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Directed Ortho Metalation. Tertiary Amide and *O*-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics[†]

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Contents

[†] It is with regret that I am unable to provide complementary reprints.

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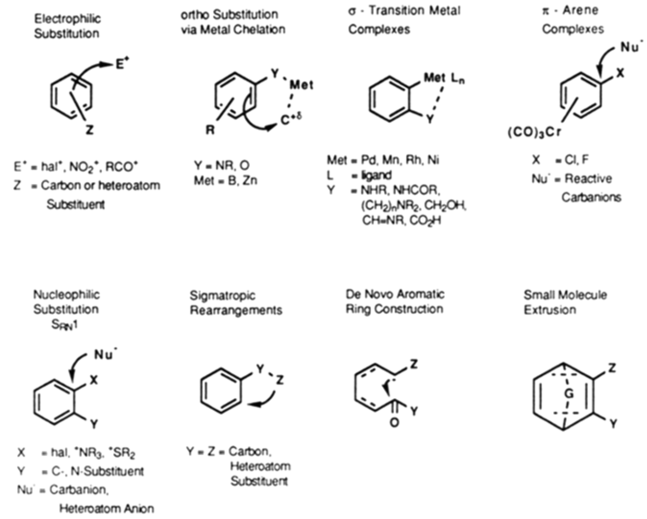
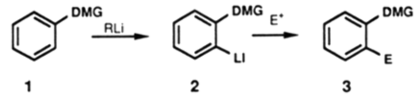
Victor Snieckus was born in Kaunas, Lithuania, and spent his childhood in Germany during World War II. He obtained his B.Sc. degree from the University of Alberta in 1959, where he was strongly influenced by R. Sandin. He studied with D. S. Noyce (M.Sc., University of California, Berkeley, 1961) and V. Boekelheide (Ph.D., University of Oregon, 1965). Following a postdoctoral year with O. E. Edwards (National Research Council, Ottawa), he joined the University of Waterloo. His major research focus is in the development of new methods and strategies in organic synthesis, with increasing emphasis on biological molecules. He can be distracted from the laboratory by good jazz and noncontact hockey.

SCHEME 1. Synthetic Approaches to Substituted Aromatics



SCHEME 2. The Directed Ortho Metalation Reaction



I. Introduction

Studies on the structure, reactions, and synthesis of aromatic compounds are steeped in the history of organic chemistry since the time of Kekulé's dream a century ago.[1,2] Today, the regiospecific preparation and modification of polysubstituted aromatic molecules constitute engaging fundamental problems in synthetic chemistry in both industrial and academic laboratories.[1,3] Many modern synthetic targets, in particular those of interest for pharmaceutical and agrochemical preparations, either are benzenoid or incorporate key aromatic or heteroaromatic components.[4,5] In these endeavors, commercially available aromatic substances are modified in a variety of ways for a variety of purposes by (a) functional group introduction into a mono- or disubstituted material, (b) functional group interconversions, (c) attachment of chains either to existing functionality or directly onto the ring, (d) hetero- or carbocyclic ring annelation, and (e) reduction (e.g., Birch) and ring destruction (e.g., ozonolysis) to carbocyclic and acyclic derivatives.

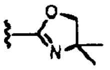
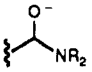
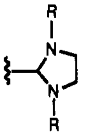
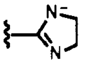
The initial response triggered by traditional pedagogy in undertaking a problem in synthetic aromatic chemistry is to apply classical electrophilic substitution.[6] While these diverse reactions are not to be denied in synthetic planning, they often suffer from harsh conditions and formation of mixtures of positional isomers. Given the normal electrophilic substitution rules, the preparation of contiguously substituted systems (1,2-, 1,2,3-, and 1,2,3,4-) can become a most demanding challenge. To aid the synthetic chemist in the fundamental task of constructing the prototype 1,2-disubstituted aromatics, an armamentarium of methods has evolved in the interim (Scheme 1):[7] electrophilic substitution via para protection–deprotection[8] and metal chelation;[9] the use of σ-transition-metal complexes, the synthesis of which σ invariably depend upon the presence of *o*-halo groups;[10,11a] similarly, $S_{RN}1$ reactions based on 1,2-disubstituted precursors;[12] nucleophilic substitution of (π-arene)metal (Cr, Mn) tricarbonyl complexes;[11b,13] sigmatropic rearrangements;[14] carbanionic de novo ring construction;[15] cycloaddition with or without small-molecule extrusion;[16,17] transformation of heterocycles;[15–17] dearomatization–rearomatization tactics.[15,18]

In 1939–1940, the independent discovery by Gilman and Bebb[19] and Wittig and Fuhrman[20] of anisole ortho deprotonation by *n*-BuLi constituted a harbinger for a new conceptual framework in synthetic aromatic chemistry. These seminal results of the directed ortho metalation (DoM) process initiated fundamental reactivity studies by Gilman[21] and, in the early 1960s, by Hauser and his students,[22] who also systematically expanded the scope of directed metalation groups (DMGs). The complementary technique of metal–halogen exchange, also discovered by Gilman[23] and Wittig,[24] provided further impetus to this area.[25] In the 1970s, the industrial use of alkyllithium bases as polymerization catalysts[26] led to their commercial availability and allowed the metalation technique to be practiced widely. In 1979, the outstanding comprehensive review by Gschwend and Rodriguez[27] brought timely appreciation of the potential of the DoM reaction.[28] The past decade has seen the evolution of this reaction as a significant fundamental methodology, demanding at least "equal time" with other methods, for the regiospecific construction of polysubstituted aromatic and heteroaromatic compounds.

II. Aim and Scope of the Review

This review[29] will focus on tertiary amide and *O*-carbamate DMGs for methodological and total syn-

TABLE 1. DMGs in Synthesis: Qualitative Evaluation

Z (pK_a) carbon based[a]	synthetic utility[b]	ref	Z (pK_a) heteroatom based[a]	synthetic utility[b]	ref
strong					
CON$^-$R	+++	27, 29f	N$^-$COR (≥40.5)	++	*c*
CSN$^-$R	++	*d*	N$^-$CO$_2$R	+++	*e*
CONR$_2$ (37.8)	+++	29a–e	OCONR$_2$ (37.2)	++	114
CONR$_2$ (31.1)[f]	++	*f*	OPO(NR)$_2$	+	139
CON(R)CH(Z)TMS, Z = H, TMS	+	104, 157	OCH$_2$OMe	+++	66, 106
			tetramer	+	*g*
			OTHP (40.0)	*c, i*	27
 (38.1)	+++	29g	OPh (38.5)	+	*i*
			SO$_3$R	+	*j*
CH=NR	++	*h*	SO$_2$N$^-$R	+	27
(CH$_2$)$_n$NR$_2$, n = 1, 2 (≥40.3)	+	27	SO$_2$NR (38.2)	+	27
			SO$_3^-$	+	*k*
CH(OH)CH$_2$NR$_2$	+	27	SO$_2$-*t*-Bu	+	*l*
CN (38.1)	+	49	SO-*t*-Bu	+	*m*
moderate					
CF$_3$	+	27	NR$_2$ (≥40.3)	+	27
			N≡C	++	*n*
			OMe (39.0)	+++	27
	++	84	OMe (33.0)[f]	+	*f*
			OCH=CH$_2$	+	*o*
			OPO(OR)$_2$	+	107
			O(CH$_2$)$_2$X, X = OMe, NR$_2$	+	*p*
			F	+	*q*
			Cl	?	*r*
			PO(NR)$_2$	+	*s*
			PS(Ph)NR$_2$	+	*t*
weak					
C(OTMS)=CH$_2$	+	27	O$^-$ (≥40.5)	+	*u*
CH(OR)$_2$	+	*v*	S$^-$	+	*w*
CH$_2$O$^-$	++	*x*			
	+	*y*			
	+	*z*			
C≡C$^-$	+	*aa*			
Ph	+	*bb*			

[a] pK_a data in parentheses are given in ref 30 and: Fraser, R. R.; Bresse, M.; Mansour, T. S *J. Chem. Soc., Chem. Commun.* **1983**, *620*. [b] +++ = well proven/extensively applied; ++ = promising/requires studies in scope, application; + = inadequately tested/new/limited use. [c] Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133. [d] Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1976**, *41*, 4029. [e] Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4758. [f] Cr(CO)$_3$ complex. Fraser, R. R.; Mansour, T. S. *J. Organomet. Chem.* **1986**, *310*, C60. [g] Kraus, G. A.; Pezzanite, J. O. *J. Org. Chem.* **1979**, *44*, 2480. [h] Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. [i] Narasimhan, N. S.; Chandrachood, P. S. *Synthesis* **1979**, 589. [j] Bonfiglio, J. N. *J. Org. Chem.* **1986**, *51*, 2833. [k] Figuly, G. D.; Martin, J. C. *J. Org. Chem.* **1980**, *45*, 3728. [l] Iwao, M.; Iihama, T.; Mahalanabis, K. K.; Perrier, H.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 24. [m] Quesnelle, C.; Iihama, T.; Perrier, H.; Aubert, T.; Snieckus, V., unpublished results. [n] Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73. [o] Muthakrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1976**, *59*, 13. [p] Wada, A.; Kanatomo, S.; Nagai, S. *Chem. Pharm. Bull. Jpn.* **1985**, *33*, 1016. [q] Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1982**, *47*, 3652. [r] Sutter, M. A.; Seebach, D. *Ann.* **1983**, 939. [s] Dashan, L.; Trippett, S. *Tetrahedron Lett.* **1983**, *24*, 2039. [t] Yoshifuji, M.; Ishizuka, T.; Choi, Y. J.; Inamoto, N. *Tetrahedron Lett.* **1984**, *25*, 553. [u] Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571. [v] Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, *20*, 4921. [w] Figuly, J. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654. Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K. *J. Am. Chem. Soc.* **1989**, *111*, 658. Smith, K.; Lindsay, C. M.; Pritchard, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 665. [x] Uemura, M.; Tokuyana, S.; Sakan, T. *Chem. Lett.* **1975**, 1195. Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *118*, 1304. [y] Harris, T. D.; Roth, G. P. *J. Org. Chem.* **1979**, *44*, 2004. [z] Houlihan, W. J.; Parrino, V. A. *J. Org. Chem.* **1982**, *47*, 5177. Houlihan, W. J.; Parrino, V. A. *J. Heterocycl. Chem.* **1981**, *18*, 1549. [aa] Hommes, H.; Verkrusse, H. D.; Brandsma, L. *Tetrahedron Lett.* **1981**, *22*, 2495. Hommes, H.; Verkruijsse, H. D.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* 1981, 366. [bb] Neugebauer, W.; Kos, A. J.; Schleyer, P. v. R. *J. Organomet. Chem.* **1982**, *228*, 107.

thesis journeys in aromatic chemistry. After a brief overview of general aspects of the DoM reaction, the utility and applications of tertiary amide and carbamate DMGs will be systematically and comprehensively developed. Where appropriate, comparison with other carbon-based (CONHR, oxazoline) and oxygen-based (OMOM) DMGs for synthetically equivalent operations will be provided.

III. The Directed Ortho Metalation (DoM) Reaction

A. General Characteristics of DoM and Scope of Directed Metalation Groups (DMGs)

The DoM reaction (Scheme 2) comprises the deprotonation of a site ortho to a heteroatom-containing

TABLE 2. Aggregation State of Organolithium Reagents

RLi	solvent	concn range, M	species	ref
MeLi	THF or Et_2O	0.2–1.2	tetramer	*a*
n-BuLi	C_6H_{12} or PhH	0.4–3.4	hexamer	*b*–*d*
	THF or Et_2O	0.1–0.7	tetramer ↔ dimer	*a*, *c*, *e*, *f*
n-BuLi·TMEDA	?	0.1	monomer	*g*
n-BuLi·TMEDA	?	high	dimer	*g*
sec-BuLi	C_5H_{10}		tetramer ↔ hexamer	*h*
	THF or Et_2O		tetramer	*d*
t-BuLi	*n*-Hex, C_6H_{12}, or PhH	0.05–0.50	tetramer	*c*, *i*
	THF		dimer	*d*

[a] West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395. [b] Margerison, D.; Newport, J. P. *Trans. Faraday Soc.* **1963**, *59*, 2058. [c] Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. [d] Eastham, J. *J. Am. Chem. Soc.* **1964**, *86*, 1076. [e] Quirck, R. P.; Kester, D. E. *J. Organomet. Chem.* **1974**, *72*, C23. [f] See ref 43. [g] See ref 26a. [h] Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 225. [i] West, P. *Inorg. Chem.* **1962**, *1*, 654.

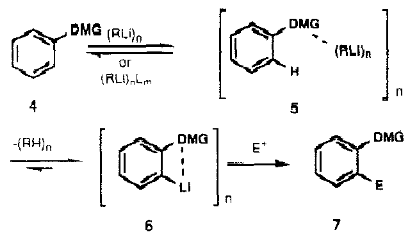
DMG (1) by a strong base, normally an alkyllithium reagent, leading to an ortho-lithiated species **2**. This species, upon treatment with electrophilic reagents, yields 1,2-disubstituted products **3**. Table 1 lists the currently available repertoire of DMGs, somewhat arbitrarily divided into strong, moderate, and weak groups,[30] together with pK_a data and qualitative evaluation of use and potential in synthesis. Of the over 40 DMGs, over half, including the $CONR_2$ and $OCONR_2$ groups, have been introduced into synthetic practice since the publication of the Gschwend and Rodriguez review.[27]

B. Bases

The DoM process normally demands the use of powerful alkyllithium bases[31–34] in organic solvents in which they exhibit high solubility due to association into aggregates of defined structure, typically as hexamers (in hydrocarbon solvents) or tetramers–dimers (in basic solvents) (Table 2). On the basis of reactivity,[31] NMR,[35] X-ray structure,[36] and calculational[37] studies, alkyllithiums are viewed predominantly as bridged structures of electron-deficient bonding arrangements of polar multicovalent C–Li bonds which in solution undergo fast equilibrium carbon–lithium and lithium–ligand bond exchanges as well as rapid conformational interconversions.

In hydrocarbon solvents, alkyllithiums are thought to react as aggregates and mixtures of aggregate or dissociated species.[38] Addition of basic solvents (ethers, amines, phosphines) causes dissociation by an acid–base reaction: e.g., THF coordination to $(n\text{-BuLi})_6$ leads to solvated $(n\text{-BuLi})_4$ (Table 2), and addition of Et_3N to $(t\text{-BuLi})_4$ leads to a 50-fold acceleration in dissociation to $(t\text{-BuLi})_2$.[39] Furthermore, bidentate ligands, in particular TMEDA, effectively break down alkyllithium aggregates, forming monomers and dimers in solution (Table 2), and thereby significantly increase their basicity.[32] X-ray crystal structure data indicate that these species are usually of the form $(RLi·TMEDA)_2$ involving fourfold-coordinated lithium.[26a,36] Their enhanced basicity is illustrated by the observed quantitative deprotonation of benzene by *n*-BuLi·TMEDA compared to its nonreactivity with *n*-BuLi alone.[26a] The *sec*-BuLi·TMEDA combination appears to be a most potent metalating agent, effecting deprotonation of Me_4Si 1000-fold faster than the *n*-BuLi·TMEDA complex.[26a] Increased understanding of the stability of RLi–solvent aggregates,[40,26] as well as the effect of metal alkoxides[41–43] and continuing evolution[44] of the powerful LICKOR bases,[45] which have not as yet been applied in DoM reactions, will undoubtedly influence future application in synthesis.

SCHEME 3



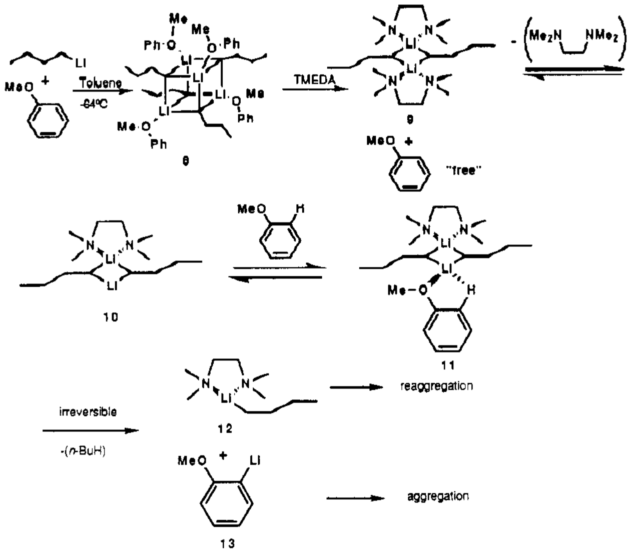
Lithium dialkylamides[46,47] are of insufficient kinetic basicity for the DoM reaction. However, reports of effects of LiX on selectivity of enolization[48] and success in aromatic and heteroaromatic deprotonations using in situ trapping combinations under thermodynamic conditions[49–51] (e.g., LiTMP/TMSCl)[49] should also be viewed with anticipated synthetic potential.

C. Mechanistic Aspects

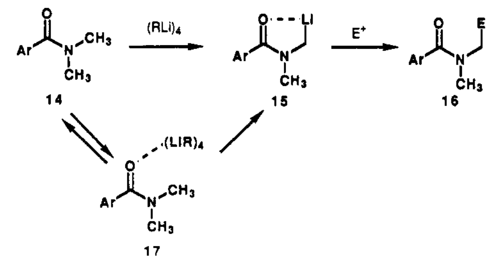
Although undoubtedly simplistic, the DoM process may be viewed as a three-step sequence (Scheme 3): coordination of the $(RLi)_n$ aggregate to the heteroatom-containing DMG, **4** → **5**; deprotonation to give the coordinated ortho-lithiated species, **5** → **6**; and reaction with electrophile to yield product, **6** → **7**. The original suggestion[52] that the ortho-lithiated species **6**, DMG = OMe, is stabilized by coordination has been supported by thermochemical data which established that proton quench of (*p*-anisyl)lithium is 3.6 kcal/mol more exothermic than that of (*o*-anisyl)lithium.[53] Studies concerning rate enhancement of anisole deprotonation relative to benzene,[54] σ Taft relationships between DMGs and partial rate factor, f_{ortho}, for base-catalyzed deuterium exchange,[55] pK_a measurements,[30] steric effects,[27,56–58] and ab initio calculations[59,60] are all consistent with the thermodynamic stabilization of an ortho-lithiated species **6**, DMG = OMe. That complexation is also kinetically acidifying was suggested initially from qualitative NMR,[30,56] kinetic isotope,[56] and steric effect[55,57,58] investigations. Recent crystal structure determinations of ortho-lithiated species indicating complex tetrameric aggregates with a high degree of lithium–heteroatom coordination[61] may be taken as circumstantial evidence for the existence of the ortho-lithiated intermediate **6**.

Using HOESY and supportive MNDO calculations, Bauer and Schleyer obtained initial mechanistic evidence for the formation of **2**.[62] In toluene at −64 °C, anisole and *n*-BuLi exist as a tetrameric aggregate **8** (Scheme 4). Addition of 1 equiv of TMEDA forms the 1:1 *n*-BuLi·TMEDA dimer **9** and free anisole (no HOESY anisole–Li interactions), which, however, does not undergo ortho lithiation. This is hypothesized to occur via a low (NMR undetectable) stationary concentration of species **10** whose newly available two co-

SCHEME 4



SCHEME 5



Ar = 2,4,6-(*i*-Pr)$_3C_6H_2$

ordination sites at Li are taken up by anisole oxygen and agostic Li–H interactions to give **11**. Irreversible deprotonation follows to give ortho-lithiated species **13** and 1:1 *n*-BuLi·TMEDA species **12**, both of which undergo aggregation. MNDO calculations support the postulated structure **11**. Thus kinetic (Li with the availability of more than one coordinating site) and thermodynamic (ortho heteroatom coordination to Li) factors appear to be significant in the DoM process. Similar observations were recorded for 1,2-dimethoxybenzene and *N*,*N*-dimethylaniline but not for fluorobenzene.

Mechanistic studies by Beak[38] and Meyers[64] on the α-deprotonation of amides and formamides, respectively, are relevant to understanding the course of the DoM reaction. For example, in the reaction of amides **14** (Scheme 5) with RLi, stopped-flow IR spectroscopy has provided evidence for the intermediacy of amide–lithium reagent complex(es) **17**, which may be en route to the α-lithiated species **15** and eventually to product **16**. Although the kinetics of this reaction are exceedingly complex, it appears that, at least in cyclohexane solution, amide–*sec*-BuLi–TMEDA complexes are involved which, contrary to expectation, become more reactive with increasing number of ligands. These results echo those of Schleyer[62] and McGarrity[43] and are inferential for preequilibrium formation of the coordinated species **6** (Scheme 3) by a complex-induced proximity effect, a concept with broader synthetic implications and unifying value in organolithium chemistry.[65] The formation of ortho-lithiated species **6** by radical and radical ion mechanisms has been invoked with marginal supporting evidence,[57,66] although the intervention of radicals in reactions of naphthalene with *n*-BuLi·TMEDA[67] and anisole with lithium naphthalide[68] has been reported.

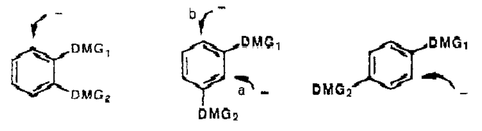
The mechanism of the reaction of **6** with electrophiles to give **7** (Scheme 3) has not been investigated for any DMG. The reaction of alkyl halides with alkyllithiums has been studied extensively and shown by CIDNP experiments to proceed by a SET process.[39,69] On the basis of kinetic and physical measurements, Brown and co-workers have suggested that PhLi reacts as a dissociated species.[39] However, Bauer and Schleyer have demonstrated that the monomer–dimer equilibrium of PhLi is shifted completely toward dimer upon addition of 1 equiv of TMEDA.[62] The evolving mechanistic studies of organic reactions that occur by SET processes[70] will undoubtedly have an impact on the understanding of the conversion **6** → **7**.

D. Nature of the DMG

For a successful deprotonation to occur, the DMG (Table 1) must exhibit the somewhat schizophrenic properties of being a good coordinating site for alkyllithium and a poor electrophilic site for attack by this strong base. A heteroatom is therefore an obligatory component of a DMG. Steric hindrance ($CONEt_2$, oxazolino, $OCONEt_2$, $P(O)NR_2$), charge deactivation (CON^-R, CSN^-R, imidazolino), or both ($^-NCO_2$-*t*-Bu, ^-NCO-*t*-Bu) may be incorporated into the design of the metalation director. On the basis of limited data on systems containing two competing DMGs, Gschwend and Rodriguez suggested[27] the operation of either a "coordination only" or an "acid–base" (inductive) mechanism. The relative significance of coordination and inductive effects of modern DMGs has not been systematically correlated with fundamental Lewis acid–base and electronic principles.[71] Inductive effects appear to play the major role in ortho deprotonation of fluorobenzene[62] and benzonitrile,[72] since neither can achive normal coordinatively stabilized ortho-lithio intermediates. pK_a determinations reflecting mainly inductive effects show little variation (Table 1) and, since qualitative observation of variation in rates as a function of DMG is common, suggest that differential coordination under the kinetic conditions normally used in synthesis determines the relative metalation priorities.

Substituent effects on the rate of ortho deprotonation are also unavailable. Gschwend and Rodriguez used[27] kinetic data of rate-determining ortho metalation of bromobenzenes as a rough but useful extrapolation of substituent effects. Br, F, and CF_3 groups located meta to the deprotonation site show strong acidifying effects that parallel those observed for the corresponding ortho series.[56] This suggests the predominant influence of inductive factors in the ortho deprotonation step for this series. On the other hand, OMe and NMe_2 groups ortho to the deprotonation site show rate enhancements greater than expected on the basis of inductive effects. To rationalize these results, a coordination component in the deprotonation step has been invoked. The acidifying effect of Ph is greater than that of OMe in the meta series but almost equal to H in the ortho series. A dominant steric effect in the latter case is a reasonable explanation for this observation.

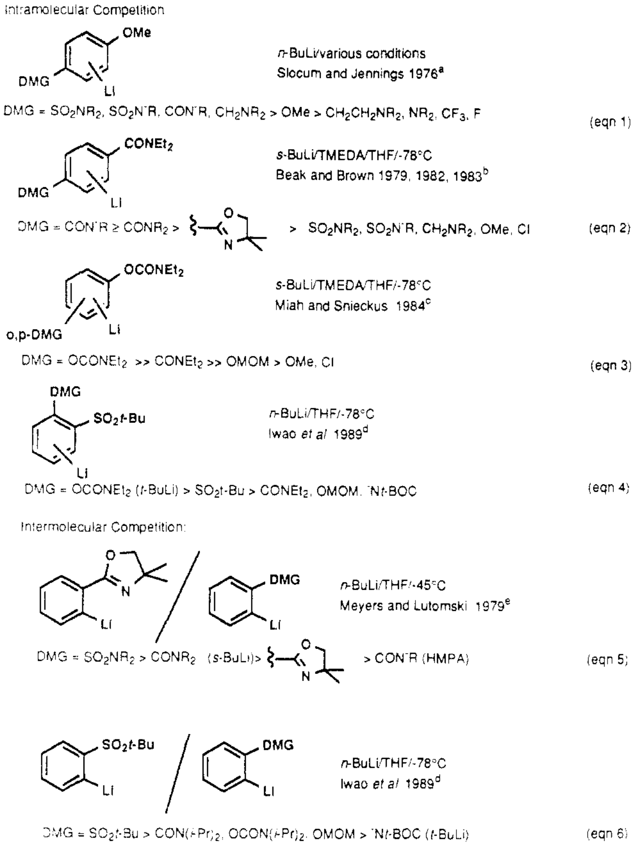
SCHEME 6



18 19* 20

$DMG_1 > DMG_2$
* a >> b in absence of steric factors

SCHEME 7. Relative Directing Abilities of Ortho Metalation Groups



[a] Table 3, footnote *b*. [b] References 73 and 86. Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. [c] Reference 117a. [d] Table 1, footnotes *l* and *m*. [e] Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464.

