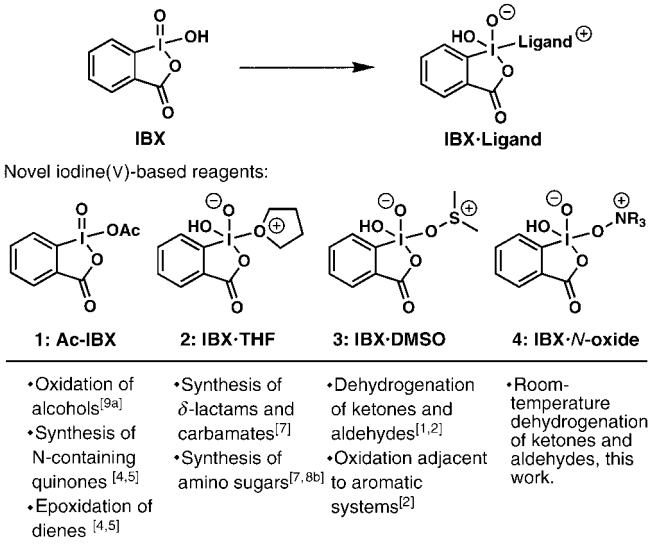
Modulation of the Reactivity Profile of IBX by Ligand Complexation: Ambient Temperature Dehydrogenation of Aldehydes and Ketones to α,β-Unsaturated Carbonyl Compounds**

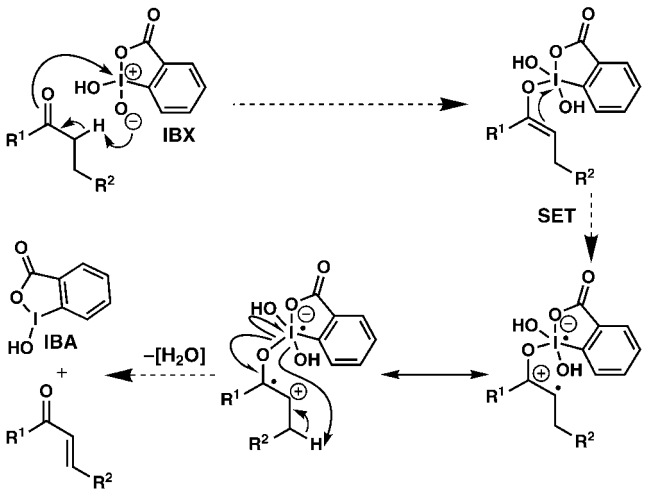
K. C. Nicolaou,* Tamsyn Montagnon, and Phil S. Baran

We have recently reported[1, 2] that the use of IBX (*o*-iodoxybenzoic acid)[3] represents a highly adept method for accessing the coveted, yet synthetically challenging, α,β-unsaturated carbonyl motif by effecting the dehydrogenation of ketones and aldehydes at elevated temperatures. Our interest[4–8] in this unique iodine(v) species has grown further owing to the tantalizing discovery that its chemistry can be modulated by complexation with a variety of ligands, thus leading to dramatic changes in its reactivity profile.[2, 8a, 10] The ligand appended to IBX not only allows moderation of the reagent's reactivity, but also differentiation between reaction pathways when a number of alternatives are available (Scheme 1).[2] Herein, we report the discovery and elucidation of this new and exciting concept and its application to the development of a room-temperature dehydrogenation reaction of carbonyl compounds which tolerates a greater breadth of functional groups than previously realized. This development became possible through the introduction of a new class of oxidants, the complexes of IBX with *N*-oxides (**4**, Scheme 1), which often exhibit superior reactivity to that of the parent reagent.



Scheme 1. Access to, and reactivity of novel iodine(v)-based reagents formed by complexation of IBX with different ligands.

