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Iodine(V) Reagents in Organic Synthesis. Part 3. New Routes to Heterocyclic Compounds via *o*-Iodoxybenzoic Acid-Mediated Cyclizations: Generality, Scope, and Mechanism

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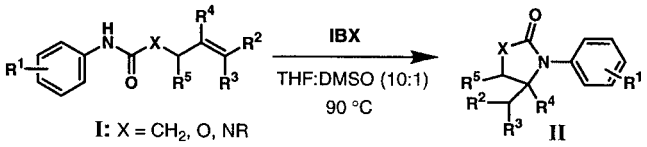
Abstract: The discovery and development of the *o*-iodoxybenzoic acid (IBX) reaction with certain unsaturated *N*-aryl amides (anilides) to form heterocycles are described. The application of the method to the synthesis of δ-lactams, cyclic urethanes, hydroxy amines, and amino sugars among other important building blocks and intermediates is detailed. In addition to the generality and scope of this cyclization reaction, this article describes a number of mechanistic investigations suggesting a single electron transfer from the anilide functionality to IBX and implicating a radical-based mechanism for the reaction.

Introduction

The task of the scientific community to develop potent, selective therapeutic agents is dependent upon methods for rapidly assembling compounds of high molecular diversity in rational and efficient ways. Furthermore, the ability of chemists to optimize newly discovered lead compounds, as well as to produce analogues or mimics of biologically active natural products, relies upon the advancement of synthetic technologies. During endeavors in total synthesis,[1] we discovered and subsequently developed a novel cyclization reaction of *N*-aryl amides (anilides) onto internally located unactivated olefins induced by the Dess−Martin periodinane.[2] This serendipitous discovery[3] led us to investigate the related and easily prepared hypervalent iodide reagent IBX[4] (*o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) as a potential agent to carry out new reactions for accessing diverse libraries of heterocycles, hydroxy amines, and amino sugars. The desirability of such reactions can be appreciated if one considers the importance of heterocyclic compounds, especially *N*-heterocycles, to chemical biology and the drug discovery process. Current methods for the formation of carbon−nitrogen bonds generally involve the displacement, by *N*-nucleophiles, of oxygen functionality, either intra-[5] or intermolecularly,[6] rearrangement of carbonyl functionalities,[7] and reductive amination. However, methods for the direct introduction of nitrogen onto non-oxygenated carbon without the formation of innocuous byproducts are rare.[8] Herein, we disclose the full account of our discovery and development of the IBX-mediated cyclization of amides, urethanes, and ureas with olefins for the rapid construction of molecular diversity employing readily available and inexpensive starting materials (Scheme 1).[9a,b]

Scheme 1. IBX-Mediated Cyclization of *N*-Aryl Amides, Urethanes, and Ureas (**I**) Furnishing an Array of Five-Membered Heterocycles (**II**)



(1) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676.

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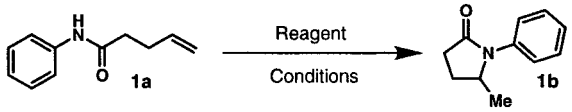
Table 1. Discovery and Optimization of the IBX-Mediated Cyclization (**1a** → **1b**)



entry	reagent	conditions	yield (%)
1	IBX (2.0 + 2.0 equiv)	THF:DMSO (10:1) (0.025 M) 90 °C, 12 h	86
2	IBX (2.0 + 2.0 equiv)	THF:DMSO (4:1) (0.025 M), 90 °C, 12 h	86
3	IBX (4.0 equiv)	DMSO, 90 °C, 12 h	0
4	IBX (4.0 equiv)	H_2O, 90 °C, 12 h	0
5	IBX (4.0 equiv)	THF:DMSO (10:1) (0.1 M), 90 °C, 12 h	38
6	IBA (10 equiv)	THF:DMSO (4:1), 90 °C, 12 h	0
7	iodosobenzene (5.0 equiv)	THF:DMSO (4:1), 90 °C, 12 h	0
8	$PhI(OAc)_2$ (5.0 equiv)	THF, 50 °C, 12 h	0
9	$PhI(CF_3COO)_2$ (5.0 equiv)	CH_3CN, 25 °C, 12 h	0
10	trifluoro IBX (5.0 equiv)	THF:DMSO (10:1), 90 °C, 12 h	0
11	$KBrO_3$ (5.0 equiv)	THF:DMSO 4:1), 90 °C, 12 h	0
12	oxone (2.0 equiv), IBX (catalyst)	THF:DMSO (10:1), 90 °C, 12 h	trace

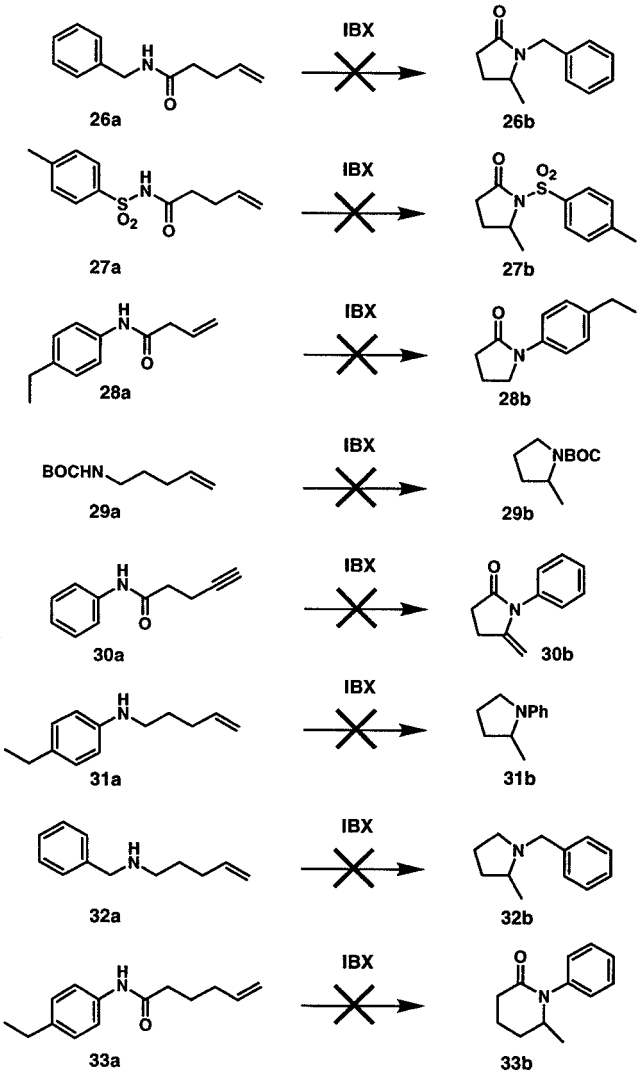
Results and Discussion

1. IBX-Mediated Cyclization of Amides. Once discovered, the development of the IBX-mediated cyclization commenced with the screening of a variety of solvent systems and reaction temperatures (see Table 1). After some experimentation, optimal conditions were found to be the heating of the anilide substrate with IBX (2.0 equiv) in a mixed solvent system of THF:DMSO (10:1) in a pressure tube at 90 °C for 8−12 h. To ensure complete conversion, the reactions were cooled to room temperature, and additional IBX (2.0 equiv) was added followed by heating at 90 °C for an additional 8 h. The concentration of substrate in THF/DMSO (10:1) was also critical (0.025 M, entries 1 and 2, Table 1). When the concentration of the substrate (**1a**) was too high, very low conversions were observed (entry 5, Table 1). Using these conditions, a diverse series of γ-lactams were prepared in good to excellent yields (Table 2). Interestingly, a variety of iodine(III)-based reagents [$PhI(OAc)_2$, $PhI(OCCF_3)_2$, and IBA] and tri-fluro-IBX or $KBrO_3$ failed to induce cyclization with **1a**, whereas oxone (3.0 equiv) in the presence of catalytic amounts of IBX gave only traces of lactam **1b** (Table 1).

As shown in Table 2, a broad range of anilides readily cyclize in the presence of IBX. The reaction is tolerant of both electron-donating and electron-withdrawing groups[10] on the *N*-aryl ring, including sensitive bromides and iodides. The ability of the process to introduce nitrogen onto monosubstituted olefins (entries 1−11, Table 2) or onto an enol silyl ether (entry 24, Table 2) without any loss in efficiency is more impressive. The efficient formation of quaternary centers is also evident from the facile construction of **20b** and **21b** (Table 2, see Figure 1 for ORTEP structure of **20b**).[9c] This remarkable reaction is highly chemoselective, as shown by the example of entry 25 (Table 2), which leads to the bis-lactam **25b** without affecting the ester functionality. Finally, it should be noted that the reaction is impervious to air or water, foregoing the requirement of an inert environment or scrupulously dried solvents.

In defining the scope and limitations of the IBX-mediated cyclization, the necessity of the anilide moiety was ascertained.

Scheme 2. Various Failures of the IBX-Cyclization Make a Compelling Case for the Essential Role of the *N*-Aryl Amide Moiety for the Success of the Reaction



As seen from Scheme 2, the case for the necessary role of the *N*-aryl amide moiety is compelling since a variety of related substrates fail to enter the reaction. These results are consistent with a single electron transfer (SET) mechanism in which the aryl group plays an active role in the initial SET process (vide

(9) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525. (c) For crystallographic information see ref 9a, footnote 4. (d) For crystallographic information see ref 9b, footnote 27.