The evolving mechanistic picture of the DoM reaction summarized above suggests that solvation, alkoxide doping,[41] in situ base–electrophile systems,[42,49–51] and complexation[38] effects will have significant future impact on the synthetic use of currently available DMGs (Table 1) and the development of new ones.

E. Hierarchy of DMGs

The scope and limitations of achievable substitution patterns by the DoM reaction will be determined by an interplay of the incipient DMG with the nature and position of other DMGs and substituents that tolerate the RLi conditions and, ultimately, by the conversion of DMGs into other functionality. Generalized expectations for the three theoretically possible bis-DMG benzenoid systems **18**, **19**, and **20** (Scheme 6) may be formulated, although only a few systematic competition studies have been carried out. In early work, using a 4-OMe anchor group under a variety of metalation conditions, Slocum and Jennings suggested the rough order indicated in eq 1, Scheme 7. These were extended by Beak and Brown under standardized conditions but using a 4-$CONEt_2$ anchor group (eq 2). This order must be treated with some caution since it was established by d_1 incorporation in which up to 15% of isomeric deuterated species may have been undetected. Nevertheless, for the moderate and weak directors, 4-OMe and 4-Cl, the metalation is overwhelmingly ortho to $CONEt_2$. Intermolecular competitions by Meyers and Lutomski (eq 5) using the oxazolino anchoring group invert the order of the CON^-R and SO_2NR_2 groups compared to the order based on the intramolecular competition results (eq 2). However, comparisons are rendered tentative by the use of different conditions for metalating $CONR_2$ (*sec*-BuLi) and CON^-R (HMPT) systems. This view is reinforced by the order in intra- and intermolecular competitions ($CON^-R > CONR_2$ = 5:1 and 1:10, respectively) under the same conditions.[73]

The intramolecular competitions of Miah and Snieckus (eq 3, Scheme 7) indicate that the $OCONEt_2$ is by far the most powerful DMG with respect to ortho and para $CONEt_2$ and OMOM groups. The essentially regiospecific metalation ortho to $OCONEt_2$ in the competitions with OMOM is of synthetic value in view of the differential deprotection sensitivities of the two DMGs. The SO_2-*t*-Bu DMG has been recently evaluated in both intra- (eq 4) and intermolecular (eq 6) competitions. While the results are again complicated by variation in conditions (*t*-BuLi for $OCONEt_2$, N-*t*-Boc), SO_2-*t*-Bu appears to outrank $CONR_2$ and perhaps $OCONEt_2$ in the hierarchy of metalation.

Interpretation of competition results must take into account steric and inductive effects that affect aggregation and complexation of alkyllithium reagents and formation of the ortho-lithiated species. This is especially true for the intramolecular competition experiments. Although further work is required to resolve the observed inconsistencies and to quantitatively understand the relative hierarchy of DMGs, the available results (Scheme 7) offer a guide for formulating synthetic strategy.

F. Cooperative Metalation Effects

A most powerful synthetic rudiment of the DoM reaction deserving separate discussion is the cooperative effect of 1,3-interrelated DMGs in promoting metalation at their common site (**19**, Scheme 6). A selection of cases illustrate the merit of this effect for the synthesis of contiguously substituted aromatics (Table 3). In the carbon-based DMG series, CON^-R, $CONEt_2$, and oxazolino groups in a meta relationship with OR, Cl, F, CH=NR, but not NMe_2 show exclusive metalation in the common site (entries 1–9). Likewise, the CH=NR group cooperates with the OR substituent (entry 10); the same species may also be obtained from the corresponding 6-Li species, generated by metal–halogen exchange, a result that constitutes a rare demonstration of thermodynamic stability of the doubly coordinated 2-Li species. The 1,3-CH_2OLi–OMOM system shows good regioselectivity reversal as a function of base, solvent, and $Cr(CO)_3$ complexation (entries 12 and 13).

Metalation of 1,3-related heteratom-based DMGs follows a parallel pattern. The N-*t*-Boc, NCO-*t*-Bu, and $OCONEt_2$ groups mostly show excellent "in between"

TABLE 3. Cooperative Effects of Meta-Related Directed Metalation Groups

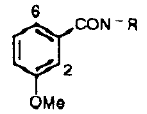
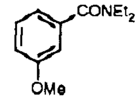
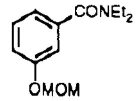
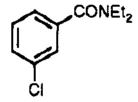
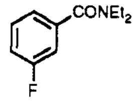
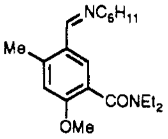
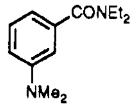
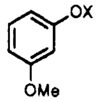
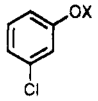
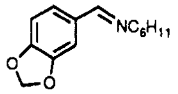
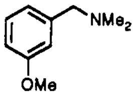
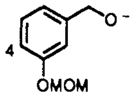
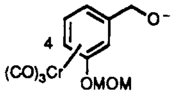
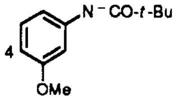
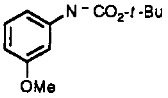
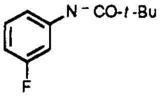
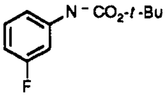
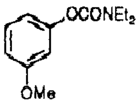
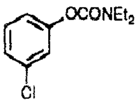
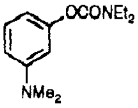
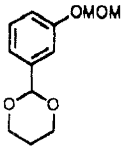
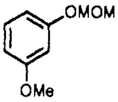
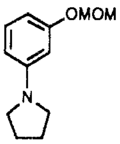
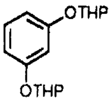
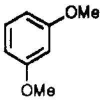
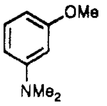
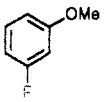
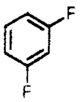
entry	substrate	metalation conditions	electrophile	yield, %	regioselectivity, % C_2:C_6[a]	ref
Carbon Based						
1		n-BuLi/TMEDA THF/–78 → –10 °C	ArCHO, Ph_2CO	48–79	95:5	b, c
		n-BuLi/THF/–75 → –10 °C	$ArCO_2R$	?	95:5	c
2		sec-BuLi/TMEDA/THF/–78 °C	D_2O, TMSCl	90	~95:5	86
3		t-BuLi/Et_2O/hexane/–78 °C	ICH_2CH_2I	35	100:0	66
4		sec-BuLi/TMEDA/THF/–78 °C	MeOD	80	95:5	86
5		sec-BuLi/TMEDA/THF/–78 °C	PhCHO	good	95:5	197
6		sec-BuLi/TMEDA/THF/–100 °C	ArCHO	60	95:5	155
7		sec-BuLi/TMEDA/THF/–78 °C	PhCHO	good	5:95	197
8		n-BuLi/THF/–45 °C	ArCHO	77–79	95:5	d
9		n-BuLi/THF/–78 °C	MeI	quant	95:5	125
10		n-BuLi/THF/–78 °C	D_2O	quant	95:5	e
11		n-BuLi/Et_2O/27 °C	Ph_2CO	79	95:5	b
12		n-BuLi/PhH/Et_2O/–78 °C	ICH_2CH_2I	78	100:0	66
		n-BuLi/TMEDA/Et_2O/–78 °C	ICH_2CH_2I	68	15:85	66
13		n-BuLi/TMEDA/Et_2O/–78 °C	$CO_2/h\nu/CH_2N_2$	45	2:98	f
Heteroatom Based						
14		n-BuLi/THF/0 °C	$(MeS)_2$	82	95:5	g
15		t-BuLi/THF/–20 °C	$I(CH_2)_3Cl$	26	95:5	h
16		n-BuLi/THF/–20 → –0 °C	benzyne formation	56–89	95:5	i
17		t-BuLi/THF/–70 → –25 °C	benzyne formation	50–85	95:5	i

TABLE 3 (Continued)

entry	substrate	metalation conditions	electrophile	yield, %	regioselectivity, % C_2:C_6[a]	ref
18		sec-BuLi/TMEDA/THF/−78 °C	CO_2	83	67:33	114
19		sec-BuLi/TMEDA/THF/−78 °C	MeI	83	95:5	129
20		sec-BuLi/TMEDA/THF/−78 °C	TMSCl DMF	93 30	0:100 0:100	j j
21		n-BuLi/C_6H_{12}/0 °C t-BuLi/TMEDA/Et_2O/−78 °C	ICH_2CH_2I ICH_2CH_2I	71 76	95:0.5 10:90	66 66
22		t-BuLi/hexane/0 °C t-BuLi/Et_2O/0 °C	ICH_2CH_2I ICH_2CH_2I	78 95	97:3 59:41	66 66
23		n-BuLi/Et_2O/reflux n-BuLi/TMEDA/C_6H_{14}/room temp	MeI DMF	78 66	0:100 28:38	j j
24		n-BuLi/Et_2O/reflux	CO_2/H^+	60	95:5	27
25		n-BuLi/Et_2O/+35 → −78 °C	$Me_2CHCOCl$	78	95:5	27, k
26		n-BuLi/TMEDA/Et_2O/35 °C	Ph_2CO	80	95:5	b
27		n-BuLi/THF/−65 °C	$B(OMe)_3/H_2O_2/HOAc$	53	95:5	b, l
28		n-BuLi/THF/−65 °C	CO_2	88	95:5	27

[a] The number "4" drawn on a structure indicates that the regioselectivity should be read as C_2:C_4. [b] Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. [c] Baldwin, J. E.; Bair, K. W. *Tetrahedron Lett.* **1978**, *19*, 2559. [d] Newman, M. S.; Kanakarajan, J. *J. Org. Chem.* **1980**, *45*, 2301. [e] Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. [f] Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 2349. [g] Table 1, footnote *c*. [h] Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725. [i] Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. [j] Skowronska-Ptasinska, M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1985**, *50*, 2690. [k] Koft, E. R.; Smith, A. B., III. *J. Am. Chem. Soc.* **1982**, *104*, 2659. [l] Furlano, D. C.; Calderon, S. N.; Chen, G.; Kirk, K. L. *J. Org. Chem.* **1988**, *53*, 3145.

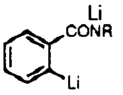
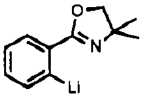
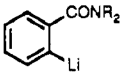
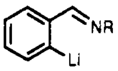
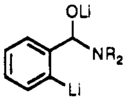
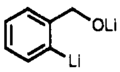
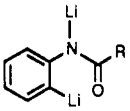
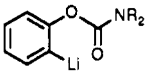
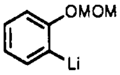
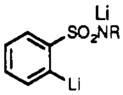
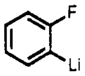
regioselectivity in concert with OMe, Cl, and F substituents (entries 14–18). Analogous to results observed with the $CONEt_2$ (entry 7), the $OCONEt_2$–NR_2 combination prefers metalation at C-6 (entry 20). The most systematically studied OMOM group shows a striking dependence on solvent effects for both OR and NR_2 meta substituents (entries 21–23). The early investigated 1,3-related OR–OR and OMe–NR_2 DMGs show clean metalation at the common site (entries 24–26). The OMe–F and F–F DMG combinations (entries 27 and 28) have not yet received wide synthetic exploitation.

The presence of a third DMG in **19** (Scheme 6) at C-4 or C-6 that is weaker than DMG_1 usually does not effect the result of C-2 metalation. With the exception of *N*,*N*-diethyl-3,5-dimethoxybenzamide,[74] such combinations have not been systematically studied.

G. Practical Aspects

The inert atmosphere–low temperature–syringe techniques used in DoM reactions are typical of modern operations in organometallic synthesis.[75–78] For exploratory experiments, the adoption of conditions based

TABLE 4. Practical Aspects of the DoM Reaction

ortho-lithiated species	base	typical conditions		temp, °C	ref
		solvent	additive		
		Carbon-Based Groups			
	*n*-BuLi	THF or Et_2O	none or TMEDA	−78 to reflux	27
	*n*-BuLi or *sec*-BuLi	THF or Et_2O	none	−45 to 0	29g
	*sec*-BuLi	THF	TMEDA	−78	86
	*n*-BuLi or LDA	THF	none	−78	*a*
	*n*-BuLi	THF	none	−78 to −20	84
	*n*-BuLi	*n*-hexane	TMEDA	reflux	*b*
		Heteroatom-Based Groups			
	*n*-BuLi[c] *t*-BuLi[e]	THF THF	none none	0 −20	*d* *f*
	*sec*-BuLi	THF	TMEDA	−78	114
	*n*-BuLi or *t*-BuLi	Et_2O	none	0–25	66
	*n*-BuLi	THF	none	−10 to +25	27
	*n*-BuLi	Et_2O	none	−50	*g*

[a] Table 3, footnote *e*. [b] Table 1, footnote *x*. [c] R = *t*-Bu. [d] Table 1, footnote *c*. [e] R = O-*t*-Bu. [f] Table, footnote *e*. [g] Table 1, footnote *q*.

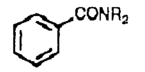
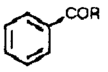
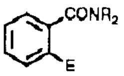
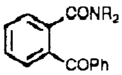
on the prototype systems (Table 4) are advised, although a systematic search for the optimum conditions by variation of alkyllithiums, solvents, and complexing agents invariably proves to be rewarding. In large-scale synthesis, the conversion from more conventional routes to those based on use of RLi reagents may result in a significant reduction in number of operational steps at a modest increase in expense. This factor coupled with the development of safe handling practices and low-temperature techniques is leading to the greater industrial use of organolithium chemistry.[79]

IV. Methodological Aspects of Tertiary Amide and O-Carbamate DMGs

A. Aromatic Tertiary Amide

In 1973, Hauser[80] reported that *N*,*N*-dimethylbenzamides undergo attack by *n*-BuLi to give aryl butyl ketones. Pursuing these observations, Beak and coworkers[81] first showed that treatment of *N*,*N*-diethylbenzamide with LiTMP gives *N*,*N*-diethyl-*o*-benzoylbenzamide, a result that implicated the formation of an ortho-lithiated intermediate by the use of a sterically hindered base and that led to the discovery of synthetically useful conditions[82] for the generation of this species. Table 5 shows the effect of conditions and N-substitution on the success of the tertiary benzamide DoM process. Metalation of the dimethylamide (*n*-BuLi, *sec*-BuLi) and the diethylamide (*n*-BuLi, *sec*-BuLi (Et_2O), and *t*-BuLi) followed by D_2O quench leads to ketone and self-condensation products (entries 1–4 and 6), although the last result was not obtained under comparable conditions. As demonstrated by Gschwend and co-workers,[83] ketone formation need not be synthetically unproductive since the carbinolamine formed by *n*-BuLi addition to a tertiary benzamide may serve as an in situ DMG and lead to ortho-substituted aryl ketones. A fundamental variation of this concept that does not involve functional group transformation, thoroughly developed by Comins and co-workers, invokes the use of carbinolamine DMGs derived from addition of dialkylamide nucleophiles to benzaldehydes.[84] In general, ortho-lithiated dimethylbenzamides cannot be generated except by metal–halogen exchange[85] or with the assistance of cooperative (meta-OR DMGs) or steric hindrance (ortho-OR

TABLE 5. **Effect of Conditions and N-Substitution on the Tertiary Benzamide DoM Reaction**

entry		base	conditions	E^+	products, yield, % 			ref
1	Me	*n*-BuLi	THF/0 °C		70			80
2	Me	*sec*-BuLi	TMEDA/THF/−78 °C	D_2O	14		26	86
3	Et	*n*-BuLi	THF/−78 °C	D_2O	31			86
4	Et	*sec*-BuLi	TMEDA/Et_2O/−78 °C	D_2O		~53	14	86
5	Et	*sec*-BuLi	TMEDA/THF/−78 °C	D_2O		>90		86
6	Et	*t*-BuLi	THF/−78 °C	TMSCl	9	28	5	206
7	*i*-Pr	*n*-BuLi, *sec*-BuLi	TMEDA/THF/−78 °C	D_2O		>90		86
8	*i*-Pr	*t*-BuLi	THF/0 °C	D_2O		91		206
9	Et,N(Et)$CH_2CH_2NEt_2$	*sec*-BuLi	TMEDA/THF/−78 °C	TMSCl		75		101
10		*sec*-BuLi	TMEDA/THF/−78 °C	TMSCl		61		*a*
11	Me, CH_2TMS	*sec*-BuLi	TMEDA/THF/−78 °C	DMF			70	157
12	*i*-Pr, CH_2TMS	*sec*-BuLi	TMEDA/THF/−78 °C	MeOD		92		*a*
13	Me, $CH(TMS)_2$	*t*-BuLi	TMEDA/THF/−78 °C	MeOD		98		104

[a] Cuevas, J.-C.; Patil, P.; Snieckus, V., unpublished results.

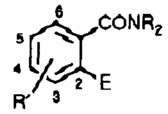
DMGs) effects and at lower temperatures as demonstrated in isolated cases (Table 6, entries 1–9). On the other hand, clean ortho metalation is observed for the diethyl- and diisopropylamides using all three alkyllithiums (Table 5, entries 5, 7, and 8). The use of *sec*-BuLi/TMEDA/THF/−78 °C in inverse addition mode established by Beak and Brown[86] has become the optimum, highly reliable conditions for ortho metalation. The "built-in" TMEDA benzamide (Table 5, entry 9) serves as a useful DMG and offers greater facility in hydrolysis (section IV.C). The piperidino amide (entry 10) is moderately effective but, similar to the pyrrolido and *N*-methylpiperazino amides, is more useful in systems with *m*-alkoxy chelation or amide carbonyl deactivating features (Table 6, entries 144–147). The mono′-α-TMS amide (Table 5, entry 11) requires the incorporation of a steric effect (entry 12) to avoid self-condensation. Increasing the effective bulk to the bis-α′,α′-TMS amide (Table 5, entry 13) gives a stable, synthetically useful ortho-lithiated species.

Table 6 provides a comprehensive list of substituted aromatic amides available by the DoM reaction and allows evaluation of functional groups that tolerate the strongly basic conditions of this process. A large number of alkoxybenzamides, of great value in natural product synthesis, have been used (e.g., entries 77–102), whereas halo (Cl, F) (entries 103, 106–108, 118, and 129), amino (Table 3, entry 7), sulfur (no entries), and carbon (Table 6, entries 27, 65, and 66) substituted systems have not been extensively explored. While C-3[86] and C-4 methylbenzamides are not deprotonated under kinetic conditions (Table 6, entries 27, 65, and 66), the C-2 methyl systems readily form *o*-toluamide anionic species of synthetic value (section VIII.A). The demonstrated bissilylation of such systems (entries 30–36) as a C–CH_3 protective expedient awaits broader synthetic exploitation (Table 21). Naphthamide DoM reactions with simple electrophiles have received limited use (Table 7), most work involving the bare *N*,*N*-diethyl-1-naphthamide, which has served as a valuable synthon for the construction of diverse polycyclic aromatic hydrocarbons (PAH) (section VIII.D.3 and Table 29). The corresponding 2-naphthamide undergoes ready 1-addition of RLi reagents,[87–89] although hindrance and deactivation effects (Table 7, entries 5 and 6) may be used to overcome this problem. Similar problems have been encountered in metalation reactions of the 2-oxazolinonaphthamide, which, however, have been turned into impressive synthetic advantage.[89] Aside from the *N*,*N*-diethyl-9-phenanthrenecarboxamides, which are valuable in alkaloid synthesis (section VIII.D.2), more highly condensed aromatic tertiary amides have not been adequately evaluated in DoM reactions.

Table 6 also offers an overview of the scope and diversity of electrophiles that may be introduced. Among carbon-based electrophiles, methyl iodide has served as the outstanding alkylating agent (e.g., entries 11, 77, 112, and 143); few examples of direct introduction of longer alkyl chains have been reported (entry 12). Presumably owing to proton exchange, allylation can only be achieved by prior transmetalation to the corresponding softer ortho Grignard reagents (entries 9, 13, 42, 56, 80, and 102). For a similar reason, successful reaction with aliphatic aldehydes can only be achieved via the same expedient (section VIII.D.2 and Table 26). Clean hydroxyalkylation reactions occur with aromatic aldehydes and benzophenone to give products that usually are directly transformed into phthalides for ease of isolation (Table 26). *o*-Formyl products or their carbinolamine precursors, invariably obtained by DMF treatment, often undergo cyclization upon workup or chromatography to hydroxyphthalides. Steric effects of 6-substitution appear to facilitate this reaction. Hydroxyphthalides are also deliberately formed by acid treatment for ease of isolation purposes (Table 26). The oxidation state of carboxylic acid in the ortho position can be achieved by isocyanate (e.g., Table 6, entries 71 and 87), by carbamoyl chloride (e.g., entries 72 and 138), and, most directly, by carbon dioxide (e.g., entries 32, 58, 78, and 96) electrophiles.

Among heteroatom electrophiles, a large number of N^+ synthons have been introduced to give anthranilamides (entries 16, 27, 36, 45, 52, 60, 66, 73, 106, 146, and 147) and *o*-anilinobenzamides (entries 1, 3, 4, 8, 10, 17, 18, 35, and 62). The synthetic utility of the former is depreciated by the difficult amide hydrolysis, while the latter serve as useful intermediates for acridones (section IX.A.2). OH^+ synthon introduction may be achieved by direct oxygenation (entries 19, 46, 59, 99,

TABLE 6. Synthesis of Ortho-Substituted Benzamides by the DoM Reaction[a]



entry	R	R′	E⁺	E	yield, %	ref
1	Me	3-OMe	$PhNMe(CN)CuLi/O_2$	N(Me)Ph	26	193
2	Me	6-OMe	MeI	Me	78	100
3	Me	6-OMe	$(CH_2)_5N(CN)CuLi/O_2$	$N(CH_2)_5$	33	193
4	Me	6-OMe	$PhNMe(Cl)CuLi/O_2$	N(Me)Ph	33	193
5	Me	6-OMe	$3\text{-}MeOC_6H_4NH(CN)CuLi/O_2$	$NHC_6H_4\text{-}3\text{-}OMe$	36	193
6	Me	3-OMOM	ICH_2CH_2Cl	I	35	66
7	Me	$3,4\text{-}OCH_2O$	$B(OMe)_3/H_2O_2, H^+$	OH	72	193
8	Me	$4,6\text{-}(OMe)_2$	$PhNMe(Cl)CuLi/O_2$	N(Me)Ph	43	193
9	Me	$4,5,6\text{-}(OMe)_3$	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	77	142
10	Me	$4,5\text{-}OCH_2O$, 6-OMe	$PhNMe(Cl)CuLi/O_2$	N(Me)Ph	48	193
11	Et	H	MeI	Me	77	86
12	Et	H	EtI	Et	70	86
13	Et	H	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	71	142
14	Et	H	HCO_2Et	CHO	23	156
15	Et	H	$MeCO_2Et$	*c*	35	142
16	Et	H	$TsN_3/NaBH_4$	NH_2	40	*g*
17	Et	H	$PhNMe(Cl)CuLi/O_2$	N(Me)Ph	46	193
18	Et	H	$2\text{-}MeOC_6H_4NH(CN)CuLi/O_2$	$NHC_6H_4\text{-}2\text{-}OMe$	50	193
19	Et	H	O_2/H^+	OH	37	*d, e*
20	Et	H	$B(OMe)_3/H_2O_2/H^+$	OH	56	86
21	Et	H	Br_2[r]	Br	93	128
22	Et	H	TMSCl	TMS	70	130
23	Et	H	$(t\text{-}BuS)_2$	*t*-BuS	88	*f*
24	Et	H	Se	$Se\text{-})_2$	31	195
25	Et	H	Bu_3SnCl	$SnBu_3$	55	197
26	Et	H	Ph_2PCl	PPh_2		197
27	Et	4-Me	$TsN_3/NaBH_4$	NH_2	82	*g*
28	Et	$4\text{-}(CH_2)_3OTHP$, 6-OMOM	MeI	Me	quant	141
29	Et	$4\text{-}(CH_2)_3OTHP$	$B(OMe)_3/H_2O_2/H^+$	OH	92[h]	141
30	Et	$6\text{-}CH(TMS)_2$	MeI	Me	91	130
31	Et	$6\text{-}CH(TMS)_2$	DMF	CHO	86	130
32	Et	$6\text{-}CH(TMS)_2$	CO_2	CO_2H[i]	78	130
33	Et	$6\text{-}CH(TMS)_2$	TMSCl	TMS	86	130
34	Et	$6\text{-}CH(TMS)_2$	$(MeS)_2$	SMe	76	130
35	Et	$6\text{-}CH(TMS)_2$	$PhNH(CN)CuLi/O_2$	NHPh	48	130
36	Et	5-OMe, $6\text{-}CH(TMS)_2$	$TsN_3/NaBH_4$	NH_2	47	*g*
37	Et	3-OH[j]	TMSCl	TMS	58–62[k]	122
38	Et	4-OH[j]	TMSCl	TMS	62–78[l]	122
39	Et	6-OH[j]	TMSCl	TMS	68	122
40	Et	6-OH	$(i\text{-}Pr)_3SiCl$	$Si(i\text{-}Pr)_3$	45–47[m]	122
41	Et	3-OMe	MeI	Me	58	139, 208
42	Et	3-OMe	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	80	142
43	Et	3-OMe	DMF	CHO	49[n]	146
44	Et	3-OMe	CO_2	CO_2H	54	146
45	Et	3-OMe	$TsN_3/NaBH_4$	NH_2	55	*g*
46	Et	3-OMe	O_2/H^+	OH	51	*d, e*
47	Et	3-OMe	TMSCl	TMS	65	195, 130
48	Et	3-OMe	S_8	SH	70	195
49	Et	3-OMe	$BrCH_2CH_2Br$	Br	25	*o*
50	Et	3-OMe	I_2	I	62	*o*
51	Et	4-OMe	MeI	Me	97	164
52	Et	4-OMe	$TsN_3/NaBH_4$	NH_2	34	*g*
53	Et	4-OMe	S_8	SH	92	195
54	Et	4-OMe	Se	$Se\text{-})_2$	30	195
55	Et	6-OMe	MeI	Me	88	100
56	Et	6-OMe	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	55	142
57	Et	6-OMe	DMF	CHO	75	146
58	Et	6-OMe	CO_2	CO_2H	70	146
59	Et	6-OMe	O_2/H^+	OH	46	*d, e*
60	Et	6-OMe	$TsN_3/NaBH_4$	NH_2	66–71	*g*
61	Et	6-OMe	$(TMS)_2N(CN)CuLi/O_2$	CN	18	193
62	Et	6-OMe	$PhNH(CN)CuLi/O_2$	NHPh	63 (54)[p]	193
63	Et	6-OMe	S_8	SH	74	195
64	Et	6-OMe	Se	$Se\text{-})_2$	32	195
65	Et	3-OMe, 4-Me	MeI	Me	90	139
66	Et	3-OMe, 4-Me	$TsN_3/NaBH_4$	NH_2	69	*g*
67	Et	3-OMe, 6-OH	TMSCl	TMS	76	122
68	Et	2-TMS, 3-OMe	S_8	SH	72	195
69	Et	5-OMe, 6-TMS	MeI	Me	74	130
70	Et	5-OMe, 6-TMS	DMF	CHO	88	130
71	Et	5-OMe, 6-TMS	PhNCS	CSNHPh	89	130
72	Et	5-OMe, 6-TMS	$ClCONEt_2$	$CONEt_2$	89	130
73	Et	5-OMe, 6-TMS	$TsN_3/NaBH_4$	NH_2	69	*g*
74	Et	5-OMe, 6-TMS	I_2	I	86	130
75	Et	5-OMe, 6-TMS	TMSCl	TMS	80	130
76	Et	5-OMe, 6-TMS	$(MeS)_2$	SMe	89	130

