO_2$ (**1e**) groups on aromatic ring were treated with I_2 (10 mol %), TBHP (2 equiv), NaN_3 (2 equiv) and Et_3N (1 equiv) in DMF:DMSO (1:1) at 25 °C, the corresponding 1,2-azido alcohols **2a–e** were obtained in 76-

Table 2: I_2-catalyzed regio- and stereodivergent azidohydroxylation of alkenes: substrate scope



Products[a] (**2a–n**)	substrates (**1a-n**)	Products[b,c] (**3a–n**)
2a (90%)	**1a** R = H	**3a** (82%) (12:1)
2b (88%)	**1b** R = CH_3	**3b** (89%) (9:1)
2c (76%)	**1c** R = OH	---
2d 82%	**1d**	**3d** (86%) (10:1)
2e 77%	**1e**	**3e** (76%) (10:1)
2f (78%)	**1f**	**3f** (83%) (9:1)
2g (79%)	**1g**	**3g** (83%) (9:1)
2h (84%)	**1h**	**3h**(74%) (8:1)
2i (74%)	**1i**	**3i** (78%) (5:1)
2j (87%) dr = 95:5	**1j**	**3j** (92%) dr = 95:5[d]
2k(87%) dr = 98:2	**1k**	**3k** (82%) dr = 92:8
2l (88%) dr = 93:7	**1l** R = H, R_1=H	**3l** (86%) dr = 97:3
2m (80%) dr = 92:8	**1m** R= OH R_1=H	**3m** (78%) dr = 94:6
2n (82%) dr = 96:4	**1n** R = OH,R_1=OMe	**3n** (80%) dr = 98:2

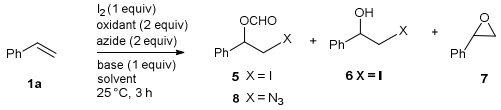
[a]Reaction condition A: styrene (1 mmol), I_2 (10 mol %), Et_3N (1 mmol), 5-6 M TBHP in decane (2 mmol), NaN_3 (2 mmol), DMSO+DMF (4 mL each), 0 °C to 25 °C, 8 h; [b] condition B: styrene (1 mmol), I_2 (10 mol %), Et_3N (1 mmol), 50% aq. H_2O_2 (2 mmol), NaN_3 (2 mmol) DMSO+DMF (4 mL each) 0 °C to 25 °C, 8 h; [c] ratio of **3**:**2**; [d] diastereomeric ratios were determined using ^{1}H NMR and HPLC analysis.

90% yields with excellent regioselectivity (>95%). In the case of disubstituted α-methyl styrene (**1f**), the azidohydroxylation product **2f** was obtained in high regioselectivity consistent with our initial findings. Also, 1-octene (**1g**) gave the desired products **2g** in high yield (79%) with high regioselectivity (>19:1). Interestingly, sterically congested and abundantly available isoprenol and prenol derivatives **1h** and **1i** too afforded **2h** and **2i** respectively in high yields with excellent regioselectivity. Cyclohexene (**1j**) and indene (**1k**) also participated in azidohydroxylation reaction affording the respective products **2j** and **2k** in predicted regioselectivity accompanied with high diastereoselectivity (Table 2) in favour of *syn* isomer. Interestingly, other open chain internal alkene **1l** gave the corresponding 1,2-azido alcohol **2l** with excellent diastereomeric ratio which is also a key intermediate for the syntheses of the psychostimulant drug, norpseudoephedrine,[22] as well as the antidepressant drug, cathinone.[22] Other allylic alcohol **1m** and **1n** were also tested and the diastereoselectivity obtained in each case remained high. Specifically, substrate with free hydroxy group was also found tolerent under this mild protocol.

On the contrary, when 50% aqueous H_2O_2 was used as co-oxidant in the reaction, azidoalcohols with complementary regioselectivity were obtained. Here again, substituted styrenes **1a-f** afforded **3a-f** in high yields (76-89%) and regioselectivities (88-95%). Also, electronically unbiased aliphatic alkenes such as octene **1g**, terminal disubstituted alkene **1h** and trisubstituted alkene **1i** smoothly underwent this transformation affording the respective azido alcohols **3g, 3h** and **3i** in high yields (74-84%) *albeit* in moderate regioselectivity (5:1). Remarkably, when symmetrical and unsymmetrical disubstituted alkenes **1j** and **1k** were tested for their diastereoselectivity under the present conditions, 1,2-azidoalcohols **3j** and **3k** were obtained with major *anti* isomer this time. No discrepancy in *anti*-diastereoselectivity was observed in substrates **1l, 1m** and **1n** thus affording **3l, 3m** and **3n** in high yields (78- 86%). However, electron deficient conjugated alkenes failed to undergo catalytic azidohydroxylation under either condition.

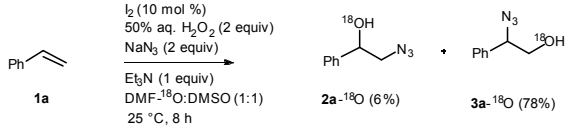
The results of experiments for the mechanistic understanding of the reaction are summarized in **Table 3**: (i) *DMF as oxygen source and role of Et_3N in hydrolysis*: When styrene was treated with I_2 (1 equiv) in DMF, the corresponding iodoformate **5** was isolated in 72% yield. In the presence of Et_3N, iodoalcohol **6** was obtained along with **5** which suggest the role of Et_3N in hydrolysis of formate **5** (entries 1 and 2). (ii) *Co-oxidants do not compete with DMF as O-nucleophile*: In the presence of co-oxidants (entries 3 and 4), iodoformate **5** was still formed. Further, when ^{18}O labelled DMF was used in the reaction, styrene gave 6% yield of **2a**-^{18}O and 78% of **3a**-^{18}O under condition B (**Scheme 2**). This clearly establishes that DMF serves as a source of oxygen and thus proves it to be more potent *O*-nucleophile as compared to TBHP, H_2O_2, H_2O or DMSO under present reaction condition. (iii) *Possibility of formation of hypervalent iodine is ruled out*: Further, on adding NaN_3 in the absence of co-oxidants (entry 5), azido alcohol product **2a** was indeed obtained in 48% yield. Therefore, reaction pathway does not involve the formation of hypervalent iodine species to yield **2** or **3** and TBHP/H_2O_2 is solely used for

