Ortho-substituted iodobenzenes as novel organocatalysts for bromination of alkenes†

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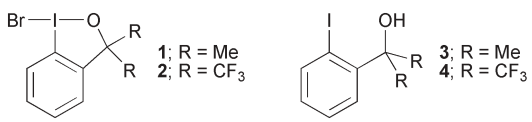
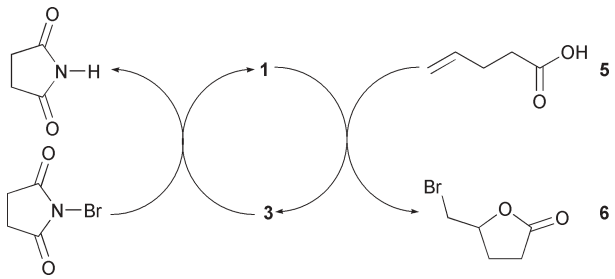
Suitably *ortho*-substituted iodobenzenes act as organocatalysts for the transfer of electrophilic bromine from *N*-bromosuccinimide to alkenes *via* the intermediacy of bromoiodinanes.

Recently we demonstrated that bromoiodinanes **1** and **2** are readily prepared in a single step by reaction of *N*-bromosuccinimide (NBS) with carbinols **3** and **4** respectively.[1] Subsequently, bromoiodinane **1** proved to be an efficient electrophilic bromine source for transfer to arenes or alkenes. A significant observation of these bromination reactions is that the only by-product observed is carbinol **3**. Since carbinol **3** is converted directly into **1** by the action of NBS, and given that carbinol **3** is the sole by-product of the subsequent bromination event, the bromination reaction should be able to be rendered catalytic in carbinol **3**. In this communication we demonstrate that the reaction can indeed be rendered catalytic in carbinol **3** with bromoiodinane **1** acting as the actual catalytic brominating agent. We also show that superior catalysts are available by increasing the nucleophilicity of the *ortho*-substituent. This is a rare example of a system which has a catalytic cycle with iodine in the I(I) and I(III) oxidation states.[2,3] To the best of our knowledge it also constitutes the first organocatalytic transfer of electrophilic bromine to alkenes.

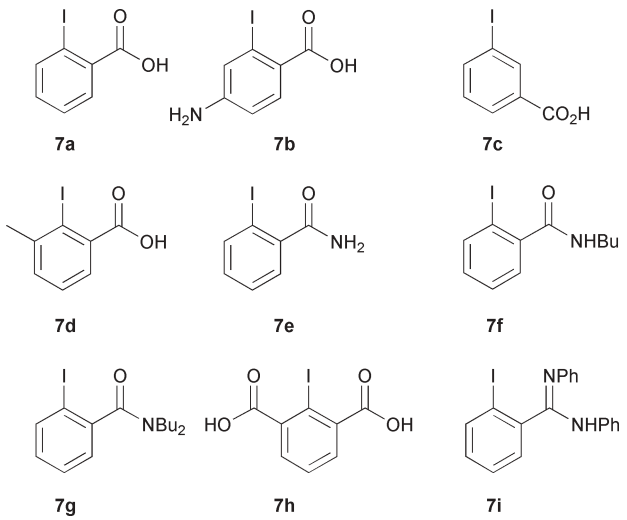


We chose to examine the bromolactonisation of 4-pentenoic acid **5** into bromolactone **6**[4] for the purpose of developing a catalytic bromination of alkenes (Table 1). In the control experiments without any catalyst (entry 1) the extent of bromolactonisation after 0.5 h is insignificant. After 15 h, 20% bromolactonisation of **5** into **6** has occurred. Thus the background bromination rate using NBS only is slow. The use of ditrifluoromethylcarbinol **4** as catalyst (25 mol%) resulted in a modest increase in conversion of **5** into **6** to 32%. At the same catalyst loading carbinol **3** catalysed the reaction to quantitative conversion in the same time period. The cyclisation is extremely clean and, apart from resonances for the catalyst and succinimide, only the desired product **6** could be detected by ^{1}H and ^{13}C NMR. The difference between the catalytic activities of **3** and **4** may be attributed to the more nucleophilic oxygen atom of **3**. A catalytic cycle invoking the intermediacy of the bromoiodinane **1** is shown below (Scheme 1).



