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Iodine(V) Reagents in Organic Synthesis. Part 4. *o*-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes

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Abstract: *o*-Iodoxybenzoic acid (IBX), a readily available hypervalent iodine(V) reagent, was found to be highly effective in carrying out oxidations adjacent to carbonyl functionalities (to form α,β-unsaturated carbonyl compounds) and at benzylic and related carbon centers (to form conjugated aromatic carbonyl systems). Mechanistic investigations led to the conclusion that these new reactions are initiated by single electron transfer (SET) from the substrate to IBX to form a radical cation which reacts further to give the final products. Fine-tuning of the reaction conditions allowed remarkably selective transformations within multifunctional substrates, elevating the status of this reagent to that of a highly useful and chemoselective oxidant.

Introduction

In the preceding three papers,[1−3] we have presented an array of useful transformations mediated by the iodine(V)-based reagents Dess−Martin periodinane (DMP), *o*-iodoxybenzoic acid (IBX), and Ac-IBX (see Figure 1). In the current paper, we expand on this theme with a description of a powerful new methodology which employs IBX for the facile and selective oxidation adjacent to carbonyl and aromatic moieties.

As a prelude to this article, we begin with a brief perspective of hypervalent iodine reagents in organic synthesis.[4] Prior to these studies, the chemistry of iodine(V)-based reagents was relegated mainly to the realm of alcohol oxidation and other closely related processes.[5] Contrary to this, iodine(III)-based reagents have been widely examined, and their chemistry plays a critical role in a plethora of well-known reactions.[6] A possible cause for the lack of extensive research into the promising iodine(V) manifold (see Figure 1 for selected examples) could

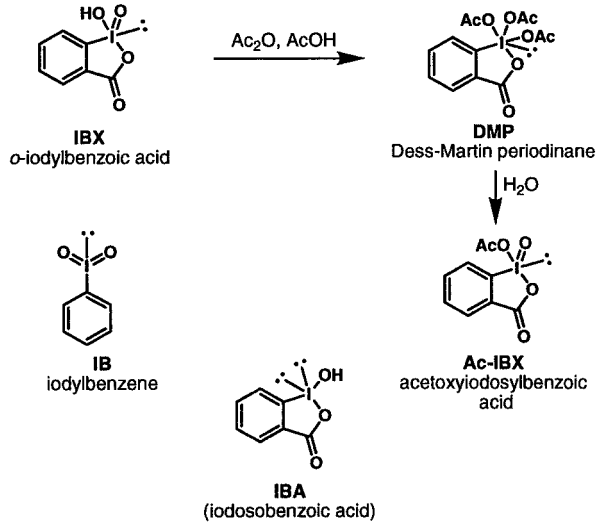


Figure 1. Selected hypervalent iodine (III and V) reagents and their relationships.

be due to the fear that these compounds are explosive and inconvenient to synthesize. Although IBX was reported to be explosive,[7] it was later found that the sample in question was contaminated with residual bromine which is likely to have contributed significantly to this negative feature.[8] Since then, a superior protocol for the oxidation of *o*-iodobenzoic acid to IBX has been developed by Santagostino et al.[9] The Santagostino method[9] is extremely simple to perform and uses inexpensive Oxone[10] in water, thus eliminating the risks posed by dangerous contaminants (e.g., bromine). All the reactions with IBX and

(1) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212−2220.
(2) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2221−2232.
(3) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233−2244.
(4) For selected recent reviews, see: (a) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (b) Varvoglis, A.; Spyroudis, S. *Synlett* **1998**, 221. (c) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (e) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. (f) Varvoglis, A., Ed. *Hypervalent Iodine In Organic Synthesis*; Academic Press: San Diego, 1996; p 256.
(5) For the oxidation of alcohols, see: (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (c) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. For closely related processes: (d) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485. (e) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945.
(6) For selected reviews see ref 4 and Kirschning, A. *J. Prakt. Chem.* **1998**, *340*, 184.
(7) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *July 16*, 3.
(8) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

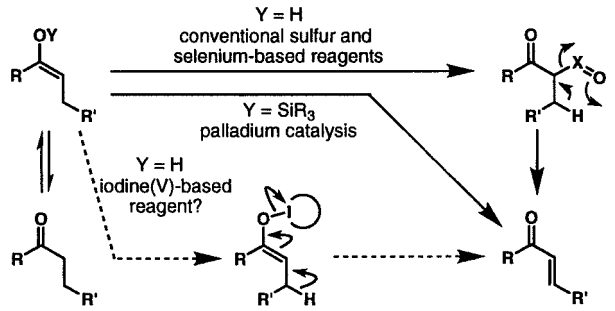


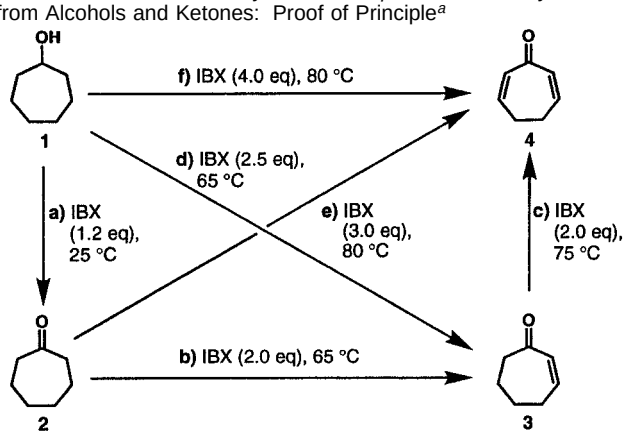
Figure 2. Mechanistically inspired design of the IBX-based process for introduction of α,β-unsaturation adjacent to a carbonyl function.

DMP reported in this series of papers are homogeneous, generally conducted at 45−90 °C, and have been repeatedly carried out on multigram scales without any incidents.

The ubiquity and utility of α,β-unsaturated compounds in organic chemistry coupled with the difficulties that are often associated with their fabrication led us to investigate the possibility of accessing them using an iodine(V)-based reagent (see Figure 2). Methods to introduce unsaturation adjacent to a carbonyl functionality have been developed over the years;[11] however, many of the protocols rely on toxic and foul selenium reagents in one- or two-step procedures.[12] Another regularly employed tactic involves preparation of the corresponding silylenol ether from the parent carbonyl compound followed by palladium-catalyzed oxidation, a sequence in which both steps require expensive reagents.[13] Prior to the realization that IBX behaves as a single electron transfer (SET) oxidant[14] at elevated temperatures, we had postulated that the enol form of a carbonyl group might be captured by IBX to effect the desired oxidation as shown in Figure 2. Because IBX is known to oxidize alcohols,[5a] the prospect of accomplishing multiple oxidative processes in one operation was particularly enticing. Indeed, we found the IBX-mediated dehydrogenation of carbonyl compounds to be mild, swift, and highly efficient.[15] Primary and secondary alcohols or aldehydes and ketones are all suitable substrates for this remarkably general reaction (vide infra).

Further investigations strongly suggested that IBX behaves as a SET-based oxidant in this dehydrogenation and in other reactions examined,[14] leading us to hypothesize that benzylic positions should also succumb to the oxidative power of this versatile reagent. If chemoselective and easily controllable, such a process would be a valuable tool in organic synthesis in view of the ready availability and robustness of the potential substrates and the widespread utility of the corresponding oxidized products.[16] As with the dehydrogenation of carbonyl compounds, the selective oxidation at the carbon adjacent to aromatic systems was found to be notably general.[17]

Scheme 1. IBX-Induced Synthesis of α,β-Unsaturated Systems from Alcohols and Ketones: Proof of Principle[a]



[a] Reagents and conditions: (a) IBX (1.2 equiv), DMSO, 25 °C, 3 h, 98%; (b) IBX (2.0 equiv), DMSO, 65 °C, 6 h, 88%; (c) IBX (2.5 equiv), DMSO, 75 °C, 12 h, 74%; (d) IBX (2.5 equiv), DMSO, 65 °C, 6 h, 82%; (e) IBX (3.0 equiv), DMSO, 80 °C, 15 h, 81%; (f) IBX (4.0 equiv), DMSO, 80 °C, 22 h, 76%.

A full account of the discovery, scope, and generality of the IBX-mediated oxidation adjacent to carbonyl and aromatic moieties is presented herein and is accompanied by discussion of the mechanistic probes which led to the conclusion that this chemistry proceeds via a SET pathway.

Results and Discussion

1. Dehydrogenation of Carbonyl Compounds Using IBX. As alluded to earlier, we found the IBX-mediated dehydrogenation of carbonyl compounds to be general and, most significantly, controllable for different oxidation states. Thus, as shown in Scheme 1, cycloheptanol (**1**) could be directly converted to 2-cyclohepten-1-one (**3**, 82% yield) or cycloheptadienone (**4**, 76% yield) simply by varying the number of equivalents of IBX and employing slightly elevated (80 °C) temperatures to access the latter. If desired, the net reaction could also be performed in a stepwise fashion proceeding from cycloheptanol (**1**) through cycloheptanone (**2**, 98% yield) to 2-cyclohepten-1-one (**3**, 88% yield) and, finally, to cycloheptadienone (**4**, 74% yield) (Scheme 1). Aside from accomplishing multiple oxidations in the same pot with admirable efficiency and ease, the synthesis of dienones is now trivial. Cycloheptadienone (**4**), for instance, has been, despite its simplicity, a constant challenge for synthetic organic chemists often requiring laborious multistep procedures for its preparation.[18]

This smooth route to cycloheptadienone (**4**) also constitutes a formal total synthesis of tropinone (**6**) as shown in Scheme 2.[19] Thus, when cycloheptadienone (**4**) was treated with methylamine hydrochloride and K_2CO_3 in MeOH for 2 h, tropinone (**6**) was isolated in 72% yield.[19] On the basis of this favorable result, we then designed a cascade transformation commencing with cycloheptanol (**1**) and affording tropinone (**6**) in one pot. Remarkably, treatment of cycloheptanol (**1**) with IBX (4.0 equiv)

(9) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. This method affords crystalline IBX (≥95% purity) in high yields. Despite the availability of such pure IBX, heating this reagent above 200 °C is still not recommended, as is the case with most oxidants. We have stored IBX at 25 °C for an excess of 6 months with no significant degradation as judged by ^{1}H NMR analysis, provided light was excluded from the container.

(10) *OXONE* [$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$] can be purchased from Aldrich at a catalogue price of $26.20 for 1 kg.

(11) For a general review of available methods for dehydrogenation α to a carbonyl moiety, see: Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, pp 119−146.

(12) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(13) Ito, Y.; Saegusa, H.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(14) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202.

(15) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

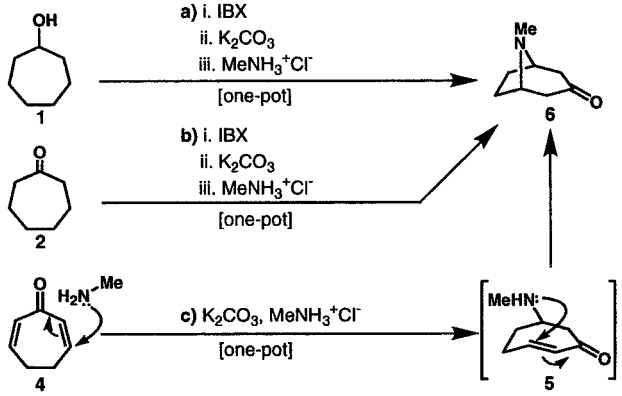
(16) Franz, G.; Sheldon, R. A. In *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Wolfgang, G., Yamamoto, Y. S., Campbell, F. T., Pfefferkorn, R., Rounsaville, J. F., Eds.; VCH: Weinheim, 1991; p 261.