TABLE 6 (Continued)

entry	R	R′	E^+	E	yield, %	ref
77	Et	3,4-$(OMe)_2$	MeI	Me	72	146
78	Et	3,4-$(OMe)_2$	CO_2	CO_2H	71	146
79	Et	3,4-$(OMe)_2$	TMSCl	TMS	95	130
80	Et	3,6-$(OMe)_2$	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	63	142
81	Et	3,6-$(OMe)_2$	DMF	CHO	80	145
82	Et	5,6-$(OMe)_2$	MeI	Me	97	146
83	Et	5,6-$(OMe)_2$	DMF	CHO	88	146
84	Et	5,6-$(OMe)_2$	3,4-$OCH_2OC_6H_3CHO$	$CH(OH)C_6H_3$-3,4-OCH_2O	76	146
85	Et	5,6-$(OMe)_2$	CO_2	CO_2H	77	146
86	Et	5,6-$(OMe)_2$	$(CO_2Et)_2$	$COCO_2Et$	88	146
87	Et	5,6-$(OMe)_2$	PhNCO	CONHPh	71	146
88	Et	5,6-$(OMe)_2$	I_2	I	70	146
89	Et	5,6-$(OMe)_2$	TMSCl	TMS	65	146
90	Et	4,5-$(OMe)_2$, 6-TMS	MeI	Me	90	130
91	Et	4,5-$(OMe)_2$, 6-TMS	DMF	CHO	56	130
92	Et	3,4-OCH_2O	MeI	Me	64	146
93	Et	3,4-OCH_2O	CO_2	CO_2H	54	146
94	Et	5,6-OCH_2O	MeI	Me	47–75	136, 146
95	Et	5,6-OCH_2O	EtI	Et	55	136
96	Et	5,6-OCH_2O	CO_2	CO_2H	50	146
97	Et	5,6-OCH_2O	$(CO_2Et)_2$	$COCO_2Et$	80	146
98	Et	4,5-OCH_2O, 6-OTBDMS	DMF	CHO	70	119
99	Et	3,4,5-$(OMe)_3$	O_2/H^+	OH	48	*d*
100	Et	3,4,6-$(OMe)_3$	DMF	CHO	50–56 (47)[q]	148a, 149a, 154
101	Et	3,4,6-$(OMe)_3$	O_2/H^+	OH	52	*d*
102	Et	4,5,6-$(OMe)_3$	$BrCH_2CH{=}CH_2$[b]	$CH_2CH{=}CH_2$	66	142
103	Et	3-F	TMSCl	TMS	88	130
104	Et	5-F, 6-TMS	MeI	Me	80	130
105	Et	5-F, 6-TMS	DMF	CHO	58	130
106	Et	3-Cl	$TsN_3/NaBH_4$	NH_2	31–36	*g*
107	Et	3-Cl	TMSCl	TMS	67	130
108	Et	3-Cl	DMF	CHO		171
109	Et	5-Cl, 6-TMS	MeI	Me	89	130
110	Et	5-Cl, 6-TMS	DMF	CHO	76	130
111	Et	6-TMS	MeI	Me	91	130
112	*i*-Pr	H	MeI	Me	86[q]	156
113	*i*-Pr	H	$BrCH_2CH{=}CH_2$	Br	60	86
114	*i*-Pr	H	DMF	CHO	90[q]	156
115	*i*-Pr	H	TMSCl	TMS	88	156
116	*i*-Pr	3-OMe	DMF	CHO	89[q]	156
117	*i*-Pr	6-OMe	DMF	CHO		156
118	*i*-Pr	6-Cl	DMF	CHO	97[q]	156
119	*i*-Pr	6-TMS	DMF	CHO		156
120	Me, *t*-Bu	6-OMe	MeI	Me	98	102
121	Et, $CH_2CH_2NEt_2$	H	MeI	Me	76	101
122	Et, $CH_2CH_2NEt_2$	H	DMF	CHO	80	101
123	Et, $CH_2CH_2NEt_2$	H	TMSCl	TMS	75	101
124	Et, $CH_2CH_2NEt_2$	H	$(MeS)_2$	SMe	56	101
125	Et, $CH_2CH_2NEt_2$	6-OMe	MeI	Me	82	101
126	Me, CH_2TMS	4-OMe	DMF	CHO	65	157
127	Me, CH_2TMS	6-OMe	DMF	CHO	65	157
128	Me, CH_2TMS	4,6-$(OMe)_2$	DMF	CHO	30	157
129	Me, CH_2TMS	6-Cl	DMF	CHO	24	157
130	Et, CH_2TMS	H	DMF	CHO	30	157
131	*i*-Pr, CH_2TMS	H	DMF	CHO	62	157
132	*i*-Pr, CH_2TMS	3-OMe	DMF	CHO	33	157
133	*i*-Pr, CH_2TMS	4-OMe	DMF	CHO	64	157
134	*i*-Pr, CH_2TMS	6-Ph	DMF	CHO	55	157
135	Me, $CH(TMS)_2$	H	MeI	Me	91	104
136	Me, $CH(TMS)_2$	H	$BrCH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	84	104
137	Me, $CH(TMS)_2$	H	DMF	CHO	87	104
138	Me, $CH(TMS)_2$	H	$ClCONEt_2$	$CONEt_2$	71	104
139	Me, $CH(TMS)_2$	H	Br_2	Br	80	104
140	Me, $CH(TMS)_2$	H	Bu_3SnCl	$SnBu_3$	98	104
141	Me, $CH(TMS)_2$	H	$(t\text{-BuS})_2$	S-*t*-Bu	68	104
142	Me, $CH(TMS)_2$	4-OMe	DMF	CHO	80	104
143		4-OMe	MeI	Me	73	101
144		3-OMe	TMSCl	TMS	72	197
145		3-OMe	TMSCl	TMS	53	197
146		3-OMe	$TsN_3/NaBH_4$	NH_2	44	197
147		3-OMOM	$TsN_3/NaBH_4$	NH_2	25	197

TABLE 6 Footnotes (Continued)

[a] Unless otherwise indicated, *sec*-BuLi/TMEDA/THF/−78 °C conditions apply. *o*-Deuteration experiments have been omitted. With DMF as electrophile, only cases of uncyclized *o*-formylated benzamides are given. Cases that lead upon workup or deliberate acid treatment to 3-hydroxyphthalides are listed in Table 26. For ortho boronation, see section IX.E. [b] Li → Mg transmetalation ($MgBr_2 \cdot 2Et_2O$) before addition of E^+. [c] 3-Methyl-3-[2-(diethylcarbamoyl)phenyl]phthalide (35%). [d] Parker, K. A.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 674. [e] Doadt, E. G.; Snieckus, V., unpublished results. [f] Table 1, footnote *l*. [g] Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795. [h] Isolated as the corresponding MOM derivative. [i] Isolated as the corresponding phthalic anhydride. [j] The silyloxy intermediate was prepared separately ($NH(TMS)_2$/neat/40 °C or Et_3SiCl/Et_3N/PhH/reflux) or in situ (*sec*-BuLi/THF/−78 °C) and subjected to the standard metalation conditions. [k] Together with *N*,*N*-diethyl-3-hydroxy-6-(trimethylsilyl)benzamide with *N*,*N*-diethyl-3-hydroxy-6-(trimethylsilyl)benzamide (5–16%) and 3-hydroxy-2,6-bis(trimethylsilyl)benzamide (4–11%). [l] Together with *N*,*N*-diethyl-4-hydroxy-2,6-bis(trimethylsilyl)benzamide (10–11%). [m] Together with *N*,*N*-diethyl-2-(triisopropylsilyl)-6-[(triisopropylsilyl)oxy]benzamide (10–30%). [n] Based on recovered starting material. [o] Sloan, C. P. M.Sc. Thesis, University of Waterloo, 1986. [p] Yield obtained with PhN(TMS)Li. [q] Without TMEDA. [r] LiTMP/$HgCl_2$/THF/0 °C conditions.

and 101) or, more reproducibly and in better yields, by the trimethyl borate/hydrogen peroxide method (entries 7 and 20). The formation of such salicylamides is especially useful in OR–amide DMG cooperative situations for the preparation of differentially functionalized oxygenated systems (entry 46). The intermediate boronic acids obtained by simple hydrolysis serve as productive partners in transition-metal-catalyzed cross-coupling methodologies (section IX.E.1). Sulfur (including S_8) (entries 23, 34, 48, 53, 63, 68, 124, and 141), selenium (entries 24, 54, and 64), phosphorus (entry 26), and tin (entries 25 and 140) electrophile incorporation has seen few applications to date (sections IX.B,D). The normally smooth and high-yield introduction of TMSCl (e.g., entries 22, 38, 75, 89, 123, and 145), even in cases of potential incomplete lithiation, is undoubtedly related to its in situ compatibility with alkyllithiums.[90] Ortho silylation plays a useful protecting group role in aromatic ring manipulations (section IX.C). Ortho silylated benzamides are also obtained, albeit in poor yields, by ortho metalation mediated oxygen to carbon silyl migration of silyloxy derivatives (entries 37–40). Notable among the halogen electrophiles introduced (entries 21, 49, 50, 74, 88, and 139) is the absence of ortho fluorination, although new F^+ reagents are known[91] and fluorobenzamides have themselves been metalated (entry 103 and Table 3, entry 5). Certain electrophiles fail in DoM reactions with tertiary benzamides,[86] whereas they have been reported to be successful with secondary amide[29f,h,i] and oxazoline[29g] DMGs. In general, most electrophiles in Table 6 serve equally well for these three DMGs.

B. Heteroaromatic Tertiary Amide

Heterocyclic amide DoM reactions are in the early stages of development. In the pyridine series (Table 8), the combination of diisopropylamide substrate and LDA or, preferably, LiTMP base is required to avoid rapid self-condensation (entries 8, 19, and 26) and addition.[92] The significance of steric effects is revealed by comparison of dimethyl- and diethylbenzamide nucleophiles (entries 15 and 16). A limited number of electrophiles may be introduced in modest yields, although utility in tandem metalation to heteroanthraquinones has also been demonstrated (Table 30). In simple reactions with electrophiles, secondary amides have comparable utility,[93] while oxazolines show dual character of ortho metalation and addition of broader synthetic scope.[29g]

N,*N*-Diethylthiophene-2-carboxamide and -3-carboxamide are useful metalation substrates. The less accessible 3-carboxamide has been used in tandem metalation sequences to obtain heteroanthraquinones (Table 30), while the 2-carboxamide allows access to a variety of 2,3- and 2,3,5-substituted thiophenes (Table 9) via silicon protection (section IX.C.1) and dianion (section VI) protocols. The corresponding furan-3-carboxamide also undergoes tandem DoM reactions to anthraquinones (Table 30), while the undetected anion of the 2-derivative **21** (Scheme 8) rapidly fragments to the enyne **22** even at low temperatures owing to the electron-withdrawing effect of the amide.[94] Complementary DoM reactions of secondary amide and oxazoline[95] furans and thiophenes provide greater scope, although further manipulation of all systems is limited by lack of mild hydrolytic conditions for these acid-sensitive π-deficient heterocycles. Recent studies by Comins[84] on furan, thiophene, and pyrrole α-amino alkoxide DMGs and by Keay[96] on furancarbinols promise to circumvent some of these difficulties.

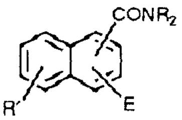
Metalation of *N*,*N*-diethylindole-2-carboxamide **23** (Scheme 9) leads to **24**,[97] a fate analogous to that observed for the corresponding furan-2-carboxamide (Scheme 8). The triazolopyridinecarboxamide **25** undergoes metalation at either C-4 (slow) or C-7 (fast); quenching with anisaldehyde gives **26**.[98]

Clearly, tertiary amide DoM chemistry in the heterocyclic area is in its infancy.

C. Amide Manipulation

The recalcitrant nature of *N*,*N*-dialkylbenzamides to acid (e.g., stable to refluxing 16 N HCl for 72 h) or base hydrolysis is well recognized. The synthetic use of the $CONEt_2$ DMG is thus seriously compromised. However, anchimeric assistance by ortho-introduced electrophiles capable of forming five- or six-membered-ring tetrahedral intermediates greatly enhances amide hydrolytic rates,[99] a feature that may be turned into synthetic benefit. Thus ortho-hydroxyalkylated and -carboxylated products of DoM reactions may be hydrolyzed under relatively mild acidic conditions to give phthalides (section VIII.D.2) and phthalic acids or anhydrides (section VIII.E). Similarly, *o*-allyl derivatives can be cyclized to benzoisocoumarins (sections VIII.A.2 and VIII.B.1), although in some cases six-membered-ring formation via attack on intermediate carbonium ions is inhibited by the diethylamide substituent.[100] In search of hydrolytic facility, Comins tested the "built-in" TMEDA benzamide **27a** (Scheme 10).[101] The developed three-step sequence affords the benzoic acid **28** in good yield but still requires relatively vigorous hydrolytic conditions. A milder three-step route for the preparation of **28**, amenable to scale up, that takes advantage of acid-catalyzed *tert*-butyl cleavage of the CON(Me)-*t*-Bu DMG **27b** has been devised by Reitz.[102] In the absence of other interfering functionality, di-

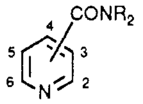
TABLE 7. Synthesis of Substituted Naphthamides[a]

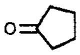
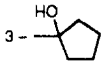
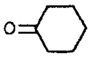
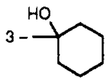
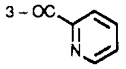
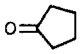
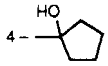
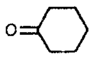
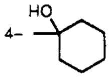
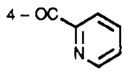
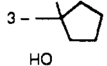
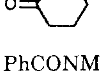
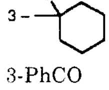
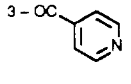


entry	CONR$_2$	R	R′	E$^+$	E	yield, %	ref
1	C-1	Et	H	TsN$_3$/NaBH$_4$	2-NH$_2$	74	192
2	C-1	Et	H	O$_2$/H$^+$	2-OH	34	*b*
3	C-1	Et	H	PhNMe(CN)CuLi/O$_2$	2-NMePh	61	193
4	C-1	Et	H	TMSCl	2-TMS	80	171
5	C-2	Et	6-OMe	EtI	1-Et	68[c]	*d*
6	C-2	*i*-Pr	6-OMe	EtI	1-Et	95[e]	*d*
7	C-2	*i*-Pr	H	DMF	CHO	22 (C-1)[f] 10 (C-3)	156
8	C-2	Et	4-OMe, 6,7-OCH$_2$O			*g*	147

[a] Unless otherwise specified, *sec*-BuLi/TMEDA/THF/−78 °C conditions apply. [b] Table 6, footnote *d*. [c] *t*-BuLi conditions. [d] Bindal, R. D.; Katzenellenbogen, J. A. *J. Org. Chem.* **1987**, *52*, 3182. [e] *n*-BuLi conditions. [f] Without TMEDA. [g] Products of C-1, C-3, and C-5 substitution by an unspecified E$^+$ in unspecified yields.

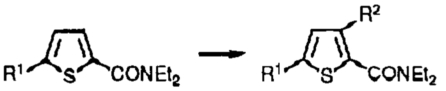
TABLE 8. Synthesis of Substituted Pyridinecarboxyamides[a]



entry	CONR$_2$	R	E$^+$	E	yield, %	ref
1	C-2	*i*-Pr	DMF	3-CHO	35	*b*
2	C-2	*i*-Pr	PhCHO	3-PhCH(OH)		*b*
3	C-2	*i*-Pr	PH$_2$CO	3-Ph$_2$C(OH)	81	*b*
4	C-2	*i*-Pr				*b*
5	C-2	*i*-Pr				*b*
6	C-2	*i*-Pr	PhCONMe$_2$	3-PhCO	52	*b*
7	C-2	*i*-Pr	TMSCl	3-TMS	54–64	*b*
8	C-2	Et			94	*c*
9	C-3	*i*-Pr	DMF	4-CHO	39	*b*
10	C-3	*i*-Pr	PhCHO	4-PhCH(OH)		*b*
11	C-3	*i*-Pr	Ph$_2$CO	4-Ph$_2$C(OH)	68	*b*
12	C-3	*i*-Pr				*b*
13	C-3	*i*-Pr				*b*
14	C-3	*i*-Pr	PhCONMe$_2$	4-PhCO	47	*b*
15	C-3	*i*-Pr	2-MeOC$_6$H$_4$CONMe$_2$	2-MeOC$_6$H$_4$CO	71[d] (6)[e]	85
16	C-3	*i*-Pr	4-MeOC$_6$H$_4$CONMe$_2$	4-MeOC$_6$H$_4$CO	98[d] (53)[e]	85
17	C-3	*i*-Pr	3,5-(MeO)$_2$C$_6$H$_3$CONMe$_2$	3,5-(MeO)$_2$C$_6$H$_3$CO	quant[d]	85
18	C-3	*i*-Pr	2,3,5-(MeO)$_3$C$_6$H$_2$CONMe$_2$	2,3,5-(MeO)$_3$C$_6$H$_2$CO	58[d]	85
19	C-3	Et			68	*c*
20	C-4	*i*-Pr	DMF	3-CHO	37 (38)[f]	156, *b*
21	C-4	*i*-Pr	PhCHO	3-PhCH(OH)		*b*
22	C-4	*i*-Pr	Ph$_2$CO	Ph$_2$C(OH)	55	*b*
23	C-4	*i*-Pr				*b*
24	C-4	*i*-Pr				*b*
25	C-4	*i*-Pr	PhCONMe$_2$	3-PhCO	36	*b*
26	C-4	Et			75	*c*

[a] Unless otherwise stated, LDA/Et$_2$O/−78 °C conditions were used. [b] Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739. Epsztajn, J.; Brezezinski, J. Z.; Jozwiak, A. J. *J. Chem. Res.* (*S*) **1986**, 18. [c] Epsztajn, J.; Bieniek, A.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735. [d] LiTMP/DME/−78 °C conditions. [e] Yield obtained with the corresponding *N*,*N*-diethylbenzamide electrophile. [f] *sec*-BuLi/THF/−78 °C conditions.

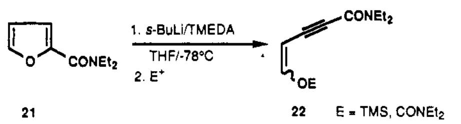
TABLE 9. Synthesis of 2,3- and 2,3,5-Substituted Thiophenecarboxamides[a]



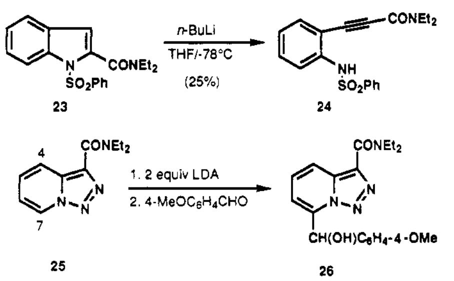
entry	reactant	electrophile		product		yield, %	ref
	R^1	E_1^+	E_2^+	R^1	R^2		
1	H	TMSCl		TMS	H	85	94
2	H	CO_2		CO_2H	H	82–85[b] (41)[b,c]	95
3	TMS	MeI		TMS	Me	56	123
4	TMS	$ClCONEt_2$		TMS	$CONEt_2$	49	123
5	TMS	$(MeS)_2$		TMS	SMe	68	123
6	H[d]	TMSCl	TMSCl	TMS	TMS	82	94
7	H[d]	$ClCONEt_2$	$ClCONEt_2$	$CONEt_2$	$CONEt_2$	82	94
8	H[d]	$(MeS)_2$	$(MeS)_2$	SMe	SMe	65	94
9	H[d]	PhCHO	PhCHO	CH(OH)Ph	CH(OH)Ph[e]	48	94
10	H[d]	MeI	MeOH	H	Me	57[f]	94
11	H[d]	$(MeS)_2$	MeOH	H	SMe	34[g]	94
12	H[d]	TMSCl	MeOH	H	TMS	40[g]	94
13	H[d]	$ClCONEt_2$	MeOH	H	$CONEt_2$	38[f]	94
14	H[d]	TMSCl	$(MeS)_2$	SMe	TMS	35[g]	94
15	H[d]	$(MeS)_2$	TMSCl	TMS	SMe	30[g]	94
16	H[d]	$(MeS)_2$	$ClCONEt_2$	$CONEt_2$	SMe	26[g]	94

[a] Unless otherwise indicated, *sec*-BuLi/TMEDA/THF/−78 °C conditions apply. [b] Using LDA/THF/−78 °C or *sec*-BuLi/THF/−78 °C conditions. [c] Accompanied by the 3-CO_2H derivative (50%). [d] Via 3,5-dilithiated intermedite; see section VI. [e] Accompanied by 10% of 3-CH(OH)Ph product. [f] Accompanied by 10–20% of starting material. [g] Accompanied by 25% of 3,5-disubstituted product of E_1^+ introduction.

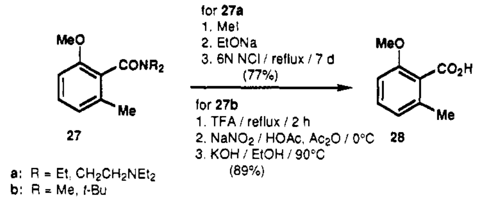
SCHEME 8



SCHEME 9



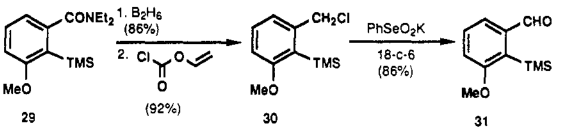
SCHEME 10



ethylbenzamides may be converted into benzaldehydes as demonstrated in the high-yield, overreduction–oxidation sequence **29** → **30** → **31** (Scheme 11).[103] Preliminary results suggest that the bis-α′,α′-TMS amide DMG may provide a general solution to the hydrolysis problem.[104] Thus **32** (Scheme 12) is readily unmasked by fluoride to the dimethylbenzamide **33**, which may be readily reduced by standard methods to aldehyde **34** or alcohol **35** oxidation states.

With the aim of developing a new aryl aldehyde and ketone synthesis, Comins has systematically explored the classical amide–alkyllithium reaction originally reported by Hauser[80] for a variety of amides, including the "built-in" TMEDA DMG system (Table 10).[101] Thus in the *N*,*N*-diethyl series, lateral metalation is suppressed by using PhH rather than THF as solvent, thereby leading to good yields of ketones from alkyllithiums (entries 2–5) but not from Grignard reagents (entry 1). The piperazine amide (entry 8) is less valuable in view of its poor DMG properties.[101] However, both of these amide types are unreliable in forming benzaldehyde products (entries 6, 7, 9, and 10). The value of "built-in" TMEDA DMGs (entries 11–20) is thus reinforced, especially in the β-(dimethylamino)ethyl series (entries 11–17), in providing ortho-substituted benzaldehydes (entries 14 and 17). Although little exploited, amide to aryl ketone conversion has been achieved via intermediate α-alkoxy amine DMGs.[83] The introduction[105] of organolanthanum reagents for this purpose has added a new dimension to the amide aryl ketone conversion (Table 11). A variety of ketones are available in excellent yield with the exception of those that suffer double-jeopardy hindrance from ortho and N substituents. Reduction methods (e.g., LAH, Dibal, Super-Hydride) that are effective on *N*,*N*-di-

SCHEME 11



SCHEME 12

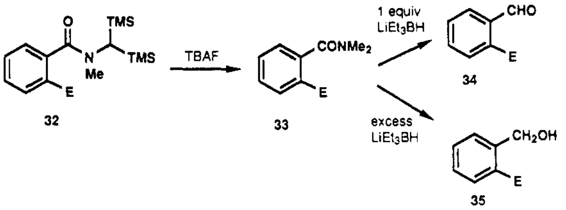
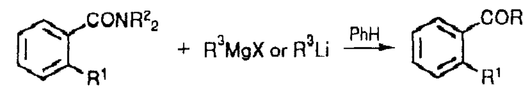
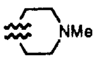
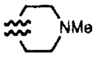


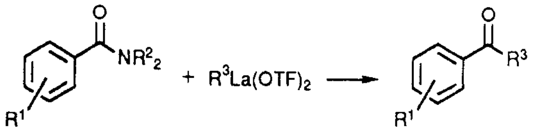
TABLE 10. Tertiary Benzamide to Ketone and Aldehyde Conversion Using RMgX and RLi Reagents[101]



	benzamide			product		
entry	R^1	R^2	R^3MgX/R^3Li	R^1	R^3	yield, %
1	Me	Et	MeMgCl	Me	Me	0
2	Me	Et	MeLi	Me	Me	72
3	Me	Et	*n*-BuLi	Me	*n*-Bu	61
4	*n*-Bu	Et	MeLi	*n*-Bu	Me	55
5	*n*-Bu	Et	*n*-BuLi	*n*-Bu	*n*-Bu	62
6	Me	Et	SmEAH[a]	Me	H	0
7	*n*-Bu	Et	SMEAH[a]	*n*-Bu	H	0
8	*n*-Bu		*n*-BuLi	*n*-Bu	*n*-Bu	58
9	Me		SMEAH[a]	Me	H	57
10	*n*-Bu		SMEAH[a]	*n*-Bu	H	0
11	Me	Me, $CH_2CH_2NMe_2$	MeMgCl	Me	Me	56
12	Me	Me, $CH_2CH_2NMe_2$	MeLi	Me	Me	82
13	Me	Me, $CH_2CH_2NMe_2$	*n*-BuLi	Me	*n*-Bu	80
14	Me	Me, $CH_2CH_2NMe_2$	SMEAH[a]	Me	H	80
15	*n*-Bu	Me, $CH_2CH_2NMe_2$	MeLi	*n*-Bu	Me	77
16	*n*-Bu	Me, $CH_2CH_2NMe_2$	*n*-BuLi	*n*-Bu	*n*-Bu	70
17	*n*-Bu	Me, $CH_2CH_2NMe_2$	SMEAH[a]	*n*-Bu	H	51
18	Me	Et, $CH_2CH_2NEt_2$	MeMgCl	Me	Me	38
19	*n*-Bu	Et, $CH_2CH_2NEt_2$	*n*-BuLi	*n*-Bu	*n*-Bu	64
20	Me	Et, $CH_2CH_2NEt_2$	SMEAH[a]	Me	H	0

[a] Modified aluminum hydride; see: Tokoyorama, T.; Kanazawa, R. *Synthesis* **1976**, 526.

