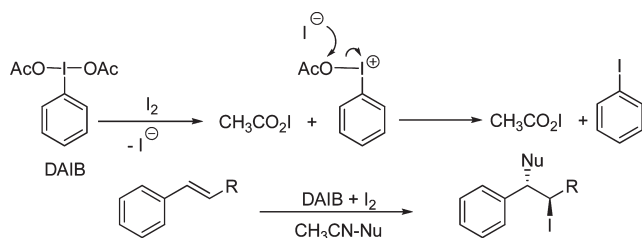# JOC Note

Versatile and Iodine Atom-Economic Co-Iodination of Alkenes

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Molecular iodine, I_2, is readily converted into 2 equiv of acetyl hypoiodite (CH_3CO_2I) via oxidation by (diacetoxyiodo)benzene (DAIB) followed by trapping of the iodide ion by acetoxyphenyl iodonium ion formed. The in situ generated CH_3CO_2I is utilized for the synthesis of 1,2-iodo-cofunctionalized derivatives of a variety of alkenes. Conversion of both iodine atoms of I_2 to I^+ sources results in 100% iodine atom economy for the reported iodo-cofunctionalization of alkenes.

Cohalogenation, the simultaneous introduction of a halogen atom and a suitable nucleophile across carbon—carbon double bonds, is a useful reaction that rapidly generates valuable synthetic intermediates bearing regio- and stereoselectively introduced vicinal functionalities for further synthetic elaborations.[1] Bromination or chlorination of alkenes carried out in the presence of nucleophilic solvents such as water, alcohols, or carboxylic acids provide ready access to halohydrins, haloethers, and halocarboxylates, three synthetically versatile intermediates.[2] In contrast, the synthesis of iodohydrins by the addition of I—OH across a carbon—carbon double bond is a difficult reaction to accomplish because of the reversibility of this addition process.[1a] Iodination of alkenes possessing tethered nucleophilic groups leads to iodocyclization and represents an important synthetic

methodology.[3] The discovery of the bioactivity of naturally occurring organohalogen compounds[4] and the continued use of organoiodo derivatives as drugs and radioactively labeled diagnostic markers[5] provides an incentive for uncovering new iodination protocols of organic compounds.[1c]

Unlike chlorination and bromination, iodination of alkenes is a considerably slower reaction due to the low electrophilicity of iodine. Activation of elemental iodine for addition to alkenes, by modifying its electrophilicity, has been achieved using transition-metal salts[6] or oxidizing agents.[7] Other electrophilic iodinating agents commonly employed for iodination of organic molecules include N-iodosuccinimide and other N—I compounds,[8] bis(pyridinium)iodonium(I) tetrafluoroborate,[9] I_2-clays,[10] and in situ generated acyl hypoidoite using a combination of elemental iodine and hypervalent iodine reagents,[11] to name a few. Though these iodinating agents are excellent sources of I^+ and provide good to excellent yields of iodinated products, the use of these reagents produces considerable waste and has no more than 50% iodine atom economy in the reaction. In keeping with the green trends in organic synthesis, environmentally benign and readily available I(III) and I(V) hypervalent iodine oxidants have also been employed for the facile oxidation of I_2 to in situ generate I^+ for iodohydrin synthesis in aqueous solvent mixtures.[7e,12] In contrast to a few select reports of in situ generation of I^+ using hypervalent iodine reagents and I_2, Suarez and co-workers have, for nearly two decades, used a combination of (diacetoxyiodo)benzene (DAIB, **1**) and I_2 as reagents to generate anomeric alkoxy radicals of glycopyrans and glycofurans en route to C1—C2 fragmentataion of the sugar molecules.[13] This apparent dichotomy, where two different reactive intermediates (I^+ vs $I^•$ or other radicals) are produced from a combination DAIB and I_2, caught our attention and we decided to explore