(17) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

(18) Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 9.

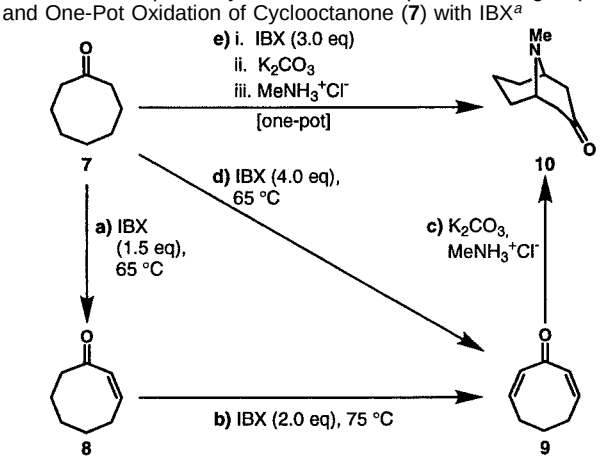
(19) Bottini, A. T.; Gal, J. *J. Org. Chem.* **1971**, *36*, 1718.

Scheme 2. One-Pot Total Synthesis of Tropinone (**6**) from Cycloheptanol (**1**), Cycloheptanone (**2**), or Cycloheptadienone (**4**) Using IBX[a]



[a] Reagents and conditions: (a) IBX (4.0 equiv), DMSO, 25−85 °C, 22 h, cool to 25 °C, add K_2CO_3 followed by $MeNH_3^+Cl^-$, 3 h, 58%; (b) IBX (3.0 equiv), DMSO, 80 °C, 22 h, cool to 25 °C, add K_2CO_3 followed by $MeNH_3^+Cl^-$, 3 h, 59%; (c) K_2CO_3, $MeNH_3^+Cl^-$, MeOH, 25 °C, 2 h, 72%.

Scheme 3. Stepwise Synthesis of the Tropinone Analogue (**10**) and One-Pot Oxidation of Cyclooctanone (**7**) with IBX[a]



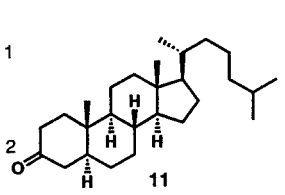
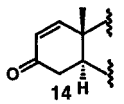
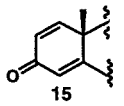
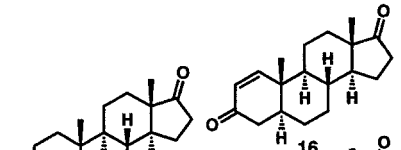
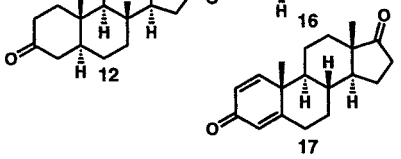
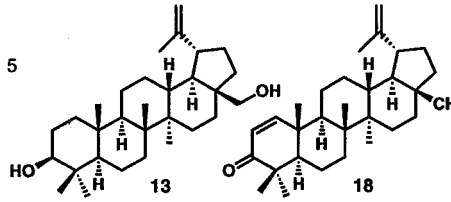
[a] Reagents and conditions: (a) IBX (1.5 equiv), DMSO, 65 °C, 6 h, **7**:**8**:**9** 1:2:1.7, 86%; (b) IBX (2.0 equiv), DMSO, 75 °C, 12 h, 82%; (c) K_2CO_3, $MeNH_3^+Cl^-$, MeOH, 25 °C, 2 h, 77%; (d) IBX (4.0 equiv), DMSO, 65 °C, 6 h, 88%; (e) IBX (4.0 equiv), DMSO, 25−85 °C, 22 h, cool to 25 °C, add K_2CO_3 followed by $MeNH_3^+Cl^-$, 3 h, 80%.

added portionwise at 25−80 °C over 22 h, followed by cooling to 25 °C and sequential addition of K_2CO_3 and methylamine hydrochloride, led to a 58% yield of tropinone (**6**) (Scheme 2). While the elegance and timeliness of this synthesis of tropinone (**6**) may not compare to the one performed by Sir Robert Robinson in 1917,[20] its efficiency and practicality does.

As shown in Scheme 3, cyclooctanone (**7**) could also be dehydrogenated to cyclooctadienone (**9**, 88% yield) in excellent yield using IBX. 2-Cycloocten-1-one (**8**) could only be obtained as the major component of a mixture (**7**:**8**:**9**, 1:2:1.7, Scheme 3). This, presumably, reflects a lower activation energy for the second oxidation when compared to that of the first and, as such, is a unique feature of the eight-membered ring. The tandem reaction to construct tropinone (**6**) (see Scheme 2) could also be applied to cyclooctanone (**7**) or cyclooctadienone (**9**) directly to furnish the tropinone analogue (**10**) in 80 and 77% yield, respectively (see Scheme 3).

The steroid backbone is often an ideal testing ground for the viability and power of a new synthetic method. As illustrated in Table 1, selective dehydrogenation of a number of steroids

Table 1. IBX-Mediated Dehydrogenation of Steroid-Based Substrates[a]

Entry	Substrate	Product	Conditions	Yield (%)[b]
1			IBX (1.5 eq) 65 °C, 24 h	80[c]
2			IBX (4.0 eq) 85 °C, 48 h	71
3			IBX (1.5 eq) 70 °C, 24 h	84[d]
4			IBX (4.0 eq) 85 °C, 48 h	72
5			IBX (6.0 eq) 85 °C, 12 h	68

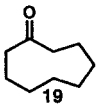
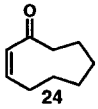
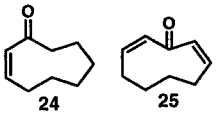
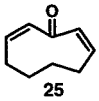
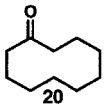
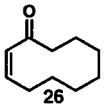
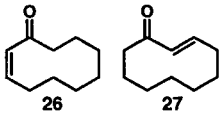
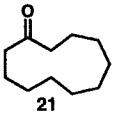
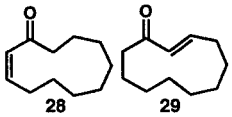
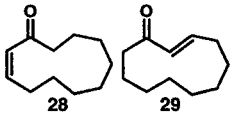
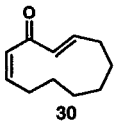
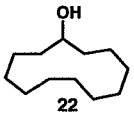
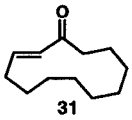
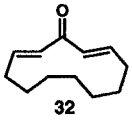
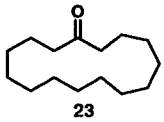
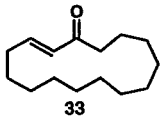
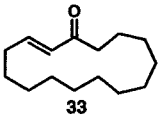
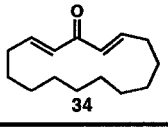
[a] Reactions were carried out on a 0.1−1.0 mmol scale in DMSO or fluorobenzene:DMSO 2:1. [b]Isolated yield of chromatographically pure compound. [c]Plus 7% isolated dienone (**15**). [d]Plus 4% isolated dienone (**17**).

(**11**−**13**) could be controlled simply by modulating the number of equivalents of IBX and the temperature employed (**14**−**18**, 68−84% yields). In this study, it was gratifying to find that the selectivity extends to the dehydrogenation of a six-membered ring in preference to a five-membered ring when both are present within the same molecule (entries 3 and 4, Table 1). The triple oxidation of diol **13** (entry 5, Table 1) to the corresponding enone-aldehyde (**18**, 68% yield) illustrates the power of this reagent to manipulate complex carbon frameworks.

When we investigated the efficacy of the oxidation with medium and large ring alcohols and ketones, we came upon a number of interesting observations. To the best of our knowledge, a systematic study of the stability and ease of formation of medium and large ring unsaturated ketones has not been reported. The product distribution of each reaction is likely to reflect the ability of the ring to accommodate an increase in the number of sp^2 hybridized carbons while balancing angle, transannular, and Pitzer strains to achieve an energy minimum.[21] Thus, when cyclononanone (**19**) (entry 1, Table 2) was submitted to the IBX reaction, clean formation of *cis*-2-cyclononen-1-one (**24**, 83% yield) was observed. On the basis of simple calculations,[22] the *cis*-enone was determined to be several kilocalories/mole more stable than the corresponding *trans*-enone. *cis*,*cis*-Cyclononadienone (**25**, 74% yield) could also be accessed

(20) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762.
(21) (a) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311. (b) Giuseppe, G. C. *Gazz. Chim. Ital.* **1986**, *116*, 683. (c) Dale, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 1000.
(22) MM3 calculations to determine total energy were performed using ChemDraw 3D (version 4.5, Cambridge Software).

Table 2. Dehydrogenation in Medium- and Large-Ring Ketones[a]

Entry	Substrate	Product(s)	Conditions	Yield (%)[b]
1	 **19**	 **24**	IBX (1.8 eq) 85 °C, 9 h	83[c]
2	"	 **24** **25**	IBX (3.0 eq) 85 °C, 30 h **24:25**, 2.1:1	62
3	"	 **25**	IBX (4.0 eq)[d] 85 °C, 22 h	74
4	 **20**	 **26**	IBX (1.8 eq) 75 °C, 9 h	88
5	"	 **26** **27**	IBX (4.0 eq) 85 °C, 30 h **26:27**, *ca* 4:1	56
6	 **21**	 **28** **29**	IBX (2.5 eq) 75 °C, 9 h **28:29**, *ca* 1:1.8	79
7	"	 **28** **29**	IBX (4.0 eq) 85 °C, 30 h **28:29**, *ca* 1:5.4	56[e]
8	"	 **30**	IBX (4.0 eq)[d] 85 °C, 22 h	81[f]
9	 **22**	 **31**	IBX (2.3 eq) 65 °C, 24 h	85
10	"	 **32**	IBX (4.0 eq) 85 °C, 24 h	71
11	 **23**	 **33**	IBX (2.0 eq) 65 °C, 24 h	83[g]
12	"	 **33**	IBX (3.0 eq) 65 °C, 60 h py (1.0 eq)	80[h]
13	"	 **34**	IBX (4.0 eq) 85 °C, 24 h	69

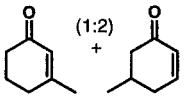
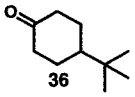
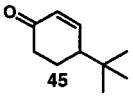
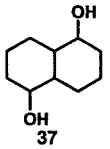
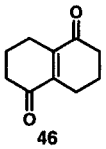
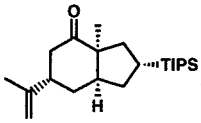
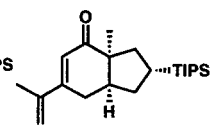
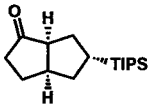
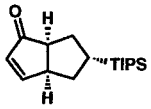
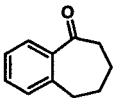
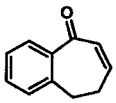
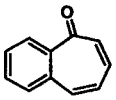
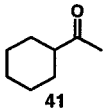
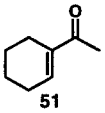
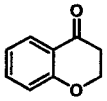
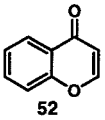
[a] Reactions were carried out on a 0.1−1.0 mmol scale in fluorobenzene: DMSO (2:1) or DMSO. [b] Isolated yield of chromatographically pure compound. [c] Plus 8% cyclononadienone (**25**). [d] IBX added in four portions at 4 h intervals. [e] Plus 3% cycloundecadienone (**3**). [f] Plus 2% cycloundecaenone (**29**). [g] Plus 8% cyclodecapentadienone (**34**). [h] Plus 6% cyclodecapentadienone (**34**); py = pyridine.