TABLE 11. Tertiary Benzamide to Aryl Ketone Conversion Using Lanthanum Triflates[105]



R^1	R^2	R^3 (equiv)	R^1	R^3	yield, %
H	Et	Me (1.2)	H	Me	95
H	Et	Ph (2.0)	H	Ph	98
H	Et	*n*-Bu (1.2)	H	*t*-Bu	94
3-Me	Et	Me (1.2)	3-Me	Me	92
4-Me	Et	Me (2.0)	4-Me	Me	98
3-Cl	Et	Me (2.0)	3-Cl	Me	95
3-OMe	Et	Me (3.0)	3-OMe	Me	96
2-OMe	Et	Me (3.0)	2-OMe	Me	91
H	*i*-Pr	Me (1.0)	H	Me	80
2-Me	*i*-Pr	Me (1.0)			NR
2-OMe, 6-(2-MeC_6H_4)	Et	Me (3.0)			NR

methylbenzamide (Scheme 12)[104] are not satisfactory for *o*- and *o*,*o*′-substituted diethylbenzamides.[105]

D. Aromatic Tertiary *O*-Carbamate

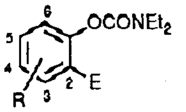
As appreciated by a glance at Table 12, electrophile introduction into ortho-lithiated *O*-aryl *N*,*N*-diethyl carbamates occurs with equal efficacy and comparable scope to that observed for the corresponding amides. Differences to note are the allylation (entry 2) and hydroxyalkylation (entry 3) reactions, which do not require transmetalation tactics. Amination and hydroxylation are effected in excellent yield by the tosyl azide–borohydride reduction (entry 11) and trimethyl borate/hydrogen peroxide (entry 12) procedures, respectively. The initial component of the latter reaction has consequences for cross-coupling chemistry (section IX.E). *m*-Methoxy (entries 27 and 28) and *m*-chloro (entries 35–37) systems show good C-2 regioselectivity, while *m*-methyl (entry 20) and *m*-dialkylamino (entries 22–25) substituents force metalation of the alternate site. Difficult to access *o*-halo-masked phenols (entries 13–15) and systems containing more than one kind of halogen (entry 41) may be obtained. *O*-Phenyl *N*,*N*-diisopropyl carbamates suffer complications in hydrolytic manipulation after DoM chemistry, while the corresponding dimethyl systems undergo rapid anionic ortho-Fries rearrangement (section V.A). Condensed aromatic carbamate metalation has been only briefly explored (Table 13) but shows excellent regioselectivities in the 1-naphthyl (entries 1–3) and 9-phenanthryl (entries 6 and 7) series.

In comparison with other oxygen-based DMGs OMe,[27] OMOM,[66] $OP(OR)_2$,[107a] and $OPO(NMe)_2$,[107b] the carbamate has advantage in the milder metalation conditions (Table 4) and complementarity in the basic conditions for hydrolysis.

E. Heteroaromatic Tertiary *O*-Carbamate

All possible isomeric *O*-pyridyl *N*,*N*-diethylcarbamates undergo smooth metalation and electrophile quench to give a rich variety of substituted derivatives that are difficult to prepare by classical substitution or de novo pyridine construction modes (Table 14).[108] The clean regiospecific 4-metalations of the 3-carbamate are complemented by the recent preliminary results[109] of efficient 2-deprotonation of 3-methoxypyridine using mesityllithium. The anionic ortho-Fries rearrangement (section V.A), iterative metalation (section VII), facile

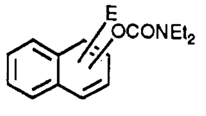
TABLE 12. Synthesis of Ortho-Substituted *O*-Aryl Carbamates[a]

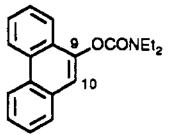


entry	R	E^+	E	yield, %	ref
1	H	MeI	Me	80	114
2	H	$BrCH_2CH=CH_2$	$CH_2CH=CH_2$	75	117a
3	H	*n*-PrCHO	*n*-PrCH(OH)	80	129
4	H	PhCHO	PhCH(OH)	90	129
5	H	Ph_2CO	$Ph_2C(OH)$	22	129
6	H	DMF	CHO	73	114
7	H	Ac_2O	COMe	32	129
8	H	CO_2	CO_2H	73-95	114, 118
9	H	$ClCONEt_2$	$CONEt_2$	86-89	114, 118
10	H	PhNCO	CONHPh	80	129
11	H	$TsN_3/NaBH_4$	NH_2	94	*b*
12	H	$B(OMe)_3/H_2O_2$, HOAc	OH	98	129
13	H	Cl_3CCCl_3	Cl	80	129
14	H	$BrCH_2CH_2Br$	Br	86	129
15	H	I_2	I	78	129
16	H	TMSCl	TMS	79	114
17	H	$(MeS)_2$	SMe	79	129
18	H	$(PhS)_2$	SPh	87	129
19	4-Me	TMSCl	TMS	83	117a
20	5-Me	TMSCl	TMS	77	117a
21	6-Me	TMSCl	TMS	54[c]	114
22	$5\text{-}NMe_2$	DMF	CHO	30	*d*
23	$5\text{-}NMe_2$	TMSCl	TMS	93	*d*
24	$5\text{-}N(CH_2CH_2)_2$	DMF	CHO	30	*d*
25	$5\text{-}N(CH_2CH_2)_2$	TMSCl	TMS	96	*d*
26	3-OMe	MeI	Me	93[e]	117a
27	3-OMe	CO_2	CO_2H	63[f]	114
28	3-OMe	I_2	I	73[g]	129
29	4-OMe	MeI	Me	72	114
30	4-OMe	DMF	CHO	88	114
31	4-OMe	CO_2	CO_2H	69	114
32	4-OMe	TMSCl	TMS	62	114
33	6-OMe	$ClCONEt_2$	$CONEt_2$	90	117a
34	6-OMe	TMSCl	TMS	68	117a
35	3-Cl	MeI	Me	83	129
36	3-Cl	PhCHO	PhCH(OH)	81	129
37	3-Cl	TMSCl	TMS	89	129
38	4-Cl	CO_2	CO_2H	69	118
39	4-Cl	$ClCONEt_2$	$CONEt_2$	77	118
40	6-Cl	$ClCONEt_2$	$CONEt_2$	78	117a
41	6-Cl	I_2	I	93	117a
42	6-Cl	TMSCl	TMS	79	117a
43	6-TMS	I_2	I	80	196

[a] All reactions were carried out under *sec*-BuLi/TMEDA/TMF/−78 °C conditions. [b] Table 6, ref *g*. [c] Together with $2\text{-}CH_2TMS$ derivative (26%) as an inseparable mixture. Under LDA/THF/−78 °C conditions, a mixture of $2\text{-}CH_2TMS$ and $2\text{-}CH(TMS)_2$ in a 5:1 ratio and 80% yield was obtained. [d] Table 3, ref *j*. [e] Combined yield with 6-Me isomer (2-Me:6-Me = 3:1). [f] 20% $6\text{-}CO_2H$. [g] 27% 6-I.

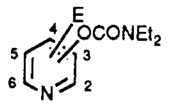
TABLE 13. Synthesis of Ortho-Substituted *O*-Naphthyl and *O*-9-Phenanthryl Carbamates[a]



entry	$OCONEt_2$	E^+	E	yield, %	ref
1	C-1	MeI	2-Me	90	114
2	C-1	$ClCONEt_2$	$2\text{-}CONEt_2$	79	117a
3	C-1	TMSCl	2-TMS	90	114
4	C-2	$ClCONEt_2$	$3\text{-}CONEt_2$	51[b]	117a
5	C-2	TMSCl	1-TMS	17	117a
			3-TMS	45[b]	117a
					
6		MeI	10-Me	92	200
7		TMSCl	10-TMS	88	200

[a] See footnote *a*, Table 12. [b] In addition, 20–25% of *N*,*N*-diethyl-3-hydroxy-2-naphthamide was obtained.

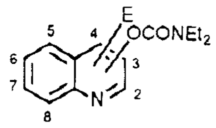
TABLE 14. Synthesis of Ortho-Substituted *O*-Pyridyl Carbamates[a]

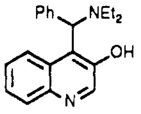
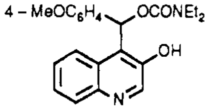
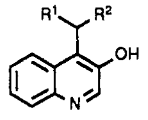


entry	$OCONEt_2$	E^+	E	yield, %
1	C-2	MeI	3-Me	72
2	C-2	$ClCONEt_2$	$3\text{-}CONEt_2$	66
3	C-2	TMSCl	3-TMS	52 (62)[b]
4	C-2	$BrCH_2CH_2Br$	3-Br	59
5	C-2	I_2	3-I	68
6	C-3	MeI	4-Me	83
7	C-3	$ClCONEt_2$	$4\text{-}CONEt_2$	64
8	C-3	$BrCH_2CH_2Br$	4-Br	71
9	C-3	TMSCl	4-TMS	69 (83)[b]
10	C-3	Me_3SnCl	$4\text{-}SnMe_3$	82
11	C-4	MeI	3-Me	75
12	C-4	$ClCONEt_2$	$3\text{-}CONEt_2$	69
13	C-4	TMSCl	3-TMS	67

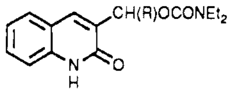
[a] Reference 108. Unless otherwise indicated, *sec*-BuLi/TMEDA/THF/−78 °C conditions were used. [b] Obtained under LDA/THF/−78 °C conditions.

TABLE 15. Synthesis of Substituted *O*-Quinolyl Carbamates[a]



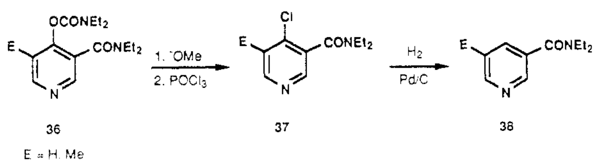
entry	OCONR$_2$	R	E$^+$	E		yield, %	ref
1	C-2	Et	EtCHO	3-EtCH(OH)		30[b,c]	116
2	C-2	Et	PhCHO	3-PhCH(OH)		24[b,c]	116
3	C-3	Me	MeCHO	4-CH(Me)NMe$_2$[d]		60	116
4	C-3	Me	EtCHO	4-CH(Et)NMe$_2$[d]		58	116
5	C-3	Me	TMSCl	4-TMS		90	116
6	C-3	Et	MeCHO	4-MeCH(OH)		25	116
7	C-3	Et	EtCHO	4-EtCH(OH)		35	116
8	C-3	Et	PhCHO	 Ph NEt$_2$ OH N		40	116
9	C-3	Et	4-MeOC$_6$H$_4$CHO	 4-MeOC$_6$H$_4$ OCONEt$_2$ OH N		53[e]	116
10	C-4	Et	MeI	3-Me		75	116
11	C-4	Et	EtCHO	3-EtCH(OH)		43	116
12	C-4	Et	TMSCl	3-TMS		95	116
13	C-5	Me	TMSCl	6-TMS		70[f]	111
14	C-6	Me	TMSCl	5-, 7-, 5,7-TMS[g]		75[f]	111
15	C-7	Me	TMSCl	8-TMS		90[f]	111
16	C-8	Me	TMSCl	7-TMS		40[f]	111
				 R^1 R^2 OH N			
				R^1	R^2		
17	C-3	Me	PhCHO	Ph	NMe$_2$	90	115
18	C-3	Me	2-MeOC$_6$H$_4$CHO	2-MeOC$_6$H$_4$	NMe$_2$	90	115
19	C-3	Me	4-MeOC$_6$H$_4$CHO	4-MeOC$_6$H$_4$	NMe$_2$	63	115
20	C-3	Me	3,4-(OMe)$_2$C$_6$H$_3$CHO	3,4-(OMe)$_2$C$_6$H$_3$	NMe$_2$	78	115
21	C-3	Me	2-ClC$_6$H$_4$CHO	2-ClC$_6$H$_4$	NMe$_2$	65	115
22	C-3	Me	2-thienyl-CHO	2-thienyl	NMe$_2$	55	115
23	C-3	Me	2-pyridyl-CHO	2-pyridyl	NMe$_2$	60	115

[a] Unless otherwise indicated, LDA/THF/−78 °C conditions were used. [b] *sec*-BuLi/THF/−100 °C conditions were used. [c] Rearranged product I (R = Et (19%), R = Ph (24%)) was also isolated. [d] The 3-OH quinoline derivative. [e] Corresponding decarboxylated material was also obtained in variable yields. [f] In situ LDA/TMSCl/−78 °C conditions. [g] Obtained in a 1:1:1 ratio.



I

SCHEME 13

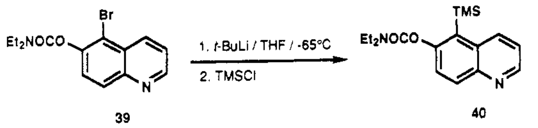


hydrolysis (especially for the 2- and 4-carbamates),[108] and latent DMG potential (**36** → **37** → **38**, Scheme 13) constitute properties of the pyridyl carbamates that make them attractive for diverse synthetic use.

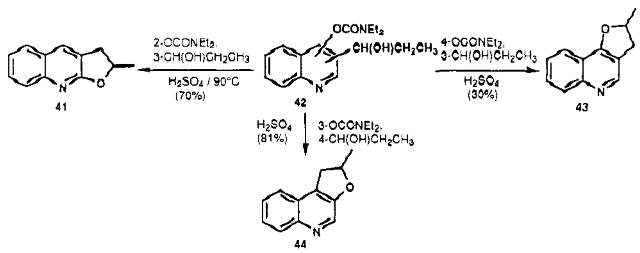
Comprehensive methoxypyridine and -quinoline DoM reactions[42,109,110] complement the carbamate results, although both DMGs have seen limited synthetic applications.[29h,i]

The DoM chemistry of isomeric *O*-quinolyl *N*,*N*-dimethyl- and *N*,*N*-diethylcarbamates has been less diversely explored (Table 15). As may be expected from the known compatibility of LDA and TMSCl,[42,50] silylation is, with two exceptions (entries 14 and 16), cleanly achieved (entries 5, 12, 13, and 15). In one of the exceptions (entry 14), formation of mixtures may be avoided via a metal–halogen exchange process, **39** → **40** (Scheme 14), at the cost of requiring the bromoquinoline precursor.[111] Hydroxyalkylation with aromatic and aliphatic aldehydes proceeds only in moderate yields and leads to some unusual products (Table 15, entries 3, 4, 8, 9, and 17–23). Some of these products **42** (Scheme 15) (entries 1, 7, and 11) have been converted into isomeric dihydrofuroquinolines **41**, **43**, and **44**.[112]

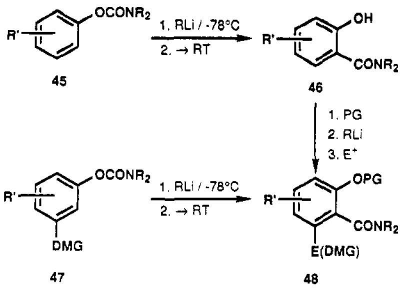
SCHEME 14



SCHEME 15



SCHEME 16



Carbamate metalation has not been as yet pursued in other heteroatomic systems, although an initial report of successful *O*-furyl phosphonate metalation may point the way.[113]

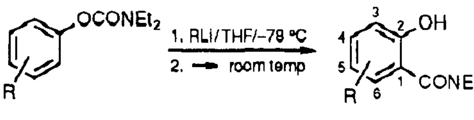
F. Carbamate Manipulation

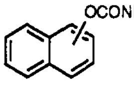
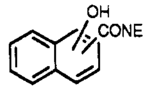
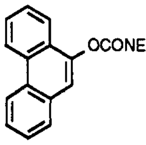
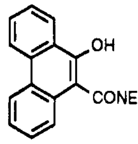
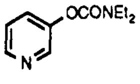
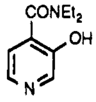
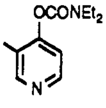
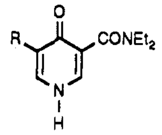
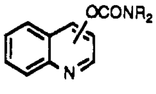
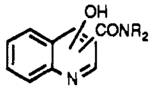
Hydrolysis of tertiary *O*-aryl carbamates to phenols normally requires vigorous basic conditions;[114] in the absence of other similarly sensitive sites, $LiAlH_4$ reduction followed by mild acid workup may be used. Similar to tertiary amides, ortho-hydroxyalkylated, -formylated, or -carboxylated carbamates suffer faster hydrolysis via anchimeric-assisted mechanisms. In the quinoline carbamate series, intermediates of such reactions have been isolated.[112,115,116]

V. The Amide–Carbamate Connection

A. Anionic Rearrangements

TABLE 16. *o*-Hydroxy Aromatic and Heteroaromatic Amides by Anionic Ortho-Fries Rearrangement[a]

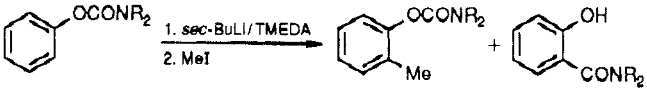


	R			
entry	reactant	product	yield, %	ref
1	H	H	75	114
2	4-Me	5-Me	70	48
3	2-Me	3-Me	70	114
4	3-Me	4-Me	48	117a
5	2-CO_2H	3-CO_2H	37[b]	118
6	2-CO_2H, 4-Cl	3-CO_2H, 5-Cl	60[b]	118
7	2-$CONEt_2$	3-$CONEt_2$	30 (59)[b]	117a
8	2-$CONEt_2$, 3-OH	3-$CONEt_2$, 4-OH	75	117a
9	2-$CONEt_2$, 4-Cl	3-$CONEt_2$, 5-Cl	42[b]	118
10	2-OMe	3-OMe	68	114
11	3-OMe	4-OMe 6-OMe	18 48	114
12	4-OMe	5-OMe	60	114
13	2,3-OCH_2O	3,4-OCH_2O	58	119
14	3-$OCONEt_2$	6-$OCONEt_2$	86	117a
15	4-$OCONEt_2$	4-$CONEt_2$, 5-OH	25[c]	118
16	2-Cl	3-Cl	72	117a
17	3-Cl	6-Cl	71	129
18	4-Cl	5-Cl	65	114
				
19	1-$OCONEt_2$	1-OH, 2-$CONEt_2$	71	117a
20	2-$OCONEt_2$	2-OH, 3-$CONEt_2$	48	117a
21			81[d]	200
22			40	108
				
23	R = H	R = H	74	108
24	R = Me	R = Me	80	108
25	R = TMS	R = TMS	60	108
				
26	2-$OCONR_2$ (R = Me, Et)	2-OH, 3-$CONR_2$ (R = Me, Et)	60[e,f]	111
27	4-$OCONMe_2$	4-OH, 3-$CONMe_2$	80[f]	116
28	5-$OCONMe_2$	5-OH, 6-$CONMe_2$		111
29	6-$OCONMe_2$	6-OH, 7-$CONMe_2$	80[e]	111
30	7-$OCONMe_2$	7-OH, 8-$CONMe_2$	60[e]	111
31	8-$OCONMe_2$	8-OH, 7-$CONMe_2$	40[e]	111

[a] Conditions: *sec*-BuLi/TMEDA/THF/−78 °C → room temperature (8–12 h) unless otherwise indicated. [b] Isolated as its methyl ether. [c] Isolated as its dimethyl ether. [d] Conditions: *t*-BuLi/THF/−78 °C → room temperature. [e] Conditions: LDA/THF/−78 °C → room temperature or −40 °C. [f] Quinolone tautomer.

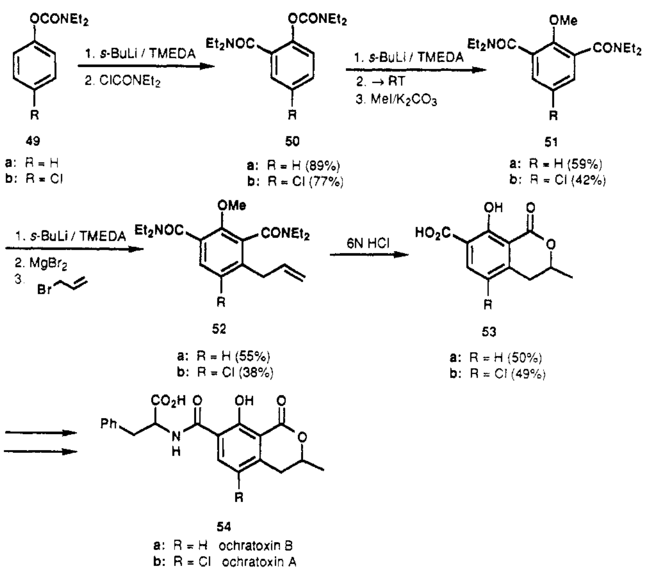
Methods for the regiospecific preparation of polysubstituted aromatics are considerably enhanced by the availability of the carbamate into salicylamide rearrangement, **45** → **46** (Scheme 16, Table 16).[114] In this anionic equivalent of the ortho-Fries rearrangement, the carbamate **45** serves as a "carrier" of the amide into an ortho site **46** from which, after suitable phenol protection, it may oblige further DoM chemistry **48**. In between metalation of 1,3-related DMG substrates **47** leading to 1,2,3-trisubstituted aromatics **48** and strategies for combinational use of amide–carbamate MGs are therefore conceptually possible. The 2-methyl carbamate migrates cleanly into the ortho site (Table 16, entry 3), while the corresponding 3-methyl derivative yields the 4-methyl product (entry 4) presumably as a consequence of a steric effect. The meta-cooperative metalation effect is demonstrated cleanly by carbamate (entry 14) and chloro (entry 17) DMGs; surprisingly, the corresponding methoxy system shows poorer regioselectivity (entry 11). An illustration of a double 1,3-carbamoyl rearrangement to a hydroquinone diamide has been recorded (entry 15). The anionic ortho-Fries rearrangement has also been observed in the naphthyl (entries 19 and 20), phenanthryl (entry 21), pyridyl (entries 22–25), and quinolinyl (entries 26–31) carbamate series. The rate of the anionic ortho-Fries rearrangement is highly sensitive to N-substitution and temperature (Table 17) and has been shown by cross-

TABLE 17. Anionic Ortho-Fries Rearrangement of o-Aryl Carbamates as a Function of N-Substituent[117a]

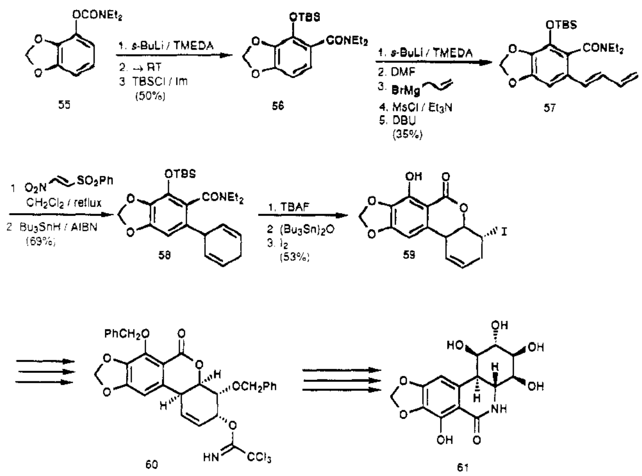


R	temp, °C	time(metalation), min	product ratio	yield, %
Et	-78	10-60	100:0	70
Me	-78	45	0:100	75
Me	-78	10	67:33	80
Me	-95	10	100:0	90

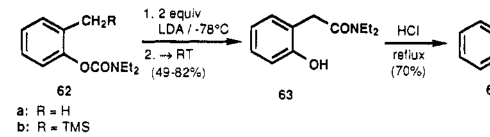
SCHEME 17



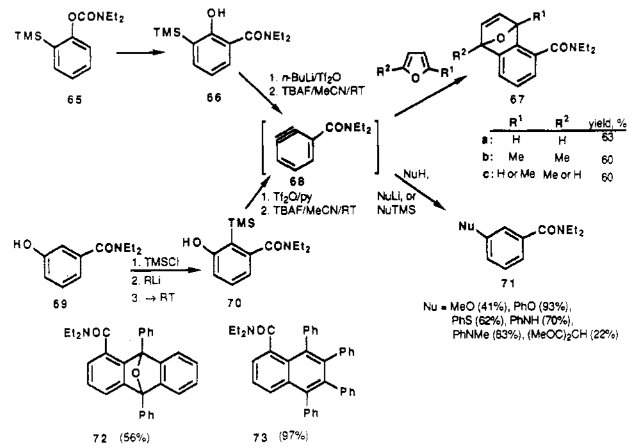
SCHEME 18



SCHEME 19



SCHEME 20



over experiments to proceed by an intramolecular mechanism.[117a]

Combinational use of amide and carbamate DoM chemistry is illustrated by the synthesis of ochratoxins A and B, toxic metabolites isolated from strains of *Aspergillus ochraceus* and *Penicillium viridicatum* (Scheme 17).[118] Metalation and carbamoylation of **49a** and **49b** led smoothly to compounds **50a** and **50b**, respectively, which, upon anionic rearrangement and methylation of the intermediate phenols, gave the isophthalamides **51a** and **51b**. The allyl group was introduced by the metalation–transmetalation sequence to afford **52a** and **52b**, which were directly treated with HCl to effect lactonization, amide hydrolysis, and demethylation in one pot to give the isocoumarincarboxylic acids **53a** and **53b** in 6–14% overall yields. These known compounds had been previously transformed into ochratoxin B (**54a**) and ochratoxin A (**54b**), respectively. An alternate route to **53b** by direct carboxylation of **49b** was accomplished in low overall yield owing to an inefficient allylation step corresponding to **51b** → **52b**.

