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Iodine(V) Reagents in Organic Synthesis. Part 1. Synthesis of Polycyclic Heterocycles via Dess−Martin Periodinane-Mediated Cascade Cyclization: Generality, Scope, and Mechanism of the Reaction

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Abstract: The scope, generality, and mechanism of the Dess−Martin periodinane-mediated cyclization reaction of unsaturated anilides discovered during the total synthesis of the CP-molecules (phomoidrides A and B) are delineated. A plethora of heterocyclic compounds are accessible by employing γ,δ-unsaturated amides (derived from anilines and carboxylic acids), urethanes, or ureas (derived from isocyanates and allylic alcohols and amines) as substrates. Optimization of the reaction led to room-temperature conditions, while isotope labeling studies allowed a mechanistic rationale for this cascade reaction.

Introduction

The importance of hypervalent iodine reagents in organic synthesis has been amply demonstrated in recent years. Useful synthetic reactions for the construction of carbon−heteroatom and carbon−carbon bonds mediated by hypervalent iodine species have been reviewed extensively.[1] One of the field's most significant advances, the discovery of the Dess−Martin periodinane (DMP),[2] opened the door to a mild oxidation procedure allowing a myriad of alcohols to be converted to the corresponding carbonyl compounds. Its widespread use over the past 10 years attests to its benign nature and its uncanny ability to succeed in the most difficult of oxidation circumstances. *o*-Iodoxybenzoic acid (IBX),[3] the precursor of DMP, has also been shown to be a mild alcohol oxidant.[4] Contemporary organic synthesis is constantly striving for discovery and design of reagents such as DMP and IBX which provide beneficial levels of chemoselectivity and efficiency. In the postgenomic age, a premium is placed on versatile, complexity-generating reactions wherein a multitude of natural product-, drug-, and lead-like compounds can be rapidly assembled and funneled into biological screening programs.[5] Recently, we unearthed a series of new paradigms for iodine(V)-mediated reactions with a variety of organic substrates which go far beyond simple alcohol oxidation.[6] These discoveries, arising from our endeavors during the total synthesis of the CP-molecules (phomoidrides A and B),[7] allow the rapid and selective construction of complex polycycles, including natural product analogues, diverse drug- and leadlike molecules, amino sugars, α,β-unsaturated carbonyl compounds, and an array of useful oxidized building blocks. In this series of papers, we describe details of these processes and provide new insights into their scope, generality, and mechanism. In this article, we present a full account of the DMP-mediated cascade polycyclization reaction of simple aryl amides (anilides), urethanes, and ureas to complex phenoxazine-containing polycycles (Scheme 1).

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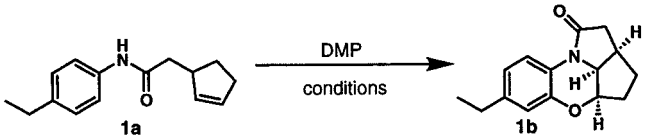
Table 1. Optimization of the DMP-Mediated Cyclization of Aryl Amides (**1a** to **1b**)



entry	DMP (equiv)	additive(s)	solvent	temp (°C)	time	yield (%)[a]
1	2.0	none (open to atmosphere)	benzene	reflux	30−40 min	34−40
2	2.0	none (open to atmosphere)	BTF	80	30−40 min	32−37
3	2.0	none (under Ar)	benzene	reflux	5 h	0
4	4.0	1.0 equiv of H_2O (under Ar)	CH_2Cl_2	23	1.5 h	15
5	4.0	0 or 1.0 equiv of H_2O (under Ar)	THF	23	20 h	0
6	2.0	0 or 1.0 equiv of H_2O (under Ar)	CH_3CN	23	24 h	0
7	4.0	0 or 1.0 equiv of H_2O (under Ar)	DMF	23	24 h	0
8	4.0	0 or 1.0 equiv of H_2O (under Ar)	DMSO	23	24 h	0
9	2.2	1.0 equiv of TFA	CH_2Cl_2	23	7 h	0
10	2.2	1.0 equiv of pyridine (under Ar)	CH_2Cl_2	23	10 h	trace
11	4.0	1.0 equiv of H_2O, excess O_2	CH_2Cl_2	23	1.5 h	15
12	4.0	1.0 equiv of H_2O, 5.0 equiv of galvinoxyl (under Ar)	CH_2Cl_2	23	7 h	14
13	4.0	2.0 equiv of H_2O (under Ar)	CH_2Cl_2	23	15 h	40−42
14	4.0	2.0 equiv of H_2O (under Ar)	toluene	80	30−40 min	27
15	4.0	none (open to atmosphere)	toluene	80	30−40 min	16

[a] Chromatographically pure **1b**. BTF = benzotrifluoride, THF = tetrahydrofuran, DMF = dimethylformamide, DMSO = dimethyl sulfoxide.

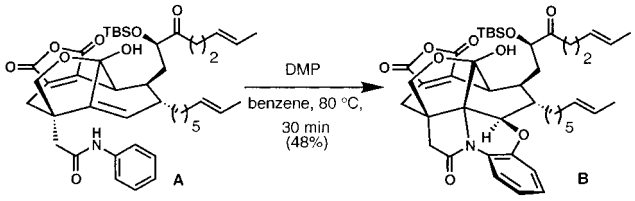
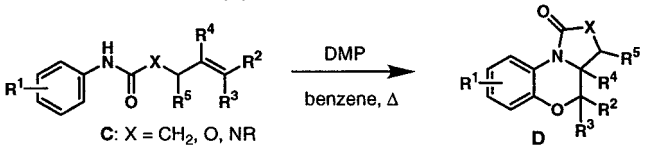


Figure 1. A serendipitous discovery during the CP-molecule campaign: initial observation of the reaction of an unsaturated anilide (**A**) to a novel heterocycle (**B**) upon heating with DMP in benzene solution at 80 °C.