(10) An exception is the nitro group. We have not been able to induce ring closure of nitro-aryl substrates.

Table 2. IBX-Mediated Cyclization of *N*-Aryl Amides

Entry	Substrate	Product	Yield (%)
1	**1a**: R = H	**1b**: R = H	86
2	**2a**: R = Br	**2b**: R = Br	79
3	**3a**: R = Et	**3b**: R = Et	89
4	**4a**: R = F	**4b**: R = F	80
5	**5a**: R = I	**5b**: R = I	85
6	**6a**: R = OMe	**6b**: R = OMe	88
7	**7a**: R = F	**7b**: R = F	80
8	**8a**: R = *t*-Bu	**8b**: R = *t*-Bu	70
9	**9a**: R = I	**9b**: R = I	45
10	**10a**	**10b**	90
11	**11a**	**11b** [*ca* 1:1]	90
12	**12a**: R = H	**12b**: R = H	90
13	**13a**: R = Et	**13b**: R = Et	90
14	**14a**	**14b**	86
15	**15a**: R = H	**15b**: R = H	90
16	**16a**: R = Br	**16b**: R = Br	84
17	**17a**: R^1, R^2 = H	**17b**: R^1, R^2 = H	93
18	**18a**: R^1 = Br, R^2 = H	**18b**: R^1 = Br, R^2 = H	89
19	**19a**: R^1 = H, R^2 = OMe	**19b**: R^1 = H, R^2 = OMe	96
20	**20a**: R = H	**20b**: R = H	90
21	**21a**: R = Br	**21b**: R = Br	84
22	**22a**	**22b**	90
23	**23a**	**23b**	55
24	**24a**	**24b** + **24c**	44 + 40
25	**25a**	**25b** (plus other syn diastereomer)	84

infra). As a result, substrates **26a**, **27a**, **29a**, and **32a** lacking the *N*-aryl moiety do not undergo the IBX-mediated cyclization (Scheme 2). The *N*-aryl amine **31a** also failed to cyclize, demonstrating the necessity of the carbonyl moiety of the anilides. Alkynes such as **30a** were also unsuitable substrates for the reaction. It should also be noted that the reaction cannot be entrusted to produce δ-lactams as suggested by the failure of **33a** to furnish **33b** under the usual reaction conditions. This reflects the known propensity of radicals, stabilized by both mesomerically donating and mesomerically withdrawing substituents, to be subject to additional stabilization to the extent that their participation in less favored cyclizations (than the 5-exo variant)[11] is quite limited. This stabilization is also

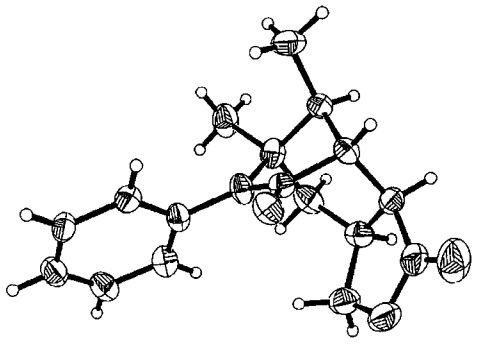


Figure 1. X-ray crystal structure of **20b**.

Table 3. IBX-Mediated Cyclization of *N*-Aryl Carbamates and Open-Chain Ureas

Entry	Substrate	Product	Yield (%)
1	**34a**: R', R'', R''' = H	**34b**: R', R'', R''' = H	88
2	**35a**: R', R'' = H, R''' = Me	**35b**: R', R'' = H, R''' = Me	70
3	**36a**: R', R'' = H, R''' = CF_3	**36b**: R', R'' = H, R''' = CF_3	30
4	**37a**: R' = H, R'', R''' = Cl	**37b**: R' = H, R'', R''' = Cl	35
5	**38a**: R' = H, R'' = Cl, R''' = OMe	**38b**: R' = H, R'' = Cl, R''' = OMe	65
6	**39a**: R' = OMe, R'', R''' = H	**39b**: R' = OMe, R'', R''' = H	66
7	**40a**	**40b**	30
8	**41a**: R = H	**41b**: R = H	90
9	**42a**: R = *n*-Bu	**42b**: R = *n*-Bu	77
10	**43a**: R', R'' = H	**43b**: R', R'' = H	85
11	**44a**: R' = OPh, R'' = H	**44b**: R' = OPh, R'' = H	76
12	**45a**: R' = Br, R'' = H	**45b**: R' = Br, R'' = H	65
13	**46a**: R' = H, R'' = Me	**46b**: R' = H, R'' = Me	80
14	**47a**: R' = H, R'' = *n*-Bu	**47b**: R' = H, R'' = *n*-Bu	83
15	**48a**: R' = H, R'' = Ph	**48b**: R' = H, R'' = Ph	68
16	**49a**: R' = H, R'' = OCF_3	**49b**: R' = H, R'' = OCF_3	70
17	**50a**: R' = H, R'' = OMe	**50b**: R' = H, R'' = OMe	73
18	**51a**: R' = H, R'' = F	**51b**: R' = H, R'' = F	70
19	**52a**: R' = H, R'' = Br	**52b**: R' = H, R'' = Br	65
20	**53a**: R' = Cl, R'' = OMe	**53b**: R' = Cl, R'' = OMe	78
21	**54a**	**54b**	72
22	**55a**	**55b**	72
23	**56a**	**56b**	88
24	**57a**: R = H	**57b**: R = H	95
25	**58a**: R = Me	**58b**: R = Me	87
26	**59a**: R = *n*-Bu	**59b**: R = *n*-Bu	86
27	**60a**: R = Ph	**60b**: R = Ph	64
28	**61a**: R = OMe	**61b**: R = OMe	75
29	**62a**	**62b**	76
30	**63a**	**63b**	83
31	**64a**	**64b**	90
32	**65a**	**65b**	70

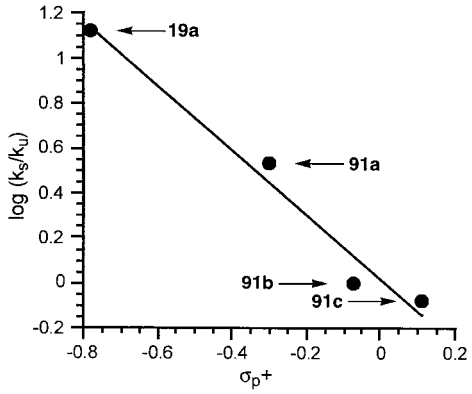


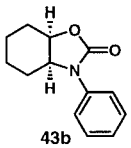
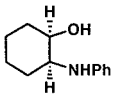
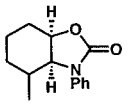
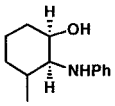
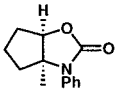
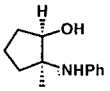
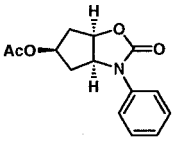
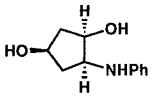
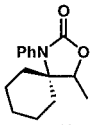
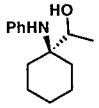
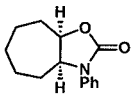
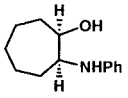
Figure 2. Hammett plot for the reaction shown in Scheme 11. See text for details.

pertinent to the ease of formation of this radical and the requirement for both the aryl and the carbonyl substituents.

2. IBX-Mediated Cyclization of Carbamates and Ureas. In an effort to address the recently heightened need for increased molecular diversity, the IBX-mediated cyclization of aryl carbamates and ureas was investigated. Such investigations were warranted not only because of the importance of the expected products, but also due to the ready and extensive availability of allylic alcohols, amines, and aryl isocyanates. Thus, a series of carbamates and ureas were prepared from the corresponding allylic alcohol (see entries 1−30, Table 3) or secondary amine (see entries 31 and 32, Table 3) by reaction with the aryl isocyanate in the presence of DBU (0.1−0.3 equiv). Using the previously described conditions [IBX (2.0 + 2.0 equiv), THF:DMSO (10:1), 90 °C, sealed tube], oxazolidinones (entries 1−30) and cyclic ureas (entries 31 and 32) were readily prepared in fair to excellent yields (Table 3). It should be noted that only ureas (**64a** and **65a**) prepared from secondary allylic amines readily cyclize. Ureas prepared from primary allylic amines slowly decomposed under the above conditions without providing any cyclized products.

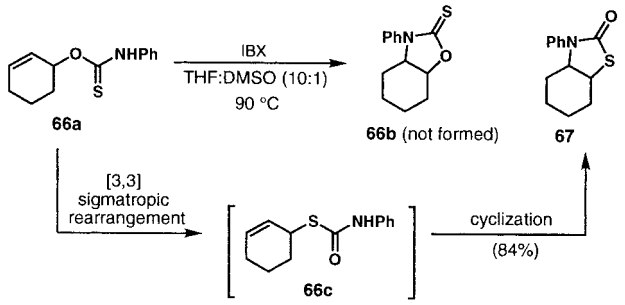
Again, a wide range of aryl substituents is tolerated, allowing for the rapid assembly of small molecule libraries. The formation of quaternary centers (entries 8, 9, 23, and 29, Table 3) and spirocyclic compounds (entry 29, Table 3) is an additional

Table 4. Preparation of 1,2-Amino Alcohols from Cyclic Carbamates[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **43b**	 **43c**	94
2	 **55b**	 **55c**	92
3	 **56b**	 **56c**	98
4	 **57b**	 **57c**	95
5	 **62b**	 **62c**	90
6	 **63b**	 **63c**	95

[a] Reactions were carried out on a 0.05 mmol scale with 1 N in EtOH at 70 °C. [b] Chromatographically pure compounds.