Extensive investigations[2] into the original IBX-mediated dehydrogenation reaction demonstrated that at elevated temperatures, IBX dissolved in DMSO acted as a single electron transfer (SET) agent and as such effected oxidation adjacent to carbonyl functionalities to furnish their α,β-unsaturated counterparts (Scheme 2). On a number of occasions, however, when these reactions were performed in deuterated DMSO and monitored by means of ^{1}H NMR spectroscopy, unexpected signals were observed which we surmised could derive from a complex between DMSO and IBX (**3**, Scheme 2). Because these observations were made only in samples that had been subjected to heating at $>50\,^{\circ}C$, and since our procedure to dehydrogenate carbonyl species required elevated temperatures, we speculated that it might be a complex of IBX and DMSO that was the active agent in these oxidation reactions. We were, therefore, pleased to find that heating IBX in DMSO at 75 °C for 30 min provided a solution, which upon cooling to 25 °C could indeed effect limited dehydrogenation of a test substrate, cyclooctanone (**5**, see Figure 1, trace d). The conversion after this activation process was greater than that observed in a parallel experiment with IBX that had merely been dissolved in DMSO at room temperature (Figure 1, trace e). With these promising results in hand, the search for other IBX complexes with improved reactivity was immediately initiated.



Scheme 2. Postulated mechanism for the IBX-mediated dehydrogenation of ketones and aldehydes to α,β-unsaturated carbonyl compounds.

A number of well-characterized complexes of IBX with hydroxy and 1,2-dihydroxy compounds and IBX analogues have been reported in the literature,[9b] having been observed during studies into the Dess-Martin periodinane (DMP)- and IBX-mediated oxidation of alcohols. Furthermore, we were mindful of the dramatic effect that a switch in reaction media

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produced during our forays into the IBX-mediated cyclization or oxidation of multifunctionalized molecules and the importance of solvent (THF) coordination in this instance.[2, 8a] We surmised, however, that heteroatom oxide ligands (e.g. DMSO), when appended to IBX, might provide a unique electronic environment around the iodine center which could enhance the propensity of these reagents to serve as electron sinks. As such, we focused our first study on this category of potential ligands; the results are illustrated in Figure 1.[11]

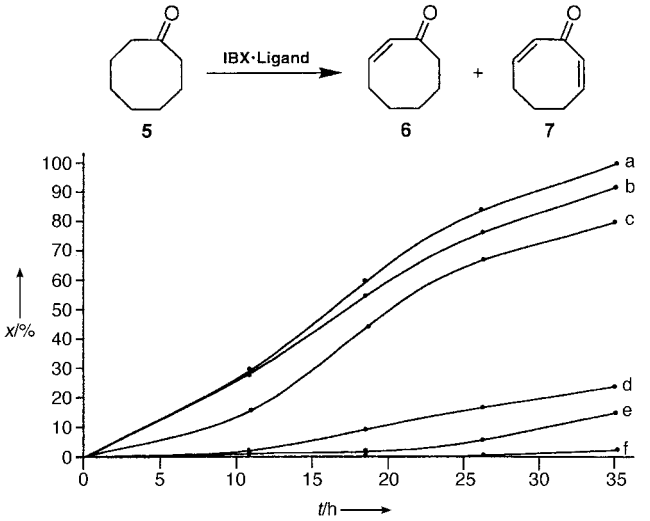

Figure 1. Graph of the rate of conversion of cyclooctanone (**5**) into dehydrogenated products (*cis* enone **6** and dienone **7**) over time, for different IBX · ligand systems: a) IBX · MPO; b) IBX · NMO; c) IBX · trimethylamine-*N*-oxide; d) IBX · DMSO formed by dissolution at 75 °C for 30 min; e) IBX · DMSO formed by dissolution at 25 °C; f) IBX · DMSO formed by dissolution at 90 °C for 20 min (leads to significant quantities of IBA from the reduction of IBX by DMSO which inhibits the desired reaction[2]). Reagents and conditions: IBX/ligand 1:1 (2.2 equiv), [D$_6$]DMSO, 25 °C, conversion monitored by means of ^{1}H NMR spectroscopy. x = Total dehydrogenation.

The formation of a distinct complex was most easily detected in the case of *N*-methylmorpholine-*N*-oxide (NMO). Thus, when NMO and IBX (1:1) were dissolved in deuterated DMSO at room temperature, 100 % conversion into a complex was clearly observed (^{1}H and ^{13}C NMR spectroscopy, see Figure 2).