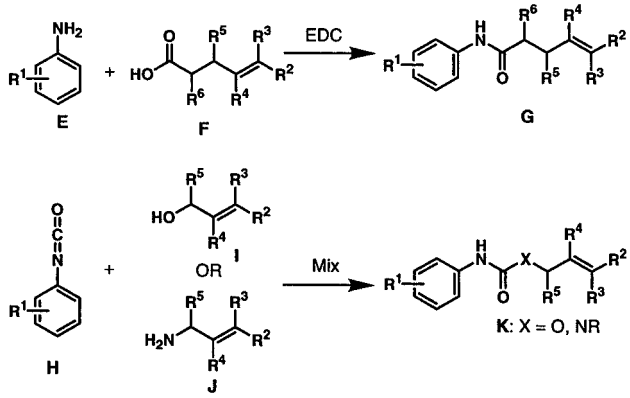
Scheme 1. DMP-Mediated Formation of Complex Heterocycles (**D**) in One Step from Readily Available Aryl Amides (Anilides), Urethanes, and Ureas (**C**)



Results and Discussion

1. Discovery and Optimization of the DMP Reaction with Anilides. In 1999, while attempting to oxidize the stubbornly resisting CP-molecule intermediate **A** (Figure 1) with DMP at elevated temperatures, we observed, much to our surprise, the formation of the novel polycyclic system **B**. Upon short reflection and mechanistic analysis we suspected a new mode of reactivity for DMP which required an aryl amide moiety and a nearby double bond as demonstrated in structure **A**. An expedient investigation of the scope and generality of the reaction led to a preliminary communication.[6a] Since our initial disclosure, we have performed extensive optimization studies of this process (Table 1) using aryl amide **1a** as a substrate. The results are shown in Table 1. Through the systematic fine-tuning of this reaction, a plausible mechanistic pathway also became clear (vide infra). When we probed solvent effects we found that benzene, benzotrifluoride (α,α,α-trifluorotoluene, BTF),[8] toluene, and CH_2Cl_2 were all suitable solvents (entries 1, 2, and 13−15, Table 1). No detectable reaction was observed in THF, CH_3CN, DMF, or DMSO. Additives such as TFA halted the reaction (entry 9, Table 1), whereas pyridine did not accelerate the reaction (entry 10, Table 1) unless water was present (vide infra). Hypothesizing that the presence or absence of water may be intimately related with reaction efficiency, we performed the reaction under strictly anhydrous conditions (entry 3, Table 1). It thus became clear that water was an essential ingredient for the reaction to proceed, and this in turn implied that Ac-IBX (see Scheme 6) was somehow involved.[9] Polycycle **1b** (Table 1) was obtained in similar yields at room temperature in CH_2Cl_2 or at 80 °C in benzene, only when the correct stoichiometry of DMP and H_2O was employed. As shown in Table 2, we found that 4.0 equiv of DMP and 2.0 equiv of H_2O was an ideal reagent combination for the reaction (entry 6, Table 2). It is interesting to note that using only DMP (no H_2O present) or DMP:H_2O (1:1) resulted in no reaction. The remarkable mechanistic implications of this finding will be discussed later (vide infra).

Scheme 2. Two Methods Utilized for the Preparation of Aryl Amides (**G**), Urethanes, and Ureas (**K**) as Substrates for the DMP-Mediated Cyclization



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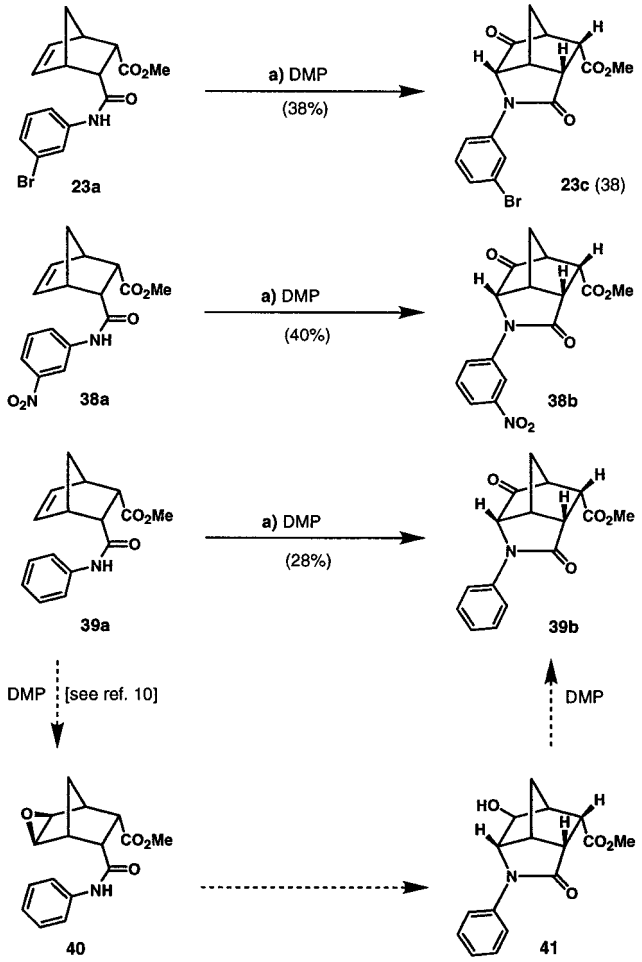
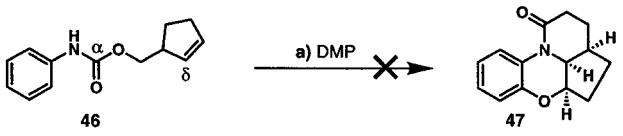
(9) (a) For the first report of Ac-IBX see ref 2b. (b) Water-induced acceleration of the DMP reagent (leading to Ac-IBX) was also observed by S. L. Schreiber in the context of alcohol oxidation, see ref 2c; see also ref 4c.

Scheme 3. Amides Such as **23a**, **38a**, and **39a** Give Rise to the Corresponding Ketones **23c**, **38b**, and **39b** Instead of the Expected Polycycles, Presumably via an Epoxide Intermediate Such as **40**[a]



[a] Reagents and conditions: (a) DMP (2.0 equiv), benzene, 75 °C, 1 h, 43% **23c**, 40% **38b**, and 28% **39b**.