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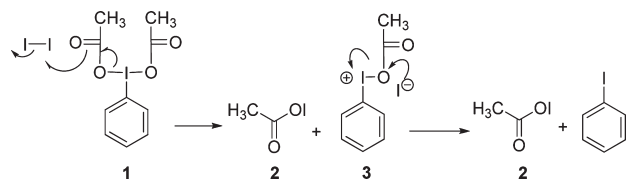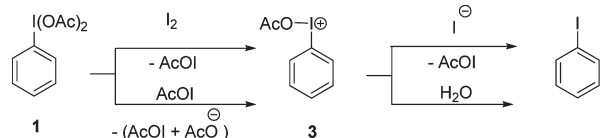
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SCHEME 1. Mechanistic Logic Behind the Hypothesis

SCHEME 2. Reductive Decomposition Pathways of DAIB

the nature of the reactive iodine moiety from this reaction further. This study was undertaken as part of an ongoing effort in our laboratory to identify green synthetic protocols using hypervalent iodine reagents.[14] We hypothesisized that oxidation of I_2 with DAIB would initially produce acetyl hypoiodite, **2**, along with acetoxyphenyl iodonium ion, **3**, which in turn can act as an iodide ion trap to ultimately yield 2 equiv of **2**, releasing iodobenzene as the reduced product as shown in Scheme 1. Such a scenario would convert both iodine atoms of I_2 into I^+ sources, enhancing the iodine atom economy to 100% in electrophilic addition to alkenes. In the absence of an alkene, the in situ formed **2** would generate radicals via homolytic fission of the O−I bond as observed by Suarez et al.[13]

Reduction of DAIB with I_2 in CD_3CN−D_2O was first examined by ^1H NMR with an eye toward developing a green co-iodination protocol for alkenes using 0.5 equiv of DAIB and I_2 in acetonitrile containing a variety of nucleophilic additives. Surprisingly, even the addition of 0.05 equiv of I_2 to an NMR sample of DAIB in 1:1 CD_3CN−D_2O showed a rapid and complete disappearance of the signals due to **1** with a concomitant formation of iodobenzene. This unexpected observation, however, was suggestive of a catalytic role of I_2 (and **2**) in the reductive decomposition of DAIB as shown in Scheme 2. The observation also indicated that in presence of an alkene the in situ generated **2** could potentially be used as an electrophilic I^+ source in the co-iodination of alkenes in solvents containing suitable nucleophilic additives. Cinnamyl alcohol **4** with its reactive allylic alcohol functional group was chosen as the initial alkene to test this hypothesis. We surmised that the rapid reaction between DAIB and I_2 would substantially reduce or completely eliminate the potential for the oxidation of the allylic alcohol functionality by the free hypervalent oxidant. ^1H NMR spectral monitoring of an equimolar mixture of DAIB and **4** in CD_3CN−D_2O with increasing amounts of I_2, as shown in Figure 1 and Table 1, shows a quantitative formation of the iodohydrin **5A** by the use of only 0.52 equiv
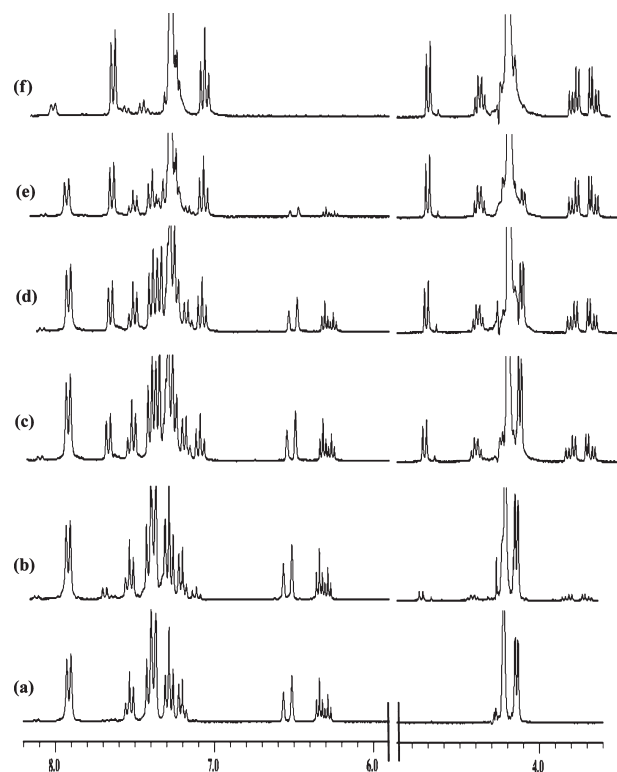
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FIGURE 1. ^1H NMR spectra in CD_3CN−D_2O of (a) 1:1 mixture of DAIB and cinnamyl alcohol, **4**, (b) with the addition of 0.075 equiv of I_2, (c) with the addition of 0.23 equiv of I_2, (d) with the addition of 0.31 equiv of I_2, (e) with the addition of 0.42 equiv of I_2, and (f) with the addition of 0.52 equiv of I_2.