efficiently by altering the temperature and stoichiometry of IBX employed (entry 3, Table 2). Cyclodecanone (**20**) (entry 4) entered the reaction smoothly to provide *cis*-2-cyclodecen-1-one (**26**, 88% yield) as the sole product. Despite the *trans*-enone possessing a greater degree of conjugation as evidenced from the chemical shifts in the ^{1}H and ^{13}C NMR spectra, calculations revealed the cis isomer to be the more stable one.[23] Despite repeated attempts, the dienone of cyclodecanone (**20**) could not be synthesized, presumably due to excessive small-angle strain. Whitman has reported[23] that *cis*- and *trans*-cyclodecenones rapidly interconvert when treated with *p*-toluenesufonic acid in refluxing benzene via an addition elimination sequence, to yield an equilibrium mixture where the cis isomer predominates (cis:trans 24:1). Because IBX is itself mildly acidic, we considered the possibility that it too might mediate interconversion; however, when *trans*-cyclodecenone[24] was subjected to heating in DMSO at 90 °C in the presence of IBX (4 equiv) for 48 h, no interconversion was observed by ^{1}H NMR spectroscopy. Calculations on cycloundecanone derivatives[22] predicted a mixture of *cis*- and *trans*-enones resulting from the IBX dehydrogenation, since the *trans*-enone (**29**) bears only a slightly higher energy. In the event, the reaction (entry 6, Table 2) provided a mixture of *cis*- and *trans*-2-cycloundecen-1-one, favoring the latter (trans:cis ca. 1.8:1) when standard reaction conditions were applied. Interestingly, when elevated temperatures, increased amounts of IBX, and a different solvent system were utilized, the bias for the *trans*-enone (**29**) was enhanced (trans:cis ca. 5.4:1), but only by incurring a sacrifice in yield (entry 7, Table 2). Extensive investigation revealed that the mixed *cis*,*trans*-dienone (**30**, 81% yield) could be synthesized in high yield by revising the protocol so that IBX was added portionwise at intervals of 4 h (entry 8, Table 2). This adaptation proved a valuable optimization of the procedure in many cases. Higher ring systems **22** and **23** can readily accommodate a trans double bond, which has reduced Pitzer strain when compared to the analogous cis double bond, without incurring energy penalties from small angle strain because of the increased conformational freedom associated with a larger number of connecting methylene units. This ensures that these compounds consistently gave rise solely to the *trans*-enones and dienones in a controllable fashion in the IBX-mediated dehydrogenation reaction (entries 9−13, Table 2).

As shown in Table 3, the reactions of a number of other assorted cyclic systems with IBX were investigated to probe further the characteristics of this oxidation method. Significantly, the reaction of 3-methylcyclohexanone (**35**) (entry 1, Table 3) can be carried out on a 0.2 mol scale with similar efficiency (74% yield) but only utilizing 1.2 equiv of IBX. The tandem oxidation of the decalin diol **37** (entry 3, Table 3) to the corresponding dienone (**46**) in one pot and in 52% isolated yield is also impressive. Oxidations of the 6-5 fused bicycle **38** (entry 4, Table 3) and the 5-5 fused bicycle **39** (entry 5, Table 3) proceeded in excellent yield (85 and 87% yield, respectively) and with complete regioselectivity. IBX-controlled dehydrogenation of the fused aromatic cyclooctanone **40** to either the corresponding α,β-unsaturated compound (**49**, 58% yield) (entry

(23) Whitham, G. H.; Zaidlewicz, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1509.
(24) *trans*-Cyclodec-2-enone was prepared according to the procedure of Carlson, R. G.; Bateman, J. H. *Tetrahedron Lett.* **1967**, *42*, 4151 with the following modifications: the solution of *cis*-cyclodec-2-enone was irradiated for 7 min using a 450 W Hanovia medium-pressure Hg lamp and purified using flash column chromatography [silica gel, hexanes:ether, 95:5].

Table 3. IBX-Induced Dehydrogenation of Functionalized Cyclic Ketones[a]

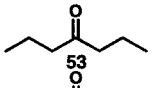
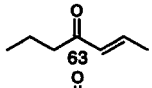
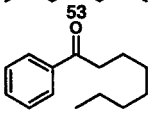
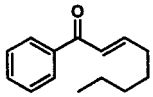
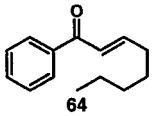
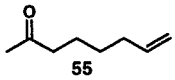
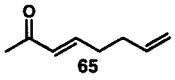
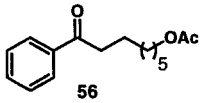
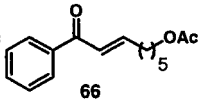
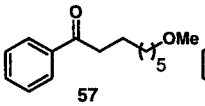
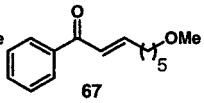
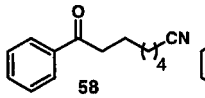
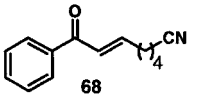
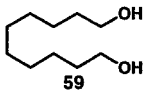
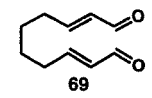
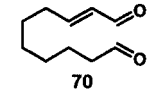
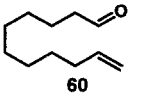
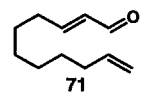
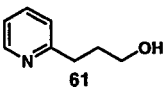
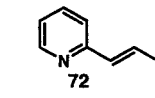
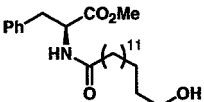
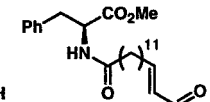
Entry	Substrate	Product	Conditions	Yield (%)[b]
1	 **35**	 **43** (1:2) + **44**	IBX (2.0 eq) 65 °C, 10 h	76[c]
2	 **36**	 **45**	IBX (1.5 eq) 70 °C, 2 h	89
3	 **37**	 **46**	IBX (6.0 eq) 85 °C, 18 h	52
4	 **38**	 **47**	IBX (4.0 eq) 85 °C, 36 h	85
5	 **39**	 **48**	IBX (2.0 eq) 85 °C, 12 h	87
6	 **40**	 **49**	IBX (2.0 eq) 70 °C, 72 h	58
7	"	 **50**	IBX (4.0 eq) 85 °C, 24 h	60
8	 **41**	 **51**	IBX (2.0 eq) 75 °C, 4 h	85
9	 **42**	 **52**	IBX (3.0 eq) 80 °C, 48 h	68

[a] Reactions were carried out on a 0.1−1.0 mmol scale in fluorobenzene: DMSO 2:1. [b]Isolated yield of chromatographically pure compound. [c]Combined isolated yield of separable isomers; TIPS = triisopropylsilyl.

6, Table 3) or the fully unsaturated benzyl tropinone (**50**, 60% yield) (entry 7, Table 3) is a notable achievement. Substitution at the α- and *β*-sites (α, entry 8; *β*, entries 1 and 4, Table 3) of the carbonyl system does not hinder the reaction, nor does it diminish its efficiency.

A variety of acyclic ketones and alcohols were then screened for reaction efficiency and functional group tolerance as depicted in Table 4. A wide range of functionalities, including acetates, methoxy groups, and primary nitriles, could be accommodated in the IBX-mediated dehydrogenation (entries 5−7, Table 4). Simple unfunctionalized systems such as **53** and **54** (entries 1 and 3, Table 4) illustrate the efficiency and ease of this oxidation. Ketone **55** (entry 4, Table 4) with an olefin group

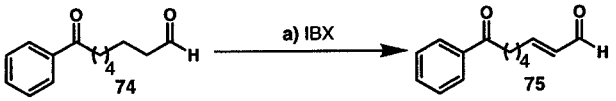
Table 4. IBX-Induced Dehydrogenation of Functionalized Acyclic Ketones[a]

Entry	Substrate	Product	Conditions	Yield (%)[b]
1	 **53**	 **63**	IBX (1.3 eq) 65 °C, 3 h	83
2	 **54**	 **64**	IBX (6.0 eq) 85 °C, 48 h	55
3	"	 **64**	IBX (6.0 eq) 85 °C, 8 h *p*-TsOH (0.3 eq)	86
4	 **55**	 **65**	IBX (2.0 eq) 80 °C, 12 h	71
5	 **56**	 **66**	IBX (2.0 eq) 80 °C, 12 h	84
6	 **57**	 **67**	IBX (3.0 eq) 80 °C, 36 h	61
7	 **58**	 **68**	IBX (1.8 eq) 80 °C, 9 h	57
8	 **59**	 **69**	IBX (8.0 eq) 80 °C, 24 h	78
9	"	 **70**	IBX (5.0 eq) 70 °C, 12 h	40[c]
10	 **60**	 **71**	IBX (2.0 eq) 80 °C, 12 h	58
11	 **61**	 **72**	IBX (4.0 eq) 70 °C, 12 h	84
12	 **62**	 **73**	IBX (2.5 eq) 65 °C, 12 h	86

[a] Reactions were carried out on a 0.1−1.0 mmol scale in fluorobenzene: DMSO 2:1 or DMSO. [b]Isolated yield of chromatographically pure compound. [c]Plus 5% isolated dienal (**69**).

embedded five carbon atoms away is of particular interest in light of the SET mechanism postulated for this reaction and because this protocol allows for the direct synthesis of a small fragile molecule that could be awkward by other means. The ease with which the reaction can be tailored to yield the desired products is ably demonstrated by the primary alcohol **59** which is conveniently converted into the corresponding α,*β*-unsaturated aldehydes **69** and **70** (entries 8 and 9, Table 4). The process works admirably well even in the presence of nitrogen-based functional groups as demonstrated by the pyridine-based alcohol **61** (entry 11, Table 4) and the protected amino acid **62** (entry 12, Table 4). A consistent observation recorded during this

Scheme 4. Chemoselective Oxidation Adjacent to an Aldehyde in the Presence of a Ketone[a]



[a] Reagents and conditions: (a) IBX (1.3 equiv), DMSO, 70 °C, 15 h, 79%.

investigation was that α-aryl ketones required a modest elevation of temperature to effect dehydrogenation (entries 2, 3, and 5−7, Table 4). This is necessary despite the tendency of such compounds to generally show an enhancement in the proportion existing as the enol tautomer when compared to similar aliphatic ketones under the same conditions;[25] it is surmised that in addition to steric hindrance the relative electron deficiency of the enol form raises the oxidation potential and thus contributes to the observed recalcitrance.