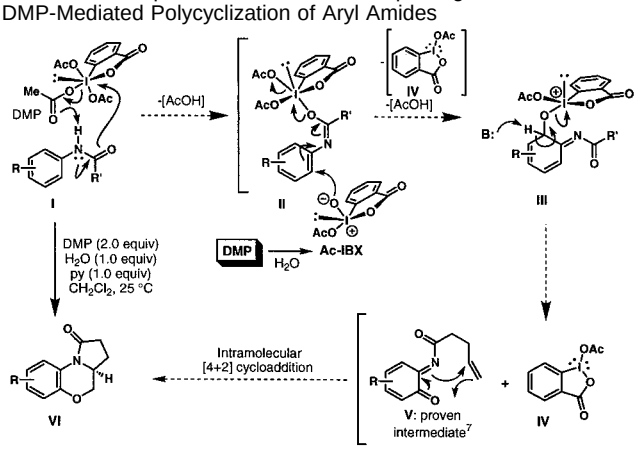
Scheme 4. Attempted Construction of Tetracycle **47** from δ-Olefinic Substrate **46** and DMP[a]



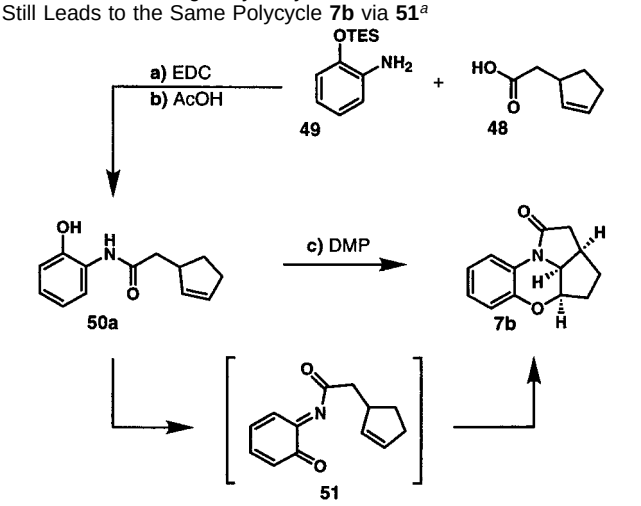
[a] Reagents and conditions: (a) DMP (4.0 equiv), benzene, 80 °C, 4 h.

2. Scope and Generality of the Reaction. With two reliable sets of conditions in hand (conditions A and B, see Table 3), we probed the generality of the DMP reaction with a variety of easily prepared anilides [from anilines (**E**) and γ,δ-unsaturated carboxylic acids (**F**), see Scheme 2 and Table 3]. Our initial attempts to determine the generality of the DMP-cascade were disappointing. As shown in entries 1−8 in Table 3, the reactions of simple anilides containing a terminal olefin led only to low yields of the desired products. We attributed this observation to a combination of two factors: (a) a high degree of conformational freedom of the olefin in these substrates and (b) the olefin's comparatively electron-poor nature. We reasoned that embedding a ring into the olefinic segment of the starting material might restrict conformational mobility and increase electron density of the olefinic bond, thereby increasing the efficiency of the reaction. Indeed, as can be seen from entries

Scheme 5. Proposed Mechanistic Underpinnings of the DMP-Mediated Polycyclization of Aryl Amides

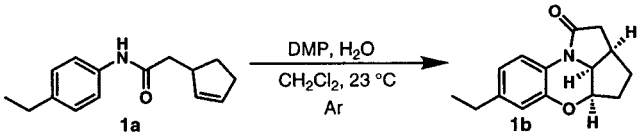


Scheme 6. Enlisting *o*-Hydroxyanilide **50a** in the DMP Cascade Still Leads to the Same Polycycle **7b** via **51**[a]



[a] Reagents and conditions: (a) EDC (1.2 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 3 h; (b) 80% aqueous AcOH, 25 °C, 1 h, 81% overall; (c) DMP (2.0 equiv), benzene, 75 °C, 0.5 h, 35%.

Table 2. Optimization of the Stoichiometry of DMP and H_2O Employed in the DMP-Induced Cyclization of Aryl Amides (**1a** → **1b**)



entry	DMP (equiv)	H_2O (equiv)	yield (%)[a]
1	1.0	0	0
2	2.0	0	0
3	2.0	1.0	30
4	2.0	2.0	0
5	4.0	0	0
6	4.0	2.0	40
7	4.0	4.0	0

[a] Chromatographically pure **1b**.

9−32 (Table 3), the cyclization yields were considerably improved with this modification to provide a variety of complex polycycles. The ability of this process to generate three new stereocenters in a diastereocontrolled manner from simple starting materials is both remarkable and highly productive in terms of achieving molecular complexity. Throughout these studies and using the new, ambient temperature-based conditions

Table 3. DMP-Mediated Construction of Novel Polycycles and Quinones from Unsaturated Aryl Amides[a]