Scheme 1 Catalytic cycle involving bromoiodinane **1**.

On the basis of the above results, it is to be expected that other *ortho*-substituted iodobenzenes with pendant nucleophilic groups should function as catalysts by formation of bromoiodinane intermediates.



Accordingly, a series of iodobenzoic acids and derivatives were screened (Table 1, entries 4–12). 2-Iodobenzoic acid **7a**‡ proved to be superior as a catalyst (10 mol%) giving quantitative conversion to **6** in 6 h at room temperature. Amino derivative **7b**,[5] which should boost the nucleophilicity of the carboxylic acid group by resonance proved still more superior. 3-Iodobenzoic acid (**7c**), where the carboxylic acid group is now *meta* to the iodine gave no increase in conversion relative to the control experiment, consistent with the need to form a bromoiodinane with an O–I–Br

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† Electronic supplementary information (ESI) available: Preparation and full characterising details of catalysts **7g** and **7i**, and substrates **10–14**. See DOI: 10.1039/b604130b

Table 1 Catalytic bromolactonisation of **5** into **6**[a]

Entry	Catalyst	Loading (mol%)	Time/h	Conversion[c] (%)
1	—	—	0.5 (15)	2 (20)
2	**4**	25	15	32
3	**3**	25	15	100
4	**7a**	10	6	100
5	**7b**	10	3	100
6	**7c**	10	24	25
7	**7d**	10	19	53
8	**7e**	10	2	72
9[b]	**7f**	10	0.5	100
10	**7g**	10	0.33	100
11	**7h**	10	<1.5	100
12	**7i**	10	<0.5	100

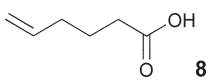
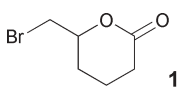
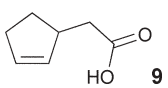
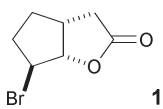
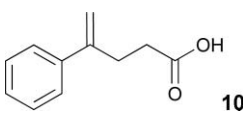
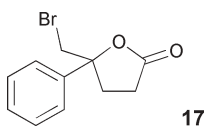
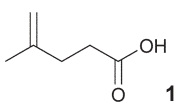
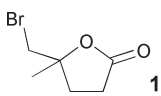
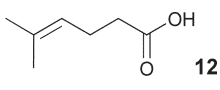
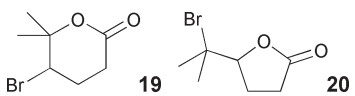
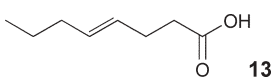
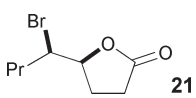
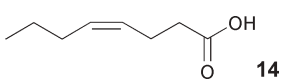
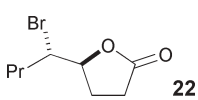
[a] All reactions performed with 1.0 eq NBS in $CDCl_3$ at rt. [b] 1.2 eq NBS. [c] Conversion determined by ^1H NMR.

three-centre four-electron bond. Control experiments with just iodobenzene or benzoic acid as potential catalysts (not shown in Table 1) gave no increase in conversion. Further evidence for the intermediacy of a bromoiodinane comes from the use of 3-methyl-2-iodobenzoic acid **7d** as catalyst, where the sp^3-hybridised carbon atom of the methyl group at the 3-position would engender a steric clash with the bromine atom in the putative bromoiodinane. This iodobenzene acts as a catalyst but the conversion relative to 2-iodobenzoic acid is much reduced.