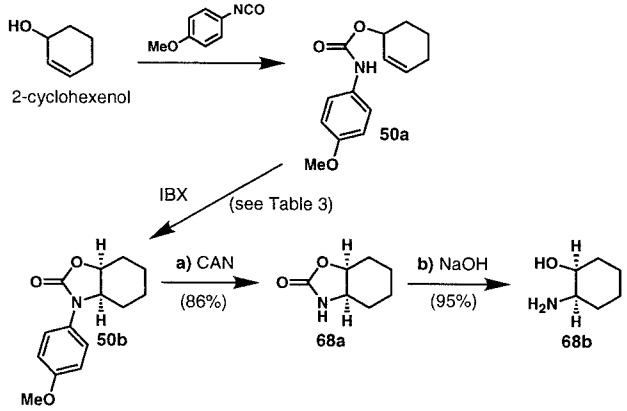
Scheme 3. Thionocarbamates in the IBX-Mediated Cyclization



feature of this new process. The exclusive stereocontrol exhibited by the cyclic scaffolds (entries 10−30, Table 3) in forming the nitrogen−carbon bond makes this an attractive procedure for preparing 1,2-amino alcohols. Direct access to this class of compounds is realized by hydrolysis (1 N NaOH) of the resulting cyclic carbamates as shown in Table 4.

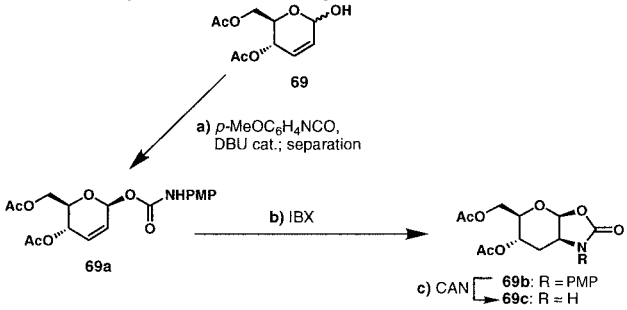
In contrast to aryl carbamates and ureas, aryl thionocarbamates do not directly cyclize to provide heterocycles. Thus, when thionocarbamate **66a** (Scheme 3) was treated with the standard conditions [IBX, THF:DMSO (10:1), 90 °C] for 12 h, thiazolidinone **67** was isolated (84% yield) instead of the cyclic thione **66b** (Scheme 3). Apparently, the thionocarbamate **66a** first

Scheme 4. IBX-Mediated Synthesis of Cyclic Urethanes and *cis*-1,2-Amino Alcohols[a]



[a] Reagents and conditions: (a) CAN (5.0 equiv), CH_3CN:H_2O (5:1), 25 °C, 20 min, 86%; (b) NaOH (10 equiv), EtOH, 75 °C, 1 h, 95%.

Scheme 5. Synthesis of Aminosugar **69c**[a]



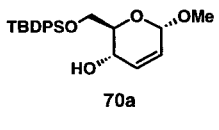
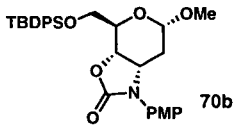
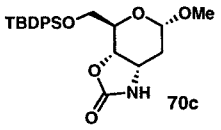
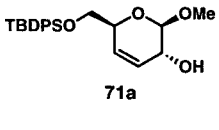
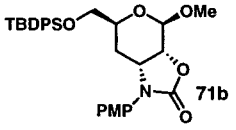
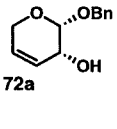
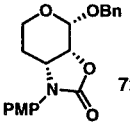
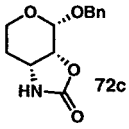
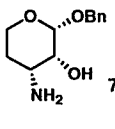
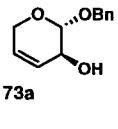
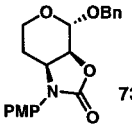
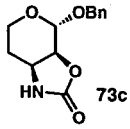
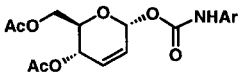
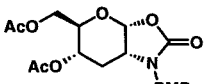
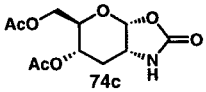
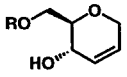
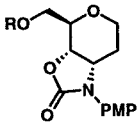
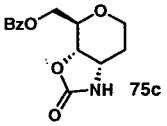
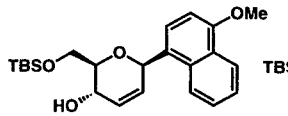
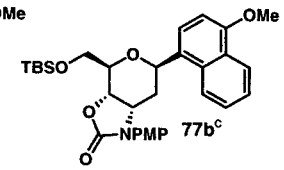
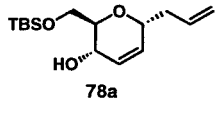
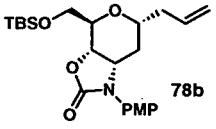
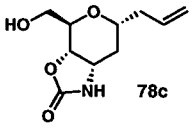
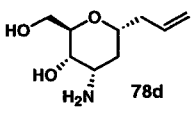
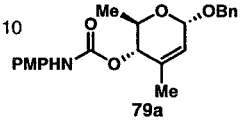
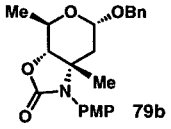
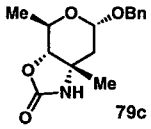
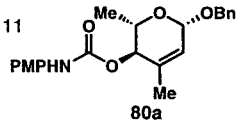
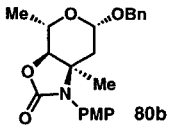
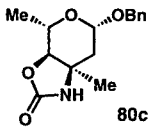
[a] Reagents and conditions: (a) *p*-$MeOC_6H_4NCO$ (1.1 equiv), DBU (0.1 equiv), CH_2Cl_2, 25 °C, 1 h, 95%; (b) IBX (2.0 equiv), THF:DMSO (10:1), 90 °C (sealed tube), 8 h; then IBX (2.0 equiv), 8 h, 84%; (c) CAN (5.0 equiv), CH_3CN:H_2O (5:1), 0 °C, 30 min, 90%.

undergoes a [3,3]-sigmatropic rearrangement to the corresponding allylic thionocarbamate (**66c**), which then undergoes the IBX-mediated cyclization to provide the observed product **67**. This laboratory has previously reported[12] the use of tertiary thionocarbamates (thionoimidazolides) to introduce allylic thiols through a highly stereoselective [3,3]-sigmatropic rearrangement. Unfortunately, application of the present method to other substrates led to a mixture of products due to competitive [1,3]-sigmatropic rearrangement and lack of stereoselectivity in this process. These results are consistent with previous findings that secondary thiocarbamates give rise to mixtures of [1,3]- and [3,3]-sigmatropic rearrangement products.[13]

3. Synthesis of Amino Sugars by the IBX-Mediated Cyclization. The efficiency of the above process for forming carbon−nitrogen bonds led us to extend our investigations to the preparation of amino sugars. As amino sugars constitute integral components of many biologically active natural products and medicinally relevant compounds, a variety of methods

(11) (a) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed.* **1979**, *18*, 917. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(12) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085. Nicolaou, K. C.; Groneberg, R. D.; Miyazaki, G. T.; Stylianides, N. A.; Schulze, T. J.; Stah, W. *J. Am. Chem. Soc.* **1990**, *112*, 8193. Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593. Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612.
(13) Harayama, H.; Nagahama, T.; Kozera, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamura, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 445.