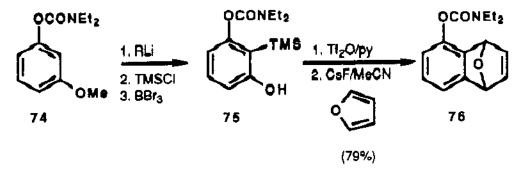
Amide–carbamate DoM reactions have also been exploited in the synthesis of pancratistatin (**61**) (Scheme 18), a phenanthridone alkaloid from *Pancratium littorale* showing promising antitumor activity.[119] Anionic ortho-Fries rearrangement on **55** followed by silylation afforded benzamide **56**, which was metalated, formylated, and subjected to chain extension and dehydration to give the arylbutadiene **57**. Cycloaddition with an acetylenic dienophile equivalent and tin hydride induced elimination afforded the cyclohexadiene **58**. Following desilylation, halolactonization to **59** was achieved by an innovative process that takes advantage of amide stannylation to effectively increase its nucleophilicity. Extensive oxygenated ring manipulation which includes a suprafacial allylic O → N transposition of **60** and terminal lactone to lactam rearrangement gave rise to pancratistatin (**61**).

In contrast to the kinetic result (Table 16, entry 3), LDA deprotonation of the o-tolyl carbamate **62a** (Scheme 19) leads to o-hydroxyphenylacetamide **63** (49%);[117a] the yields of **63** are improved by using silylated starting carbamate **63b**.[117b] The demonstrated conversion of **63** into **64** in good yields suggests that this methodology may have general synthetic utility for difficult to access benzofuran-2-ones.

B. Benzyne Generation

The discovery by Kobayashi[120] that o-TMS aryl triflates serve as benzyne precursors led to the development of two routes for the generation of the synthetically useful benzamide benzyne intermediate **68** (Scheme 20).[121] Precursor isomeric TMS phenols **66** and **70** were secured by anion-induced ortho-Fries **65** → **66** or O → C silicon **69** → **70** rearrangements, re-

SCHEME 21



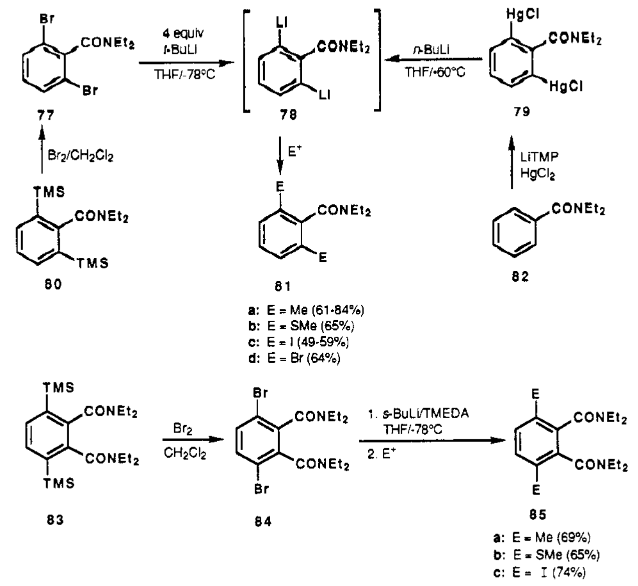
spectively. The latter reaction, proceeding via intra- or intermolecular paths, depending on the position of the silyloxy substituent, has modest, as yet incompletely explored, scope for the preparation of *o*-silylbenzamides (Table 6, entries 37–40).[122] The triflates of **66** and **70**, obtained by standard procedures, upon treatment with TBAF in the presence of an excess of appropriate dienes afford products **67a–c**, **72**, and **73** in good yields. In the solitary pertinent case studied (**67c**), the reaction shows no regioselectivity. Using the same benzyne-generating conditions but in the presence of excess of nucleophiles in protio, lithio, and TMS precursor forms allows rapid access to a variety of meta-functionalized benzamides **71**. As observed by Kobayashi,[120] the success of this reaction with protio nucleophiles such as MeOH is consistent with a mechanism that involves either rapid loss of OTf from a desilylated precursor or concerted formation of the benzyne. These reactions, which are under further exploration,[123,124] parallel and complement observations by Meyers and co-workers on benzyne species derived from (*m*-chlorophenyl)oxazolines under strongly basic RLi metalation conditions.[125] Aside from participating in cycloaddition similar to that observed for **68**, the oxazoline benzynes have been shown to react in situ with organolithiums and cuprates at either C-2 or C-3 dictated by kinetic or thermodynamic control conditions. The resulting anions may be treated with electrophiles, thus providing an innovative tandem route to 1,2,3-trisubstituted benzenes.

Similarly, carbamate benzynes may be generated from analogous precursors (Scheme 21).[123,124] Thus conversion of **74** into the ortho-silylated phenol **75** followed by triflation and fluoride-induced benzyne formation in the presence of furan affords cycloadduct **76** in good yields.

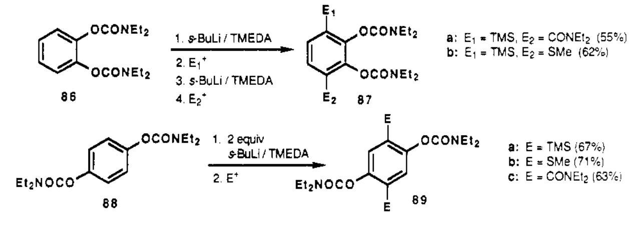
VI. 2,6-Dianion Equivalents

The successful generation of a dimetalated or higher order metalated aromatic species promoted by one or more DMGs will be dependent upon electrostatic repulsion, additional complexity in aggregation, and solubility, among other factors. Utility in synthesis has only recently been explored.[34,126] In the context of the tertiary amide DMG, the formal dilithiated species **78** (Scheme 22) cannot be generated directly by double DoM reaction, but may be obtained by metal–halogen exchange from the 2,6-dibromobenzamide **77**[127] or by reverse transmetalation from the dimercurial **79**.[128] Compound **77** is available by double ipso bromodesilylation of **80**, which, in turn, is readily accessible by one-pot sequential bissilylation of *N*,*N*-diethylbenzamide; **79** is obtained from the bare benzamide **82** under in situ trap thermodynamic conditions using the compatible LiTMP/$HgCl_2$ base–electrophile combination. Electrophile quench of **78** leads to satisfactory yields of otherwise poorly accessible 2,6-disubstituted benzamides **81a**,[127,128] **81b**,[127] **81c**,[127,128] and **81d**.[128] High d_2 incorporation (95%)[127] and clean disubstitution by electrophiles (e.g., MeI) that would expose highly acidic sites in potential monosubstituted intermediates strongly suggest that the dilithiated species **78** is generated in these reactions.

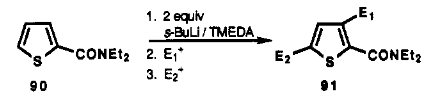
SCHEME 22



SCHEME 23



SCHEME 24

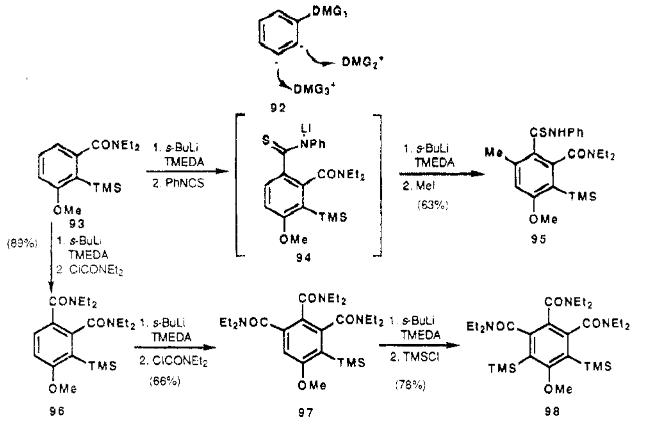


The generation of dianion equivalent synthons may be extended to phthalamides. Thus the dianion from dibromophthalamide **84**, obtained analogously by bromodesilylation of **83**, has been shown to react with similar electrophiles to give 3,6-disubstituted products **85a–c**.[127] The generation of the corresponding dianions of isophthalamides and terephthalamides was impeded at the dibromo and bis-TMS precursor stages, respectively.[127]

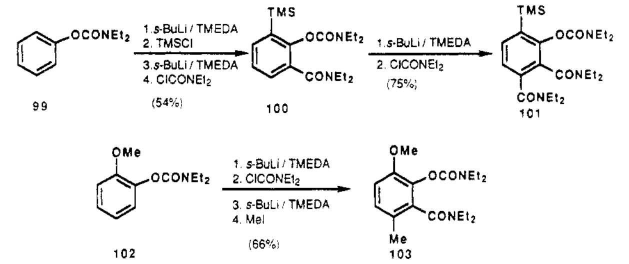
In contrast to the phthalamide **84**, the catechol and hydroquinone dicarbamates **86** and **88** (Scheme 23) undergo direct dilithiation under the standard *sec*-BuLi/TMEDA conditions and lead, after electrophile treatment, to products **87a,b**[129] and **89a–c**,[127] respectively. The evident potential for sequential introduction of two different electrophiles (**87a,b**) may have application in these and related systems for the synthesis of unsymmetrically substituted benzoquinones.

In the solitary study of a dimetalated DMG heteroaromatic system, the thiophene-2-carboxamide **90** (Scheme 24) has been shown to serve as a 3,5-dianion equivalent and to produce, following the expected carbanion reactivity order, a variety of thiophenes with

SCHEME 25



SCHEME 26



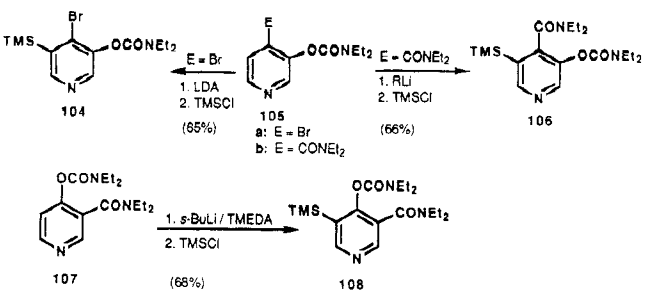
the same or different 3,5-substituents in modest yields (Table 9, entries 6–16).[94]

VII. Iterative DoM Reactions

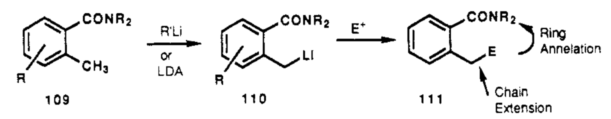
Iterative DoM processes, as yet little exploited, are potentially valuable for rapid access to diverse polysubstituted aromatics. The concept (**92**, Scheme 25) involves sequential introduction of electrophiles that serve as DMGs for subsequent metalation in an overall "walk-around-the-ring" regimen. The relative hierarchy of the introduced DMG_2 and the original DMG_1 dictates the position of the incomimg DMG_3 and is a repetitive consideration. Illustrative of possibilities are the conversions of **93** and **96** into the polysubstituted systems **95** and **98**, respectively.[130] Metalation of **93** followed by phenyl isothiocyanate quench gave the lithiated thioamide **94**, which, without isolation, was metalated and treated with methyl iodide to give **95** in good overall yield. Alternatively, a sequence of metalations on **93**, involving two carbamoyl chloride and one trimethylsilyl chloride electrophile quenches, led, via isolated intermediates **96** and **97**, to the hexasubstituted aromatic **98**, a highly crowded molecule with a nonplanar benzene ring as established by X-ray crystallographic analysis.[130]

Similarly, broader synthetic potential of iterative metalations initiated by the carbamate DMG is suggested by the conversion of **99** and **102** into the tetrasubstituted systems **101** and **103**, respectively (Scheme 26).[117a] Thus a one-pot sequence of metalation, silylation, metalation, and carbamoylation gave the trisubstituted derivative **100**, which was isolated and subjected to a second metalation-carbamoylation treatment to give the tetrasubstituted derivative **101**. A similar one-pot sequence on the *o*-methoxy carbamate **102** gave a different contiguously substituted aromatic **103**.

SCHEME 27



SCHEME 28



Iterative metalation processes have also been demonstrated for *O*-pyridyl carbamates (Scheme 27).[108] Thus the 4-bromo derivative **105a** (Table 14, entry 8), when subjected to known conditions for metalation of the bromopyridine prototype,[131,132] afforded the 3,4,5-trisubstituted pyridine **104**. In a parallel series of reactions, the intermediate isonicotinamide **105b** (Table 14, entry 7) furnished a different trisubstituted derivative **106**. On the other hand, the nicotinamide **107** (Table 14, entry 12) led to yet another variation of pyridine trisubstitution (**108**). The final products in all three cases indicate that the last metalation occurs at C-5 irrespective of the DMG. Complementary 2-metalation of unsubstituted 3-methoxypyridine has been achieved by using mesityllithium.[109]

VIII. Synthetic Consequences of o-Carbon Electrophile Introduction

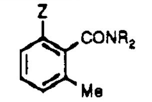
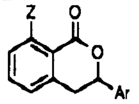
Products derived from regiospecific DoM reactions may be further manipulated by standard functional group interconversions into a variety of useful polysubstituted aromatics. Of equal synthetic value is the potential, as yet in the early stages of exploration, to parlay DoM processes, via the initially introduced electrophile, into chain extension, carbo- or heteroring annelation, and other carbon–carbon bond-forming protocols. These synthetic consequences are discussed according to the nature of the initially introduced electrophile.

With the exception of the areas of cross-coupling chemistry (section IX.E) and anionic rearrangement (section V), few results are available for the $OCONEt_2$ DMG and, as the discussion will make evident, the majority of synthetic applications is the exclusive domain of the $CONR_2$ DMG.

A. *o*-Methyl

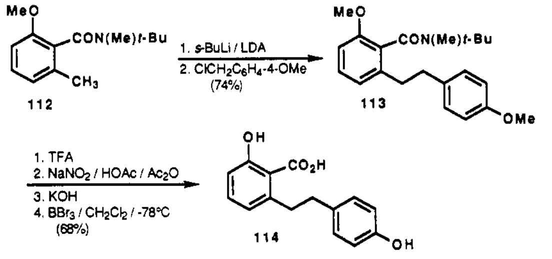
The simple expedient of methylation of an ortho-lithiated benzamide to give **109** (Scheme 28) provides a handle for further electrophilic functionalization via the easily generated (usually burgundy red) *o*-tolyl anion **110**, thus offering avenues for chain extension and ring annelation strategies **111**. For annelations, introduced olefinic, imine, nitrile, carboxy, and hydroxyalkyl functionalities serve as electrophilic or nucleophilic sites

TABLE 18. Synthesis of 3-Aryl-3,4-dihydroisocoumarins

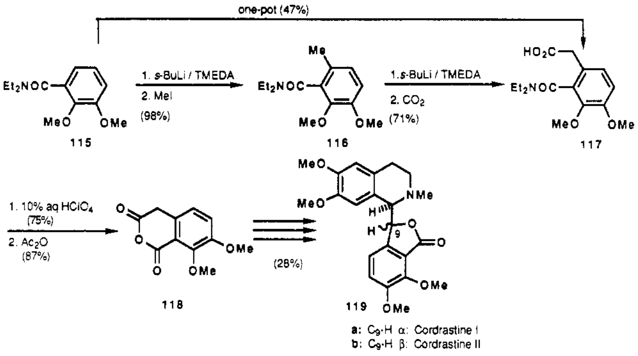
						
R	Z	ArCHO	Z	Ar	yield, %	ref
Et	H	PhCHO	H	Ph	30 (62)[a]	100, 101
Et	H	$2\text{-MeOC}_6\text{H}_4\text{CHO}$	H	$2\text{-MeOC}_6\text{H}_4$	45	100
Et	H	$3\text{-MeOC}_6\text{H}_4\text{CHO}$	H	$3\text{-MeOC}_6\text{H}_4$	40	100
Et	H	$4\text{-MeOC}_6\text{H}_4\text{CHO}$	H	$4\text{-MeOC}_6\text{H}_4$	65	100
Et	H	$3\text{-PhCH}_2\text{O}, 4\text{-MeOC}_6\text{H}_3\text{CHO}$	H	$3\text{-PhCH}_2\text{O}, 4\text{-MeOC}_6\text{H}_3$	32	100
Et	H	furan-2-carbaldehyde	H	2-furyl	30	100
Et	H	thiophene-2-carbaldehyde	H	2-thienyl	30	100
Me	OMe	$4\text{-MeOC}_6\text{H}_4\text{CHO}$	OMe	$4\text{-MeOC}_6\text{H}_4$	35 (46)[b]	100
Me	OMe	$3\text{-PhCH}_2\text{O}, 4\text{-MeOC}_6\text{H}_3\text{CHO}$	OMe	$3\text{-PhCH}_2\text{O}, 4\text{-MeOC}_6\text{H}_3$	32 (21)[b]	100

[a] Using starting benzamide, R = Me, $\text{N(Me)CH}_2\text{CH}_2\text{NMe}_2$, Z = H. [b] By a one-pot procedure from *N,N*-dimethyl-2-methoxybenzamide.

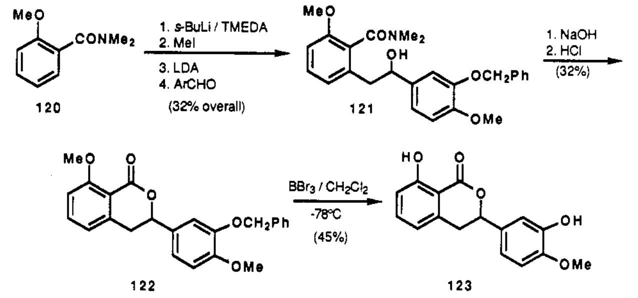
SCHEME 29



SCHEME 30



SCHEME 31



for cyclization by amide participation. This partly confers a chameleon character to the CONR_2 in that it originally withstands attack by potent RLi reagents. Complementary routes are available from *o*-tolyl secondary amides,[29h,i] oxazolines,[29g] α-amino alkoxides,[84] and esters,[133] although the last species, while widely used, clearly cannot be derived via initial DoM chemistry. As documented below, a large body of literature attests to the synthetic value of the *o*-tolyl tertiary amide anion **110**.

1. Chain Extension

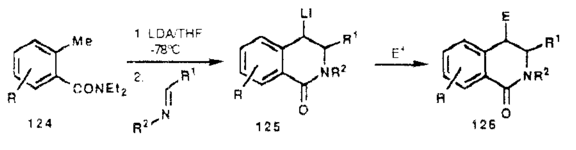
With the exception of ethylation (Table 6, entry 12), introduction of long chains into ortho-lithiated *N,N*-diethylbenzamides has not been reported, perhaps due to intervention of elimination reactions. The less basic *o*-tolyl anion is recommended for such processes as illustrated by the short synthesis of lunularic acid **112** → **113** → **114** (Scheme 29) using the more easily hydrolyzed CON(Me)-*t*-Bu DMG.[102]

2. Heteroannelation via o-Tolyl Anions

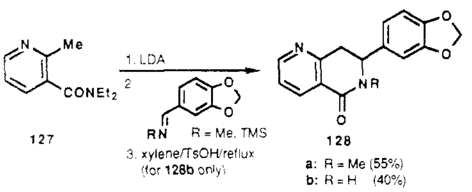
The carboxylation of the *o*-tolyl anion of **116** (Scheme 30), obtained from the benzamide **115**, leads to the homophthalic acid amide **117**.[134] This overall two-carbon chain extension, not achievable directly by treatment of **116** with ethyl α-bromoacetate, can also be carried out in a one-pot procedure and provides convenient access to the homophthalic anhydride **118**, previously available by a classical route in nine steps and low overall yield. The heteroring annelation product **118** served as one component for a convergent and abbreviated synthesis of the phthalide isoquinoline alkaloids cordrastine I (**119a**) and cordrastine II (**119b**), which also embodied a key bromohomophthalic anhydride–phthalide α-carboxamide rearrangement. 5-Methoxyhomophthalic anhydride has been similarly prepared for use in a naphthoquinone ring construct (Scheme 36).

An alternate annelation method leading to the same ring system at a different oxidation state **123** (Scheme 31) may be achieved via amide alcohol intermediate **121**.[100,101] A typical sequence[100] of some generality (Table 18) begins with a rare case of an *N,N*-dimethylbenzamide **120** metalation followed by methylation, a second metalation, and treatment with *O*-benzylisovanillin in a one-pot process to give amide alcohol **121** in modest overall yield. Compound **121** is also available by condensation of the intermediate *o*-toluamide with the appropriate benzoate ester followed by sodium borohydride reduction. Base-induced cyclization to **122** followed by deprotection affords phyllodulcin (**123**), a natural product with a sweetness index 400 times that of sucrose. Base hydrolysis of the tertiary amides was necessitated by the derailment of the synthesis to a stilbene derivative under the standard TsOH-catalyzed conditions. This problem appears to be circumvented by the use of the TMEDA-like DMG (Table 18).[101] A single case of condensation of lithiated

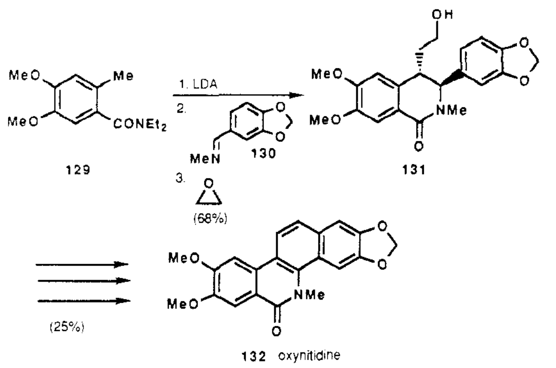
SCHEME 32



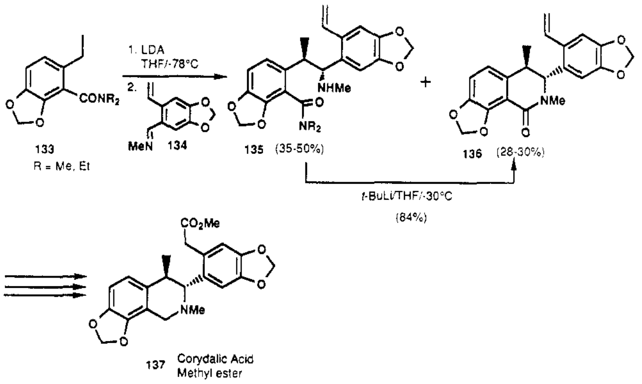
SCHEME 33



SCHEME 34



SCHEME 35



N,*N*-dimethyl-2-methoxy-6-methylbenzamide with an aliphatic aldehyde has been recorded.[135]

N-Heteroring annelation using imine electrophilic partners has been demonstrated and applied to alkaloid synthesis by Clark and Jahangir (Schemes 32–35, Tables 19 and 20).[136,137] In this rapid heteroring construct related to several other methods of isoquinoline synthesis,[138] *o*-toluamides **124** (Scheme 32) are condensed with a variety of aromatic and aliphatic imines to give satisfactory yields of 3-substituted isoquinolones **126** (E = H) via the 4-lithiated species **125**. Among the derivatives available by this procedure are functionalized amine (Table 19, entries 7 and 8), spiro (entry 16), and fused (entries 17 and 18) systems. In contrast to the acid-mediated synthesis of isocoumarins (Table 18), this route involves amide participation as an electrophilic site in what appears to be a stepwise process. As a consequence of the generation of the 4-lithiated species **125** (formed by proton exchange with the in situ generated $LiNEt_2$), quench with electrophiles other than a proton source leads to 3,4-disubstituted products **126** (E = alkyl), thereby adding a valuable feature to this heteroannelation method. The scope of this stereospecific tandem reaction has been explored (Table 20) and extended to heterocyclic analogues (**127** → **128**, Scheme 33).[137] Instructive applications of this methodology for the construction of protoberberines (Table 19, entries 17 and 18), a benzophenanthridine alkaloid (**129** + **130** → **131** → **132**, Scheme 34),[136a] and a proposed common biosynthetic intermediate (**133** + **134** → **135** + **136** → **137**, Scheme 35)[136b] for these two classes of natural products have been demonstrated. In the last case, the inability to obtain **136** by the tandem sequence, presumably owing to decreased acidity of the C-4 hydrogens, necessitated the use of the 2-ethyl starting material **133**.

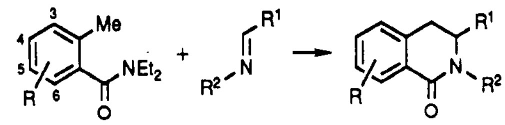
Condensation of *o*-tolyl amide anions **139** (Scheme 36)[139] with homophthalic anhydride **138** leads to adducts **140** in a reaction that embodies overtones of polyketide biogenesis.[15b] Since both reacting partners may be prepared by DoM, the overall process has considerable scope. Sequential Claisen–aldol condensation, base-catalyzed aerial oxidation, and amide hydrolysis on **140** afford the hydroxynaphthoquinones **141** in good overall yields. The pendant quinone hydroxy group presumably assists the hydrolysis step under these relatively mild conditions.[134] These compounds were converted into pyranonaphthoquinones, one of which (**142**) was shown to be identical with the antibiotic WS-5995A isolated from *Streptomyces auranticolor*. This convergent synthesis illustrates the use of the *o*-tolyl amide anion as a lynchpin for the C/D rings of compounds **142** and the amide as a terminal electrophile for heteroannelation.