Because IBX could act as a mild acid in this reaction, we probed the effect of adding a base or an acid. Addition of *p*-TsOH (0.3 equiv)[26] tended to significantly accelerate the reaction (entry 3, Table 4), while addition of pyridine (1.0 equiv) decreased the rate of the reaction (entry 12, Table 2), yet did not effect the isolated yield after extended reaction times. This feature should allow even acid-labile carbonyl compounds and alcohols to enter smoothly into this process of unsaturation. The acceleration in rate seen upon inclusion of *p*-TsOH as an additive may be due to an increase in the population of the enol form of the carbonyl group (vide infra), or the *p*-TsOH may act as an activating ligand on IBX.[27] Because aldehydes enolize more readily than ketones and are less sterically encumbered, we expected the former to be dehydrogenated faster than the latter with IBX. Indeed, when keto aldehyde **74** (Scheme 4) was treated with IBX (1.3 equiv), the reaction proceeded to yield exclusively the α,β-unsaturated aldehyde **75** in high yield (79%) providing an indication of the degree to which selectivity can be expected when IBX is used.

Although an ionic mechanism was originally envisaged (see Figure 3A) for this IBX-mediated oxidation, the cumulative results of mechanistic investigations of other IBX-based reactions[14] at elevated temperatures led us to develop the hypothesis that the current process is more likely to proceed via a SET-based pathway as shown in Figure 3B. To gather empirical verification of our SET hypothesis, we sought evidence for the intermediacy of a radical species by using the well-established fragmentation of cyclopropylmethyl radicals.[28] The radical species proposed as an intermediate in the IBX oxidation is stabilized by resonance, and, therefore, the substrate used to test for its existence ought to be loaded with a diphenyl moiety to ensure that the equilibrium would lie at a position strongly favoring the open-chain adduct.[29] Additionally, it has been shown that the rate constant for the opening of 2,2-diphenylcyclopropylmethyl radicals is significantly larger than that of the unsubstituted cyclopropylmethyl radical,[29] thus permitting a much more unequivocal assessment of the presence or absence of a radical, when its fragmentation is used as a mechanistic probe. Thus, cyclopropyl aldehyde **81** was designed and synthesized (see Scheme 5) and was exclusively converted, in 98% yield, to conjugated diene **82** upon treatment with IBX in DMSO at 70 °C for 7 h, as shown in Scheme 5. The opening of the cyclopropyl ring was taken to provide strong support for a single electron-transfer mechanism for this process; however, further investigation was deemed desirable. Hammett analysis[30] has a

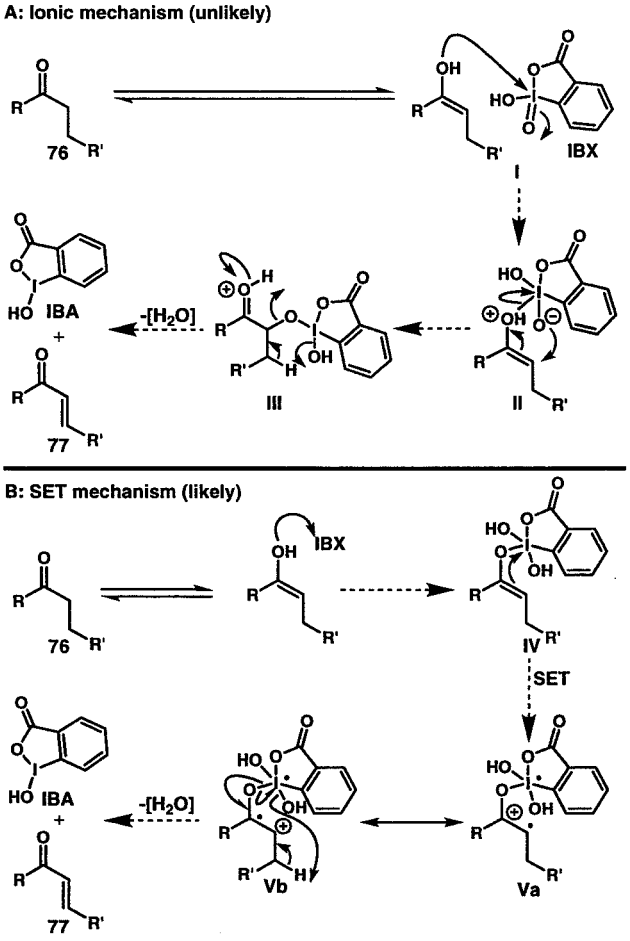
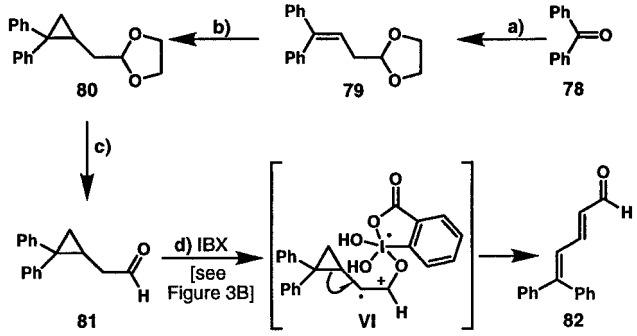


Figure 3. Possible ionic- (A) and SET-based (B) mechanisms for the dehydrogenation of carbonyl compounds by IBX. Alternatively IBX may also be considered to effect the initial enolization of the carbonyl compound to yield **IV** directly.

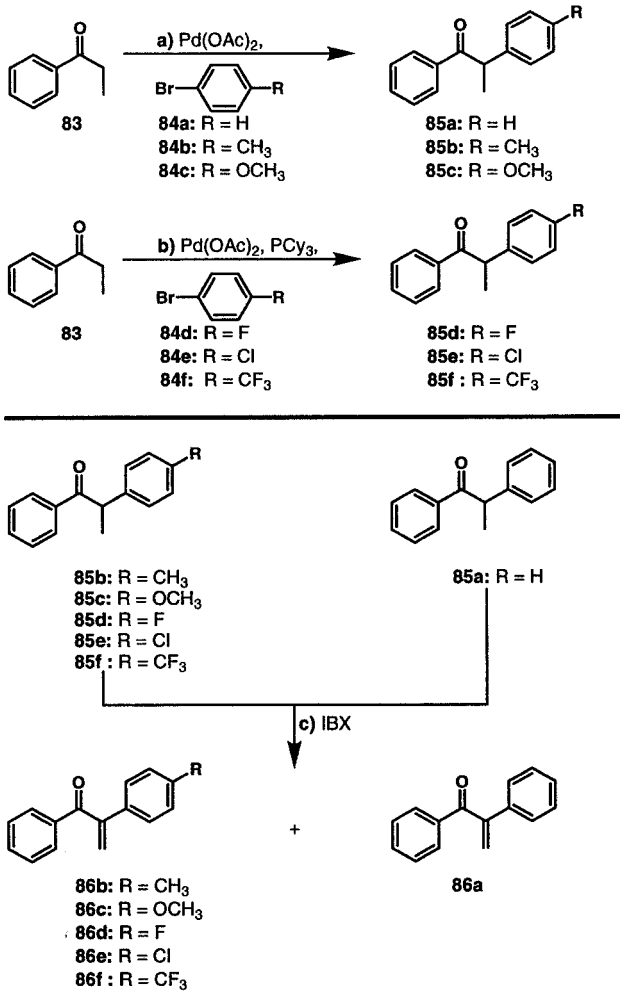
Scheme 5. Reaction of Cyclopropyl Aldehyde **81** with IBX Leads to the Ring-Opened Dienal **82**, Thus Supporting the Intermediacy of Radical Species (i.e., **VI**)[a]



[a] Reagents and conditions: (a) [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide[43] (2.0 equiv), *t*-BuOH (2.0 equiv), THF, 25 °C, 72 h, 43%; (b) Zn−Ag couple,[44] CH_2I_2 (1.3 equiv), Et_2O, reflux, 22 h, 78%; (c) AcOH:H_2O 1:1, 25 °C, 12 h, 81%; (d) IBX (2.0 equiv), DMSO, 70 °C, 7 h, 98%.

(25) Gero, A. *J. Org. Chem.* **1954**, *19*, 469.
(26) Addition of one full equiv of *p*-TsOH acid has the opposite effect and causes deceleration in the reaction rate.
(27) Zhdankin, V. V. *FIV Report* **2000**, No. 3, 140.
(28) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981.
(29) Newcomb, M.; Johnson, C. C.; Beata Manek, M.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915.

Scheme 6. Synthesis of Substrates **85a**−**f** and Determination of Relative Reaction Rates for Derivation of a Hammet Relationship and Plot[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$ (1 mol %), toluene, 80 °C, 10 h, (**85a**, 88%), (**85b**, 92%), (**85c**, 93%); (b) $Pd(OAc)_2$ (1 mol %), PCy_3 (2 mol %), toluene, 80 °C, 6 h, (**85d**, 87%), (**85e**, 72%), (**85f**, 79%); (c) IBX (2.5 equiv), *p*-TsOH (0.3 equiv), DMSO, 85 °C, 22 h.

venerable history as a means of elucidating the development and distribution of charge in the transition state of a given reaction, so it was to this method that we next turned. An array of α-aryl ketones (**85a**−**f**) with different *p*-substituents were synthesized using chemistry developed by Buchwald et al.[31] and Hartwig and Kawatsura[32] as depicted in Scheme 6. By comparing the relative rates of the reaction of substituted aryl ketones (**85b**−**f**) with the unsubstituted ketone (**85a**), a Hammett free energy relationship was derived and plotted as shown in Figure 4. A linear correlation between the ratio of reaction rate constants (k_s/k_u) and the σ_p^+ parameters[33a,b] with a negative slope ($\rho = -0.75$, $R^2 = 0.99$) was obtained, provided the data obtained from the methoxy-substituted ketone **85c** were regarded as an anomaly. It is our contention that the methoxy-substituted ketone **85c** coordinates at the iodine center via the lone pair of electrons on the ethereal oxygen thus distorting the reaction progress and leading to a unique set of kinetic data for this compound. In

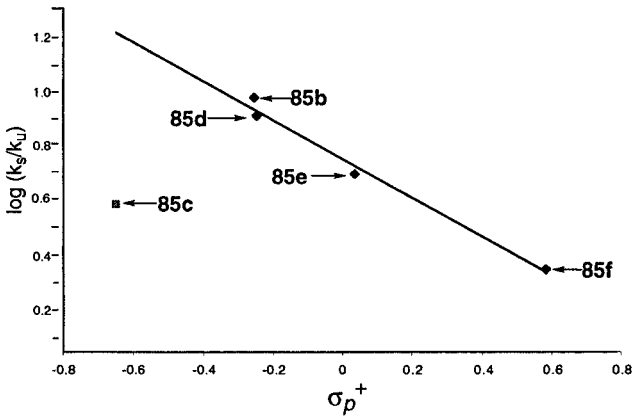


Figure 4. Plot derived using Hammett analysis of the competition reactions of substituted α-aryl ketones (**85b**−**f**) with ketone (**85a**). The gradient (ρ) = −0.75 and regression analysis give a value $R^2 = 0.99$.

this context, we have observed a number of stable IBX complexes with oxygen-bearing ligands by ^{1}H NMR spectroscopy, and this has provided the basis for current ongoing research. With this caveat in mind, the remaining data are strongly suggestive of a SET pathway. The magnitude of ρ is small, indicating only a slight dependence in this reaction on the polarizing influence of the aromatic substituents appended to the α carbon. This is consistent with a transition state bearing a radical cation and not a true oxonium ion at the center α to the carbonyl. The negative sign of ρ leads to the inference that the transition state is electron deficient when compared to the ground state which again is in accord with the proposed radical cation species. Generally, most radical reactions thoroughly investigated involve species that are regarded as being essentially neutral, and, therefore, there is no acceleration in rate when solvent polarity is increased. Radical cations are different because of the evolution from radical cation to true oxonium ion during the course of the reaction. Newcomb and Horner[34] have shown a large kinetic acceleration associated with increased solvent polarity for radical cation cyclizations which fits favorably with the use of DMSO as solvent in our protocol for the dehydrogenation of carbonyl compounds. Fluorobenzene was used in the original protocol to ensure that hydrophobic substrates were fully dissolved in the reaction media; however, it was subsequently found that addition of fluorobenzene caused a deceleration in the rate of reaction. The fluorobenzene content of the solvent mixture should, therefore, be minimized.