Incorporating a more nucleophilic oxygen atom as part of an amide group *ortho* to the iodo group gives even more superior catalysts. The inductive effect of added alkyl groups on moving along the 1° (**7e**),[6] 2° (**7f**)[7] and 3° (**7g**)§ amide series is also clearly evident. Dicarboxylic acid **7h**[8]—a catalyst with a pendant nucleophilic group at both *ortho* positions of the iodobenzene—was found to be a superior catalyst compared to 2-iodobenzoic acid **7a**. Finally, amidine **7i**¶ proved to be an excellent catalyst too, as expected on the basis of nucleophilicity. The above experiments demonstrate that (i) the pendant functional group is required to be positioned *ortho* to the iodine atom on the benzene ring, (ii) for a given *ortho*-positioned functional group increasing its nucleophilicity results in superior catalysts and (iii) substitution of an sp^3-hybridised group at the other *ortho* position retards the catalytic ability. All these effects are consistent with the intermediacy of a bromoiodinane which is the electrophilic bromine source. Further, catalysts of higher activity are available by introduction of two pendant nucleophilic groups at both *ortho* positions of the iodobenzene *cf.* **7h** *vs.* **7a**.

A series of other bromolactonisation substrates **8–14**‖ were screened using highly active catalyst **7i** (Table 2). All the substrates cyclised smoothly to give bromolactone products **15–22**.** The

Table 2 Catalytic bromolactonisation of substrates **8–14** with catalyst **7i**[a]

Entry	Substrate	Time/h	Product(s)	Conversion[b] (%)	Isolated yield[c] (%)
1	 **8**	1	 **15**	100 (<5)	89
2	 **9**	0.5	 **16**	100 (0)	91
3	 **10**	0.5	 **17**	100 (14)	93
4	 **11**	0.5	 **18**	100 (100)	98
5	 **12**	1.5	 **19** **20**	100 (13)[d]	83[e]
6	 **13**	1	 **21**	100 (12)[f]	81[g]
7	 **14**	0.25	 **22**	100 (0)	90

[a] All reactions performed with 10 mol% **7i** and 1.0 eq NBS in $CDCl_3$ at rt. [b] Conversion determined by ^1H NMR. The percentage conversion in the control experiment without catalyst is given in parentheses. [c] Isolated yield after chromatography. [d] The ratio of **19** : **20** was 1 : 1 in the catalysed reaction and 8 : 2 in the uncatalysed reaction. [e] Combined yield: 43% of **19**; 40% of **20**. [f] A minor isomer (<10%) was observed in both the catalysed and uncatalysed reaction. [g] A 6-ring lactone was isolated in 6% yield. It was identified by the characteristic IR stretch at 1719 cm^{-1}.

products are all consistent with the intermediacy of bromonium ions followed by intramolecular attack of the nucleophilic carboxylate. Two factors are at play in determining the ring-size of the bromolactone product. The nucleophile prefers to attack the bromonium ion at its most substituted carbon, consistent with the stabilisation of partial positive charge there. Secondly, the *exo* ring-closing process is preferredto the *endo* mode. With the exception of substrate **12**, both these factors are reinforcing and a single bromolactone product is observed. For substrate **12**, a "mis-matched" substrate, both the 5 and 6-ring lactones are observed. It is interesting to note that the product distribution changes markedly in the catalysed *versus* uncatalysed reaction for this substrate. Finally, the isomeric *E* and *Z* unsaturated acids **13** and **14** give two different diastereoisomers, consistent with the stereospecific ring-opening of a bromonium ion. For all the bromolactonisation products, the ring sizes were readily identified by inspection of the lactone stretching frequency in the IR spectra. For example 5-ring lactone **20** displays a stretching frequency of 1780 cm^{-1}, whereas 6-ring lactone **19** shows a characteristic stretch at 1724 cm^{-1}.

In conclusion we have developed the first organocatalytic method for the transfer of electrophilic bromine to alkenes. We invoke a catalytic cycle involving I(I) and I(III) oxidation states. These results should provide a platform for the development of a highly efficient asymmetric bromination reaction of prochiral alkenes.