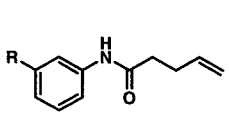
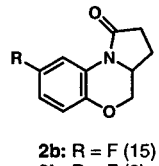
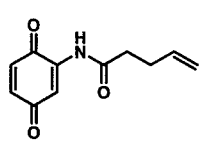
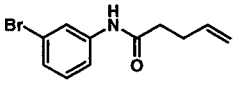
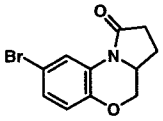
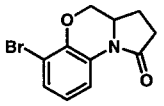
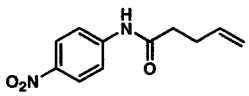
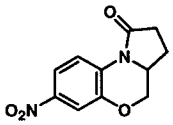
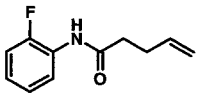
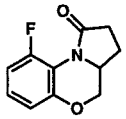
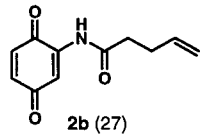
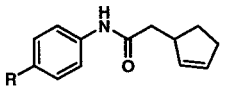
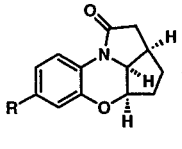
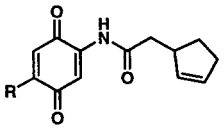
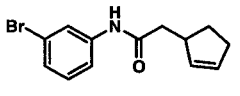
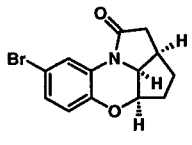
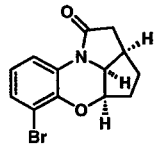
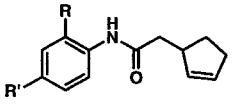
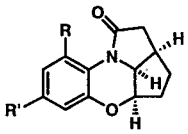
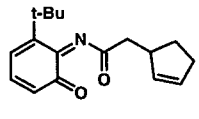
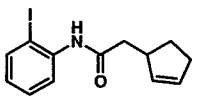
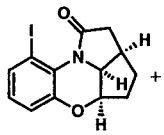
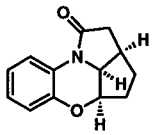
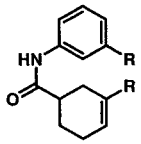
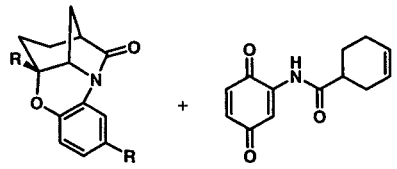
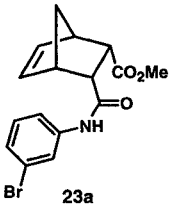
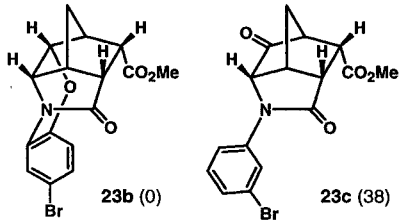
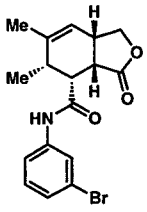
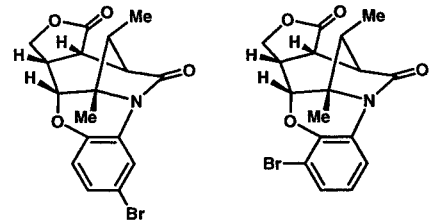
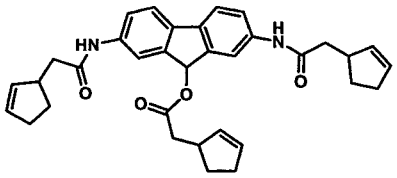
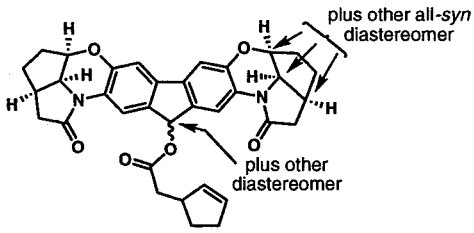
Entry	Substrate	Conditions, Time	Product(s) (Yield %)[b]	
		Conditions A: DMP (2.0 equiv), benzene, reflux, open to atmosphere Conditions B: DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 23 °C, Ar	 + 	
1	**2a:** R = F	A, 40 min	**2b:** R = F (15)	
2	**2a:** R = F	B, 48 h	**2b:** R = F (0)	**2c** (10%)
3	**3a:** R = NO_2	A, 35 min	**3b:** R = NO_2 (10)	
4	**3a:** R = NO_2	B, 40 h	**3b:** R = NO_2 (11)	
			 + 	
5	**4a**	A, 45 min	**4b** (11%, *ca* 1:1)	
6	**4a**	B, 80 h	**4b** (7%, *ca* 2:1)	
				
7	**5a**	B, 36 h	**5b** (13)	
			 + 	
8	**6a**	B, 36 h	**6b** (20)	**2b** (27)
			 + 	
9	**7a:** R = H	A, 1 h	**7b:** R = H (52)	
10	**7a:** R = H	B, 24 h	**7b:** R = H (40)	**7c:** R = H (10)
11	**1a:** R = Et	A, 40 min	**1b:** R = Et (40)	
12	**1a:** R = Et	B, 15 h	**1b:** R = Et (44)	**1c:** R = Et (7)
13	**8a:** R = Cl	B, 14h	**8b:** R = Cl (48)	**8c:** R = Cl (11)
14	**9a:** R = Br	B, 14 h	**9b:** R = Br (26)	
15	**10a:** R = I	B, 18 h	**10b:** R = I (24)	
16	**11a:** R = NO_2	B, 16 h	**11b:** R = NO_2 (37)	
17	**12a:** R = CF_3	B, 12 h	**12b:** R = CF_3 (57)	
18	**13a:** R = Ph	B, 27 h	**13b:** R = Ph (29)	**13c:** R = Ph (8)
19	**14a:** R = *t*-Bu	B, 36 h	**14b:** R = *t*-Bu (27)	**14c:** R = *t*-Bu (8)
20	**15a:** R = OMe	B, 24 h	**15b:** R = OMe (17)	**15c:** R = OMe (41)
			 + 	
21	**16a**	A, 35 min	**16b** (49%, *ca* 2:1 ratio)	
22	**16a**	B, 18 h	**16b** (21%, *ca* 2:1 ratio)	
			 + 	
23	**17a:** R = *t*-Bu, R' = H	B, 36 h	**7b:** R = H, R' = H (12)	**17b** (56)
24	**18a:** R = CF_3, R' = H	B, 120 h	**18b:** R = CF_3, R' = H (39)	
25	**19a:** R = Me, R' = F	B, 36 h	**19b:** R = Me, R' = F (25)	
			 + 	
26	**20a**	B, 24 h	**20b** (31)	**7b** (20)

Table 3. (continued)

Entry	Substrate	Conditions, Time	Product(s) (Yield %)[b]
27	 **21a:** R = F, R' = H	A, 40 min	 **21b:** R = F (36), R' = H
28	**21a:** R = F, R' = H	B, 84 h	**21b:** R = F (8), R' = H **21c** (12)
29	**22a:** R = Br, R' = Me	A, 40 min	**22b:** R = Br (37), R' = Me
30	 **23a**	A, 1 h	 **23b** (0) **23c** (38)
31	 **24a**	A, 1 h	 **24b** (42, *ca* 2:1 mixture of regioisomers)
32	 **25a**	A, 2 h	 plus other all-*syn* diastereomer; plus other diastereomer **25b** (30)

[a] Reactions were carried out on 0.1−0.3 mmol scale. [b]Chromatographically pure compounds.