2. Selective Oxidation at Carbon Adjacent to Aromatic Systems with IBX. Assuming that the IBX-mediated oxidation of carbonyl compounds proceeded through a SET from the

(30) For discussion of Hammett plots, see: Lowry, T. H.; Richardson, S. K. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 748.
(31) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
(32) Hartwig, J. F.; Kawatsura, M. *J. Am. Chem. Soc.* **1999**, *121*, 1473.
(33) (a) For σ_p^+ values, see: Gardner Swain, C.; Lupton, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 4328 and references therein. (b) k_u: Rate constant of reaction **85a** → **86a**; k_s: Rate constants for reactions **85b**−**f** → **86b**−**f**. For the determination of ρ the following expression[28] was used: $k_s/k_u = \log[1 - s_r/s_t]/\log[1 - u_r/u_t]$. ρ = reaction constant; u_r and s_r = millimoles of α-aryl ketone **85a** and *p*-substituted α-aryl ketone **85b**−**f**, respectively, that reacted, or by analogy, millimoles of products **86a** and **86b**−**f** formed; u_t and s_t = initial millimoles of α-aryl ketone **85a** and *p*-substituted α-aryl ketone **85b**−**f**, respectively. (c) k_u: Rate constant of reaction **90** → **102**, k_s: Rate constants for reactions **90a**−**d**, **91**, and **94** → **102a**−**d**, **103**, and **106**. For the determination of ρ the following expression[28] was used: $k_s/k_u = \log[1 - s_r/s_t]/\log[1 - u_r/u_t]$. ρ = reaction constant; u_r and s_r = millimoles of toluene **90** and *p*-substituted toluenes **90a**−**d**, **91**, and **94**, respectively, that reacted, or by analogy, millimoles of products **102a**−**d**, **103**, and **106** formed; u_t and s_t = initial millimoles of toluene **90** and *p*-substituted toluenes **90a**−**d**, **91**, and **94**, respectively.
(34) Newcomb, M.; Horner, J. H. *J. Am. Chem. Soc.* **2001**, *123*, 4364.

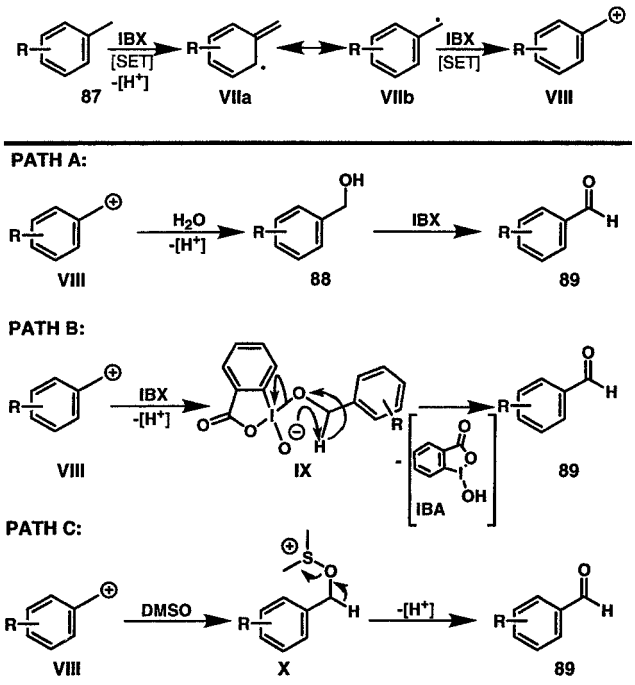


Figure 5. Postulated mechanistic pathways for benzylic oxidation using IBX.

electron-rich enol tautomer, it was reasoned that the same principle may be applicable to the oxidation of other electron-rich sites, such as the benzylic position of an aromatic ring. The postulated mechanistic underpinnings of such an IBX-mediated process are shown in Figure 5. Thus, SET from the aromatic ring of compound **87** to IBX followed by loss of a proton would lead to the radical intermediate **VIIa**. Depiction of the canonical form of this species **VIIb** illustrates how this could then undergo a second, IBX-facilitated oxidation to give the benzylic carbocation **VIII**. At this juncture, three divergent paths from intermediate **VIII** are conceivable, each using a different source of oxygen for construction of the carbonyl functionality. In path A (Figure 5), the trace amounts of water present would intercept intermediate **VIII** to furnish the benzylic alcohol **88** which would be rapidly oxidized with an additional equivalent of IBX to afford the product, aldehyde **89**. Path B involves the trapping of intermediate **VIII** with a second molecule of IBX to give intermediate **IX** whose rearrangement would then lead to aldehyde **89**. This pathway is statistically improbable since it requires the interaction of a reactive intermediate which has only a short lifetime, with a second molecule of IBX. In path C, capture of the intermediate **VIII** would occur by the solvent, DMSO (which is necessary to solubilize IBX), forming the Kornblum-type intermediate **X** which would then collapse to yield the product (**89**) upon loss of a proton. It is, however, tempting to consider another mechanism for the IBX-mediated oxidation of benzylic positions based on literature precedent for aryl π-iodine complexes and their role in single electron-transfer redox reactions[35] (Figure 6). Thus, we invoked the possibility that IBX may form a similar charge-transfer complex (**XI**, Figure 6) which could then lead to the benzyl alcohol (**88**) via intermediate species **XII**−**XV**. This requires that IBX is not only responsible for the initial

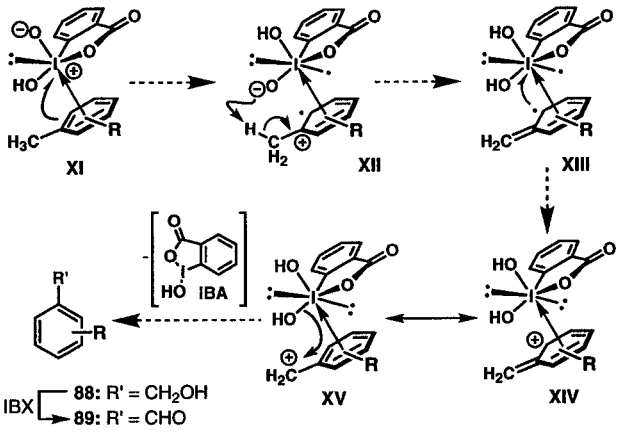


Figure 6. Concerted mechanism for the IBX-mediated benzylic oxidation.

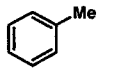
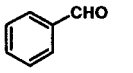
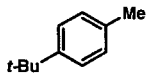
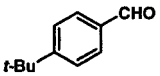
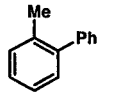
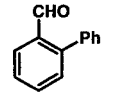
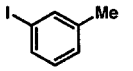
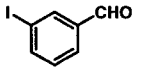
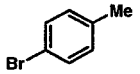
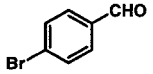
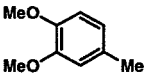
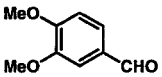
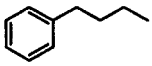
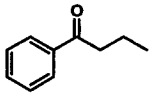
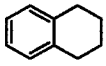
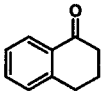
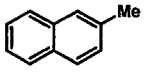
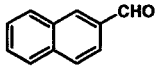
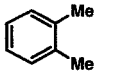
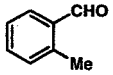
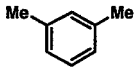
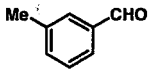
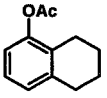
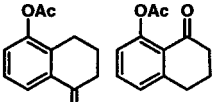
SET, but also for the ensuing oxygen transfer which could occur via intramolecular delivery and expulsion of IBA using the oxide ligand of IBX as a nucleophile (vide supra). Of course, a second molecule of IBX is then required for the oxidation of benzyl alcohol (**88**) to benzaldehyde (**89**).

With a mechanistic rationale in hand, we set out to determine the feasibility of the proposed reaction. To our delight, the oxidation of a variety of substituted toluenes and related systems proceeded in good to excellent yield as shown in Table 5 (entries 1−7). In general, the reaction was clean and efficient, proceeding in fluorobenzene:DMSO (2:1) or DMSO alone, at 80−90 °C. Overoxidation to the corresponding carboxylic acid, a common feature of transition metal-based benzylic oxidants, was not observed even in electron-rich substrates (e.g., entry 7, Table 5). The presence of halogens (entries 5 and 6, Table 5) did not deter the desired oxidation from occurring, nor did the steric hindrance of *o*-substituents (entries 4, 9, and 11, Table 5). The reaction was not limited to production of benzylic aldehydes as seen in several examples which gave benzylic ketones; thus, *n*-butylbenzene **96** smoothly enters into the reaction to furnish *n*-butyrophenone **108** (entry 8, Table 5), and similarly tetrahydronaphthalene derivatives **97** and **101** could be readily oxidized (entries 9 and 13, Table 5). Because selective mono-oxidation of aromatic rings with more than one alkyl group appended is often a challenge, we were eager to employ the IBX reaction as a possible solution to this problem. Thus, the expected retardation of the reaction by electron-withdrawing substituents (vide infra) was exploited to bring about the selective oxidation of 1,2-xylenes (**99** and **100**) and tetrahydronaphthalenes (**97** and **101**) leading to the corresponding monocarbonyl systems (entries 9, 11, 12, and 13, Table 5).

It should be emphasized that whereas the presence of olefins, *N*-heterocycles, amides, and aldehydes would ordinarily interfere with benzylic oxidations mediated by conventional reagents, the present IBX-based method performs admirably in such circumstances as shown in Table 6. Thus, oxidation of the unsaturated substituted toluenes **115** and **116** (entries 1 and 2, Table 6) with IBX proceeded smoothly in direct contrast to the use of DDQ, PDC, or ceric ammonium nitrate (CAN), all of which led to low conversion or decomposition. It was also interesting to observe the stepwise oxidation of substrate **117**. At 65 °C (2.5 equiv of IBX) the product obtained was the α,β-unsaturated aldehyde **122** (72% yield), while under more forcing conditions (4.0 equiv of IBX, 85 °C) the bis-aldehyde **123** was isolated in

(35) Lehmann, F.; Pedro, A. *J. Med. Chem.* **1972**, *15*, 404.