TABLE 1. Correlation of Yields of 5A and Iodobenzene
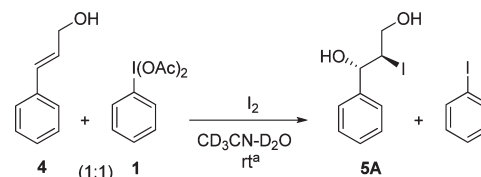
entry	I_2 (equiv)	yield[b] (%) of **5A**	yield[b] (%) of iodobenzene
1	0.0		
2	0.075	12	10
3	0.23	40	30
4	0.31	53	40
5	0.42	83	53
6	0.52	100	100

[a]Spectra were recorded after 10 min of stirring subsequent to each addition of I_2. [b]Determined by ^1H NMR.

of I_2 in the reaction, attesting to the postulated 100% iodine atom economy for the conversion. The extent of iodobenzene produced after each addition of I_2 is slightly more than what is expected from the reductive decomposition of DAIB by I_2 alone. The complete reduction of DAIB to iodobenzene when **4** is completely consumed from the reaction (entry 6) clearly indicates that the reaction of **2** with **4** is considerably faster than the reduction of DAIB by **2**.

Next, we decided to test the scope of other nucleophiles in the reaction for the synthesis of a wide range of co-iodinated products of **4**. We were cognizant of the fact that success of such an attempt would depend on the amount of the

TABLE 2. Co-Iodination Derivatives of Cinnamyl Alcohol, 4

entry	nucleophile	product	yield,%[a]
1	methanol	**5B**	87
2	ethylene glycol	**5C**	84
3	1-butanol	**5D**	72
4	2-chloroethanol	**5E**	62
5	3-chloro-1-propanol	**5F**	69
6	1,3-propanediol	**5G**	75
7	benzyl alcohol	**5H**	60
8	Sodium azide	**5I**[b]	72

[a]Isolated yield. [b]Isolated from a solid-state reaction.

TABLE 3. Co-Iodination Derivatives of Select Alkenes

Alkene		Product	yield, %
6	methanol	**13**	93
	benzyl alcohol	**14**	65
	1,3-propanediol	**15**	72
7	benzyl alcohol	**16**	60
8	water	**17A**	58
		17B	32
9	water	**18A**	70
		18B	trace
10	RCO₂H(int)	**19**	65
11	methanol	No reaction	
12	water	**20**	72

nucleophilic additive present in the reaction medium and how effectively I⁻ is trapped by acetoxyphenyl iodonium ion **3**, suppressing the formation of the diiodo derivative. With nucleophilic cosolvents, as in the case of the synthesis of **5A−C**, the formation of the diiodo derivative was not a major concern nor was an observed contaminant when 1.0 equiv of DAIB was used along with 0.6 equiv.of I₂. Two approaches were taken to minimize the formation of the diiodo derivative when the nucleophilic component could not be employed as a cosolvent in the reaction. Apart from the obvious use of an excess of the nucleophile (5.0 equiv), we also observed that the use of 1.5 equiv of DAIB in conjunction with 0.75 equiv of I₂ in the reaction improved the yield of the desired co-iodinated derivatives **5D−I**. The reactions reported in Table 2 were carried out at rt with most reaching completion within 2 h. No other regioisomeric products were observed. The anti stereochemistry of the addition was deduced from mechanistic considerations and in comparison with the literature reported spectral data for the known derivatives, **5A** and **5B**.[15] The nucleophiles employed for