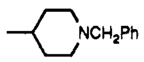
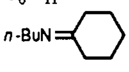
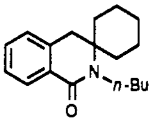
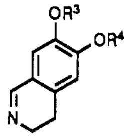
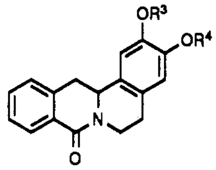
N-Heteroring annelation to the α-lithiated *o*-toluamide synthon may be achieved by use of nitrile electrophiles as demonstrated in the instructive synthesis of the potent antitumor antibiotic fredericamycin A (**148**) (Scheme 37).[140] Thus starting with simple indan **143** or dihydroisocoumarin **146** precursors, intermediates **144** were prepared, which, upon LiTMP-induced condensation with diethoxyacetonitrile, produced **145** in good yield on a multigram scale. Conversion into the silyl anion **147** followed by coupling with an appropriate naphthalene anhydride set the stage for the successful completion of the total synthesis of fredericamycin A (**148**). The heteroannelation tactic has also been used for the construction of the isoquinolone **151**, initiated by a comprehensive DoM approach on **149** and involving the intermediate **150**, with the same target molecule as a goal.[141]

3. α-Silylated o-Toluamides

The α-silylated *o*-toluamides **153a,b** (Scheme 38) are formally *o*-tolylamide anion synthons through the expediency of fluoride ion. As demonstrated by several examples, TBAF-induced carbodesilylative hydroxylation on the α-silyl *o*-toluamides **153a**, available in high yield from precursors **152**, gives products **154a–d** in good yields.[130] Since this process is carried out under essentially neutral conditions, it complements the direct chain extension of the anion derived from **152** with benzaldehyde to give **154** and may be valuable for the preparation of substituted systems that cannot tolerate strongly basic conditions. α-Bromination of derivatives

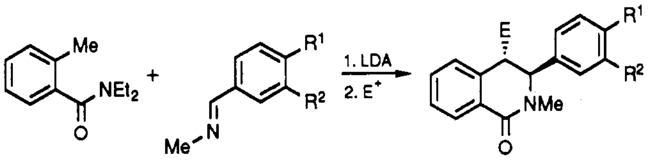
TABLE 19. Synthesis of 3-Substituted 3,4-Dihydro-1(2*H*)-isoquinolones



entry	R	R^1	R^2	yield, %	ref
1	H	Ph	CH_2Ph	55	137
2	H	Ph	TMS	*a*	137
3	H	$2\text{-}MeC_6H_4$	Me	56	137
4	H	$3\text{-}MeC_6H_4$	C_6H_{11}	42	137
5	H	$4\text{-}MeOC_6H_4$	*n*-Bu	42	137
6	H	$4\text{-}MeOC_6H_4$	C_6H_{11}	48	137
7	H	$4\text{-}MeOC_6H_4$	$CH_2CH_2NMe_2$	37	137
8	H	$4\text{-}MeOC_6H_4$	 NCH2Ph	24	137
9	H	$3,4\text{-}(MeO)_2C_6H_3$	Me	37	137
10	H	$3,4\text{-}OCH_2OC_6H_3$	Me	47	137
11	5,6-OCH_2O	$3,4\text{-}OCH_2OC_6H_3$	Me		136b
12	4,5-$(MeO)_2$	$3,4\text{-}OCH_2OC_6H_3$	Me	10[b]	136a
13	5,6-OCH_2O	$2\text{-vinyl-}4,5\text{-}OCH_2OC_6H_2$	Me	61	*b*
14	H	4-pyridyl	Me	30	137
15	H	C_6H_{11}	Me	44	137
16	H	 n-BuN	 N n-Bu O	44	137
		 OR3 OR4 N	 OR3 OR4 N O		
17	H	$R^3 = R^4 = Me$		43	137
18	H	$R^3 + R^4 = CH_2$		59	137

[a] Obtained after cyclization (TsOH/xylene/reflux) of initially isolated open-chain intermediate. [b] Byproduct from tandem reaction, **129** → **131** (Scheme 34).

TABLE 20. Synthesis of 3,4-Disubstituted 3,4-Dihydro-1(2*H*)-isoquinolones

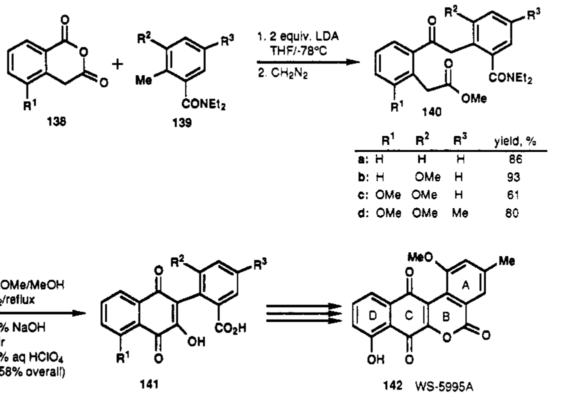


E^+	E	product R^1	product R^2	yield, %	ref
MeI	MeI	H	H	45	136b
MeI	Me	OCH_2O		62	137
n-BuI	*n*-Bu	OCH_2O		68[a]	137
$CH_2{=}CHCH_2Br$	$CH_2CH{=}CH_2$	OCH_2O		51	137
$PhCH_2Cl$	CH_2Ph	OCH_2O		59	137
$ClCH_2TMS$	CH_2TMS	OCH_2O		58	137
TMSCl	TMS	OCH_2O		32	137
$BrCH_2CH(OMe)_2$	$CH_2CH(OMe)_2$	OCH_2O		54	136a

[a] Using *n*-BuBr and *n*-BuCl gave yields of 53% and 59%, respectively.

153a is also possible (section VIII.C.2). Fluoride-mediated Peterson olefination may be effected on the equally accessible α,α-disilylated *o*-toluamide **153b** with an aromatic aldehyde leading to a stilbene derivative **157**. The reduced counterpart of the monosilylated amide **153a** is useful as an *o*-quinodimethane precursor **155** to the tetralin **156**.[130] α′,α′-Disilylated derivative **153b** undergoes further kinetic metalation at aromatic C-6 rather than methine site as evidenced by products of electrophile quench (Table 21).[130] Fluoride-induced desilylation to contiguously substituted aromatics with diverse functionality concludes this methodology, which has been applied (Table 29, entries 3 and 4; Scheme 62) and deserves further attention.

SCHEME 36

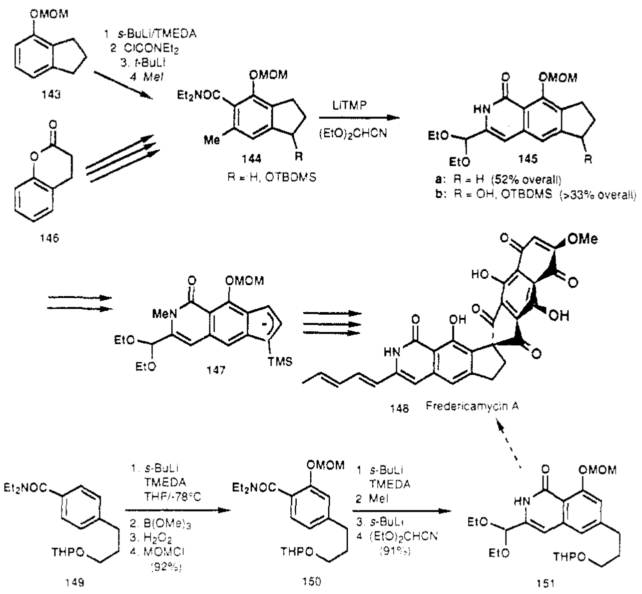


	R^1	R^2	R^3	yield, %
a:	H	H	H	86
b:	H	OMe	H	93
c:	OMe	OMe	H	61
d:	OMe	OMe	Me	80

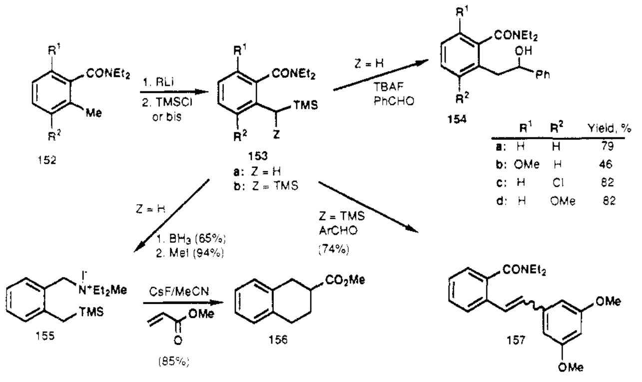
B. *o*-Allyl

N,*N*-Diethyl-*o*-allylbenzamides may assume either cationic **158** (Scheme 39) or anionic **159** annelation modes. In the former, the amide is internally hydrolyzed by anchimeric assistance from the developing carbocation; in the latter, it reveals its chameleon electrophilic character which is not granted to RLi reagents.

SCHEME 37

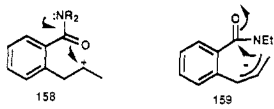


SCHEME 38



	R¹	R²	Yield, %
a:	H	H	79
b:	OMe	H	46
c:	H	Cl	82
d:	H	OMe	82

SCHEME 39



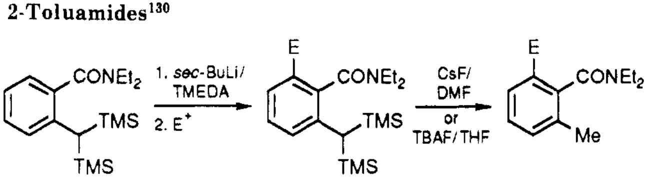
1. Isocoumarins

o-Allylbenzamides **161** (Scheme 40), readily prepared from the parent **160** by the ortho metalation–transmetalation technique, are converted into substituted isocoumarins **162** under acid-catalyzed conditions.[142] The vigorous conditions of this reaction lead, in part, to demethylation but this result has, at times, advantage in that two natural products, mellein (**162b**) and kigelin (**162e**), are directly formed. The synthesis of ochratoxin (Scheme 17) demonstrates the application of this cyclization to a more complex system. Secondary toluamides[29h,i] and o-tolyl oxazolines[29g] have been adapted for similar ring construction.

2. 1-Naphthols

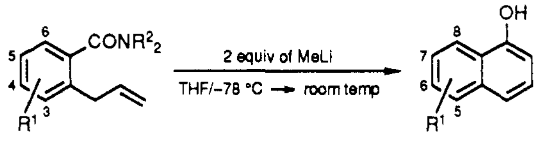
In contrast to the nature of the above isocoumarin ring closure, the electrophilic character of the tertiary amide in o-allylbenzamides is manifested in a methyllithium-induced regiospecific construction of 1-naphthol derivatives (Table 22).[143] Although not thoroughly evaluated in scope and mechanistically ambiguous,[143] this anionic carboannelation reaction provides rapid and regiospecific assemblage of several significant oxygenated naphthols. The operation of a steric factor is evident from comparison of yields of products from diethyl- and dimethylamides (entries 4 and 5), although it appears not to have a detrimental effect for a number of oxygenated cases. The o-crotyl derivative **164a** (dotted bond) (Scheme 41), prepared by Ni-catalyzed cross coupling, allows access to 2-methyl-1-naphthol **163** while the (trimethylsilyl)allyl counterpart **164b**, obtained by metalation–silylation of the parent system, affords 1-(diethylamino)naphthalene (**165**), a product of an intramolecular amide Peterson olefination. A useful, potentially general, adjunct to this method is the regiospecific preparation of oxygenated naphthoquinones as illustrated by the conversion of **167** (Scheme 42) into both **166** and **168** (juglone acetate) in unoptimized yields.

TABLE 21. Silicon Protection Route to 6-Substituted 2-Toluamides[130]



E	yield, %	E	yield, %
D	94	SMe	96
Me	81	TMS	83
CHO	78		

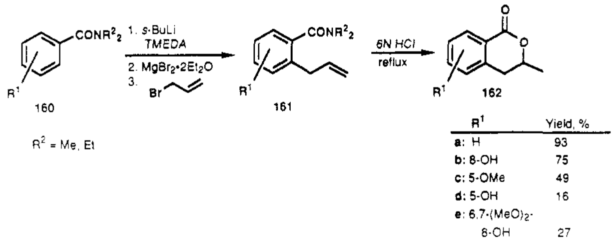
TABLE 22. Synthesis of 1-Naphthols[143]



entry	reactant R¹	reactant R²	product R¹	yield,[a] %
1	H	Et	H	86 (65)
2	3-OMe	Et	5-OMe	90 (58)
3	4-OMe	Et	6-OMe	64
4	6-OMe	Et	8-OMe	35 (16)
5	6-OMe	Me	8-OMe	81
6	3,6-$(OMe)_2$	Et	5,8-$(OMe)_2$	77 (37)
7	4,6-$(OMe)_2$	Et	6,8-$(OMe)_2$	62

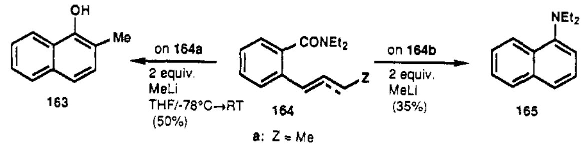
[a] Yields in parentheses are for reactions using 2.2 equiv of LDA.

SCHEME 40

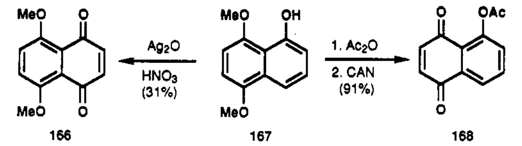


R¹	Yield, %
a: H	93
b: 8-OH	75
c: 5-OMe	49
d: 5-OH	16
e: 6,7-$(MeO)_2$-8-OH	27

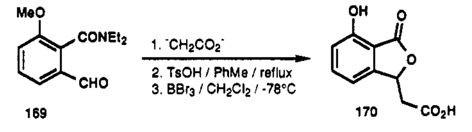
SCHEME 41



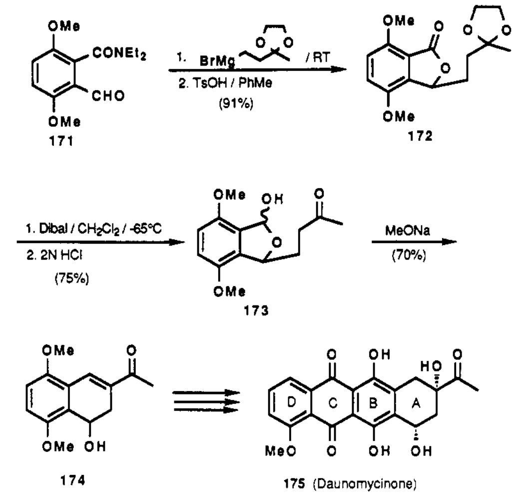
SCHEME 42



SCHEME 43



SCHEME 44



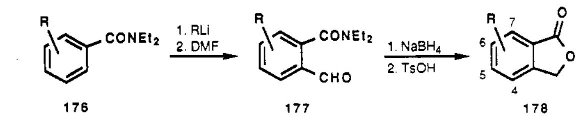
C. *o*-Formyl

The *N*,*N*-diethyl-*o*-formylbenzamide synthon, readily available in a variety of substitution patterns (Table 6), may, in principle, partake in the large body of fundamental carbonyl chemistry. The expedient of anchimerically assisted hydrolysis to 3-hydroxyphthalide derivatives has dominated the utility of *o*-formylbenzamides in synthesis (section VIII.C.2); however, chain extension by an acetic acid dianion **169** → **170** (Scheme 43)[144] is a simple illustration of further synthetic potential. Compound **170** represents isoochracinic acid, a rare phthalide natural product isolated from the parasitic fungus *Alternaria kikuchiana* which is responsible for black spot disease on Japanese pears. Similarly, chain elongation via Grignard reagents (Schemes 18, 44) has been exploited. The efficient construction of the A/B ring synthon **174** (Scheme 44)[145] of the antitumor antibiotic daunomycinone (**175**) was initiated by the incorporation of a four-carbon Grignard into the *o*-formylbenzamide **171**. The phthalide **172**, resulting from subsequent acid-catalyzed cyclization, was partially reduced and carefully hydrolyzed to give the hemiacetal **173**, which upon intramolecular aldol condensation furnished **174** in 38% overall yield.

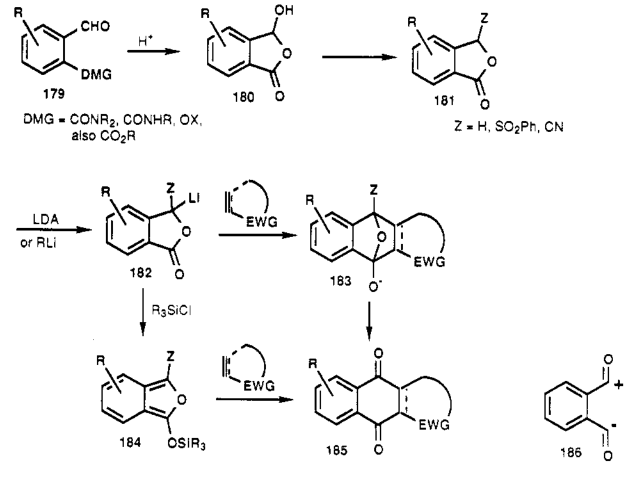
1. Phthalides by Reduction

As a consequence of the inconvenience and poor reproducibility of tertiary benzamide DoM reactions with various sources of formaldehyde, the preparation of C-3-unsubstituted phthalides has been pursued by the three-step process **176** → **177** → **178** (Scheme 45, Table 26, entries 1–4).[146] Analogous sequences have been effected via DoM chemistry of secondary amides[29h,i] and oxazolines.[29g,147] This general and invariably high-yield protocol is particularly valuable for the preparation of oxygenated phthalides, useful synthons for natural products, which have been previously available only by tedious and inefficient routes.[148]

SCHEME 45



SCHEME 46

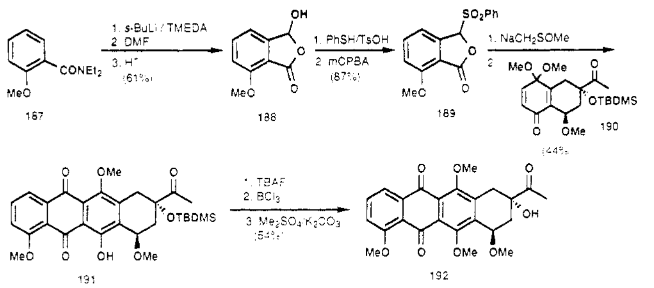


2. 3-Hydroxyphthalides and Isobenzofurans

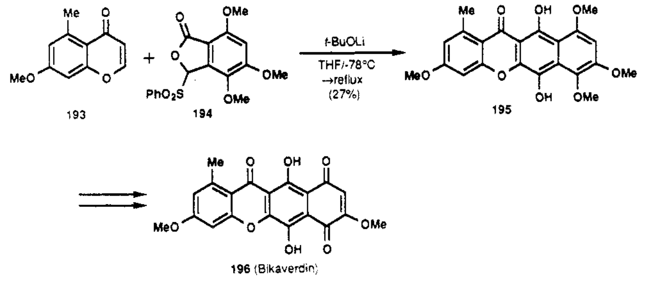
The easily achieved, acid-driven cyclization of *o*-formyl DMG aromatics **179** (Scheme 46) to 3-hydroxyphthalide **180** has served as the basis for the development of several new important annelation methods. The hydroxyphthalides are usually converted into carbanion-activating derivatives **181** which proceed by metalation (**182**) and condensation (**183**) with Michael acceptors to give quinones **185**. In this sequence, the 3-hydroxyphthalide synthon **180**, easily available in a variety of substitution patterns (Table 26, entries 46–54), acts as a 1,4-dipole equivalent **186**.[149] The assumed two-step anionic process in the conversion **182** → **183** is synthetically equivalent to a $(4 + 2)\pi$ cycloaddition **184** → **185**, the 3-(silyloxy)isobenzofuran **184** being generated by an in situ silicon trap of the ambident anion **182**.[150] The contribution of benzamide DoM chemistry to these two types of protocols is indicated in Schemes 47–51 and Schemes 52–54, respectively.

A convergent synthesis of the 7-deoxy-7-epimethoxydaunomycinone derivative **192** (Scheme 47)[149b] commences with the hydroxyphthalide **188**, obtained in satisfactory yield from the anisamide **187**. Conversion into the corresponding sulfone **189** and condensation with the quinone monoketal **190** led directly to the tetracyclic product **191**. Cosmetic modification gave the daunomycinone derivative **192** in good overall yield. In a synthesis of the antiprotozoal pigment bikaverdin (**196**) (Scheme 48),[149a] a more highly oxygenated phthalide sulfone **194** was coupled with the chromone

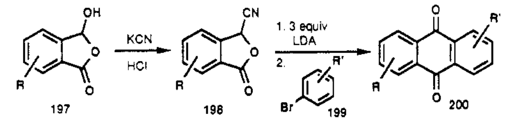
SCHEME 47



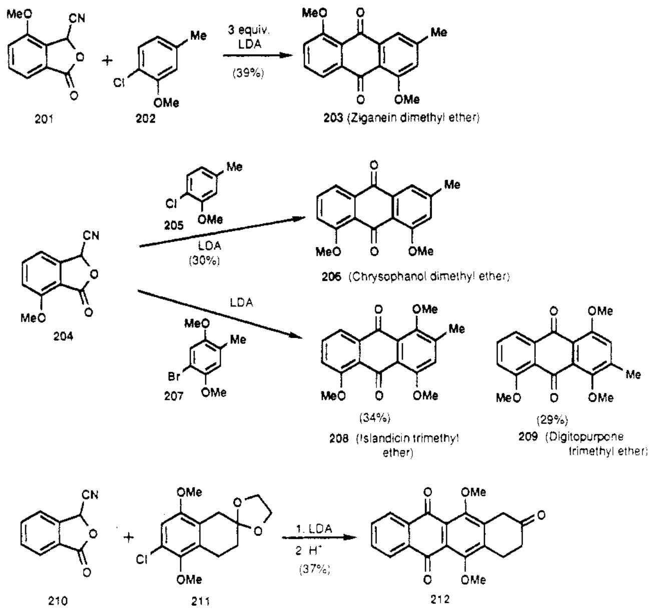
SCHEME 48



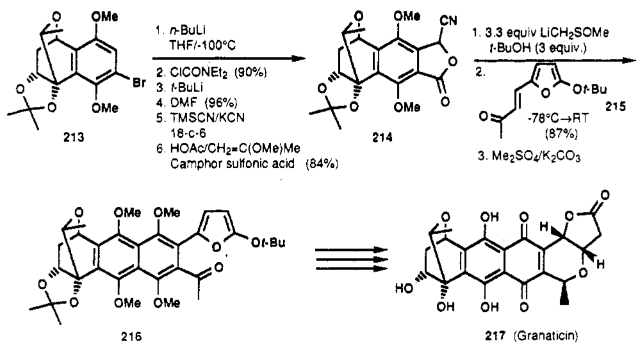
SCHEME 49



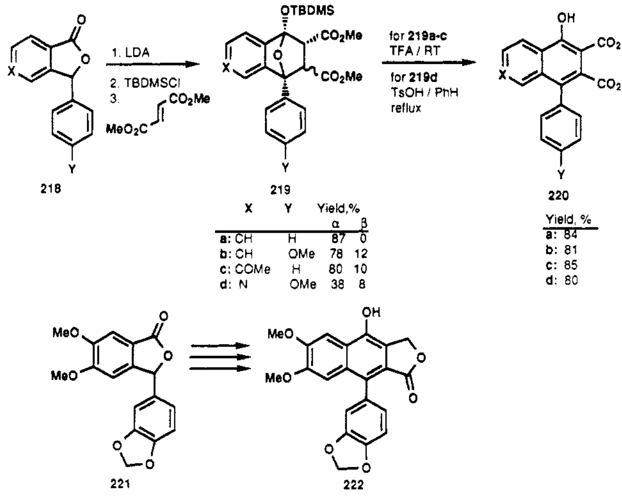
SCHEME 50



SCHEME 51



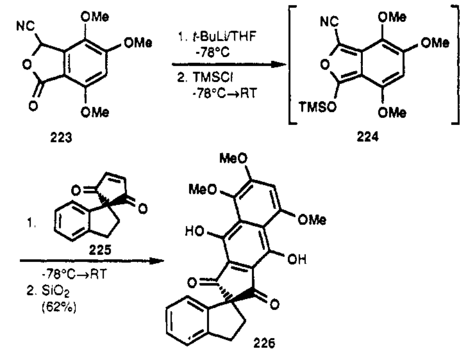
SCHEME 52



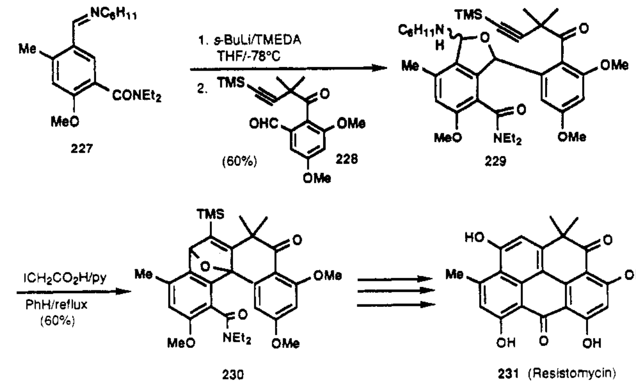
X	Y	Yield, % α	β
a: CH	H	87	0
b: CH	OMe	78	12
c: COMe	H	80	10
d: N	OMe	38	8

220 Yield, %
a: 84
b: 81
c: 85
d: 80

SCHEME 53



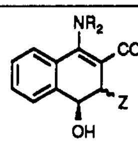
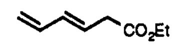
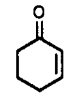
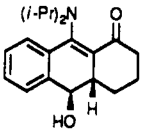
SCHEME 54



193 to give the annelated product **195**, which was oxidized and demethylated to complete the brief synthesis of **196**.