Table 5. IBX-Mediated Synthesis of Amino Sugar Derivatives from Allylic Alcohols and Aryl Isocyanates

Entry	Substrate	Cyclization product	Yield(%)[a]	CAN-product	Yield(%)[a]	Hydrolysis product	Yield(%)[a]
1	 **70a**	 **70b**	84	 **70c**	91	—	
2	 **71a**	 **71b**	80	—		—	
3	 **72a**	 **72b**	81	 **72c**	90	 **72d**	95
4	 **73a**	 **73b**	85	 **73c**	96	—	
5	 **74a**	 **74b**	66	 **74c**	95	—	
6	 **75a**: R = Bz	 **75b**: R = Bz,	82	 **75c**	90	—	
7	**76a**: R = TBS	**76b**: R = TBS[b]	83				
8	 **77a**	 **77b**[c]	83	—		—	
9	 **78a**	 **78b**	82	 **78c**	94	 **78d**	88
10	 **79a**	 **79b**	69[d]	 **79c**	90	—	
11	 **80a**	 **80b**	71[d]	 **80c**	88	—	

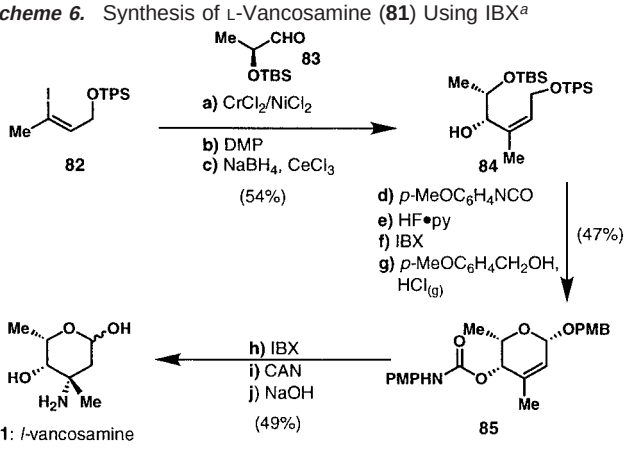
[a] Reagents and conditions: (i) (urethane formation) PMPNCO (1.1 equiv), DBU (0.1−0.3 equiv), CH_2Cl_2; (ii) (cyclization) IBX (4.0 equiv), THF:DMSO (10:1), 90 °C (sealed tube), 12 h; then IBX (2.0−4.0 equiv), 12 h; (iii) (removal of PMP group) CAN (5.0 equiv), CH_3CN:H_2O (5:1), 0 °C. [b] $NaHCO_3$ (4.0 equiv) was added to prevent TBS cleavage. [c] The CAN reaction was not performed due to the presence of the naphthalene ring. [d] $NaHCO_3$ (4.0 equiv) was added to prevent hydrolysis of the benzyl glycoside. [e] Yield over two steps. PMP = *p*-methoxyphenyl; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethyl silyl; Bn = benzyl; Bz = benzoyl; Ac = acetate. For the synthesis of compounds **79a** and **80a**, see Experimental Section.

for their synthesis have been reported and extensively reviewed.[14] However, a general method that is highly stereoselective, relies upon inexpensive materials, and does not introduce unwanted carbon functionality, remains an elusive goal in this area. To develop such a method, the issue of removing the extraneous but enabling aryl moiety required further research, and there was also the question of whether carbohydrate-based scaffolds would be compatible with the reaction conditions.

The first of these issues was addressed and clarified by the employment of *p*-methoxyphenyl (PMP) isocyanate to convert

(14) (a) Anonymous in *Carbohydr. Chem.* **1998**, *30*, 123. (b) Jurczak, J. *Prepr. Carbohydr. Chem.* **1997**, 595. (c) ref 8d.

Scheme 6. Synthesis of L-Vancosamine (**81**) Using IBX[a]



[a] Reagents and conditions: (a) $CrCl_2$ (4.0 equiv)/$NiCl_2$ (0.04 equiv), DMSO, 25 °C, 12 h, 61%; (b) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 30 min, 98%; (c) $NaBH_4$ (1.0 equiv), $CeCl_3$ (1.0 equiv), MeOH, −20 °C, 30 min, then 0 °C, 30 min, 90%; (d) p-$MeOC_6H_4NCO$ (2.0 equiv), DBU (0.3 equiv), CH_2Cl_2, 25 °C, 5 h, 86%; (e) HF•py (5.0 equiv), THF, 25 °C, 5 h, 90%; (f) IBX (1.2 equiv), THF:DMSO (10:1), 25 °C, 20 min, 79%; (g) p-$MeOC_6H_4OH$ (10.0 equiv), HCl (g), CH_2Cl_2, 0 °C, 30 min, 77%; (h) IBX (4.0 equiv), $NaHCO_3$ (4.4 equiv), THF:DMSO (10:1), 90 °C, 24 h, 76%; (i) CAN (3.0 equiv), CH_3CN:H_2O (5:1), 3 h, 0 °C, 92%; (j) NaOH (3 N), 90 °C, 1 h, 70%. DMP = Dess−Martin periodinane; CAN = ceric ammonium nitrate; PMP = p-methoxyphenyl.

2-cyclohexenol to the corresponding carbamate **50a** (Scheme 4, Table 3). The IBX-mediated cyclization of the latter compound [IBX (4.0 + 2.0 equiv), THF:DMSO (10:1), 90 °C] cleanly provided the bicyclic carbamate **50b** (73% yield). Removal of the PMP group with ceric ammonium nitrate (CAN),[15] followed by hydrolysis of the resulting cyclic carbamate **68a**, cleanly provided the deprotected amino alcohol **68b** (95% yield).

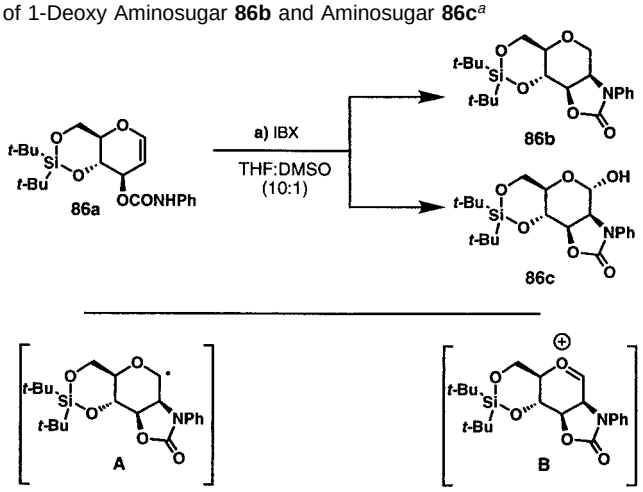
An extension of this method to carbohydrate scaffolds was carried out as shown in Scheme 5. Thus, treatment of allylic system **69** with PMP isocyanate in the presence of catalytic amounts of DBU, followed by separation of the resulting anomers,[16] IBX-mediated cyclization of the β-anomer (**69a**), and PMP group removal of the resulting protected amino sugar **69b**, successfully provided the protected amino sugar **69c** (72% yield over three steps). The exclusive formation of the cis ring fusion was assured due to the necessity of proper orbital alignment between the nitrogen-centered radical (vida infra) and the olefinic π-system.

The generality and scope of this reaction are displayed in Table 5. The simplicity of the process as a means for introducing nitrogen into carbohydrates makes it appealing, an attractiveness augmented by its stereospecific and high yielding nature, and the fact that the conditions involved do not interfere with a wide variety of protecting groups. Acid labile groups can be accommodated by buffering the reaction medium with solid sodium bicarbonate (entries 7, 10, and 11, Table 5). The process remains efficient even when forming quaternary centers (entry 11, Table 5) and in the presence of an additional olefin (entry 9, Table 5).

To further demonstrate the synthetic utility of this process, an expeditious synthesis of L-vancosamine (**81**)[17] was designed and executed (Scheme 6). Thus, intermolecular Kishi−Nozaki coupling of the readily available vinyl iodide **82** and aldehyde **83** provided a mixture of alcohols that was oxidized to afford a ketone which was reduced under Luche conditions[18] to furnish only the desired isomer **84** (54% overall yield from **83**). Carbamate formation [PMP isocyanate, DBU (catalyst)] and silyl group removal (HF•py), followed by selective oxidation of the primary hydroxyl group (IBX) and treatment with p-methoxybenzyl alcohol in the presence of HCl, provided glycoside **85** in 47% overall yield. L-Vancosamine (**81**) was then reached, in 49% overall yield, by IBX-mediated cyclization, removal of the PMB and PMP groups (CAN), and basic hydrolysis (3 N NaOH) of the carbamate moiety. This short sequence provides one of the most direct syntheses of **81** and attests to the potential of this new technology for amino sugar construction.

During further investigations directed at the extension of this methodology to the glycal arena, further benefits of the IBX-

Scheme 7. Reaction of Urethane **86a** with IBX Leads to a Mixture of 1-Deoxy Aminosugar **86b** and Aminosugar **86c**[a]



[a] Reagents and conditions: (a) IBX (2.0 equiv), THF:DMSO (10:1), 90 °C, 12 h, 85%, (**86b**:**86c**, ca. 1:2).

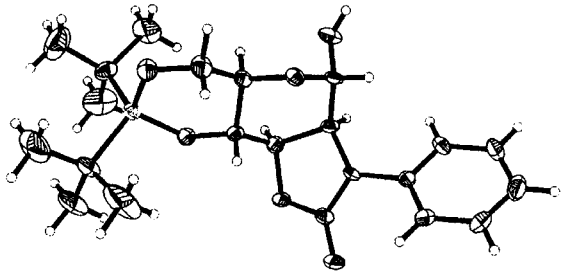


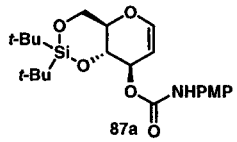
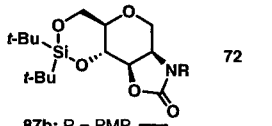
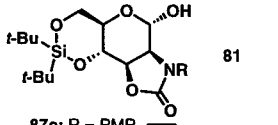
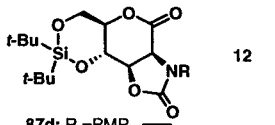
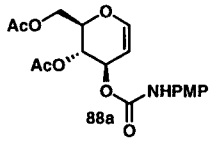
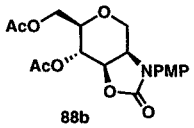
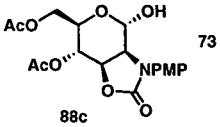
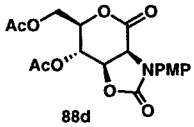
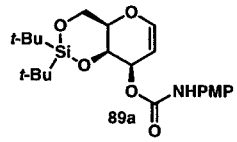
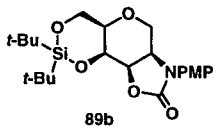
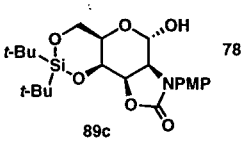
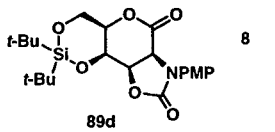
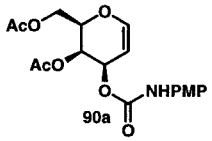
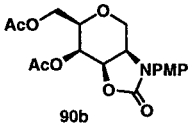
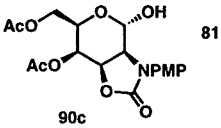
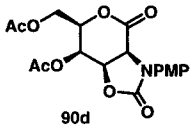
Figure 3. X-ray structure of aminosugar **86c**.