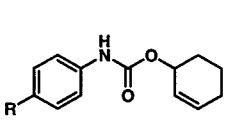
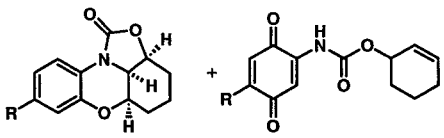
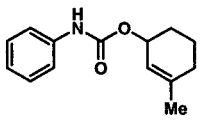
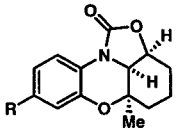
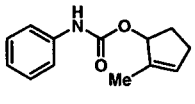
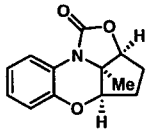
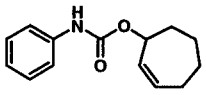
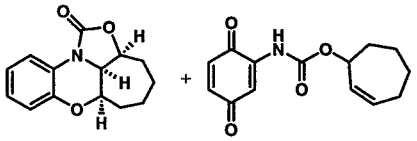
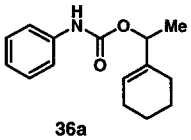
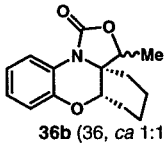
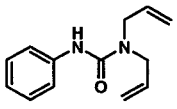
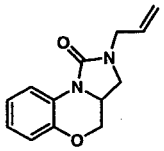
(conditions B, Table 3; entry 13, Table 1), we often observed the formation of *p*-quinones along with the desired polycycles. When we enlisted the original conditions (conditions A, Table 3; entry 1, Table 1), the *p*-quinone byproducts were not observed, presumably due to their thermal instability. It should also be mentioned that a neutral workup protocol was essential to isolate the *p*-quinone compounds in the case of the room temperature experiments. Under basic workup conditions (5% aqueous $NaHCO_3$), the *p*-quinones were removed.

As seen from inspection of Table 3, a wide variety of groups are tolerated on the aryl residue, ranging from the electron-withdrawing nitro and trifluoromethyl groups (entries 16, 17, and 24, Table 3) to the synthetically fertile halides (entries 13−15, 21, 22, 25, and 27−31, Table 3). Remarkably, even the electron-rich and overoxidation prone methoxy group (entry 20, Table 3) was tolerated in this reaction leading to polycycle **15b**. In this case, however, the corresponding *p*-quinone was also found in appreciable amounts (41%) (entry 20, Table 3). Although the bulky *tert*-butyl group was well tolerated at the *p*-position of the anilide (entry 19, Table 3), substitution at the ortho position led to the novel *o*-imidoquinone **17b** along with the polycycle **7b**, the latter missing the *tert*-butyl group. A reasonable mechanistic scenario for the puzzling loss of the *t*-Bu group in this reaction may involve ipso attack on the *tert*-butyl bearing carbon (of intermediate **II**, Scheme 5) by Ac-IBX followed by loss of the *tert*-butyl cation. A pathway leading to the defluorinated *p*-quinone byproducts observed (entries 2 and 8, Table 3) is offered in the following paper, wherein the scope of *p*-quinone generation is explored.[10] Disubstitution on the aromatic moiety was tolerated as seen in entry 25 (Table 3). Given the complexity of the CP-based polycycle (Figure 1, **B**) formed in the initial discovery of this reaction,[7] we were not surprised that even the amide **24a** (entry 31, Table 3) cyclized smoothly under the influence of DMP to give the complex polycycle **24b** with six contiguous stereocenters (one of them quaternary). As a further test of the power of this process to deliver complex molecular diversity, we enlisted the diamide **25a** (entry 32, Table 3) as a substrate and observed the formation of the complex polycycle **25b**, harboring 10 rings and seven stereocenters in 30% yield (mixture of four diastereomers).

Upon further investigation, substrate **23a** (entry 30, Table 3), first reported[6a] to furnish the polycycle **23b**, actually gives rise

(10) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2221−2232.

Table 4. DMP-Mediated Construction of Novel Polycycles and Quinones from Urethanes, Thiourethanes, and Ureas[a]

Entry	Substrate	Conditions, Time	Product(s) (Yield %)[b]
		Conditions A: DMP (2.0 equiv), benzene, reflux, open to atmosphere Conditions B: DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 23 °C, Ar	
1	**26a:** R = H	A, 35 min	**26b:** R = H (50)
2	**26a:** R = H	B, 84 h	**26b:** R = H (42) **26c:** R = H (10)
3	**27a:** R = Et	B, 60 h	**27b:** R = Et (30) **27c:** R = Et (27)
4	**28a:** R = Ph	B, 63 h	**28b:** R = Ph (20) **28c:** R = Ph (13)
5	**29a:** R = OMe	B, 117 h	**29b:** R = OMe (25)
6	**30a:** R = OCF_3	B, 168 h	**30b:** R = OCF_3 (17)
7	**31a:** R = CN	B, 240 h	**31b:** R = CN (37)
8	**32a:** R = NO_2	B, 109 h	**32b:** R = NO_2 (25)
			
9	**33a**	A, 40 min	**33b** (42)
10	**33a**	B, 84 h	**33b** (39)
			
11	**34a**	A, 1 h	**34b** (40)
			
12	**35a**	A, 1 h	**35b** (38)
13	**35a**	B, 84 h	**35b** (35) **35c** (16)
			
14	**36a**	A, 45 min	**36b** (36, *ca* 1:1 mixture of diastereomers)
			