Table 3: Stoichiometric control experiments for azidohydroxylation of styrene[a]



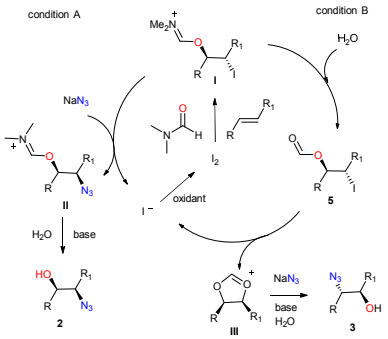
no.	solvent	base	oxidant	azide	products [b]
1	DMF	---	---	---	**5**(72%)
2	DMF	Et_3N	---	---	**5** (38%) + **6** 42%)
3	DMF + DMSO	Et_3N	anhyd. TBHP	---	**5** (34%) + **6** (22%) + **7** (11%)
4	DMF + DMSO	Et_3N	aq.50% H_2O_2	---	**5** (32%) + **6** (26%) + **7** (18%)
5	DMF + DMSO	Et_3N	---	NaN_3	**8** (22%) + **6** (18%) + **2a** (48%)
6	DMF + DMSO + H_2O	Et_3N	---	NaN_3	**5** (35%) + **3a** (48%)

[a] Reaction condition: styrene (1 mmol), I_2 (1 mmol), oxidant (2 mmol), NaN_3 (2 mmol), base (2 mmol), solvent, 25 °C, 3 h; [b] Isolated yields after column chromatographic purification



Scheme 2. Isotopic labelling experiment using DMF-^{18}O

regeneration of I_2. (iv) *Account for reversal in regio and stereoselectivity of the product*: However, when the above reaction was performed under aqueous conditions (DMSO: DMF:H_2O = 1:1:0.4), iodoformate **5** and product **3a** were isolated (entry 6). Further reaction of iodo formate **5** with NaN_3 (2 equiv) and Et_3N (1 equiv) in DMF:DMSO:H_2O (1:1:0.4) gave **3a** in 54% yield suggesting the formation of cyclic intermediate **III**, which can account for the reversal in regio- and stereoselectivity of azidohydroxylation under the aqueous conditions.

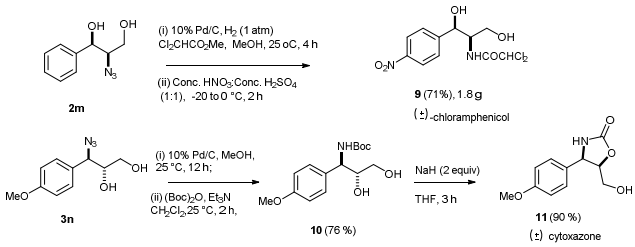


Scheme 3: Plausible mechanism for I_2-catalyzed azidohydroxylation of alkenes

Based on the above experiments and literature precedence,[18,21] the above mechanism has been proposed (**Scheme 3**). Initially, alkene reacts with iodine to form iodonium ion which

undergoes regioselective ring opening with DMF to give the corresponding iodo intermediate **I** followed by subsequent stereoselective displacement with azide ion to form species **II.** This on hydrolysis affords *syn* azido alcohols **2**. On the other hand, under aq. H_2O_2 condition, the iodo intermediate **I** is hydrolyzed in situ to form iodoformate **5**. The proposed species **III** formed from **5** by the anchimeric assistance shown by the formate group, reacts with azide anion in a regioselective manner to give *anti* azido alcohol **3** with the liberation of iodide ion, which is then reoxidized with TBHP/H_2O_2 to regenerate I_2 in the catalytic cycle.

The application of this novel method is amply illustrated in the concise total synthesis of (±)-chloramphenicol (**9**),[23] an antibiotic drug and (±)-cytoxazone (**11**),[24] a cytokine modulator. 1,2-*syn* azido alcohol **2m**, prepared by the present protocol was subjected to simple reduction-protection sequence



Scheme 4. Total Synthesis of (±)-chloramphenicol and (±)-cytoxazone

followed by regioselective nitration gave (±)-chloramphenicol (**9**) in 71% yield. Also, azidodiol **3n**, prepared from **1n** using condition B, on reduction-Boc protection sequence, gave aminodiol **10** in 76% yield, which under basic condition underwent cyclization to give (±)-cytoxazone (**11**) in 90% yield (**Scheme 4**).

To summarize, we have developed, for the first time, regio- and diastereoselective azidohydroxylation of alkenes to give vicinal azidoalcohols in high yields. The regio- and stereodivergence observed in the process is driven by the oxidants chosen in combination with catalytic I_2. Mechanistic study revealed that DMF is crucial for regiodivergence and acts as an *O*-source in this azidohydroxylation reaction. This methodology has successfully been applied to the concise syntheses of (±)-chloramphenicol and (±)-cytoxazone. We believe that this mild, environmentally benign and operationally simple method would find tremendous application in streamlining the synthesis of various drugs and synthetically useful intermediates. Chiral version of this azidohydroxylation process is currently underway in our laboratory and will be reported in due course.

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