(15) (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765. (b) Knapp, S.; Kukkola, P. J.; Sharma, S. *J. Org. Chem.* **1990**, *55*, 5700.

(16) The corresponding β-isomer was used in Table 4, entry 5.

(17) For selected syntheses of L-vancosamine and derivatives thereof, see: (a) Thang, T. T.; Winternitz, F. *J. Chem. Soc., Chem. Commun.* **1979**, 153. (b) Dyong, I.; Friege, H. *Chem. Ber.* **1979**, *112*, 3273. (c) Thang, T. T.; Winternitz, F. *Tetrahedron Lett.* **1980**, *21*, 4495. (d) Ahmad, H. I.; Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. N. *Carbohydr. Res.* **1981**, *93*, 288. (e) Dyong, I.; Friege, H.; Luftmann, H.; Merten, H. *Chem. Ber.* **1981**, *114*, 2669. (f) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 5073. (g) Brimacombe, J. S.; Mengech, A. S.; Rahman, K. M. M.; Tucker, L. C. N. *Carbohydr. Res.* **1982**, *110*, 207. (h) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Carbohydr. Chem.* **1983**, *2*, 225. (i) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5413. (j) Hauser, F. M.; Ellenberger, S. R. *J. Org. Chem.* **1986**, *51*, 50. (k) Dyong, I.; Weigand, J.; Thiem, J. *Liebigs Ann. Chem.* **1986**, 577. (l) Klemer, A.; Wilbers, H. *Liebigs Ann. Chem.* **1987**, 815. (m) Hamada, Y.; Kawai, A.; Matsui, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823. (n) Greven, R.; Jutten, P.; Scharf, H.-D. *Carbohydr. Res.* **1995**, *275*, 83. (o) Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rübsam, F.; Rodríguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871.

Table 6. IBX-Mediated Synthesis of 1-Deoxy Amino Sugar, Amino Sugars, and Amino Sugar Lactones from Glycals via Their PMP-Protected Urethanes[a]

Entry	Glycal	1-Deoxy amino sugar	Yield(%)	Amino sugar	Yield(%)	Amino sugar lactone	Yield(%)[b]
1	 **87a**	 **87b:** R = PMP, **87e:** R = H	72	 **87c:** R = PMP, **87f:** R = H	81	 **87d:** R =PMP, **87g:** R = H	12
		CAN (85%)		CAN (67%)		CAN (72%)	
2	 **88a**	 **88b**	68	 **88c**	73	 **88d**	18
3	 **89a**	 **89b**	76	 **89c**	78	 **89d**	8
4	 **90a**	 **90b**	71	 **90c**	81	 **90d**	16

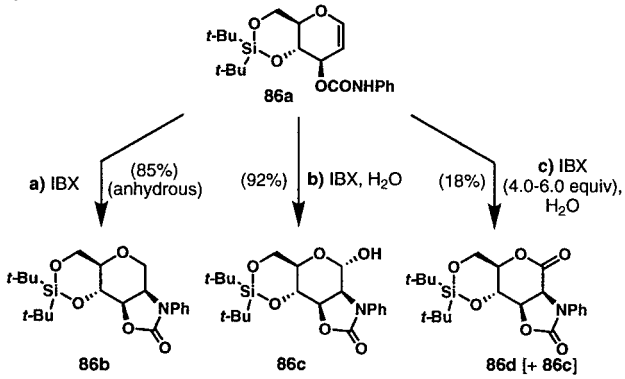
[a] Reagents and conditions: (i) (1-deoxy amino sugar formation) IBX (2.0 equiv), THF, 90 °C (sealed tube), 5 h; then IBX (2.0 equiv), 5 h; (ii) (amino sugar formation) IBX (2.0 equiv), THF:DMSO:H_2O (10:1:0.05), 12 h, 90 °C; (iii) (amino sugar lactone formation) IBX (6.0 equiv), THF:H_2O (100:1), 8 h, 90 °C (sealed tube); then IBX (6.0 equiv), 8 h; (iv) (removal of PMP group) CAN (5.0 equiv), CH_3CN:H_2O (5:1), 0 °C, 30 min. [b] In addition to the lactones the corresponding lactols (series c compounds) were obtained in yields ranging from 50 to 60%.

mediated cyclizations were discovered. When glycal **86a** (Scheme 7) was treated with IBX (2.0 equiv) in the typical solvent system (THF:DMSO, 10:1), a mixture of 1-deoxy amino sugar **86b** and amino sugar **86c** (see Figure 3 for ORTEP structure)[9d] was produced in 85% combined yield and ca. 1:2 ratio (Scheme 7). Consistent with mechanistic studies (vide infra), it became apparent that radical **A**, produced from the IBX-mediated cyclization, now being heteroatom-stabilized, is capable of undergoing further oxidation to the corresponding oxocarbenium ion (**B**) which serves as a precursor to **86c**. It should be noted that, in principle, oxocarbenium ion **B** could also lead to 1-deoxy amino sugar **86b** via hydride transfer from the large excess of THF present.[19]

Following this hypothesis, treatment of **86a** with IBX under anhydrous conditions (dry THF) provided the 1-deoxy amino sugar **86b** in 85% yield (Scheme 8). However, exposure of **86a** to IBX (2.0 + 2.0 equiv) in the presence of water (THF:DMSO:H_2O, 10:1:0.5) provided the amino sugar **86c** in 92% yield with complete control of both newly formed stereocenters. Use of a larger excess of IBX (6.0 + 6.0 equiv) provided the lactone **86d** in 18% yield (along with 61% of **86c**). These key observations led us to probe the generality of this process for the construction of diverse amino sugars from readily available glycals. Table 6 summarizes these studies.

Thus, beginning with either glucal- or galactal-derived glycals, 1-deoxy amino sugars, amino sugars, and amino sugar lactones were readily obtained using the described conditions. The enabling PMP group may also be removed from these products by employing ceric ammonium nitrate (CAN) as demonstrated in entry 1 (Table 6). The IBX-mediated route to 1-deoxy amino sugars and amino sugars is general and highly efficient. In contrast, the direct, one-pot entry into the amino sugar lactones is low yielding (the products being accompanied by the corresponding lactols), and a stepwise approach is, therefore, recommended in accessing these compounds.

Scheme 8. Complete Control in the Synthesis of 1-Deoxy Aminosugars, Aminosugars, and Aminosugar Lactones from Glycal **86a**[a]

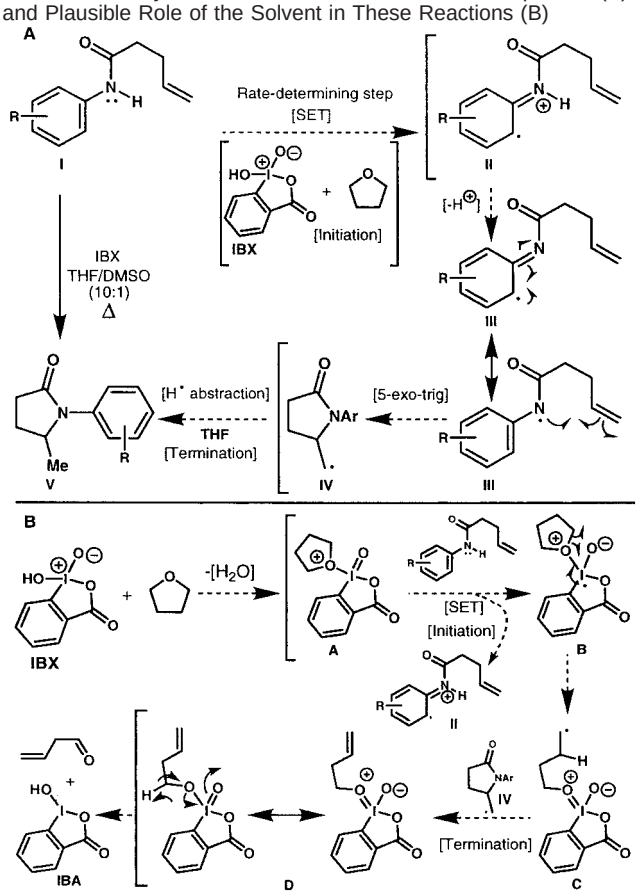


[a] Reagents and conditions: (a) IBX (2.0 equiv), THF, 90 °C (sealed tube), 5 h; then IBX (2.0 equiv), 5 h, 85%; (b) IBX (2.0 equiv), THF:DMSO:H_2O (10:1:0.05), 12 h, 90 °C, 92%; (c) IBX (6.0 equiv), THF:H_2O (100:1), 8 h, 90 °C (sealed tube); then IBX (6.0 equiv), 8 h, 18% **86d** plus 61% **86c**.