15	**37a**	A, 30 min	**37b** (56)
16	**37a**	B, 26 h	**37b** (48)

[a] Reactions were carried out on 0.1−0.3 mmol scale. [b]Chromatographically pure compounds.

to the ketone **23c**. As shown in Scheme 3, the same type of reactivity is observed with nitro-substituted amide **38a** and unsubstituted amide **39a**. Presumably, the lowered reactivity of this type of amide coupled with the unique reactivity profile[11] of the appended bicyclic olefin lead to an epoxidation with DMP (leading to **40**, Scheme 3) followed by ring opening with the nearby amide (leading to **41**) and oxidation of the resulting alcohol to furnish the observed ketone **39b**. The ability of DMP to epoxidize certain substrates is addressed in the following article.[10]

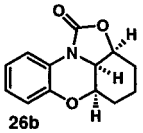
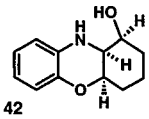
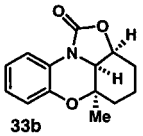
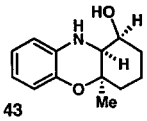
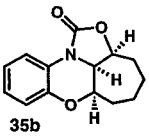
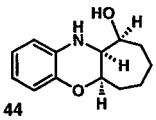
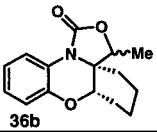
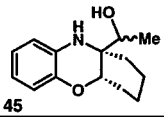
Recognizing that the scope and versatility of the reaction could be considerably enhanced if the pool of starting materials was expanded to other effortlessly available compounds, we considered the nucleophilic attack of allylic alcohols (**I**) or amines (**J**) on phenyl isocyanates (**H**) as a means to secure such substrates (**G**, **K**) as shown in Scheme 2.[12] Although in our initial disclosure[6a] we reported the use of phenyl isothiocyanates, we later found that a majority of the resulting allylic thiourethanes undergo rearrangement to give a mixture of products.[13] As seen in Table 4, urethanes react efficiently to produce the corresponding polycycles. As with the amides (Table 3), using the room temperature conditions (conditions B, Table 4), we were able to isolate the formed *p*-quinones in many cases (entries 2−5 and 13, Table 4). Electronic influences of the aromatic

(11) Pinkerton, A. A.; Schwarzenbach, D.; Birbaum, J.-L.; Carrupt, P.-A.; Schwager, L.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 701.

(12) Patai, S., Ed. *The Chemistry of Cyanates and Their Thio Derivatives, Part 1*; Wiley: Chichester, 1977; p 618. Patai, S., Ed. *The Chemistry of Cyanates and Their Thio Derivatives, Part 2*; Wiley: Chichester, 1977; p 700.

(13) Harayama, H.; Nagahama, T.; Kozera, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamura, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 445.

Table 5. Hydrolysis of Protected Phenoxazines to Amino Alcohols[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **26b**	 **42**	95
2	 **33b**	 **43**	95
3	 **35b**	 **44**	95
4	 **36b**	 **45**	90

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

ring substituents on the reaction course were similar to those observed for the aryl amides (Table 3). The presumption that restriction of conformational freedom should enhance reactivity (vide supra) in these reactions appears to hold, since the more rigid urea **37a** cyclized to polycycle **37b** in good yield (56%, entry 15, Table 4).

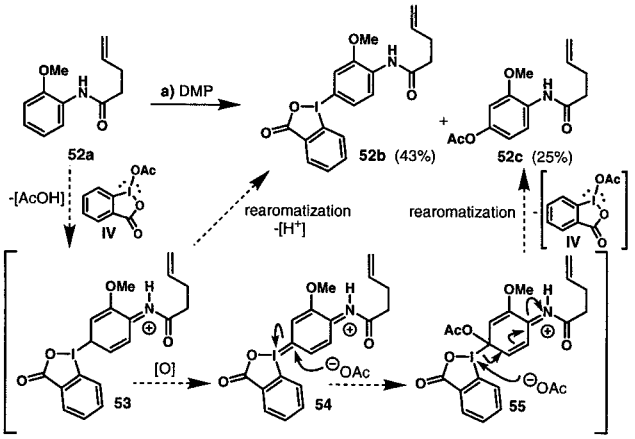
As illustrated in Table 5, the phenoxazine derivatives produced according to Table 4 could be easily hydrolyzed (NaOH, EtOH, 70 °C) to the corresponding amino alcohols in high yield (90−96%).

To extend the scope of the DMP-induced ring closure reaction, we attempted the cyclization with a substrate in which the olefin was located δ rather than γ to the carbonyl of the amide or urethane group. Unfortunately, compounds such as **46** did not furnish the desired polycycle (**47**, Scheme 4).

3. Mechanistic Studies. One of the most interesting facets of the new periodinane-based reactions reported in this series of papers is the unique mechanism by which each appears to be operating. A closer examination of the mechanism of the DMP-mediated cascade cyclization led us to revise our original[6a] mechanistic proposals to the one depicted in Scheme 5. Thus, we now believe that an anilide molecule (**I**, Scheme 5) engages DMP from the oxygen of the amide functionality leading to intermediate **II**. Indeed, upon addition of freshly prepared DMP to a solution of the model anilide *N*-phenylacetamide (**I**: R = H; R′ = Me) in $CDCl_3$, a dark brown coloration appeared along with new ^{1}H NMR signals. This supported the formation of a transient intermediate, presumed to be **II** (Scheme 5), although TLC analysis (silica gel) revealed only starting materials and traces of decomposition products. The performance of the reaction even in the presence of the radical inhibitor galvinoxyl (entry 12, Table 1) suggests that the reaction does not involve discreet radical intermediates.