The most gratifying result to emerge from this initial survey of potential ligands was observed with 4-methoxypyridine-*N*-oxide (MPO), which resulted in the clean and effective conversion of cyclooctanone (**5**) into the dehydrogenated products (**6** and **7**, Figure 1, trace a). The success of this ligand relative to other *N*-oxides[11] can be rationalized as resulting from two key features of MPO: mesomeric stabilization of the positive charge by the methoxy substituent, and the inclusion of the *N*-oxide moiety on the aromatic nucleus, thus preventing oxidative degradation of the ligand under the reaction conditions. Subsequent experimentation demonstrated that this complex, when employed in the dehydrogenation reaction of carbonyl substrates, is not only general but also mild and highly efficient (see Table 1). However, for optimal results, certain conditions must be fulfilled, particularly with

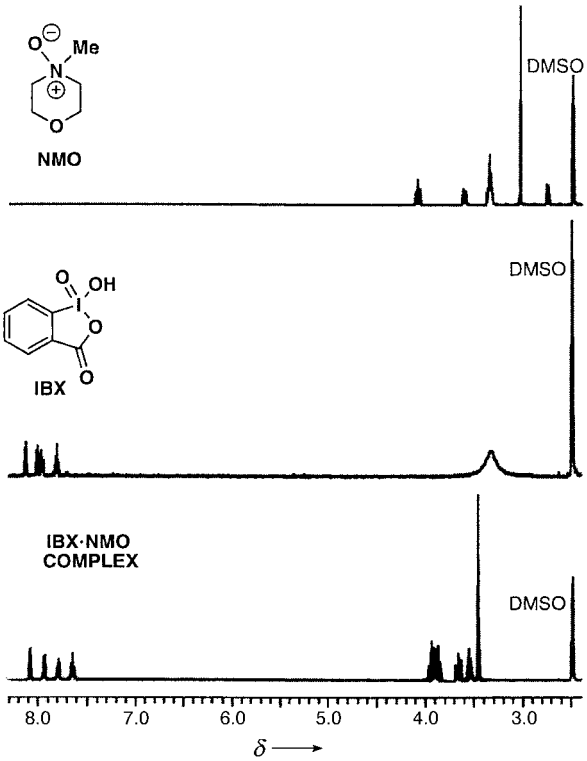

Figure 2. ^{1}H NMR spectra (500 MHz, [D$_6$]DMSO) of NMO (top), IBX (center), and the observed NMO · IBX complex (bottom).

respect to the quality of IBX, the concentration, and the substrate solubility (see Table 2 and Experimental Section).

Substrates that previously did not lead to products in satisfactory yields for a variety of reasons, perform well under the present conditions (Table 1, entries 8, 10, 12, and 17). Thus, the advantages of this method are particularly apparent with acid-labile substrates and in cases in which β-elimination is possible. Furthermore, the first productive example of the inclusion of an alkyl amine in a substrate subjected to IBX-mediated dehydrogenation was observed (Table 1, entry 17). The success of the reaction of this challenging substrate can be attributed directly to the lower temperature employed, since substrates with an amine functionality decompose readily when exposed to IBX at elevated temperatures. The IBX · MPO complex is the reagent of choice for the dehydrogenation of reactive or volatile aldehydes, because the method is particularly efficient and mild, and minimal purification is required (Table 1, entries 5 – 8). Furthermore, other IBX-induced SET reactions[2, 8a] such as benzylic oxidations[8c] do not compete with carbonyl dehydrogenation (Table 1, entries 15 and 16).