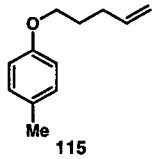
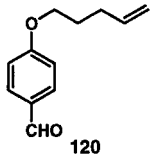
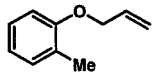
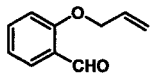
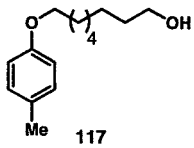
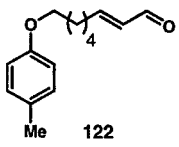
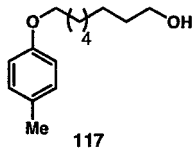
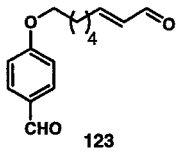
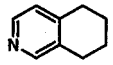
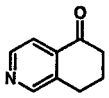
Table 5. Oxidation at Benzylic Carbon Centers with IBX[a]

Entry	Substrate	Product	Conditions	Yield (%)[b]
1	 **90**	 **102**	IBX (3.0 eq) 85 °C, 12 h	85
2	 **91**	 **103**	IBX (3.0 eq) 80 °C, 8 h	95
3	"	"	IBX 3.0 eq) 80 °C, 8 h H_2O (100 eq)	90
4	 **92**	 **104**	IBX (3.0 eq) 90 °C, 24 h	78
5	 **93**	 **105**	IBX (4.0 eq) 85 °C, 16 h	72
6	 **94**	 **106**	IBX (3.0 eq) 80 °C, 16 h	73
7	 **95**	 **107**	IBX (3.0 eq) 75 °C, 5 h	80
8	 **96**	 **108**	IBX (3.0 eq) 80 °C, 8 h	72
9	 **97**	 **109**	IBX (3. 0 eq) 80 °C, 12 h	70
10	 **98**	 **110**	IBX (3.0 eq) 80 °C, 20 h	90
11	 **99**	 **111**	IBX (3.0 eq) 85 °C, 16 h	82
12	 **100**	 **112**	IBX (3.0 eq) 85 °C, 16 h	85
13	 **101**	 **113** O (1:1) **114**	IBX (3.0 eq) 85 °C, 24 h	70

[a] Reactions were carried out on a 0.1−1.0 mmol scale in DMSO or DMSO:fluorobenzene 1:2. [b]Isolated yield of chromatographically pure compound.

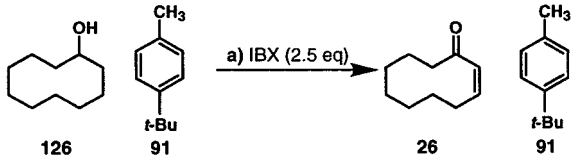
62% yield (entries 3 and 4, Table 6). The finding that the dehydrogenation of carbonyl compounds can be performed selectively over benzylic oxidation was also confirmed by the intermolecular competition experiment in which cyclodecanol (**126**) and *p*-*tert*-butyltoluene (**91**) were allowed to react with IBX (2.5 equiv, 65 °C, fluorobenzene:DMSO 2:1). The sole product isolated was *cis*-2-cyclodecen-1-one (**26**, 78% yield) with no aromatic aldehyde detected (Scheme 7).

Table 6. IBX-Induced Oxidation of Benzylic Positions in Functionalized Substrates[a]

Entry	Substrate	Product	Conditions	Yield (%)[b]
1	 **115**	 **120**	IBX (3.0 eq) 80 °C, 8 h	88
2	 **116**	 **121**	IBX (3.0 eq) 80 °C, 12 h	80
3	 **117**	 **122**	IBX (2.5 eq) 65 °C, 8 h	75
4	 **117**	 **123**	IBX (4 eq) 85 °C, 12 h	62
5	 **118**	 **124**	IBX (3.0 eq) 85 °C, 24 h	70
6	 **119**	 **125**	IBX (4.0 eq) 90 °C, 36 h	52

[a] Reactions were carried out on a 0.1−1.0 mmol scale in DMSO or DMSO:fluorobenzene 1:2. [b]Isolated yield of chromatographically pure compound.

Scheme 7. Competition Experiments Revealing that Alcohol Oxidation and Subsequent Carbonyl Dehydrogenation with IBX Are Significantly Faster Processes than Benzylic Oxidation[a]



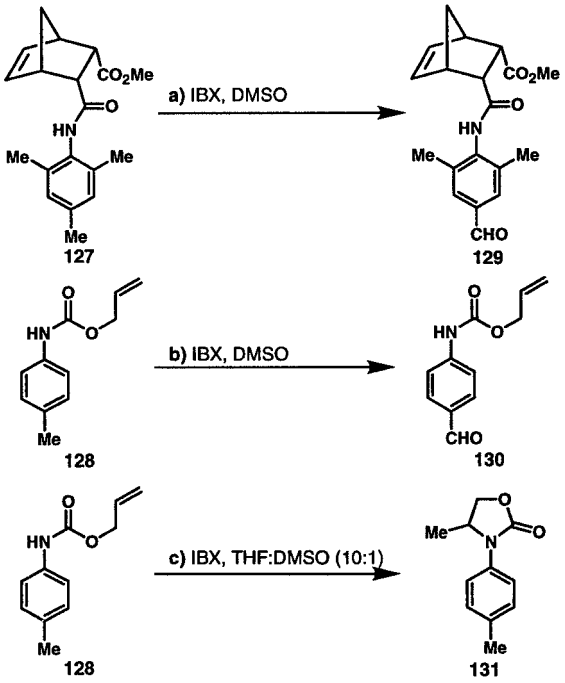
126 **91** **26** **91**

[a] Reagents and conditions: (a) IBX (2.5 equiv), DMSO or DMSO: fluorobenzene 1:2, 65 °C, 3 h, 78%.

While a slightly longer reaction time or higher temperature was necessary to effect the oxidation of N-containing aromatic systems, it is noteworthy that no N-oxidation was observed in such cases (**118** to **124** and **119** to **125**; entries 5 and 6, Table 6).

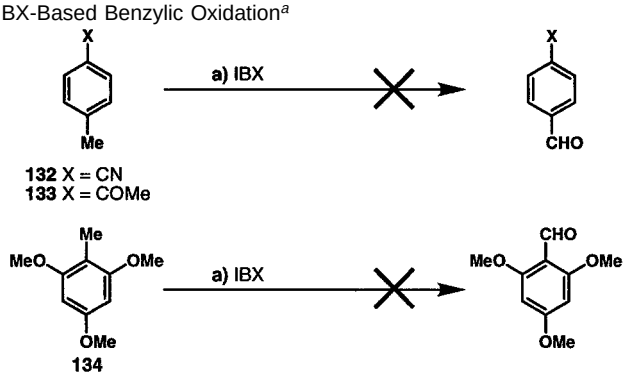
On the basis of mechanistic insights gained during our studies with the IBX-mediated N-cyclization of unsaturated anilides,[14] we predicted it was likely that we would be able to perform a benzylic oxidation in the presence of a cyclization-prone amide, and more crucially, vice versa, by simply altering the solvent

Scheme 8. Highly Selective IBX-Mediated Oxidation/Cyclization of Substrates **127** and **128**[a]



[a] Reagents and conditions: (a) IBX (3.0 equiv), DMSO, 90 °C, 24 h, 75%; (b) IBX (3.0 equiv), DMSO, 85 °C, 12 h, 60%; (c) IBX (4.0 equiv, added in two portions at 0 and 4 h), THF:DMSO 10:1, 85 °C, 8 h, 89%.

Scheme 9. Failure of Substrates **132**−**134** To Enter the IBX-Based Benzylic Oxidation[a]



[a] Reagents and conditions: (a) IBX (10.0 equiv), DMSO, 100 °C, 12 h, most starting material recovered.

employed. To our delight this was indeed the case, as demonstrated in Scheme 8. Thus, it proved possible to selectively oxidize substrates **127** and **128** to the corresponding aldehydes **129**, 75% and **130**, 60% in the presence of IBX when DMSO was employed as solvent. Remarkably, the reaction of urethane **128** could be deviated from this pathway to afford the cyclized oxazolidinone (**131**, 89%) simply by switching from DMSO (or fluorobenzene:DMSO 2:1) to THF:DMSO (10:1) as solvent.

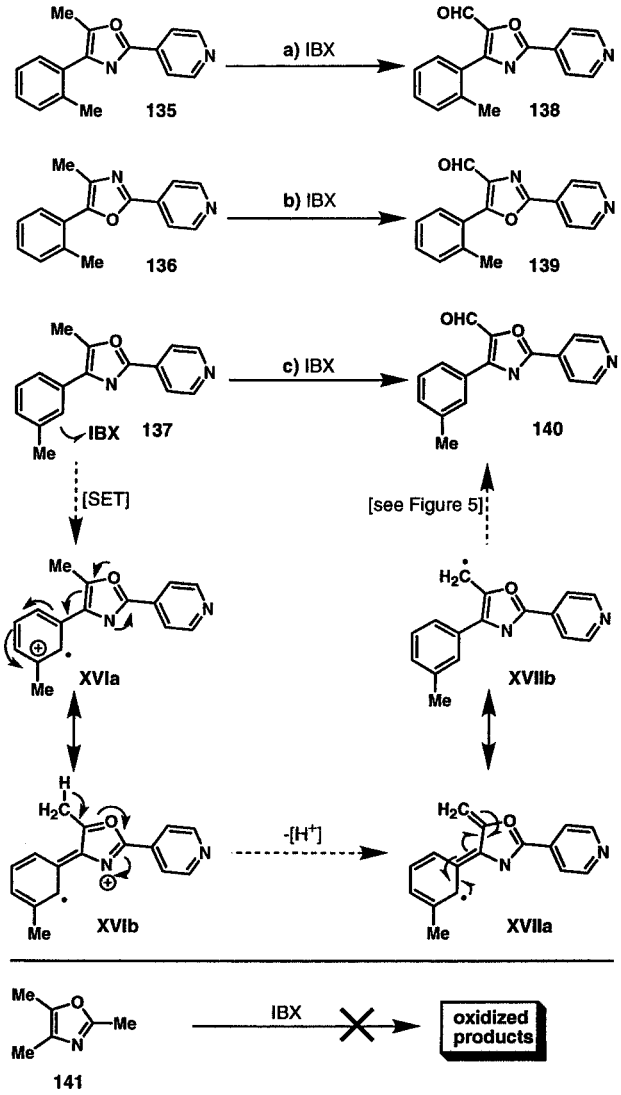
The present reaction can clearly be considered as a SET-based process if analogy is drawn to the SET mediated N-cyclization reaction (vide infra). Accordingly and as expected, aromatic systems with higher oxidation potentials (electron-donating substituents) were generally found to be oxidized faster than those with lower oxidation potentials (electron-withdrawing substituents). Herein lies an explanation for the failure of the substituted toluenes **132** and **133** (Scheme 9) to enter into the benzylic oxidation reaction. The clean mono-oxidation of xylenes **99** and **100** (entries 11 and 12, Table 5) can also be attributed to the inability of the initial product, an electron-deficient aldehyde, to submit to further oxidation. However, the failure of 2,4,6-trimethoxytoluene (**134**, Scheme 9) to yield the corresponding aldehyde (starting material recovered) illustrates the requirement of a free *o*-position for this benzylic oxidation, just as is the case for the IBX-mediated N-cyclization.[14] We note that substrates containing ethereal oxygen functionality react more slowly than expected. We speculate that this is related to coordination of the substrate to IBX (or IBA) via this functionality which may undermine the desired reaction course.