During the optimization of the DMP-cascade (vide supra) we had found that water was essential for the reaction to proceed. If DMP was pretreated with H_2O, thereby producing an equal amount of Ac-IBX (as it is well documented),[2] the result was identical to treatment of the reaction mixture (DMP, substrate, CH_2Cl_2) with H_2O. As shown in Table 2, using only DMP (strictly anhydrous conditions) or only Ac-IBX (DMP:H_2O (1:1)) led to no reaction. Recognition of the key synergy between DMP and Ac-IBX in this process led to the proposition that Ac-IBX acts as a nucleophile descending upon intermediate **II** as depicted in Scheme 5 and leading to species **III** along with a molecule of AcOH and the known byproduct **IV**. Subsequent oxidative collapse of intermediate **III** then furnishes the *o*-imidoquinone **V**[14] which is accompanied by an additional equivalent of **IV**. The fleeting *o*-imidoquinone system of **V** then engages the proximate olefin in an inverse electron demand hetero Diels−Alder reaction[15] to furnish the observed polycycle **VI**.

Scheme 7. Informative Byproducts from the Reaction of Amide **52a** with DMP and a Possible Mechanism for Their Formation[a]



[a] Reagents and conditions: (a) DMP (2.0 equiv), benzene, 75 °C, 1 h, 43% **52b** plus 25% **52c**.

Because, at first, we had no hope of isolating the short-lived *o*-imidoquinone intermediate **V** (at the higher temperatures employed), we utilized the *o*-hydroxy anilide **50a** to indirectly implicate it in the cascade (Scheme 6). Indeed, treatment of **50a** with DMP (2.0 equiv) in refluxing benzene led to the desired polycycle **7b**, presumably through the intermediacy of *o*-imidoquinone **51**. As our studies progressed, however, we were able to isolate, at ambient temperature, pure *o*-imidoquinones and study their chemistry (vide infra).

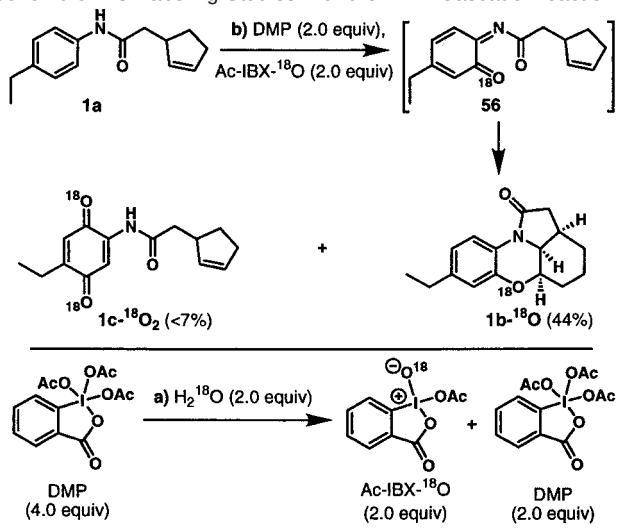
A unique observation was made in the case of the *o*-methoxyanilide **52a** (Scheme 7) which afforded the acetate **52c** and iodinane **52b** upon treatment with DMP in refluxing benzene. A possible mechanistic rationale for the formation of these interesting byproducts is illustrated in Scheme 7, although other plausible mechanisms cannot be excluded at present. Presumably, the electron-rich anilide **52a** attacks from the aromatic ring (para to the NH group) rather than from the amide-oxygen, leading to intermediate **53** whose fate diverges to give **52b** and **52c**, the latter via intermediates **54** and **55** (Scheme 7).

Isotope labeling studies using $H_2{}^{18}O$ were then initiated to verify that the new oxygen atom in these reactions is derived from Ac-IBX (Scheme 8). Thus, $H_2{}^{18}O$ (2.0 equiv) was added

(14) A multistep route to this type of diene is known; however, the reaction requires the presence of chlorine substituents on the aryl ring, see: Heine, H. W.; Barchiesi, B. J.; Williams, E. A. *J. Org. Chem.* **1984**, *49*, 2560.

(15) Boger, D. L.; Weinreb, S. M. *Organic Chemistry, Vol. 47: Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; p 366.

Scheme 8. ^{18}O Labeling Studies with the DMP Cascade Reaction[a]

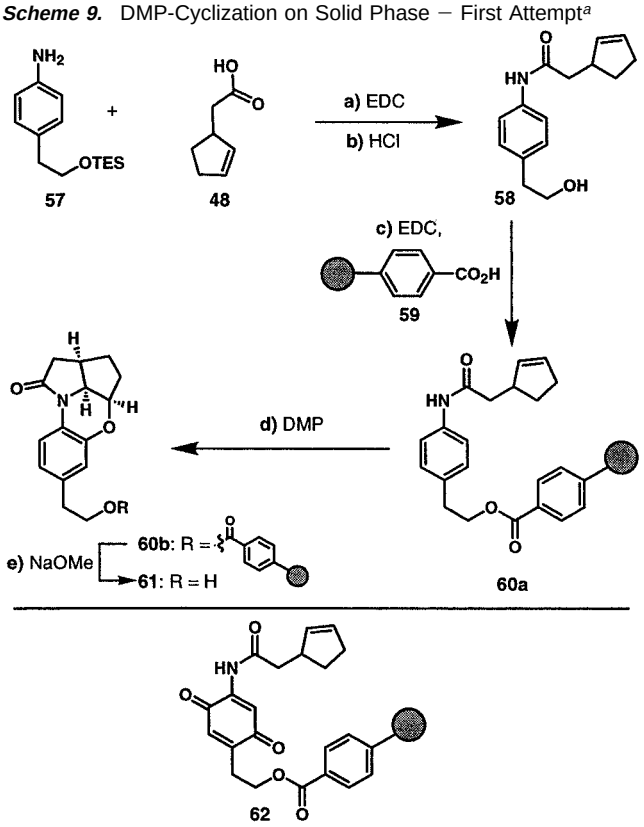


[a] Reagents and conditions: (a) $H_2{}^{18}O$ (2.0 equiv), CH_2Cl_2, 25 °C, ultrasound, 1 min; then 25 °C, 10 min; (b) solution of Ac-IBX-^{18}O/DMP, **1a** (1.0 equiv), CH_2Cl_2, 25 °C, 4 h.