In conclusion, we have unearthed new details about the nature of the oxidant in the IBX-mediated dehydrogenation of carbonyl compounds originally discovered in these laboratories[1, 2] which suggest that the active species in this reaction is most likely a complex between IBX and DMSO. By using insight gained in the rational design of new oxidants, IBX · MPO was developed as an effective dehydrogenation reagent for carbonyl compounds and exhibits high selectivity under remarkably mild conditions. The precise origins of the accelerating effect induced by the *N*-oxide complexes **4** in this

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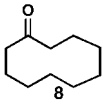
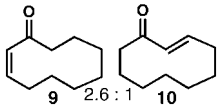
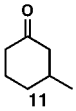
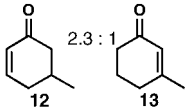
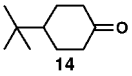
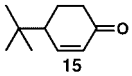
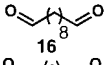
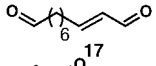
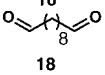
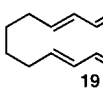
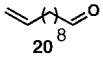
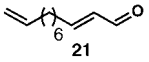
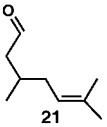
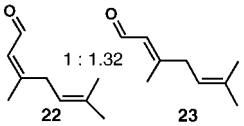
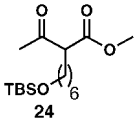
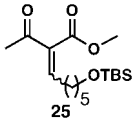
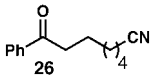
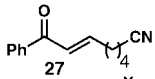
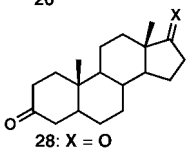
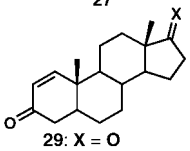
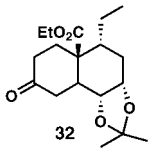
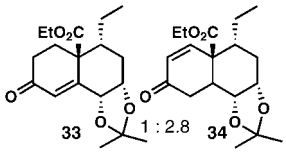
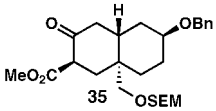
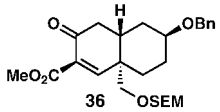
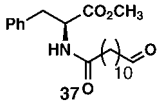
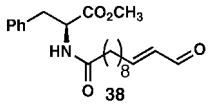
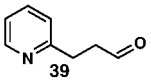
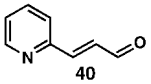
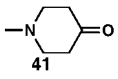
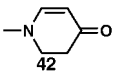
Tabelle 1. Facile room temperature dehydrogenation of ketones and aldehydes using IBX · MPO.[a]

Entry	Substrate	Product(s)	Conditions IBX · MPO [equiv]	Conditions t [h]	Yield [%][b]
1	 5	 7	3.5	18	96
2	 8	 9 2.6 : 1 10	1.8	24	78
3	 11	 12 2.3 : 1 13	2.5	32	79
4	 14	 15	1.8	36	86
5	 16	 17	2.2	22	84
6	 18	 19	4.0	48	78[c]
7	 20	 21	2.5	30	88
8	 21	 22 1 : 1.32 23	1.4	42	72
9	 24	 25	1.8	20	77
10	 26	 27	2.5	24	74
11	 28: X = O	 29: X = O	2.2	32	92
12	30: X = α-H, β-OTBS	31: X = α-H, β-OTBS	1.8	40	81
13	 32	 33 1 : 2.8 34	2.2	48	78
14	 35	 36	1.5	15	91
15	 37	 38	1.5	15	88
16	 39	 40	3.0	45	43[e]
17	 41	 42	2.2	48	62[f]

[a] Reactions were carried out on a 0.1 – 1.0 mmol scale in DMSO. [b] Yield of isolated chromatographically pure compound. Some starting material was always recovered; however, the quantity is only specified when it exceeds 20 %. [c] Plus 11 % enone. [d] Plus 21 % recovered starting material. [e] Plus 37 % recovered starting material. [f] Plus 34 % recovered starting material. MPO = 4-methoxypyridine-*N*-oxide; SEM = 2-(trimethylsilyl)ethoxymethyl; Bn = benzyl; TBS = *tert*-butyldimethylsilyl.