3-Cyanophthalides appear to be even more effective 1,4-dipole equivalents (**186**). In a comprehensive study, Biehl and co-workers have demonstrated a rapid construction of anthraquinones **200** (Scheme 49)[151] by base-mediated condensation of 3-cyanophthalides **198**, readily available from benzamides via the corresponding hydroxy derivatives **197**, with benzynes derived from haloaromatic precursors **199**. A variety of alkoxy, aldehyde, and condensed anthraquinones are available by this reaction, whose regioselectivity is dictated by methoxy substituents ortho to the incipient benzyne site. A selection of natural products and natural product precursors available by this protocol from simple 3-cyanophthalides and haloaromatics is shown in Scheme 50: **201** + **202** → **203** (ziganein dimethyl ether),

TABLE 23. Reaction of *N*,*N*-Diisopropyl-2-(diazomethyl)benzamides with Dienophiles[156]

				
method (see Scheme 55)	dienophile	R	Z	yield, %
A	$H_2C{=}CHCO_2Me$	*i*-Pr	H	52[a]
B	$H_2C{=}CHCO_2Me$	Et	H	44
C	$H_2C{=}CHCO_2Me$	*i*-Pr	H	55
A	(Z)-$MeO_2CCH{=}CHCO_2Me$	*i*-Pr	β-CO_2Me	75[a]
B	(Z)-$MeO_2CCH{=}CHCO_2Me$	Et	α,β-CO_2Me	27:40[b]
A	(E)-$MeO_2CCH{=}CHCO_2Me$	*i*-Pr	α-CO_2Me	43[a,c]
B	(E)-$MeO_2CCH{=}CHCO_2Me$	Et	α-CO_2Me	44
C	(Z)-$MeO_2CCH{=}CHCO_2Me$	*i*-Pr	β-CO_2Me	51
A	$MeO_2CC{\equiv}CCO_2Me$	*i*-Pr	CO_2Me	49,[c,d] 28[d,e]
B	$MeO_2CC{\equiv}CCO_2Me$	Et	CO_2Me	71[d]
A	$CH_2{=}CHCON(Me)Ph$	*i*-Pr	H	56[a]
A	$CH_2{=}CHSO_2Ph$	*i*-Pr	H	39[c]
C	$CH_2{=}CHSO_2Ph$	*i*-Pr	H	46
A		*i*-Pr	(E)-CH=CHMe	6[c,f]
A				33,[a] 44[c]

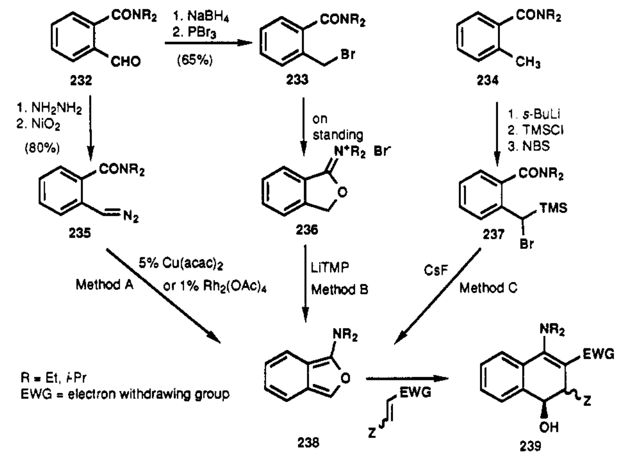
[a] Using $Cu(acac)_2$ catalyst. [b] *N*,*N*-Diethyl-2,3-bis(methoxycarbonyl)naphthalene (17%) byproduct. [c] Using $Rh_2(OAc)_4$ catalyst. [d] The aromatized ($-H_2$) product was obtained. [e] 30 mol % of $Cu(acac)_2$ was used. [f] The regioisomer from addition at the α,β-double bond was obtained (35%) as a separable cis:trans = 21:13 mixture.

204 + **205** → **206** (chrysophanol dimethyl ether), **204** + **207** → **208** (islandicin trimethyl ether) + **209** (digitopurpone trimethyl ether). In addition, the coupling of **210** and **211** leads to **212**, a valuable intermediate for 4-demethoxydaunomycinone.

The total synthesis of granaticin (**217**) (Scheme 51),[152] an antibiotic with powerful and diverse biological activity, incorporates a complex cyanophthalide **214**, available from the aryl bromide **213** by a six-step sequence which was initiated by incorporation of the tertiary amide DMG by a metal–halogen exchange–carbamoylation ($ClCONEt_2$) process. Disciplined conditions for the condensation of **214** with the furan enone **215** gave **216**, which was converted into the natural product **217** by a series of equally carefully executed steps.

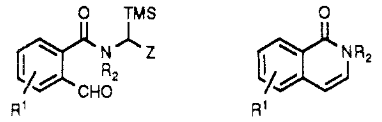
The utility of Diels–Alder cycloaddition to in situ generated 3-(silyloxy)isobenzofurans (**184** → **185**, Scheme 46) is illustrated by a procedure for rapid aromatic ring annelation (Scheme 52).[153] Thus phthalides **218**, available by benzamide DoM methodology, provided mixtures of cycloadducts **219a–d**, which upon acid treatment were smoothly aromatized to the naphthols **220a–d** in high yields. In a non-DoM-mediated application of this method, phthalide **221**, prepared via metal–halogen exchange, was converted into the aryl naphthalide lignan diphyllin (**222**). The Diels–Alder approach has also been used for the construction of the spiroindandione **226** (Scheme 53),[154] a model for fredericamycin A (**148**, Scheme 37). The cyanophthalide **223**, derived by DoM chemistry from the appropriate benzamide, was deprotonated and silylated to give **224**, whose solution NMR spectrum at room temperature could be recorded. Treatment with the enedione **225** at low temperatures gave the fredericamycin A model **226** in good yield. In an elegant and instructive study, Keay and Rodrigo used an isobenzofuran intermediate derived by benzamide DoM chemistry for the total synthesis of the aptly named antibiotic resistomycin (**231**) (Scheme 54).[155] Cooperative imine–amide DMGs in **227** promoted regiospecific lithiation and condensation with **228** to afford **229**. Special conditions of iodoacetic acid–pyridine led to the cycloadduct **230**, which, in several steps, was transformed into resistomycin (**231**).

SCHEME 55



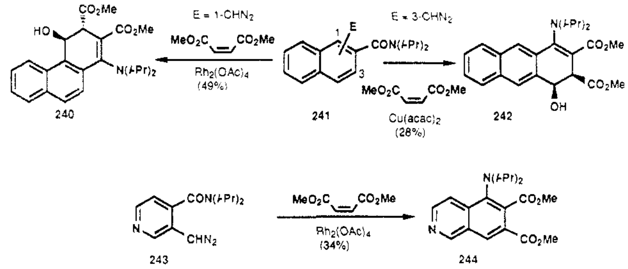
A tertiary amide DMG based generation of 1-aminoisobenzofurans **238**, R = *i*-Pr (Scheme 55),[156] allows the construction of a variety of dihydronaphthalene derivatives (Table 23). The undetectable species **238** were generated by DoM chemistry from the pivotal *o*-formylbenzamide **232** via the easily accessible diazomethyl (**235**), imidate salt (**236**), and bromo(trimethylsilyl)methyl (**237**) intermediates. These were treated with reactive dienophiles under copper or rhodium catalytic (method A), LiTMP (method B), and CsF (method C) conditions, respectively, to give prod-

TABLE 24. Synthesis of 2-Isoquinolones from α'- and α',α'-Silylated Benzamides

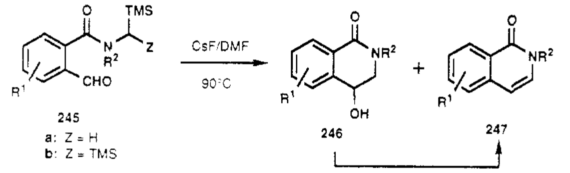


Z	R^1	R^2	R^1	R^2	overall yield, %	ref
H	H	i-Pr	H	i-Pr	44	157
H	3-OMe	i-Pr	5-OMe	i-Pr	26	157
H	4-OMe	i-Pr	6-OMe	i-Pr	49	157
H	6-OMe	Me	8-OMe	Me	46	157
H	4,6-$(OMe)_2$	Me	6,8-$(OMe)_2$	Me	23	157
H	6-Cl	Me	8-Cl	Me	20	157
H	6-Ph	i-Pr	8-Ph	i-Pr	51	157
TMS	H	Me	H	Me	36	104
TMS	4-OMe	Me	6-OMe	Me	21	104

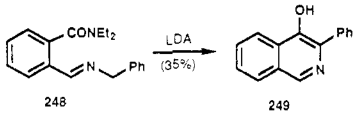
SCHEME 56



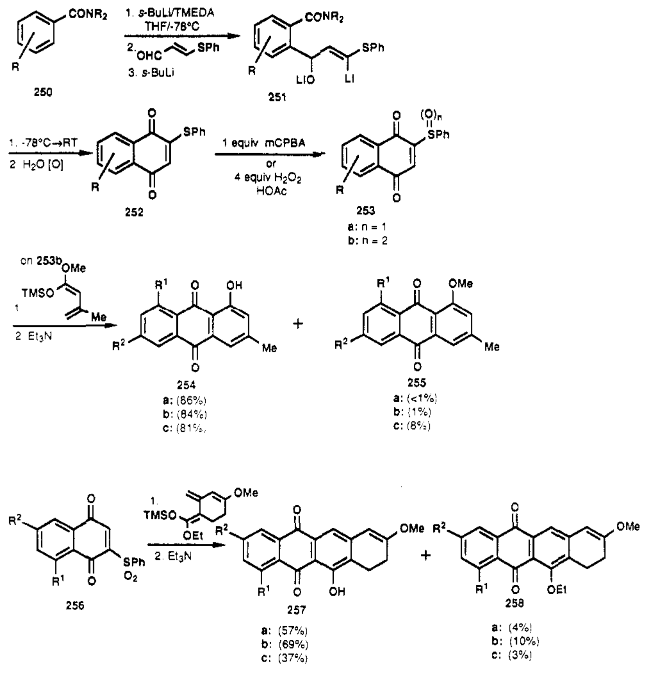
SCHEME 57



SCHEME 58



SCHEME 59



a: $R^1 = R^2 = H$; b: $R^1 = H$, $R^2 = OMe$; c: $R^1 = R^2 = OMe$

ucts **239**. Ring annelation using diethylamides **235**, R = Et, gives products in low yields. Although substituted benzamide precursors **232** have been only briefly investigated, the cycloaddition provides good scope for the preparation of non-aromatic ring functionalized systems **239**, including some condensed and heterocyclic analogues (**241** → **240** and **242**; **243** → **244**; Scheme 56).[156]

3. Isoquinolones

The development of α'- and α',α'-silylated tertiary carboxamide DMGs has provided a rational basis for a fluoride-induced intramolecular carbodesilylative route to isoquinolines **247** (Scheme 57, Table 24).[104,157] Clean metalation–formylation of α'-silylated benzamide **245a** cannot be achieved without competing self-condensation of the ortho-lithiated species unless a steric effect (R^2 = i-Pr) or ring deactivation (R^1 = OMe) (Table 6, entries 126, 128, and 129) is incorporated in the precursor. On the other hand, the corresponding α',α'-disilylated **245b** (and a variety of other ortho-functionalized products) may be obtained in high yields for R^2 = Me (Table 6, entries 135–142). Treatment of **245a** with CsF leads to the hydroxydihydroisoquinolones **246**, which by acid-catalyzed dehydration furnish product **247**.[157] The same conditions applied on the disilylated substrates **245b** result in intramolecular Peterson olefination to afford mixtures of **246** and **247**, the former being readily converted into the latter by acid treatment.[104] Preliminary results on both substrates promise generalization (Table 24). Furthermore, the reactivity of **245a,b** as amide dipole-stabilized carbanion equivalents in lateral condensation and 1,3-dipolar cycloaddition protocols has been demonstrated.[104,157] This coupled with the ready transformation of **245b** into other functionality (Scheme 12) provides a new focus for DoM-mediated chemistry.

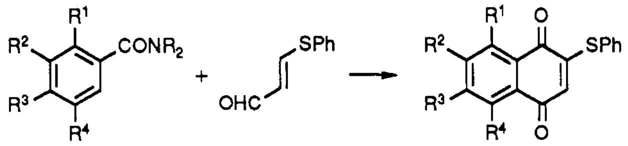
As an early indication of the additional utility of o-formylbenzamides, the simple imine derivative **248** (Scheme 58) has been converted into 3-phenyl-4-hydroxyisoquinoline (**249**).[158]

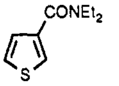
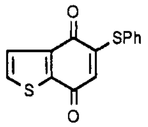
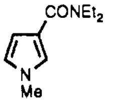
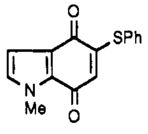
D. Ortho Hydroxyalkylation

1. Naphthoquinones

The previously encountered (Scheme 41) chameleon character of the tertiary amide DMG is further evidenced in the general synthesis of naphthoquinones (Scheme 59).[159] A variety of benzamides **250** were sequentially ortho metalated under standard conditions, treated with 3-(phenylthio)acrolein, and α-metalated to give transient dianions **251**, which, upon warming to room temperature, led to products **252**. Good yields of alkoxy-substituted (phenylthio)naphthoquinones (Table 25) may be obtained by this regioselective tandem metalation process, although use of o-methoxy (entries 10–12), naphthalen-1-amide (entry 13), and m-fluoro (entry 3) derivatives gives lower yields presumably due to steric hindrance effects in the former two cases and competitive benzyne formation in the latter sample.

TABLE 25. Synthesis of 2-(Phenylthio)-1,4-naphthoquinones[159]



entry	amide R	product R1	R2	R3	R4	yield, %
1	Et	H	H	H	H	59
2	Et	H	H	Me	H	66
3	Et	H	H	F	H	33
4	Et	H	H	OMe	H	66
5	Et	H	H	H	OMe	58[a]
6	Et	H	OMe	H	OMe	52
7	Et	H	H	OMe	OMe	52
8	Et	H	H	OCH_2O		49
9	Et	H	Me	H	OMe	53[a]
10	Me	OMe	H	H	H	22
11	Me	OMe	H	OMe	H	31
12	Me	OMe	H	H	OMe	46[a]
13	Et	CH=CH—CH=CH		H	H	21
14	 CONEt2 S			 O SPh S O		44
15	 CONEt2 N Me			 O SPh N Me O		63

[a] Yield after Ag_2O oxidation.

Potential extension of this methodology to heterocyclic quinones is indicated by entries 14 and 15.

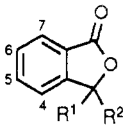
Removal of the phenylthio α-metalation director may be achieved by sequential treatment of **252** with MCPBA and Bu_3SnH.[159] However, more significant is its use in controlling the regiochemistry of subsequent Diels–Alder reaction.[160] Thus a variety of naphthoquinone sulfoxides or sulfones **253a,b**, readily obtained from **252**, have been shown to undergo cycloaddition with vinylketene acetals to give, after base-catalyzed aromatization, anthraquinones **254** and **255**. In this comprehensive study, Iwao demonstrated that sulfoxides and sulfones **253a,b** show greater regioselectivity and rate of reaction compared to the corresponding sulfides. For example, the naturally occurring anthraquinones pachybasin (**254a**), phomarin 6-methyl ether (**254b**), and emodin 6,8-dimethyl ether (**254c**) were obtained in high yield together with small amounts of corresponding methyl ethers **255a**, **255b**, and **255c**, respectively. Similarly, the cycloaddition of sulfones **256a–c** with a cyclic vinylketene acetal produced anthracyclinone analogues **257a–c** and **258a–c** in somewhat lower yields but good selectivities favoring phenols **257**.

2. Phthalides and Derived Anthraquinones

Hydroxyalkylation of ortho-lithiated benzamides followed by anchimerically assisted[161] acid-catalyzed cyclization constitutes a convenient entry into 3-substituted phthalides (Tables 26 and 27). A diverse and extensive group of 3-arylphthalides (Table 26, entries 17–34; Table 27), heterophthalides (Table 26, entries 63–74), and, by transmetalation, 3-alkylphthalides (Table 26, entries 8–12) are rapidly available by this tactic. Comparable routes are known by secondary amide[29h,i] and oxazoline[29g] DoM technology. A solitary attempt to induce optical activity by the reaction of (*S*)-*O*-methyl-*N*-methylbenzoylleucinol with 1-naphthaldehyde was unsuccessful.[73] In contrast, optically active oxazolines serve as excellent chiral auxilliaries in numerous preparative applications.[29g] As summarized below, phthalides derived from tertiary benzamides are useful intermediates for a variety of more highly condensed systems such as anthraquinones (Schemes 61, 62, and 64; Tables 28 and 30), heterocyclic quinones (Schemes 65 and 66), anthracyclinones (Scheme 63), several classes of alkaloids (Schemes 68–70), and polycyclic aromatic hydrocarbons (PAH) (Scheme 72, Table 29).

Classical approaches to unsymmetrically oxygenated anthraquinones **263** and **264** (Scheme 60) initiated from phthalic acids and phenols by double Friedel–Crafts reactions are, as illustrated for a specific bond construct, plagued by lack of regiocontrol (initial Friedel–Crafts step **259** + **260** → **261** + **262**), inefficiency (electron-withdrawing benzoyl substituent in **261** and **262** in the second Friedel–Crafts step), and ambiguity (potential Hayashi rearrangement of the equilibrating acylium ions corresponding to **261** and **262**). According to DoM retrosynthetic analysis (illustrated only for **263**), four modes of initial coupling of two appropriately substituted and usually readily accessible lithiated benzamide (**267**, **269**) and benzaldehyde (**268**, **270**) partners are eminently feasible; the productive dissections a and b focus on the regiospecific positioning of the bond to ring A (→**265**, **266**), thus avoiding the ambiguity in the first Friedel–Crafts step of the classical approach. Although

TABLE 26. Synthesis of Phthalides and Phthalic Anhydrides from Ortho-Lithiated Tertiary Aromatic Amides^a



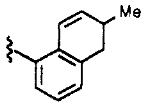
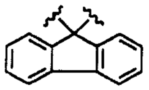
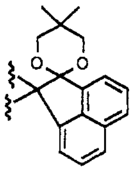
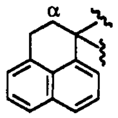
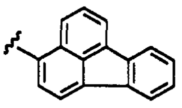
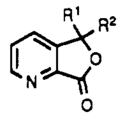
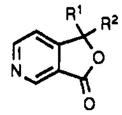
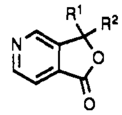
entry	R^1	R^2	substituent C-4	C-5	C-6	C-7	yield, %	ref
1	H	H	OMe	H	H	H	93	146
2	H	H	H	H	H	OMe	97	146
3	H	H	H	H	OMe	OMe	90	146
4	H	H	OMe	OMe	H	OMe	44	148a
5	O		OMe	H	H	H	70–80	146
6	O		OMe	OMe	H	H	70	146
7	Me	H	H	H	H	H	61^b	142
8	*n*-Pr	H	H	H	H	H	64^b	142
9	*n*-Pr	H	OMe	H	H	H	59^b	142
10	*n*-Pr	H	H	H	H	OMe	60^b	142
11	*n*-Pr	H	OMe	H	H	OMe	75^b	142
12	Me	Me	H	H	H	H	54	86
13	Me	2-$(CONEt_2)C_6H_4$	H	H	H	H	35	142
14	Ph	H	H	H	H	H	48, 50, 56	86, 101, 130, 153
15	Ph	H	H	OMe	H	H		153
16	Ph	H	OMe	OMe	H	H	49, 74	87, 130
17	3-MeC_6H_4	H	H	OMe	H	H	5	163
18	4-MeC_6H_4	H	H	OMe	H	H	11	163
19	4-$MeOC_6H_4$	H	H	H	H	H		153
20	3-$MeOC_6H_4$	H	H	H	Me	OMe	76	162
21	4-$MeOC_6H_4$	H	H	Me	H	OMe	45	160
22	2,5-$(MeO)_2C_6H_3$	H	OMe	OMe	OMe	H	21	159
23	3,5-$(MeO)_2C_6H_3$	H	H	OMe	H	Me	51^c	164
24	2,5-$(MeO)_2$-4-MeC_6H_2	H	OMe	H	H	H	68	162
25	2,5-$(MeO)_2$-4-MeC_6H_2	H	H	H	H	OMe	62	162
26	2,5-$(MeO)_2$-4-MeC_6H_2	H	OMe	H	OMe	H	64	162
27	2,5-$(MeO)_2$-4-MeC_6H_2	H	OMe	H	H	OMe	63	162
28	3,4-$(MeO)_2C_6H_3$	H	H	H	H	Me	65^c	130
29	1-naphthyl	H	H	H	H	H	20	87
30	2-naphthyl	H	H	H	H	H	22	164
31	1-naphthyl	H	H	H	H	Me	58^c	164
32	2-naphthyl	H	H	H	H	Me	52^c	164
33	9-phenanthryl	H	H	H	H	H	24	87
34	9-phenanthryl	H	H	H	H	Me	63	164
35	2-(NCH_2Ph)pyrrolyl	H	H	H	H	H	89	175
36	2-furyl	H	H	H	OMe	OMe	75	169
37	2-pyridyl	H	H	H	H	H	88^b	142
38	1-[6,7-$(MeO)_2$-isoquinolyl]	H	H	H	OMe	OMe		173
39	Ph	Ph	H	H	H	H	65	86
40	Ph	Ph	H	OX^d	H	H	46	86
41	Ph	Ph	H	CONHMe	H	H	7^e	86
42	Ph	Ph	H	$CONEt_2$	H	H	20^e	86
43	Ph	Ph	H	Cl	H	H	60	86
44	Ph	Ph	H	SO_2NHMe	H	H	41	86
45	Ph	Ph	H	SO_2NEt_2	H	H	21	86
46	OH	H	H	H	H	H	80	101
47	OH	H	OMe	H	H	H	54	*f*, 151
48	OH	H	OMe	OMe	H	OMe	47, 81	149a, 154
49	OH	H	OMe	H	H	H	54	*f*, 148b, 151
50	OH	H	H	H	H	OMe	39, 61	149b, 151
51	OH	H	H	Me	H	OMe	39	151
52	OH	H	OMe	H	OMe	H	40	151
53	OH	H	F	H	H	H	<15	*f*
54	OH	H	H	H	H	F	10	148b
55	CO_2H	H	H	H	OMe	OMe	72	146
56	CO_2H	H	H	H	OCH_2O		37	146
57		H	H	H	H	H	77	168
58		H	H	H	H	H	70	182
59		H	H	H	H	H	93	183

TABLE 26 (Continued)

			substituent					
entry	R^1	R^2	C-4	C-5	C-6	C-7	yield, %	ref
60		H	H	H	H	H	22 (50)[g]	176
61		H	*t*-Bu	H	H	H	39[h]	179
62		H	H	H	H	H	80[i]	184
								
63	R^1 = Ph; R^2 = H						*j*	*k*
64	$R^1 + R^2 = (CH_2)_4$						*j*	*k*
65	$R^1 + R^2 = (CH_2)_5$						*j*	*k*
66	$R^1 = R^2$ = Ph						77[j]	*k*
								
67	R^1 = Ph; R^2 = H						*j*	*k*
68	$R^1 + R^2 = (CH_2)_4$						*j*	*k*
69	$R^1 + R^2 = (CH_2)_5$						*j*	*k*
70	$R^1 = R^2$ = Ph						63[j]	*k*
								
71	R^1 = Ph; R^2 = H						*j*	*k*
72	R^1 = 4-$MeOC_6H_4$; R^2 = H							153
73	$R^1 + R^2 = (CH_2)_4$						*j*	*k*
74	$R^1 + R^2 = (CH_2)_5$						*j*	*k*
75	$R^1 = R^2$ = Ph						51[j]	*k*

[a] Unless otherwise noted, *N,N*-diethylbenzamide starting materials were employed. The phthalides resulted from spontaneous cyclization of intermediate alcohol amides upon workup or chromatography or upon deliberate treatment with acid. [b] Table 6, footnote *b*. [c] Fluoride desilylation of the unisolated $CH(TMS)_2$ intermediate prior to acid-catalyzed cyclization. [d] 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl). [e] Obtained from a competitive metalation reaction of a 1:1 mixture of *N*-methylbenzamide and *N,N*-diethylbenzamide. The yield was improved to 55% of a 3:1 mixture of products of entries 42:41. entries 42:41. [f] Morrow, G. W.; Swenton, J. S.; Filippi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* 1987, *52*, 713. [g] Yield obtained with the α,α-dideuterated 2,3-dihydrophenalen-1-one. [h] Yield of the benzoic acid obtained by Zn–Cu/KOH reduction of the phthalide. [i] *N*-[2-(Diethylamino)ethyl]-*N*-ethylbenzamide starting material. [j] *N,N*-Diisopropylamide starting material. [k] Table 8, footnote *b*.

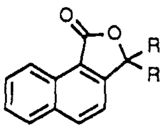
the second bond formation to ring C is carried out by Friedel–Crafts technology and is therefore dictated by normal electronic substitution rules, regioselectivity may be decided by appropriate choice of benzaldehyde reactant. Furthermore, the Hayashi rearrangement is precluded by use of intermediate benzyl benzoic acids obtained from amide alcohol intermediates **265** and **266**.