reactions listed in Table 2 provided cofunctionalized derivatives carrying a broad range of functional groups amenable for further synthetic manipulations. It is noteworthy that the benzyl derivative **5H** carries both a protected secondary alcohol group as well as the unprotected primary alcohol group of the original alkene substrate. The labile azido derivative **5I** was obtained through a solid state reaction. A mixture of **4**, DAIB, **1**, I₂, and NaN₃ was carefully ground[16] with a mortar and pestle after the mixture self-reacted to form a paste. The azido derivative **5I** was isolated from the reaction mixture by dichloromethane extraction.

Using the developed reaction procedure, we extended the co-iodination protocol to include a diverse array of alkenes to test the generality of the method.[17] As shown in Table 3,

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desired reaction products were generally obtained in good to excellent yields. Use of water or methanol as cosolvents in the reaction gave exclusively the co-iodinated product(s). Alkenes **4**, **6**, and **7** gave only the indicated and expected regioisomeric product. Alkenes **8** and **9** gave both regioisomeric products with the major product obtained by the attack from the least hindered side of the presumed iodonium ion intermediate by the nucleophile. The O*H* signal in the ^{1}H NMR spectra of **17A** and **17B** appeared coupled to the α C*H*/C*H*$_2$ protons, making the identification facile. Identification of **18A** and **18B** was made on the basis of chemical shift arguments with the −C*H*$_2$OH signal in **18A** more deshielded than −C*H*$_2$I in **18B**. While iodolactone **19** was readily obtained form **10**, the electron-deficient double bond in **11** failed to react.[18] When subjected to the co-iodination protocol, the diene **12** provided a 72% yield of **20**, establishing an apparent selectivity of the procedure for electron-rich alkenes.

In conclusion, we have developed a versatile and iodine atom-economic co-iodination protocol for alkenes. A variety of nucleophiles could be employed to readily access a wide range of functionalized derivatives for further synthetic elaborations, and the procedure appears to be selective toward electron-rich double bonds in diene substrates.

Experimental Section

General Procedure for Co-Iodination of Alkenes. To a solution of alkene (2.0 mmol) and the nucleophilic additive (10 mmol) in acetonitrile (12 mL) were added (diacetoxyiodo)benzene, **1** (3.0 mmol), and I$_2$ (1.5 mmol) in one portion, and the mixture was stirred at rt for 2 h, during which time the solution turned reddish orange in color. The reaction mixture was then poured in water (40 mL) and extracted with dichloromethane (2 × 30 mL) subsequent to decolorizing the reaction mixture with the addition of required amount of solid NaHSO$_3$. The combined organic extract was dried over anhydrous MgSO$_4$ and evaporated to yield the crude product along with iodobenzene, which was conveniently removed by evaporation by placing the crude product in an open beaker in a well-ventilated fumehood overnight. The crude product was then purified by column chromatography (petroleum ether/dichloromethane) on silica.

2-Iodo-3-(2-hydroxyethoxy)-3-phenylpropan-1-ol, 5C. ^{1}H NMR, δ (300 MHz, CDCl$_3$): 7.35 (m, 5H, Ar-H), 4.70 (d, *J* = 9.0 Hz, 1H,

C3-*H*), 4.35 (m, 1H, C2-*H*), 4.13 and 3.83 (d of AB, *J* = 3.0, 12.0 Hz, C*H*$_2$OH), 3.73 (m, 2H, −OC*H*$_2$CH$_2$OH), 3.49 (m, 2H, −OCH$_2$C*H*$_2$OH), 2.51 (brs, 2H, −O*H*s). ^{13}C NMR, δ (75 MHz, CDCl$_3$): 138.8, 128.8, 128.7, and 127.6 (Ar-*C*s), 85.3 (Ar-*C*HO−), 71.0, 65.8, and 61.7 (O*C*H$_2$CH$_2$− and *C*H$_2$OH), 39.9 (*C*HI). HRMS (EI): *m/z* calcd for C$_{11}$H$_{15}$O$_3$I 322.00664, found 322.00443.