Armed with key information regarding the scope of this methodology, we then turned our attention to more complex substrates in which more than one aromatic position could potentially be oxidized. The bis-methyl-substituted pyridyl oxazoles **135**−**137**[36] (Scheme 10) were chosen as examples for their resistance to oxidation at either methyl group with a variety of known oxidants.[36] In the event, compounds **135**−**137** could be oxidized at 110 °C by employing 8 equiv of IBX in DMSO to furnish aldehydes **138**−**140** in 75−78% isolated yields and with ca. 20% starting material being recovered. HMQC and HMBC NMR experiments confirmed that the position of oxidation was the oxazole-bearing methyl group and not the benzylic methyl group in all cases. When trimethyl oxazole (**141**, Scheme 10) was submitted to the same conditions, the corresponding aldehyde was not detected; application of more forcing conditions led only to traces of aldehyde, accompanied by several unidentified products. These intriguing results led to the proposal of the mechanistic rationale presented in Scheme 10, which seemingly contradicts the observations (vide supra) that a free *o*-position is required for oxidation. Specifically, it is postulated that the phenyl moiety of 2-methyl-3-tolyl-5-pyridyl oxazoles such as **137** initiates the reaction by transferring an electron to IBX, leading to the radical cation **XVIa** which can also be depicted by its resonance structure **XVIb**. Loss of a proton from **XVIb** would then lead to **XVIIa** which, in turn, may proceed to form 2-formyl-3-tolyl-5-pyridyl oxazole **140** via the mechanism already delineated in Figure 5 (vide supra). The radical species **XVII** reacts exclusively at the oxazole methylene position as opposed to the phenyl methyl position. This can be explained as being a result of the proposed minor contribution made by the resonance form **XVIIa** to the actual structure of **XVII**, a feature that would result from the greater aromatic stabilization of a phenyl moiety when compared to the oxazole heterocycle. Further support for this postulated mechanism comes from the reluctance of the electron-deficient (low oxidation potential) trimethyl oxazole **141** (Scheme 10) to enter into the IBX-mediated benzylic oxidation when treated under similar conditions.

These results coupled with mechanistic considerations led us to speculate on the possible IBX-mediated oxidation product of 5,5′,8-trimethylpsoralen (trioxsalen) (**142**, Scheme 11). All intelligence gathered thus far and mechanistic evaluation summarized and shown in Scheme 11B pointed to the oxidation affording furanaldehyde **143** (Scheme 11A) as the most logical regioisomer. Indeed, treatment of **142** with IBX (5.0 equiv) at 120 °C for 24 h in DMSO led to **143** (50% yield) as the sole aldehyde produced.

(36) Finney, N.; Fang, A. Department of Chemistry and Biochemistry, University of California, San Diego, unpublished results. Professor Finney is gratefully acknowledged for generous samples of oxazoles **135**−**137**.

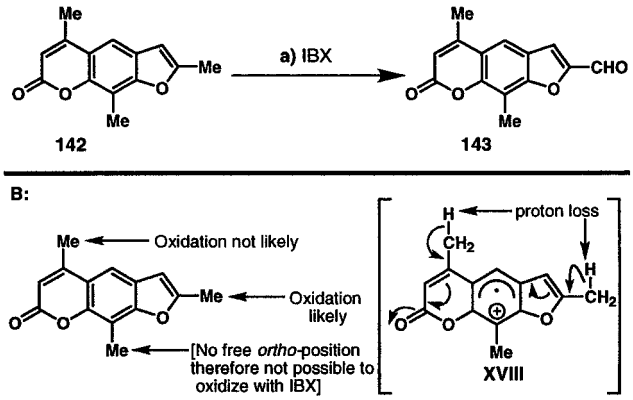
Scheme 10. Selective Oxidation of 2-Methyl-3-tolyl-5-pyridyl Oxazoles to 5-Formyl-3-tolyl-5-pyridyl Oxazoles and Postulated Mechanistic Rationale (Mechanism Supported by Failure of Trimethyl Oxazole To Be Oxidized with IBX under Similar Conditions)[a]



[a] Reagents and conditions: (a) IBX (8.0 equiv, added in four portions at $t = 0$, 3, 6, and 12 h), DMSO, 110 °C, 24 h, 78%; (b) IBX (8.0 equiv, added in four portions at $t = 0$, 3, 6, and 12 h), DMSO, 110 °C, 24 h, 75%; (c) IBX (8.0 equiv, added in four portions at $t = 0$, 3, 6, and 12 h), DMSO, 110 °C, 24 h, 78%.

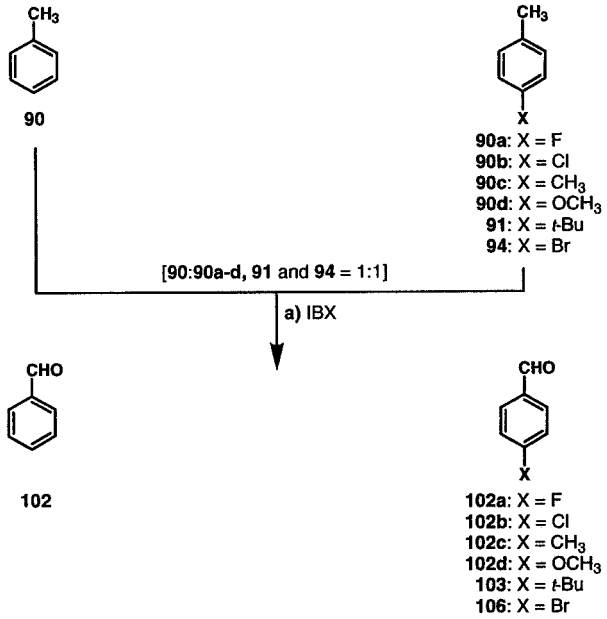
To obtain additional experimental support for the SET-based mechanism proposed for this oxidation (Figures 5 and 6), we ran a series of competition experiments utilizing substituted toluenes **90a**−**d**, **91**, and **94** versus toluene **90**, as shown in Scheme 12. A Hammett plot drawn from these results (Figure 7) showed a linear correlation, with negative slope, between the ratio of reaction rate constants (k_s/k_u) and the σ_p^+ parameters ($\rho = -0.91$, $R^2 = 0.97$).[33a,c] This is consistent with SET from the substrate to IBX in the rate-determining step. The magnitude of ρ falls into a region suggestive of a radical-type intermediate since it reveals a relatively small dependence on the polarizing ability of substituents in this step of the transformation. Furthermore, the transition state has lower electron density than the ground state, as evidenced by the negative gradient. This validates the supposition that a radical cation is formed in the initial step (see Figure 5). Despite repeated attempts, methyl anisole, interestingly and once again, gave anomalous data which did not fit into this linear correlation, reinforcing the conclusion drawn earlier from when the carbonyl dehydrogenation reaction was examined using this analysis method (vide supra).

Scheme 11. Chemoselective Oxidation of Trioxsalen (**142**) to Furanaldehyde **143** Using IBX and Mechanistic Rationale[a]



[a] Reagents and conditions: (a) IBX (5.0 equiv), DMSO, 120 °C, 24 h, 50%.

Scheme 12. Competition Experiments of Toluene with Substituted Toluenes To Derive a Hammett Plot for the IBX-Mediated Benzylic Oxidation[a]



[a] Reagents and conditions: (a) IBX (4.0 equiv), DMSO, 85 °C, 22 h.

When *p*-cresol (**144**, Scheme 13) was employed in the IBX reaction, we observed a rapid color change. After only a few minutes at room temperature, the dark reaction mixture was composed primarily of polymeric material and a small amount of the bis-phenol **146** as the only identifiable product. Because the reaction was rapid at room temperature, we propose the ionic mechanism shown in Scheme 13 to account for this interesting product and to explain the polymeric material formed, by virtue of the ready polymerization that would be expected from a reactive diene such as **145**, presumably formed via **XIX** and **XX**. The regiochemistry of the product **146** is strongly suggestive of an intramolecular delivery of an oxygen nucleophile, see **XIX** (vide infra). The similarly complex mixtures obtained

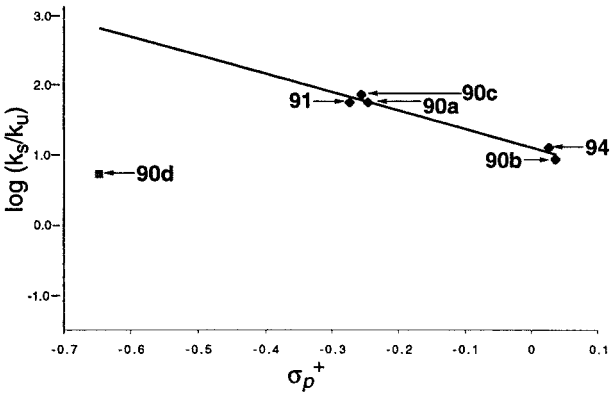
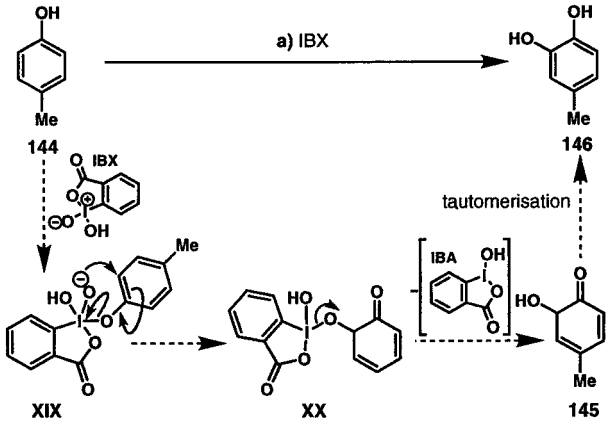


Figure 7. Plot derived using Hammett analysis of the competition reactions of substituted toluenes (**90a**−**d**, **91**) and **94** with toluene (**90**). The gradient (ρ) = 0.91 and regression analysis give a value R^2 = 0.97.

Scheme 13. Isolation of bis-Phenol **146** from *p*-Cresol (**144**) upon Treatment with IBX and Mechanistic Rationale[a]



[a] Reagents and conditions: (a) IBX (1.0 equiv), DMSO, 25 °C, 17%.

in the IBX-mediated reactions of anilines[37] may also be due to such a degradation pathway.