4. Mechanistic Studies of IBX-Mediated Cyclizations of *N*-Aryl Amides. Although the IBX-mediated cyclization readily provided access to a host of diverse heterocyclic compounds and other nitrogen-containing systems, the exact mechanism of the reaction was not readily apparent. Other than observing the

(18) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(19) For a study of hydride transfer kinetics from THF to triphenylmethyl cation, see: Kabir-ud-Din; Plesch, P. H. *J. Chem. Soc., Perkin Trans. 2* **1978**, 937.

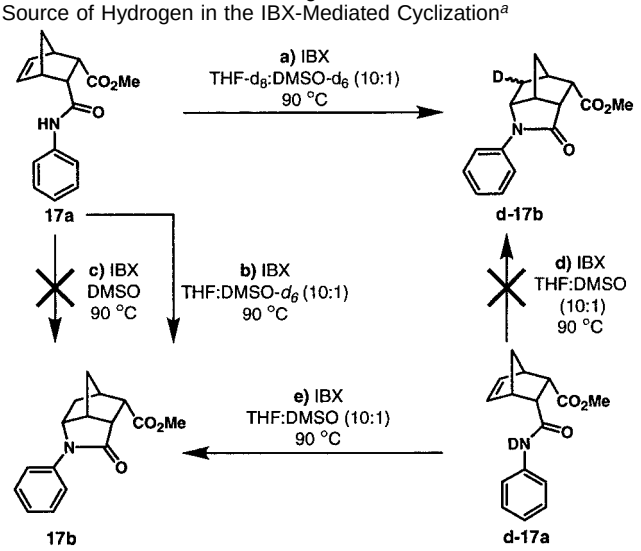
Scheme 9. Mechanistic Rationale for the SET-Based IBX-Mediated Cyclization of Anilides and Related Compounds (A) and Plausible Role of the Solvent in These Reactions (B)



necessity of THF for successful ring closure, the factors influencing the reaction were not satisfactorily resolved. Perhaps the most critical question was whether, as suspected, the reaction was initiated by single electron transfer (SET) as shown in Scheme 9.[20] Second, the role of THF along the reaction pathway required clarification. Next, the nature, and apparent requirement, of the nitrogen aryl group required further study in the hope that light could be shed on the electronic nature and properties of the reactive species involved in the cascade. In so doing, it was hoped that the structural features of substrates could be clearly defined to fully exploit the scope and limitations of this new synthetic tool.

To probe the possibility of a SET mechanism, it was critical to determine whether the hydrogen atom that must quench the radical resulting from cyclization (**IV** → **V**, Scheme 9) originated from the substrate, IBX, or the solvent (THF). Thus, when the reaction of **17a** (Scheme 10) was performed in THF-d_8/DMSO-d_6 (10:1), deuterium was detected (NMR) in product ***d*-17b** at the carbon predicted from the proposed mechanism. However, carrying out the reaction of **17a** in THF/DMSO-d_6 (10:1) or of deuterated amide ***d*-17a** in THF/DMSO (10:1) led to **17b** containing no deuterium. Use of DMSO as solvent in the absence of hydrogen-donating solvents (such as THF or dioxane) returned only starting material, along with small amounts of a number of unidentified decomposition products. This strong reliance of the reaction on solvent choice led to the conclusion that the solvent (THF) actually plays an active role

Scheme 10. Deuterium Labeling Studies To Determine the Source of Hydrogen in the IBX-Mediated Cyclization[a]



[a] Reagents and conditions: (a) IBX (4.0 equiv), THF-d_8:DMSO-d_6 (10:1), 90 °C, 24 h, 24%; (b) IBX (1.0 equiv), THF:DMSO-d_6 (10:1), 80 °C, 10 min, 15% conversion (NMR); (c) IBX (4.0 equiv), DMSO, 90 °C, 24 h; (d) see (e); (e) IBX (4.0 equiv), THF:DMSO (10:1), 90 °C, 24 h, 40%.

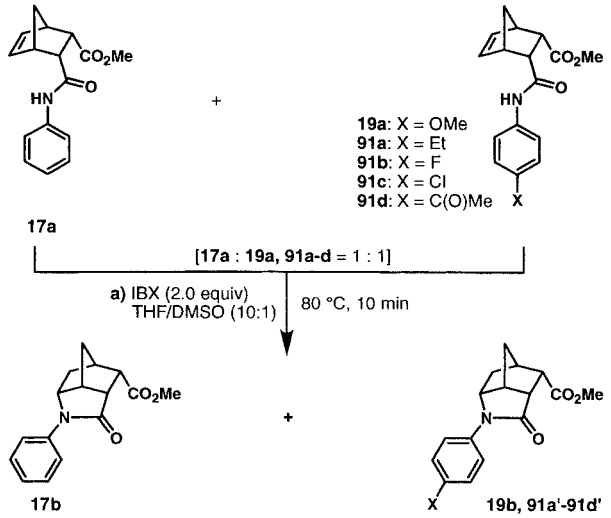
in the process, besides being a source of the hydrogen atom as shown in Scheme 9B. The combined investigations[21] into IBX-mediated reactions emanating from these laboratories have strongly suggested that heteroatom coordination to IBX is facile. THF is uniquely suited for this transformation not only because of its low α C−H bond dissociation energy (BDE), but because it may readily coordinate to IBX through the oxygen atom lone pair. A viable scenario accommodating the observed phenomena might involve coordination of a molecule of THF to IBX, leading to intermediate **A** (Scheme 9B). This species is expected to be an extraordinarily strong oxidant, one that could initiate the cyclization by SET to the aryl amide, furnishing intermediates **II** (Scheme 9A) and **B** (Scheme 9B). Rearrangement of **B** to **C** followed by hydrogen abstraction may then lead to product **V** (Scheme 9A) along with **D** (Scheme 9B), the latter rapidly collapsing to iodosobenzoic acid (IBA) and 3-butenal (Scheme 9B). Notably, treatment of THF with only IBX at 90 °C for 24 h led to the isolation of 2-iodobenzoic acid along with polymeric material and unidentified compounds containing aldehyde residues, as judged by ^{1}H NMR spectroscopy. In addition, when IBA or other hypervalent iodine reagents were employed in the cyclization (**I** → **V**, Scheme 9), no reaction was observed (vide supra, entries 7−10, Table 1).

Further support for the SET mechanism was gained in a straightforward fashion through a systematic evaluation of the kinetics of the reaction with substrates designed to probe the electronic effects of aromatic substituents on the rates of the entire process (**I** → **V**) and of step **III** → **IV** (Scheme 9A). A Hammett plot was generated by comparing the relative rates of the *para*-substituted aromatic amides **19a**, **91a**−**d** with the unsubstituted aromatic amide **17a** (Scheme 11). Competing equimolar mixtures of **17a** and **19a**, **91a**, **91b**, **91c**, or **91d** were heated with 2.0 equiv of IBX in THF:DMSO (10:1) at 80 °C for 10 min. The ratios between the unsubstituted product **17b** and the *para*-substituted products **19b**, **91a′**−**d′**

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

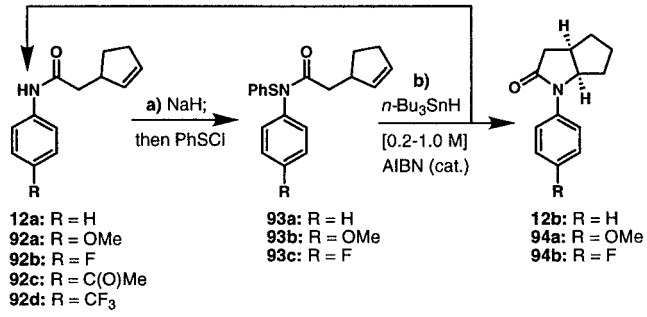
(21) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.

Scheme 11. NMR-Monitored Competition Reactions between Anilides **17a** and **19a**, **91a**−**d**[a]



[a] Reagents and conditions: (a) IBX (2.0 equiv), THF:DMSO (10:1), 80 °C, 10 min.