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Notes and references

‡ **7a**, **7c** and **7d** are all commercially available iodobenzoic acids.

§ **7g** was prepared by *N*,*N*-alkylation of benzamide **7e** with bromobutane. Full details are given in the ESI.†

¶ Amidine **7i** was prepared by the method of Daoust and Lessard for amidine preparation from amides [ref. 9] starting from 2-iodo-*N*-phenylbenzamide [ref. 10]. Full details are given in the ESI.†

‖ Acids **8–14** are all known compounds. 5-Hexenoic acid **8** and 2-cyclopentene-1-acetic acid **9** are commercially available. γ,δ-Unsaturated acids **11**, **12** and **13** are prepared by Johnson–Claisen rearrangement [ref. 11] of the appropriately substituted prop-2-en-1-ol with triethylorthoformate, followed by hydrolysis of the resulting ethyl ester. Acid **10** is prepared by the action of a Wittig reagent on ethyl 4-oxo-4-phenylbutyrate, followed by ester hydrolysis. *Z*-Unsaturated acid **14**, was prepared by the Wittig reaction of the phosponium salt of ethyl 4-bromobutyrate with butyraldehyde followed by ester hydrolysis. Full details are given in the ESI.†

** Data for bromolactones **15–22**: 6-Bromomethyltetrahydropyran-2-one (**15**): R_f 0.30 (2 : 8, EtOAc : petroleum ether); FT IR (NaCl) ν_{max} 1738 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.52–4.42 (m, 1H, OC*H*), 3.55–3.41 (m, 2H, CH_2Br), 2.65–2.37 (m, 2H, CH_2), 2.16–1.61 (m, 4H, CH_2CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.4, 78.6, 33.8, 29.4, 26.3, 18.1; MS (CI^+) 212, 210 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_6H_{13}{}^{79}BrNO_2$ 210.0130, found 210.0120.

6-Bromohexahydrocyclopenta[*b*]furan-2-one (**16**): R_f 0.30 (1 : 9, EtOAc : petroleum ether); FT IR (NaCl) ν_{max} 1778 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.04 (d, *J* = 6.2 Hz, 1H, OC*H*), 4.41 (d, *J* = 4.5 Hz, 1H, C*H*Br), 3.20–3.03 (m, 1H, C*H*), 2.85 (dd, *J* = 18.5, 10.2 Hz, 1H, C(O)C*H*H), 2.47–2.00 (m, 4H, CH_2), 1.62–1.49 (m, 1H, C*H*H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.5, 90.5, 52.9, 36.0, 35.9, 33.1, 31.4; MS (CI^+) 224, 222 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_7H_{13}{}^{79}BrNO_2$ 222.0130, found 222.0122.

5-Bromomethyl-5-phenyldihydrofuran-2-one (**17**): R_f 0.13 (4 : 6, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1783 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40–7.35 (m, 5H, Ar*H*), 3.72 (d, *J* = 11.3 Hz, 1H, H*H*CBr), 3.67 (d, *J* = 11.3, 1H, *H*HCBr), 2.85–2.73 (m, 2H, CH_2), 2.60–2.44 (m, 2H, CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.6, 140.8, 128.9, 128.8, 125.0, 86.5, 41.2, 32.5, 29.2; MS (CI^+) 274, 272 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_{11}H_{15}{}^{79}BrNO_2$ 272.0286, found 272.0274; Anal. calcd for $C_{11}H_{11}BrO_2$ C, 51.79; H, 4.35; found: C, 51.86; H, 4.39.

5-(Bromomethyl)-5-methyl-γ-butyrolactone (**18**): R_f 0.26 (3 : 7, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1776 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.52 (d, *J* = 10.8 Hz, 1H, CH*H*Br), 3.44 (d, *J* = 10.8 Hz, 1H, C*H*HBr), 2.61–2.68 (m, 2H, CH_2), 2.41–2.29 (m, 1H, CH*H*), 2.13–1.97 (m, 1H, CHH_2), 1.54 (s, 3H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.9, 84.2, 39.6, 31.6, 29.3, 25.5; MS (CI^+) 212, 210 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_6H_{13}{}^{79}BrNO_2$ 210.0130, found 210.0125.