In a separate study we found that the concentration of IBX employed had an important effect upon the oxidation of aromatic systems. To achieve maximum conversion, for example, of methyl anisole (**90d**) to anisaldehyde (**102d**), an optimum concentration of ca. 1.25 M in IBX was employed (see Figure 8). If the concentration of IBX was too low, competitive reduction of IBX to IBA by DMSO (present in large excess) leads to a lower yield, while higher concentrations resulted in solubility problems. During the reaction course, a heavy white precipitate forms which is not soluble in DMSO. This material is primarily composed mainly of IBA, but may also draw some IBX out of solution by trapping it in a complex secondary bonding network, thus having a deleterious effect on the reaction rate.[38]

To aid elucidation of the source of the oxygen atom in the oxidized products, we carried out the reaction with varying amounts of water. Interestingly, the reaction was faster when anhydrous DMSO (dried according to the literature[39] and verified as containing <250 ppm of water by titration) was employed. The addition of varying amounts of water decelerated the reaction, but after extended reaction times the conversion

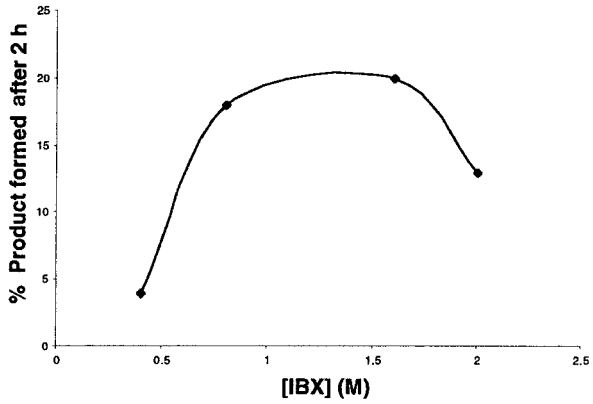


Figure 8. Effect of IBX concentration on conversion of methyl anisole (**90d**) to anisaldehyde as measured by ^{1}H NMR spectroscopy. Reagents and conditions: IBX (2.0 equiv), 80 °C, 2 h.

to product was unaffected. In the cases where the dried DMSO was employed at standard concentrations used for this reaction (which translate to a 1−5 mol % water content with respect to the oxidation substrate), conversion to the ketone or aldehyde was still routinely seen to be in excess of 70%. This result indicates that water is not the source of the oxygen atom in the final product of IBX-mediated benzylic oxidation. An isotope labeling study using $H_2{}^{18}O$ was considered as a further means of tracing the carbonyl oxygen in the oxidized products; ultimately, however, this study was considered to offer little hope of a conclusive answer and was, therefore, not pursued.[40] Our results to date cannot unequivocally determine the source of oxygen in the IBX-mediated oxidation of benzylic positions; however, it is hoped that detailed kinetic studies might allow for differentiation between the postulated pathways for this process (Figures 5 and 6). These new investigations are expected to form the basis of further reaction designs and are currently being pursued. Whatever the detailed profiling uncovers, it can be confidently stated that IBX shows a unique and multifaceted reactivity profile that, until now, has been underappreciated.

3. Chemoselective and Controllable IBX-Mediated Cyclizations and Oxidations. The potential utility of IBX-mediated benzylic oxidation and carbonyl dehydrogenation reactions occurring in tandem has not escaped our attention. Thus, we synthesized chromane **147** (Scheme 14) and exposed it to IBX (4.0 equiv) in DMSO at 80 °C leading to the isolation of the flavanoid **148** in 68% yield as the product of a double oxidation.

At this juncture it was critical to demonstrate that IBX is not only a versatile oxidant, capable of a variety of transformations, but also a highly chemoselective reagent. Thus, we designed and synthesized compound **149** (Scheme 15) as a flexible substrate for entering into IBX-mediated N-cyclization, alcohol

(37) Crich, D.; Mo, X.-S. *Synlett* **1999**, 67.
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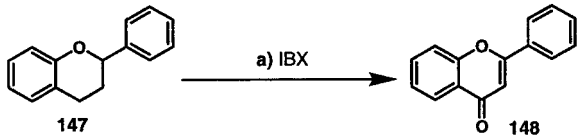
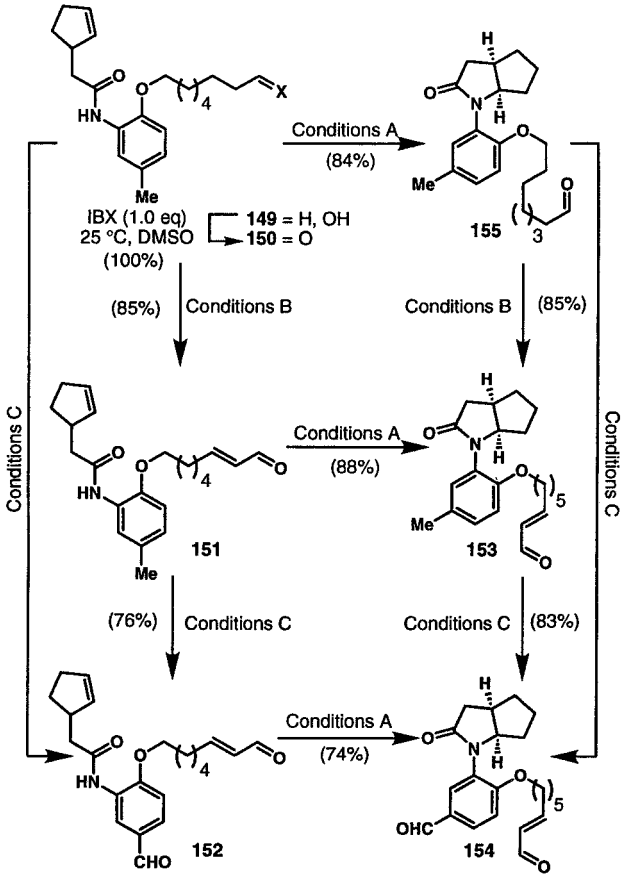
(40) The following factors persuaded us not to pursue an O^{18} labeling study: the propensity of a carbonyl bearing species to enrich or deplete an ^{18}O label via hydrate formation under mildly acidic or basic conditions,[41] the dynamic equilibrium that exists with IBX and free unbound water, and the demanding set of criteria required to obtain a molecular ion that could be readily observed in a crude reaction mixture by ESI mass spectrometry (no technique involving a matrix could be used due to catalysis of the hydrate formation reaction in an aqueous environment).
(41) Cohn, M.; Urey, H. C. *J. Am. Chem. Soc.* **1938**, *60*, 679.
(42) See refs 3, 14, 15, and 17 in addition to (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2000**, *39*, 625.
(43) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.
(44) Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 8908.

Scheme 14. IBX-Mediated Synthesis of Flavone **148** from Chromane **147**[a]



[a] Reagents and conditions: (a) IBX (4.0 equiv), DMSO, 80 °C, 22 h, 68%.

Scheme 15. Selective Chemical Transformations with IBX[a]



[a] Conditions A: IBX (2.2 equiv), THF:DMSO (10:1), 85 °C, 8 h. Conditions B: IBX (2.0 equiv), TsOH (0.2 equiv), DMSO, 65 °C, 5 h. Conditions C: IBX (3.0 equiv), DMSO, 90 °C, 2 h.

oxidation/carbonyl dehydrogenation, and benzylic oxidation. Using only three standard sets of conditions, substrate **149** could be easily converted into any of the compounds **150**−**155** (shown in Scheme 15) as desired. Thus, treatment of **149** with 2.0 equiv of IBX at 65 °C in fluorobenzene:DMSO (2:1) in the presence of catalytic amounts of *p*-TsOH (conditions B, Scheme 15) led to α,*β*-unsaturated aldehyde **151** in 85% isolated yield. Further oxidation of **151** with 3.0 equiv of IBX in DMSO at 90 °C (conditions C) furnished fully oxidized product **152** in 76% yield. Compounds **149**−**152** could be converted to **153**−**155** simply by employing an IBX and THF:DMSO (10:1) mixture as the solvent system (conditions A). Alternatively, **155** could also be cleanly converted by conditions B to **153**, which, in turn, was smoothly transformed to **154** by conditions C. This series of reactions ably illustrates the ease with which IBX-mediated oxidations can be manipulated to furnish a diverse spectrum of highly functionalized products. We strongly suspect that the ability of certain solvents to form discrete complexes with IBX may be responsible for these rather dramatic reactivity patterns, and we are, therefore, pursuing further experiments to clarify the situation.

Conclusion

In this series of papers,[1−3] we describe significant extension of the utility of iodine(V) reagents (see Figure 1) far beyond the realm of alcohol oxidations. Within the present paper, we presented a full account of a new and general synthetic reaction for the oxidation of a range of alcohols, ketones, and aldehydes to the corresponding α,*β*-unsaturated systems and under mild conditions in one pot employing the cheap, nontoxic, and readily available reagent IBX. Adjusting the stoichiometry of IBX, temperature, and time scale of the reaction, the process can readily be programmed to provide varying degrees of unsaturation. In many instances, this frequently encountered objective is accomplished where other established methods fail to perform well. As such, these IBX-based technologies are expected to find widespread applications in organic synthesis. Furthermore, the mild conditions employed allow cascade reaction sequences leading to a rapid increase in molecular complexity by simple one-pot operations. On the basis of the presumption that IBX acts as a SET-based oxidant, we also developed a selective oxidation reaction of benzylic and other similarly activated positions and demonstrated its scope, generality, and usefulness in organic synthesis. Both of these transformations fit well as chemospecific tools within the diverse family of IBX-mediated reactions recently reported from these laboratories.[14,15,17] Consequently, in multiply functionalized substrates, one can orchestrate, with confidence, the desired oxidation pathway by merely choosing the proper conditions for the reaction. Detailed mechanistic studies of these reactions have shown that they are SET-based processes and have led to some remarkable insights into the underexplored iodine(V) manifold. The isolation of novel byproducts during the course of these studies points to future expansions of the repertoire of transformations that can be accessed using such iodine(V)-based reagents.

Most importantly, and once again, the fact that a serendipitous observation made in the course of the synthesis of the CP-molecules opened the gates to this underexplored field of chemistry emphasizes the importance of total synthesis as a catalyst for the development of powerful new reactions and synthetic technologies.

Experimental Section

General Procedure for Dehydrogenation α,*β* to a Carbonyl Function. This procedure represents an updated version[15] and includes many optimizations that significantly enhance reproducibility of this reaction in more complex substrates. To a solution of alcohol (or carbonyl compound) in DMSO:fluorobenzene (the ratio should be substrate dependent with the fluorobenzene content being minimized so that the substrate is soluble but the rate of reaction is reduced as little as possible, 0.3 M with respect to IBX) was added IBX (1.5 equiv per alcohol or C−C bond to be oxidized; the use of large excesses of IBX is not recommended since the IBA formed on decomposition of IBX by its oxidation of DMSO retards the reaction rate). The solution was heated to 55−85 °C, and the reaction was monitored by TLC (thin-layer chromatography) until complete consumption of starting material was observed. The reaction mixture was cooled to room temperature and diluted with Et_2O. The organic layer was washed with 5% $NaHCO_3$ (3×), H_2O (1×), and dried ($MgSO_4$), followed by removal of solvent in vacuo, leading to crude compounds which could be purified using flash column chromatography (silica gel).

General Procedure for Benzylic Oxidation. This procedure represents an updated version[17] and includes many optimizations that significantly enhance reproducibility of this reaction in more complex substrates. To a solution of oxidation substrate (1.0 mmol) in DMSO:fluorobenzene (the ratio should be substrate dependent with the fluorobenzene content being minimized so that the substrate is soluble but the rate of reaction is reduced as little as possible, 1.25 M with respect to IBX) was added IBX (3.0 mmol), and the mixture was typically heated to 85−95 °C. The reaction was monitored by TLC (thin-layer chromatography) until complete consumption of starting material was observed. The reaction mixture was cooled to room temperature and diluted with Et_2O. The organic layer was washed with 5% $NaHCO_3$ (3×), H_2O (1×), and dried ($MgSO_4$), followed by removal of solvent in vacuo, leading to crude compounds which could be purified using flash column chromatography (silica gel).

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Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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