to a solution of DMP (4.0 equiv) in CH_2Cl_2. After ensuring that all of the labeled water was consumed (sonication for 1 min, stirring for an additional 10 min at ambient temperature), the resulting DMP/Ac-IBX-^{18}O combination was added to substrate **1a**, leading to the ^{18}O-labeled polycycle **1b-^{18}O** (44% yield) as confirmed by mass spectrometric analysis (Scheme 8). This observation supports the notion that the newly installed oxygen atom arises from Ac-IBX rather than from H_2O, air, or the substrate itself. Attempts to intercept the postulated *o*-imidoquinone intermediate **56** were unsuccessful; however, we were able to isolate and characterize the *o*-*tert*-butyl substituted *o*-imidoquinone **17b** (entry 23, Table 3). The minor product of the labeling study, *p*-quinone **1c-^{18}O$_2$** (Scheme 8), was also isolated, characterized, and shown to have incorporated two ^{18}O atoms by mass spectrometry. This intriguing observation led to an understanding of the relation between the fleeting *o*-imidoquinone **56** and *p*-quinone **1c-^{18}O$_2$**, thus opening the door to the design of a series of new reactions commencing with DMP-accessible *o*-imidoquinones and leading to a variety of diverse and complex polycyclic molecular architectures.[10]

4. Solid-Phase Synthesis with DMP. To explore the feasibility of employing the discovered DMP-cascade on solid phase to generate libraries of medicinally relevant compounds,[16] we synthesized the resin-bound aniline **60a** as shown in Scheme 9. Thus, EDC-mediated coupling of carboxylic acid **48** with aniline **57** followed by desilylation (H_3O^+) led to the hydroxy anilide derivative **58**. Esterification (EDC) of the latter compound (**58**) with resin-bound **59** furnished the desired anilide **60a** which upon treatment with DMP in CH_2Cl_2 for 48 h led to the resin-bound polycycle **60b**. It was presumed that the corresponding *p*-quinone byproduct **62** was also formed, although, upon basic cleavage (K_2CO_3/MeOH), only the polycycle **61** and uncyclized anilide **58** were isolated, the quinone being too labile to survive these conditions. TLC and ^1H NMR analysis of the crude reaction mixture following hydrolysis were clean, showing only polycycle **61** and uncyclized amide **58** (ratio ca. 5:1) and in 28% overall yield from **58** (based on weight difference of the resin **60a** after loading of the alcohol **58**). This study provides proof of principle for the viability of a cyclization on solid phase for possible large-scale combinatorial chemistry efforts.

Scheme 9. DMP-Cyclization on Solid Phase − First Attempt[a]



[a] Reagents and conditions: (a) EDC (1.5 equiv), Et_3N (1.5 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 2 h; (b) 1 M aqueous HCl, 25 °C, 20 min, 95% overall; (c) EDC (1.5 equiv), Et_3N (1.5 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 16 h, 37%; (d) DMP (5.0 equiv), H_2O (3.5 equiv), CH_2Cl_2, 25 °C, 12 h; (e) NaOMe (10 equiv), MeOH, 25 °C, 2 h, 25% **61** plus 20% **58**.

Conclusion

In this article, we described the development of a serendipitous observation made en route to the CP-molecules into a new synthetic technology for the construction of complex phenoxazine-containing heterocycles relevant to biological systems. Requiring only two operations from ubiquitous and commercially available starting materials, this reaction delivers impressively complex structures equipped with numerous heteroatoms, useful functionalities, and stereochemical centers. Systematic optimization of the reaction conditions led to a mild, ambient temperature protocol for this fertile process and to further observations which facilitated the accumulation of important mechanistic insights. The significant discovery that two periodinane species, DMP and Ac-IBX, are intimately involved in this unique cascade sequence was verified empirically and through isotope labeling studies. Further evolution of the understanding of this elaborate mechanism led to the recognition of the potential of *o*-imidoquinones in organic synthesis. This potential has been explored to a considerable extent as will be discussed in the following paper.[10]

(16) Phenoxazines as amyloid fibril inhibitors: Petrassi, H. M.; Klabunde, T.; Sacchettini, J.; Kelly, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 2178. Phenoxazines have been found to reverse drug resistance in cancer cells, see: Horton, J. K.; Thimmaiah, K. N.; Harwood, F. C.; Kuttesch, J. F.; Houghton, P. J. *Mol. Pharmacol.* **1993**, *44*, 552. For a review of antitumor phenoxazines, see: Motohashi, N.; Mitscher, L. A.; Meyer, R. *Med. Res. Rev.* **1991**, *11*, 239.

Experimental Section

General Procedures for the DMP Cyclization. Conditions A: To a solution of aryl amide **G**, urethane, or urea **K** (0.1 mmol) in benzene (or BTF)[8] (4 mL) was added DMP (2.0 equiv) in one portion. The solution (open to the atmosphere) was heated at reflux (or at 80−85 °C for the case of BTF) for ca. 30 min (precise times listed in Tables 3 and 4), at which point TLC indicated complete consumption of the starting material. Dilution with EtOAc followed by washing with 5% aqueous $NaHCO_3$ solution (2 × 5 mL) and brine (5 mL), drying over $MgSO_4$, and concentration led to the crude polycylic products. Pure compounds were isolated in the yields listed below and are shown in Tables 3 and 4 after flash column chromatography (silica gel, EtOAc:hexane 1:2) (see Supporting Information Available). **Conditions B:** To a solution of aryl amide **G**, urethane, or urea **K** (0.1 mmol) in dry CH_2Cl_2 (4 mL) under an argon atmosphere was added DMP (4.0 equiv) followed by water (2.0 equiv). The solution was stirred at room temperature for the time indicated in Tables 3 and 4, at which point TLC indicated complete consumption of the starting material. Dilution with EtOAc followed by washing with water (2 × 5 mL) and brine (5 mL), drying over $MgSO_4$, and concentration led to the crude polycylic products. Pure compounds were isolated in the yields listed below and are shown in Tables 3 and 4 after flash column chromatography (silica gel, EtOAc:hexane 1:2) (see Supporting Information Available).

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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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