5-Bromo-6,6-dimethyltetrahydropyran-2-one (**19**): mp 45–47 °C; R_f 0.30 (3 : 7, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1724 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 8.0, 4.0 Hz, 1H, C*H*Br), 2.80 (ddd, *J* = 18.4, 7.9, 6.3 Hz, 1H, C*H*H), 2.60 (ddd, *J* = 18.5, 7.5, 6.3 Hz, 1H, C*H*H); 2.52–2.24 (m, 2H, CH_2), 1.53 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.2, 83.3, 52.5, 28.2, 27.8, 27.4, 26.1; MS (CI^+) 226, 224 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_7H_{15}{}^{79}BrNO_2$ 224.0286, found 224.0279.

5-(1-Bromo-1-methylethyl)-γ-butyrolactone (**20**): mp 43–45 °C; R_f 0.40 (3 : 7, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1780 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.30 (t, *J* = 7.2 Hz, 1H, OC*H*), 2.72–2.48 (m, 2H, CH_2), 2.43–2.16 (m, 2H, CH_2); 1.76 (s, 3H, CH_3), 1.74 (s, 3H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.5, 85.9, 65.6, 30.5, 29.5, 28.7, 24.6; MS (CI^+) 226, 224 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_7H_{15}{}^{79}BrNO_2$ 224.0286, found 224.0280; Anal. calcd for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35; found: C, 40.74 H, 5.46.

(1*R**,2*S**)-5-(1-Bromobutyl)-γ-butyrolactone (**21**): R_f 0.34 (4 : 6, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1781 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.50 (q, *J* = 7.0, 1H, *H*CO), 4.04 (ddd, *J* = 10.0, 6.9, 3.4 Hz, 1H, *H*CBr), 2.67–2.35 (m, 3H, CH_2), 2.21–2.05 (m, 1H, CH*H*), 1.98–1.85 (m, 1H, CH*H*), 1.81–1.54 (m, 2H, CH_2), 1.52–1.33 (m, 1H, CH*H*), 0.92 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.4, 81.4, 57.6, 36.7, 28.6, 26.0, 20.4, 13.4; MS (CI^+) 240, 238 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_8H_{17}{}^{79}BrNO_2$ 238.0443, found 238.0442.

(1*S**,2*S**)-5-(1-Bromobutyl)-γ-butyrolactone (**22**): R_f 0.32 (4 : 6, petroleum ether : Et_2O); FT IR (NaCl) ν_{max} 1782 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.61 (ddd, *J* = 7.0, 6.0, 3.0 Hz, 1H, OC*H*), 4.03 (ddd, *J* = 8.0, 5.0, 3.0 Hz, 1H, *H*CBr), 2.66 (ddd, 17.5, 11.0, 6.0 Hz, 1H, C*H*H), 2.53 (dd, *J* = 10, 7.5 Hz, 1H, C*H*H), 2.47–2.31 (m, 1H, C*H*H), 2.22–2.09 (m, 1H, C*H*H), 1.94–1.75 (m, 2H, CH_2), 1.70–1.54 (m, 1H, C*H*H), 1.51–1.32 (m, 1H, C*H*H), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3): ^{13}C NMR (68 MHz, $CDCl_3$) δ 176.6, 81.0, 57.8, 36.6, 28.4, 25.5, 20.9, 13.4; MS (CI^+) 240, 238 (M + NH_4^+); HRMS calcd for (M + NH_4) $C_8H_{17}{}^{79}BrNO_2$ 238.0443, found 238.0433; Anal. calcd for $C_8H_{13}BrO_2$: C, 43.36; H, 5.93; found: C, 43.53; H, 5.93.

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