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Tabelle 2. Effect of concentration and solvent composition on the outcome of the IBX · MPO-mediated dehydrogenation reaction.[a]

Entry	Substrate (M)	Solvent	IBX · MPO [equiv]	Time [h]	Yield [%][b]
1	**35** (0.20)	DMSO	1.5	15	0
2	**35** (0.20)	DMSO/THF (1:1)	1.5	15	< 40
3	**35** (0.20)	DMSO/CH_2Cl_2 (2:1)	1.5	6	92
4	**35** (0.20)	DMSO/CH_2Cl_2 (1:1)	1.5	15	91
5	**14** (0.40)	DMSO	2.0	40	68
6	**14** (0.50)	DMSO	2.0	40	72
7	**14** (0.75)	DMSO	2.0	40	87
8	**16** (0.36)	DMSO	2.2	22	82
9	**16** (0.48)	DMSO	2.2	22	76
10	**16** (0.55)	DMSO	2.2	22	73
11	**16** (0.55)	DMSO/CH_2Cl_2 (2:1)	2.2	22	86

[a] Reactions were carried out on a 1.0 mmol scale. [b] Yield of isolated chromatographically pure compound.

dehydrogenation reaction is the subject of continuing research. Elucidation of these features should facilitate further rational designs toward expanding this new area of chemistry whose applications in organic synthesis are expected to be widespread. These results introduce a new paradigm for modifying the iodine(V) nucleus and, hence, controlling its reactivity profile.

Experimental Section

IBX (1.2 mmol) and MPO[12] (1.2 mmol) were added to DMSO (see Table 2 for concentration effect) and stirred at ambient temperature until complete dissolution (15–60 min). The carbonyl compound (0.5 mmol) was added, and the mixture was stirred vigorously at the same temperature. The reaction progress was monitored by thin-layer chromatography. The reaction mixture was diluted with an equal volume of aqueous $NaHCO_3$ (5%) solution and extracted with diethyl ether (3×). The combined organic phase was filtered through a pad of celite and then washed with saturated $NaHCO_3$ solution, water, and brine. After drying ($MgSO_4$), the organic layer was concentrated to yield the crude product, which could be further purified by column chromatography (silica gel).

For optimal results in this reaction the following points should be noted: a) in cases in which the substrate was not soluble in the DMSO solution of IBX · MPO, increasing amounts of CH_2Cl_2[13] were added as co-solvent until dissolution, and/or the rate was optimized (see Table 2); b) a large excess of IBX · MPO complex is not recommended, as the rather insoluble IBA formed under these conditions causes precipitation of IBX; in this respect it is also important that the IBX quality is assured by preparation in strict accordance to the method of Santagostino[14] and subsequent checking by means of ^1H NMR spectroscopy; c) commercial DMSO (Aldrich) was used directly without prior drying; furthermore, it was noted that anhydrous solvent (sequential drying over activated 4-Å molecular sieves) was deleterious to the yield; d) IBX is light-sensitive, thus the reaction vessel was covered with aluminum foil.[15]

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[11] In addition to the ligands shown in Figure 1, nBu$_3$P=O, tBuOH, 2-picoline-*N*-oxide, and 4-phenylpyridine-*N*-oxide were examined, but the rate of reaction for these complexes was lower than that of uncomplexed IBX under the same conditions.

[12] The commercially available hydrate of MPO, which is considerably less hygroscopic than NMO, was used. The IBX · NMO complex is prepared in the same manner and can also be successfully employed at ambient temperature, although the reaction times are longer and the yields show greater variation with this reagent.

[13] When CH_2Cl_2 is used as cosolvent the reaction rate is retarded; however, its addition was frequently necessary to obtain complete solubility of the substrate (see Table 2, entries 1–4).

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Oxidation of Silyl Enol Ethers by Using IBX and IBX · *N*-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones**

K. C. Nicolaou,* David L. F. Gray, Tamsyn Montagnon, and Scott T. Harrison

Our recent explorations into the chemistry of iodine(V) reagents have highlighted their remarkable synthetic utility.[1–8] In particular, IBX (*o*-iodoxybenzoic acid) has proved to have a rather unique set of properties which can be appropriately exploited to manipulate the course of a reaction.[7, 9] In the preceding paper,[9] we delineated the

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