Scheme 12. Synthesis and Reactions of *N*-Thiophenyl Amides **93a**−**c** with *n*-Bu_3SnH[a]

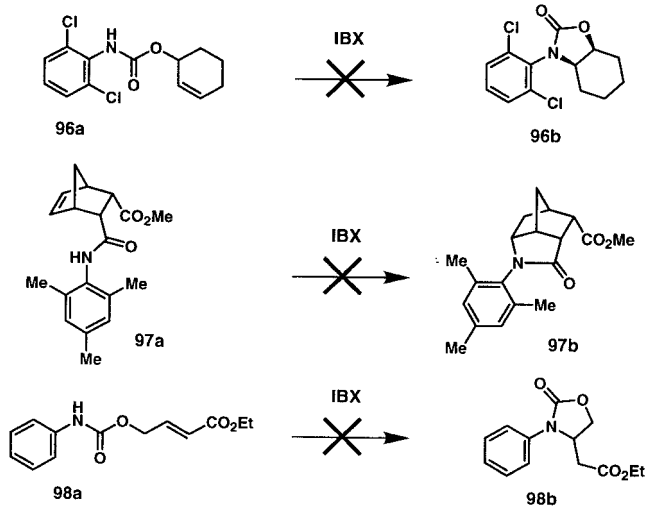


[a] Reagents and conditions: (a) NaH (1.3 equiv), THF, reflux, 4 h; then PhSCl (ca. 1 equiv, added until yellow color of PhSCl persisted), −78 °C, 1 h, 74−86%; (b) *n*-Bu_3SnH (0.2−1.0 M), toluene, 65 °C, 2−5 h, 85−92% total yield of cyclized product plus uncyclized anilide.

were determined by ^{1}H NMR spectroscopy. Electron-donating substituents [X = OMe (**19a**) and Et (**91a**)] increased the rate of cyclization, whereas electron-withdrawing substituents [X = Cl (**91c**) and C(O)Me (**91d**)] caused a decrease in the reaction rate or had no significant effect on the rate [X = F (**91b**)] relative to the unsubstituted substrate. For amides of type **91** where X = NO_2 and CF_3, no appreciable reaction was observed under the reaction conditions utilized in the kinetic study.

The Hammett plot,[22] based on the ratio of the reaction rate constants (k_s/k_u) and σ_p^+ parameters,[23] gave a linear graph with a negative slope ($\rho = -1.4$, $R^2 = 0.97$; Figure 2).[24] This ρ value

Scheme 13. Failure of Substrates **96a**−**98a** to Cyclize under the Influence of IBX



is typical for a radical reaction[22] and indicates a lower electron density in the transition state relative to the initial ground state of the substrate. It supports the hypothesis that the first step of the reaction involves SET from the aromatic ring of the amide to IBX to form a radical anion/radical cation pair as shown in Scheme 9. After loss of a proton, radical cation **II** is converted to radical **III**, which then undergoes cyclization onto the double bond in a 5-*exo-trig* fashion to furnish the carbon-centered radical species **IV**. Subsequent quenching of the latter species (**IV**) by hydrogen atom transfer from THF then leads to product **V**.

To determine if the rate-determining step of the reaction was **I** → **II** or **III** → **IV** (Scheme 9A), a series of *N*-(phenylthio)-amides[25] (i.e., **93a**−**c**) were prepared[26] from **12a** and **92a**,**b** (Scheme 12). Three cyclization experiments for each *N*-(phenylthio)amide (**93a**−**c**) were conducted at 65 °C in toluene in the presence of excess *n*-Bu_3SnH at concentrations ranging from 0.2 to 1.0 M. After determining the relative yields of cyclized product (**12b**, **94a**,**b**, Scheme 12) and acyclic amide (**12a**, **92a**,**b**) formed in the reactions by HPLC, and assuming the rate of trapping of tin hydride to be the same for all radicals,[25] the relative rate constants for cyclization of the amide centered radicals were inferred. According to this method, the relative rates of cyclization for **93a**, **93b**, and **93c** were determined to be (0.66 ± 0.1), (0.30 ± 0.1), and (0.40 ± 0.1) M, respectively. Because the opposite trend is observed when the overall rate is evaluated (see Figure 2), and because the amidyl radical cyclization is rapid for **93a**−**c**, we concluded that SET from the aromatic nucleus of the anilide to the IBX·THF complex (**I** → **II**, Scheme 9A) is the rate-determining step of the reaction.

Determination of the oxidation potentials of anilides **12a** and **92a**−**d** (see Scheme 12) provided further insights into the electronic requirements for this cylization process. Thus, by performing cyclic voltammetry on CH_2Cl_2 solutions of **12a** and

(22) σ_p^+ values: Zuman, P.; Patel, R. C. *Techniques in Organic Reaction Kinetics*; Krieger Publishing Company: Malabar, Florida, 1992; p 230. For a discussion of Hammett plots, see: Lowry, T. H.; Richardson, S. K. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987.

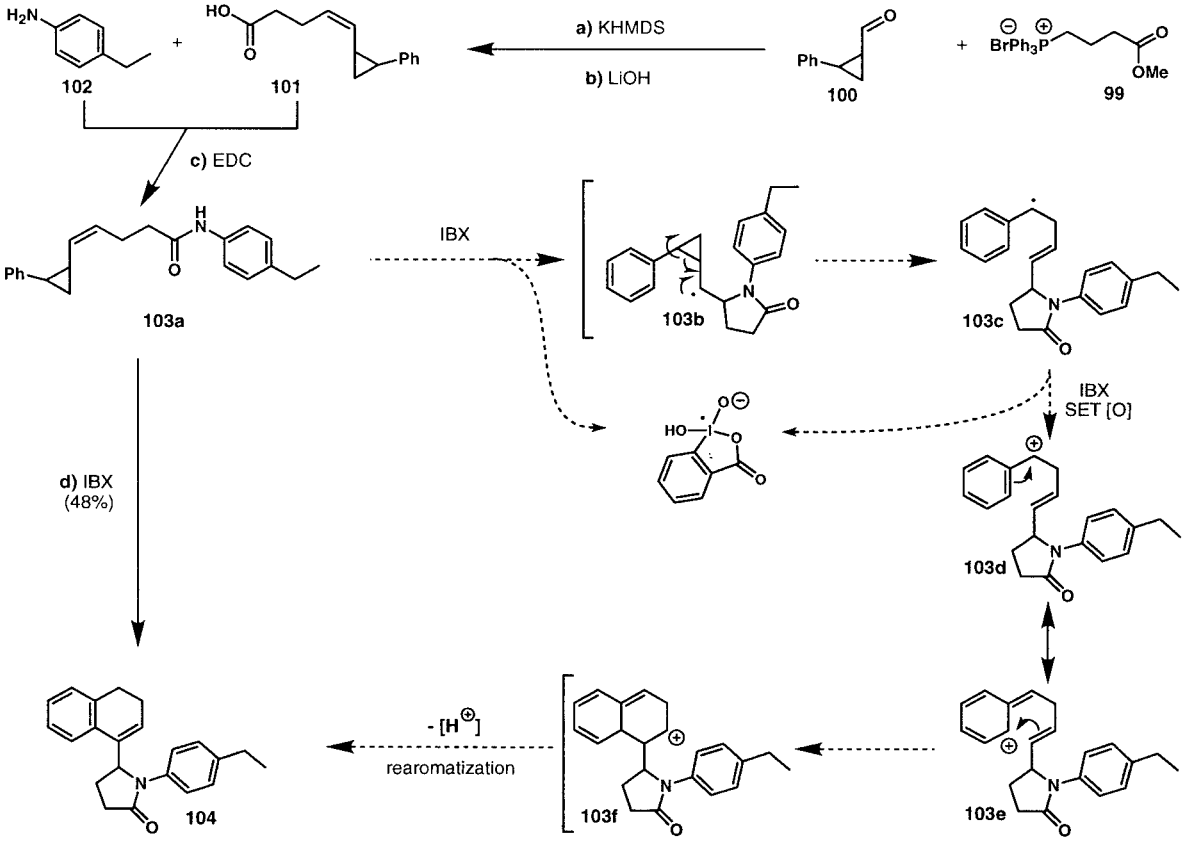
(23) k_u: Rate constant of reaction **17a** → **17a**; k_s: Rate constants of reactions **91a**−**d** and **19a** → **91a′**−**d′** and **19b**. Because the σ_p^+ parameter for the acetate group was not defined in ref 20, substrate **91d** was not plotted. For the determination of ρ the following expression[19] 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 anilide **19a** and *p*-substituted anilides **91a**−**d** that reacted, or by analogy, millimoles of products **19b** and **91a′**−**d′**; u_t and s_t = initial millimoles of anilide **19a** and *p*-substituted anilides **91a**−**d**.

(24) Higgins, R.; Foote, C. S.; Cheng, H. *ACS Symp. Ser*. **1968**, *77*, 102.

(25) For seminal work in the area of amide-centered radicals, see: Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738. Newcomb, M.; Tanaka, N.; Bouvier, A.; Tronche, C.; Horner, J.; Musa, O. M.; Martinez, F. N. *J. Am. Chem. Soc.* **1996**, *118*, 8505. Newcomb, M. *Tetrahedron* **1993**, *49*, 1151 and references therein. Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katrizky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, p 1.

(26) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877.

Scheme 14. Cascade Reaction Sequence Supporting the Radical Nature of the IBX-Mediated Cyclizations[a]



[a] Reagents and conditions: (a) **99** (1.2 equiv), KHMDS (1.0 equiv), THF, 0−25 °C, 1 h, then **100**, −78 °C, 2 h, warm to 25 °C, 6 h; (b) LiOH (5.0 equiv), THF:H_2O (4:1), 25 °C, 24 h, 70% overall; (c) EDC (1.2 equiv), 4-DMAP (1.2 equiv), CH_2Cl_2, 25 °C, 10 h, 95%; (d) IBX (4.0 equiv every 24 h), THF:DMSO (10:1), 90 °C, 48 h, 48%.