2-Iodo-3-benzyloxy-3-phenylpropan-1-ol, 5H. ^{1}H NMR, δ (300 MHz, CDCl$_3$): 7.36 (m, 10H, Ar-H), 4.69 (d, *J* = 6.0 Hz, 1H, C3-*H*), 4.46 and 4.30 (AB, *J* = 12.0 Hz, −OC*H*$_2$Ph), 4.42 (m, 1H, C2-*H*), 3.84 (m, 2H, −C*H*$_2$OH), 2.82 (t, *J* = 6.0 Hz, 1H, −CH$_2$O*H*). ^{13}C NMR, δ (75 MHz, CDCl$_3$): 138.9, 137.3, 128.9, 128.7, 128.2, 128.1, and 127.8 (Ar-*C*s), 85.3 (Ar-*C*HO−), 71.7 and 64.5 (−O*C*H$_2$Ph− and −*C*H$_2$OH), 39.4 (*C*HI). HRMS (tof ES+): *m/z* calcd for (MH$^+$) C$_{16}$H$_{18}$O$_2$I 369.0352, found 369.0355.

17A. ^{1}HNMR, δ (300 MHz, CDCl$_3$): 7.36−7.26 (m, 10H, Ar-H), 6.90 (s, 1H, Ar$_2$C*H*O−) 4.73 (m, 1H, −C*H*I), 4.47 (m, 1H, −C*H*I), 3.76 (t, *J* = 7.0 Hz, −C*H*$_2$OH), 3.24 and 3.14 (dAB q, 2H, *J* = 16.0, 6.0, 7.0 Hz, −COC*H*$_2$CHI−), 2.08 (t, *J* = 7.0 Hz, −CH$_2$O*H*, D$_2$O exchangeable). ^{13}C NMR, δ (75 MHz, CDCl$_3$): 169.9 (−*C*O), 139.7, 128.6, 127.3, and 127.2 (Ar-*C*s), 77.8 and 68.1 (Ar$_2$*C*O− and −*C*H$_2$OH), 44.8 (−*C*HI), 28.1 (−CO*C*H$_2$−). HRMS (electrospray): *m/z* calcd for C$_{17}$H$_{17}$NaO$_3$I (M + Na) 419.0120, found 419.0127.

17B. ^{1}H NMR, δ (300 MHz, CDCl$_3$): 7.35−7.26 (m, 10H, Ar-H), 6.90 (s, 1H, Ar$_2$C*H*O−) 4.00 (m, 1H, −C*H*I), 3.32− 2.76 (two sets of overlapping dAB q, −COC*H*$_2$CHI−), 4.47 (m, 1H, −C*H*I), 3.76 (t, *J* = 7.0 Hz, −C*H*$_2$OH), 3.24 and 3.14 (dAB q, 2H, *J* = 16.0, 6.0, 7.0 Hz, −COC*H*$_2$CH(OH)− and −CH(OH)-C*H*$_2$I), 2.77 (d, *J* = 7.0 Hz, −CHO*H*, D$_2$O exchangeable). ^{13}C NMR, δ (75 MHz, CDCl$_3$): 170.9 (−*C*O), 139.7, 128.7, 127.2, and 127.1 (Ar-*C*s), 77.8 and 67.5 (Ar$_2$*C*O− and −*C*HOH), 41.8 (−*C*H$_2$I), 12.2 (−CO*C*HI−). HRMS (EI): *m/z* calcd for C$_{17}$H$_{17}$O$_3$I 396.02228, found 396.02108.

Supporting Information Available: All experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra of newly synthesized derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See the Supporting Information for experimental details and spectral data of all isolated products.

(18) Electron-deficient double bonds of *trans*-chalcone and coumarin also failed to produce any cofunctionalized derivatives.