92a−**d**, the *p*-substituted anilides were determined to be more difficult to oxidize than ferrocene by the following amounts: 1.20 V (**12a**), 0.82 V (**93a**), 1.23 V (**93b**), 1.48 V (**93c**), and ≥1.57 V (**93d**).[27] By comparing the measured oxidation potentials with the observed relative rates of the reactions, a direct correlation was immediately apparent. Thus, anilides with lower oxidation potentials (i.e., **12a**, **92a**, and **92b**) proceeded to cyclize rapidly, while anilides with higher oxidation potentials (i.e., **92c**−**d**) entered the reaction only sluggishly.

In light of these findings, a number of unexplained failures of the IBX-mediated cyclization previously encountered in these laboratories can now be rationalized (see Scheme 13). The need for an open position *ortho* to the nitrogen atom is evident since **96a** and **97a** (Scheme 13) do not undergo the reaction. This could be explained by an increase in the oxidation potential caused by deconjugation of the lone pair of electrons on the nitrogen atom from the arene ring,[28] by a decreased rate for the 5-*exo-trig* cyclization, or simply by the lack of deprotonation of the radical cation (**II** → **III**, Scheme 9A). The mildly electrophilic nature of the nitrogen-centered radical[25] is supported by the failure of α,β-unsaturated ester **98a** to react (Scheme 13). The notion that only *N*-aryl amides should undergo the IBX-mediated cyclization is supported by the fact that substrates **26a**, **27a**, and **29a** are unresponsive to the conditions, while **31a** and **32a** lead rapidly to decomposition products (Scheme 2).

Further evidence pointing to the radical-based mechanism of the cyclization is provided by the designed cascade reaction depicted in Scheme 14. Thus, when cyclopropyl anilide **103a** was treated with IBX (4.0 equiv in two portions) in THF:DMSO (10:1) at 90 °C for 48 h, the novel tetracycle **104** was obtained in 48% yield. This striking transformation is rationalized by invoking a radical-based mechanism involving species **103b**, which is postulated to lead to benzylic radical **103c** by rupture of the cyclopropyl ring as shown. A second SET from this species to IBX provides benzylic cation **103d** ↔ **103e**, which after cationic cyclization and re-aromatization, provides the observed product **104** via species **103f**.

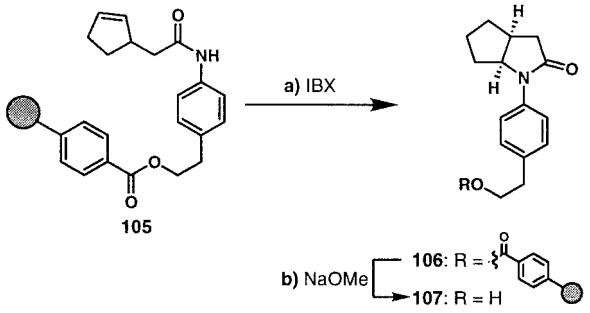
5. Solid-Phase Synthesis with IBX. After gaining significant insight into the mechanism of the IBX-mediated cyclization, we sought to determine the reaction's applicability to solid phase synthesis. Treatment of **105**[29] with IBX (excess) in THF/DMSO (10:1) at 85 °C for 3 days led to the resin-bound product **106**, which upon cleavage with NaOMe in MeOH afforded only 15% yield of γ-lactam **107** (based on 1.0 mmol/g loading of **105**) (Scheme 15).

The low efficiency observed in these reactions is likely due to oxidative damage of the resin by IBX. Nevertheless, this

(27) Anodic peak potentials, 0.2 M *n*-Bu_4NBF_4 in CH_2Cl_2, Pt disk electrode, Pt wire auxiliary and pseudo-reference electrodes, 23 °C, 200 mV s^{-1}, referenced to internal $FeCp_2$ at +0.30 V. Irreversible and rapid fouling of the electrode was observed, and, therefore, measured potentials are on first scan only (reproducible on several independent runs). Professor M. G. Finn is gratefully acknowledged for his assistance in these measurements. For a systematic study of the bond dissociation energies of the N−H bonds in anilines and their oxidation potentials see: Bordwell, F. G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* **1993**, *58*, 6410.

(28) For an insightful study of steric inhibition of resonance, see: Böhm, S.; Exner, O. *Chem.-Eur. J.* **2000**, *6*, 3391 and references therein.

Scheme 15. Solid Phase Version of the IBX-Mediated Cyclization of *N*-Aryl Amides[a]



[a] Reagents and conditions: (a) IBX (excess), THF:DMSO (10:1), 90 °C, 72 h; (b) NaOMe (10 equiv), MeOH, 25 °C, 2 h, 15% **107**.

IBX-mediated cyclization protocol may still be amenable to further optimization through exploitation of other more appropriate resins or in parallel solution formats yet to be implemented.

Conclusion

The discovery of the IBX-mediated cyclization of *N*-aryl amides, carbamates, and ureas provides access to novel, structurally diverse lactams and other heterocycles, as well as various amino alcohols. Additionally, amino sugars and 1-deoxy amino sugars are readily prepared from glucals and other carbohydrate-based scaffolds. The operational simplicity of this reaction, coupled with the ease of preparation of the cyclization precursors, allow for the rapid diversification of allylic alcohols to provide small molecule libraries for biological screening and other applications. Furthermore, the ability to selectively introduce nitrogen functionality onto unactivated alkenes provides opportunities for the synthesis of natural and unnatural alkaloid-type compounds. The versatility of IBX as a controllable SET-based oxidation reagent is further demonstrated in the following article.[21]

Experimental Section

General Procedure for IBX-Induced Cyclization. IBX (59.4 mg, 0.20 mmol) was added to a solution of amide (0.1 mmol) in THF:DMSO (10:1, 4 mL total volume). The solution was placed in a sealed tube and heated at 90 °C for 12 h, followed by another addition of IBX (59.4 mg, 0.20 mmol) and heating for a further 12 h period at the same temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with 5% aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. After purification by preparative thin-layer chromatography (PTLC, silica gel, EtOAc:hexanes, 1:2) or flash column chromatography (silica gel), the desired product was obtained in pure form.

General Procedure for the Hydrolysis of Cyclic Urethanes to Amino Alcohols. To a solution of cyclic urethane (0.05 mmol) in ethanol (0.5 mL) was added NaOH (20 mg, 0.5 mmol), and the reaction was heated to 70 °C until TLC indicated complete consumption of the starting urethane. The reaction mixture was then diluted with EtOAc (1 mL) and washed with water (3 × 2 mL) and brine (2 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel) to provide the free amino alcohols.

General Procedure for the CAN-Induced Deprotection of Amino Sugar Derivatives. To a solution of amino sugar derivative (0.05 mmol) in $CH_3CN:H_2O$ (5:1, 0.6 mL) was added ceric ammonium nitrate (CAN, 137 mg, 0.25 mmol) at 0 °C. After TLC indicated complete consumption of the starting material, the reaction mixture was diluted with EtOAc (2 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 1 mL), water (2 × 2 mL), and brine (3 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel) to provide pure deprotected amino sugar derivatives.

General Procedure for the Synthesis of 1-Deoxy-Aminosugars (Procedure A). IBX (59.4 mg, 0.2 mmol) was added to a solution of glycal-urethane (0.1 mmol) in anhydrous THF (4 mL). The solution was placed in a sealed tube and heated at 90 °C for 5 h, followed by another addition of IBX (59.4 mg, 0.20 mmol) and heating for a further 5 h period at the same temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with 5% aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. After purification by preparative thin-layer chromatography (PTLC, silica gel, EtOAc:hexanes, 1:2) or flash column chromatography (silica gel), the desired product was obtained in pure form.

General Procedure for the Synthesis of Aminosugars (Procedure B). IBX (59.4 mg, 0.2 mmol) was added to a solution of glycal-urethane (0.1 mmol) in THF:DMSO:H_2O (10:1:0.5, 4 mL total volume). The solution was placed in a sealed tube and heated at 90 °C for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with 5% aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. After purification by preparative thin-layer chromatography (PTLC, silica gel, EtOAc:hexanes, 1:2) or flash column chromatography (silica gel), the desired product was obtained in pure form.

General Procedure for the Synthesis of Aminosugar Lactones (Procedure C). IBX (178.2 mg, 0.6 mmol) was added to a solution of glycal-urethane (0.1 mmol) in THF:H_2O (100:1, 4 mL total volume). The solution was placed in a sealed tube and heated at 90 °C for 8 h, followed by another addition of IBX (178.2 mg, 0.6 mmol) and heating for a further 8 h period at the same temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with 5% aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. After purification by preparative thin-layer chromatography (PTLC, silica gel, EtOAc:hexanes, 1:2) or flash column chromatography (silica gel), the desired product was obtained in pure form. In all cases, amino sugar lactones were isolated as the minor products with the corresponding lactols predominating. The lactols could be easily oxidized to the lactones using Dess−Martin periodinane (DMP) in CH_2Cl_2 at 25 °C.

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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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