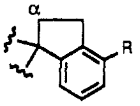
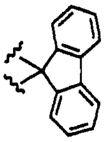
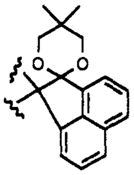
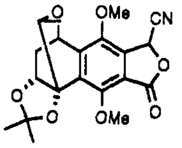
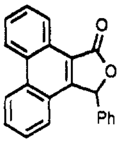
This strategy, which is also viable via secondary amide[29h,i] and oxazoline[29g] DMG protocols, has been applied to the synthesis of anthraquinones, including several natural products (Table 28).[159,160,162–165] Early illustrations are delinated in Scheme 61.[162] Metalation of **271** followed by condensation with an appropriate benzaldehyde and TsOH cyclization afforded phthalide **272**, which upon hydrogenolysis and mild Friedel–Crafts cyclization led to the anthracenol **273**. Chromium trioxide oxidation to the corresponding anthraquinone followed by selective deprotection afforded either catenarin (**274a**) or erythroglaucin (**274b**). Significantly, acidic methyl hydrogens in aldehyde and, in certain cases, amide (e.g., soranjidiol, Table 28) components are tolerated in the metalation–condensation stages of this route.

The synthesis of desoxyerythrolaccin trimethyl ether (**278**) (Scheme 62)[164] involves a similar strategy but illustrates the silicon protection of reactive *o*-methyl hydrogens in toluamide **275** for the construction of this peri-methyl anthraquinone. Thus α,α-disilylation of **275**, prepared by DoM, furnished **276**, which upon metalation, condensation with 3,5-dimethoxybenzaldehyde, and, without isolation of intermediates, CsF-mediated desilylation and cyclization gave the phthalide **277**. A simple three-step conversion afforded the trimethyl ether of the natural product **278** in 51% overall yield. The use of the silicon protection tactic for simpler systems has also been demonstrated (Table 26, entries 23, 28, 31, and 32).

Similarly, ketone **285** (Scheme 63), a key intermediate in several syntheses of daunomycinone, has been prepared by a route that is initiated from **279** and **282** by amide DoM tactics and that converges into the phthalide **281**.[166] Thus treatment of lithiated **279** and aldehyde **282**, which are interrelated by DoM reactions, with aldehydes **280a,b** and lithiated **283**, respectively, led, after TsOH cyclization, to the phthalides **281a,b** in good overall yields. Standard manipulation provided

TABLE 27. Synthesis of Phthalides from Ortho-Lithiated Naphthamides



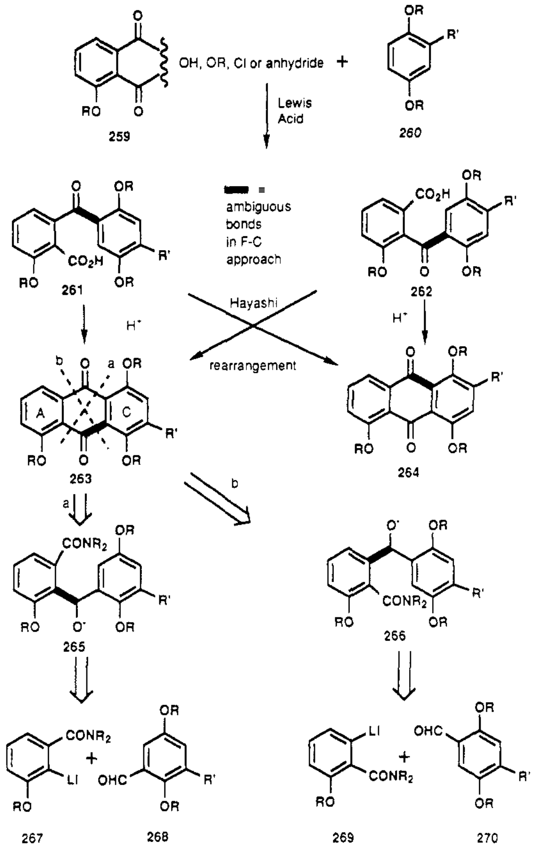
entry	R^1	R^2	yield, %	ref
1	Ph	H	81	87
2	Ph	Me	71	176
3	1-naphthyl	H	81, 67	87, 176
4	2-naphthyl	H	70	87, 176
5	1-naphthyl	Me	52	176
6	2-naphthyl	Me	58[a]	176
7	2-pyridyl	H	80	175
8	2-(NCH_2Ph)pyrrolyl	H	89	175
9	Ph	Me	72[a]	177
	5,8-$(OMe)_2$			
				
10	R = H		50[b]	180
11	R = Me		30 (52)[b]	176
12			70	182
13			87	183
14			66[c]	152
15			24	87

[a] Yield of corresponding benzoic acid obtained after Zn–Cu/KOH reduction of the phthalide. [b] Yield obtained with the α,α-dideuterated indan-1-one. [c] Overall yield from amide after treatment of *o*-CHO intermediate with Me_3SiCN, KCN-18-c-6; HOAc; $CH_2{=}C(OMe)Me$, camphorsulfonic acid.

the anthraquinone **284**, which upon epoxidation and acid-catalyzed rearrangement afforded the anthracyclinone **285**. Syntheses of this class of antitumor antibiotics via analogous convergent approaches involving the secondary amide DMG have been reported.[167]

A maximum convergence approach is also portrayed by the synthesis of the "angular" anthracyclinone antibiotics X-14881C (**290a**) and ochromycinone (**290b**) isolated from several strains of *Streptomyces* (Scheme 64).[168] Thus treatment of the metalation-interrelated tetralin derivatives **286** and **287** with appropriate anisamides followed by acid-induced cyclization afforded the phthalide **288**. The first route involving the use of the CH_2OLi DMG proved to be the more efficient one. Standard conversion into an anthraquinone was followed by a regioselective selenohydroxylation to give **289**. Oxidation and deselenylation yielded X-14881C (**290a**), which was demethylated ($AlCl_3$) to ochromycinone (**290b**), thus concluding these short syntheses (21% overall yields).

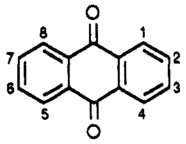
SCHEME 60



Phthalide-mediated routes to anthraquinones may be extended to heterocyclic analogues as shown by the synthesis of the cytotoxic furanonaphthoquinone **295** (Scheme 65).[169] Thus treatment of lithiated benzamide **291** with furfural (**292**) and cyclization afforded the furanophthalide **293** in good yield. Zinc chloride promoted acylation at the highly reactive furan 2-position followed by protection gave the ketal **294**, which was converted into the unnamed natural product **295** by standard steps.

The synthesis of the rare azaanthraquinone bostrycoidin (**301**) (Scheme 66) involves analogous steps but also illustrates an interesting pyridine methylation reaction.[170] Although 4-silylation of the methylnicotinamide **296a** was achieved under *sec*-BuLi/TMEDA/THF/−78 °C conditions,[171] metalation using LiTMP followed by dimethylbenzamide[170] or benzaldehyde[171] quench led to products of lateral substitution, e.g., **297**. This result necessitated the introduction of the methyl group at a later stage in the synthesis. Optimized metalation of **296b** using LiTMP followed by condensation with an appropriate *N*,*N*-dimethylbenzamide, a reaction of some generality (Table 8, entries 6 and 14–18), afforded the keto amide **298**. Regioselective 2-methyl group introduction was achieved via the *N*-oxide of **298** involving an acetoacetic ester synthon which suffers hydrolysis, decarboxylation, and deacylation in the last acid-catalyzed step. The resulting product **299** was reduced and cyclized to furnish the phthalide **300**, which was conventionally manipulated

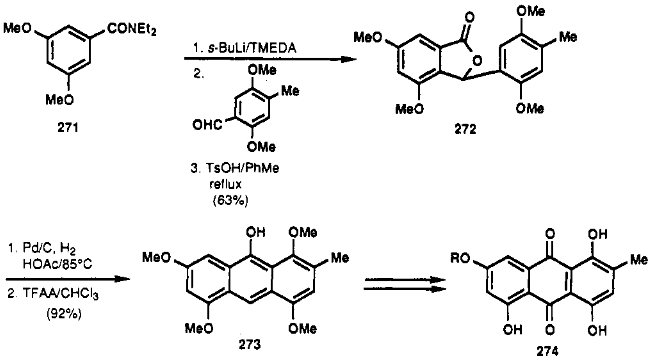
TABLE 28. Synthesis of Anthraquinones from Ortho-Lithiated Tertiary Benzamides via Phthalide Intermediates



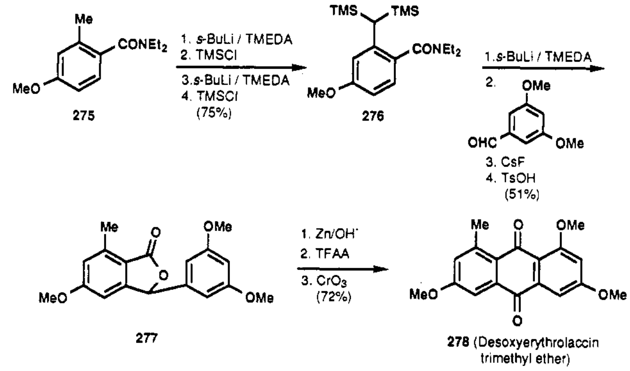
name	substitution								overall yield, %	ref
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8		
islandicin	OH	Me	H	OH	OH	H	H	H	41[a]	162
digitopurpone	OH	H	Me	OH	OH	H	H	H	39[a]	162
erythroglaucin	OH	Me	H	OH	OH	H	OMe	H	22	162
catenarin	OH	Me	H	OH	OH	H	OH	H	29	162
cyanodontin	OH	Me	H	OH	OH	H	H	OH	23	162
soranjidiol	H	H	OH	H	H	H	Me	H	21	162
desoxyerythrolaccin	OH	H	OH	H	H	OH	H	Me	61[a]	164
	H	Me	H	H	H	OMe	H	H		163
	H	H	Me	H	H	OMe	H	H		163
	OH	H	Me	H	H	H	OMe	H	11	160
emodin	OH	H	Me	H	H	OH	H	OH	38[a]	165
7-hydroxyemodin	OH	H	Me	H	H	OH	OH	OH	37[b]	165
helminthosporin	OH	H	Me	H	OH	H	H	H	23	165
chrysophanol	OH	H	Me	H	H	H	H	OH	35[c]	165

[a] Yield of trimethyl ether. [b] Yield of tetramethyl ether. [c] Yield of dimethyl ether.

SCHEME 61



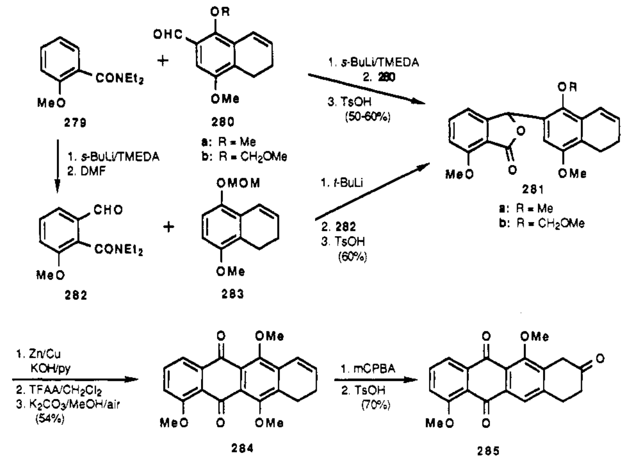
SCHEME 62



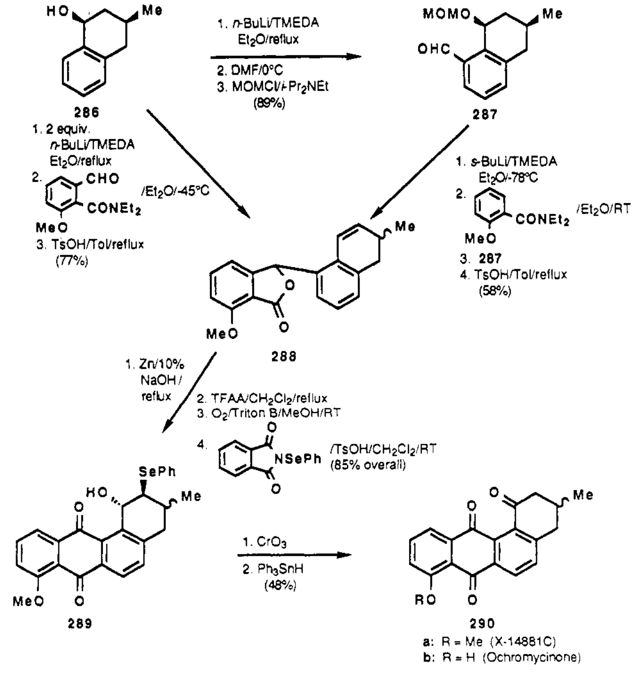
into the antibiotic bostrycoidin (301).

In a further application of pyridine amide DoM, the conformationally rigid analogue of the tricyclic antidepressant imipramine (306) (Scheme 67) was prepared by condensation of metalated nicotinamide 302 with the dibenzazepine carbaldehyde 303, which was also obtained by DoM chemistry.[172] Surprising difficulty was encountered in the hydrolysis of the initial product 304 or the corresponding diisopropylamide, which was similarly secured. However, hydrogenolysis of 304 in acetic acid followed by $POCl_3$ treatment gave the lactam 305,

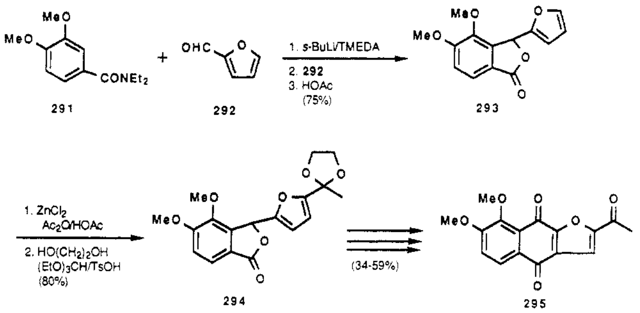
SCHEME 63



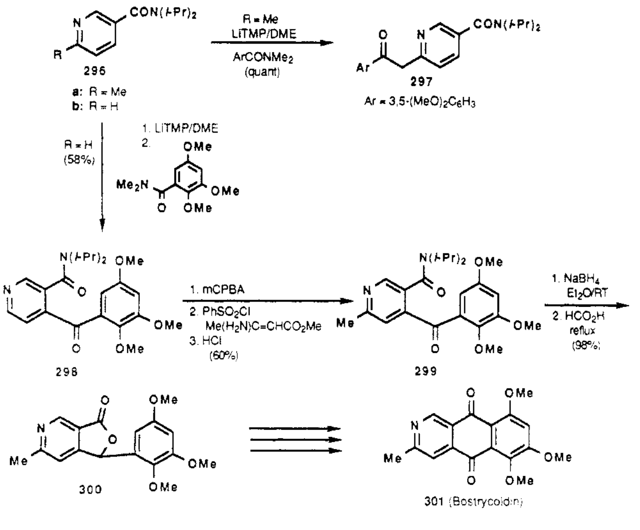
SCHEME 64



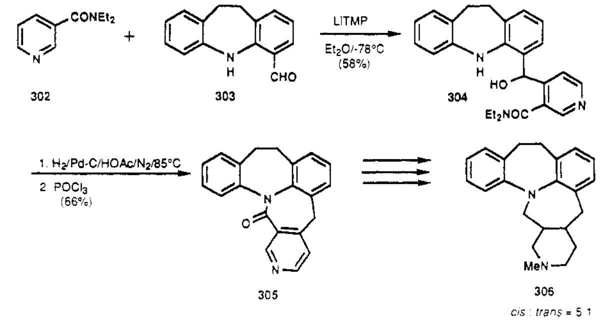
SCHEME 65



SCHEME 66



SCHEME 67

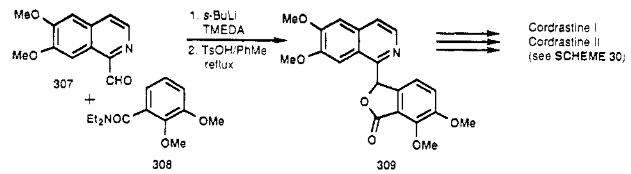


a sequence that likely proceeds via a phthalide intermediate. Unexceptional steps led to the target molecule **306** as a separable cis–trans mixture.

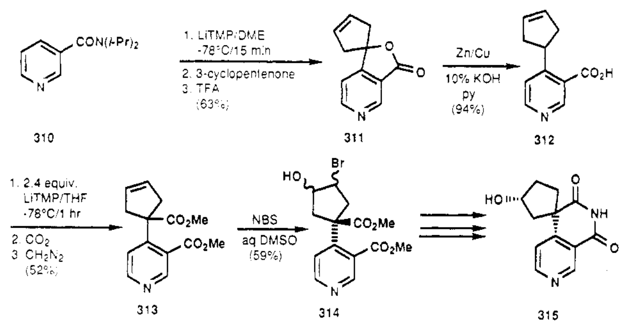
Concurrent with a DoM approach to the phthalide isoquinoline alkaloids cordrastine I and II (Scheme 30), a second, more direct, synthesis was also formally achieved by simple condensation of the isoquinolinecarbaldehyde **307** (Scheme 68) with the ortho-lithiated species derived from **308** to give, after acid-catalyzed cyclization, phthalide **309** (also Table 26, entry 38).[173]

Following careful experimentation in pyridinecarboxamide metalation, Iwao devised an innovative synthesis of the antileukemic pyridinecarboximide sesbanine (**315**) (Scheme 69).[174] The spirophthalide **311** was secured by metalation of the diisopropylnicotinamide **310** in preference to the corresponding diethylamide (e.g., Table 8, entries 8 vs 9–11), followed by condensation with 3-cyclopentenone and acid-mediated cyclization. Chemical hydrogenolysis usefully completed the circumscribed amide "hydrolysis" to afford

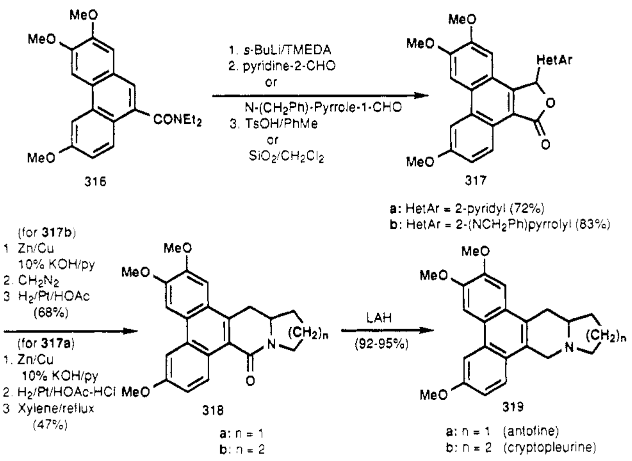
SCHEME 68



SCHEME 69



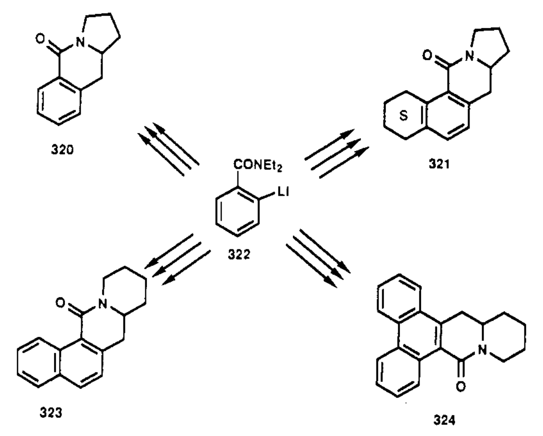
SCHEME 70



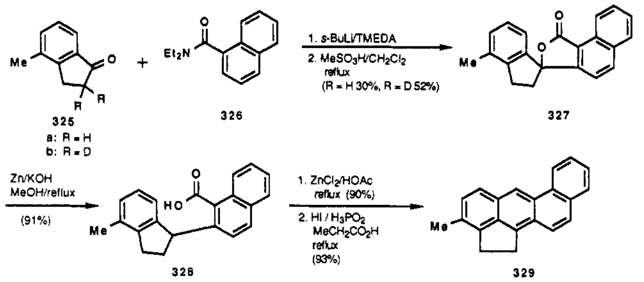
the nicotinic acid **312**, which upon benzylic metalation, carbonation, and esterification afforded the diester **313**. Nonstereoselective bromohydrin formation, **314**, was later recouped when both of the corresponding debrominated products were converted into sesbanine (**315**) (12.5% overall yield).

An abbreviated synthesis of the phenanthroindolizidine and -quinolizidine alkaloids antofine (**319a**) and cryptopleurine (**319b**) was achieved by using the common phenanthrenecarboxamide **316** as starting material (Scheme 70).[175] Metalation of **316** followed by condensation with pyridine-2-carbaldehyde and *N*-benzylpyrrole-2-carbaldehyde and TsOH cyclization afforded the phthalides **317a** and **317b**, respectively, in good yields. These were subjected to sequential C–O bond hydrogenolysis and heterocyclic ring hydrogenation with slight additional procedural variation to give lactams **318a** and **318b**, which were reduced to antofine (**319a**) and cryptopleurine (**319b**), respectively. The *N*-methoxymethylpyrrole phthalide corresponding to **317b**, obtained in 72% yield, proceeded smoothly through the Zn/Cu hydrogenolysis stage but suffered hydrogenolytic OMe cleavage during pyrrole ring catalytic reduction, thus thwarting this approach. The five-step heteroannelation process was generalized to prepare the condensed lactams **320**, **321**, **323**, and **324** in modest to good yields from the ortho-lithiated amide

SCHEME 71



SCHEME 72



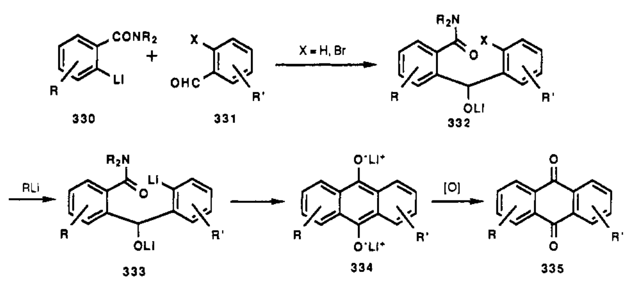
322 and respective pyrrole- or pyridine-2-carbaldehyde precursors (Scheme 71).[175]

3. Polycyclic Aromatic Hydrocarbons via Phthalides

The facile and generally high-yield condensation of ortho-lithiated benzamide with aromatic aldehydes provides a general principle for the regiospecific construction of polycyclic aromatic hydrocarbons (PAH). In view of the significant environmental presence of this class of carcinogenic substances, the development of regiospecific syntheses that avoid isomeric mixtures and extended handling of intermediates is of considerable merit. Application of the amide DMG has led to the rapid and efficient preparation of a variety of PAH (Table 29) of value in analytical, metabolism, and carcinogenicity studies. Thus condensation of simple lithiated *N*,*N*-diethylbenzamides, *N*,*N*-diethylnaphthamides, and, in one case, the "built-in" TMEDA benzamide (entry 26) with aryl aldehydes or ketones, normally readily obtained by classical electrophilic (e.g., Villsmeier) substitution, leads to the following PAH: benz[*a*]anthraquinones (entries 1–4),[164,171] whose reduction to the corresponding PAH is well documented, benz[*a*]anthrancenes (entries 5 and 6),[176,177] dibenz[*a*,*j*]anthrancenes (entries 7–10),[176,178] dibenz[*a*,*h*]anthracenes (entries 11 and 12),[176] benzo[*a*]pyrenes (entries 13–15),[176,179] cholanthrenes (entries 16–21),[176,180,181] benzo[*a*]fluoranthene (entry 22),[182] naphtho[2,1-*a*]fluoranthene (entry 23),[182] 1,12-methylenebenz[*a*]anthracene (entry 24),[183] 1,14-methylenedibenz[*a*,*h*]anthrancene (entry 25),[183] and dibenz[*e*,*k*]acephenanthrylene (entry 26).[184]

The preparation of 3-methylcholanthrene (**329**) (Scheme 72)[176] is representative but also illustrates the advantage of deuteration of α-carbonyl sites to diminish proton exchange in strong-base-mediated processes.

SCHEME 73



Thus condensation of the indanone **325a** with the lithiated species of naphthamide **326** followed by acid-catalyzed cyclization afforded the spirophthalide **327** in low yield. In contrast, under the same conditions, the α,α-dideuterated indanone **325b** gave the product **327** in substantially improved yield. This marked isotope effect, which evidently attenuates proton exchange, has also been used to enhance the yields of analogous condensation reactions (Table 29, entries 14 and 17–21). Hydrogenolysis of phthalide **327** led to **328**, which was converted into 3-methylcholanthrene (**329**) in excellent overall yield.

The regiospecific and efficient preparation of peri-methyl-substituted benz[*a*]anthraquinones (Table 29, entries 3 and 4), using silicon protection of methyl groups of *o*-toluamides (Table 21), invites broader application of this tactic.

4. Anthraquinones Not via Phthalides

Tandem benzamide DoM processes may be used to effect one-pot regioselective synthesis of anthraquinones (Scheme 73).[87] In this sequence of potential broader application for other DMGs, the initial ortho-lithiated benzamide (**330**)–benzaldehyde (**331**, X = H) condensation to give intermediate **332**, X = H, is followed by a second metalation that takes advantage of the presence of the CH_2OLi DMG to give **333**. Although metalation ortho to the more powerful amine DMG undoubtedly occurs, equilibration of anions is assumed, with cyclization to an anthracene diphenolate **334** constituting a driving force for the overall reaction. Aerial oxidation to the anthraquinone **335** is a well-documented process. The success of this reaction using acetophenone or benzophenone as the carbonyl reactants[87] does not preclude an alternate mechanism involving benzylic deprotonation of **332**, X = H, and cyclization. On the other hand, **333** is the likely species in the more efficient tandem DoM metal–halogen exchange involving intermediate **332**, X = Br.[185]

In spite of mechanistic uncertainty, this method has considerable synthetic utility for the rapid construction of complex anthraquinones, including diverse heterocyclic analogues (Table 30). Illustrative of scope and generality is the synthesis of a variety of substituted and condensed anthraquinones (entries 1–20), thus constituting an alternate abbreviated route to PAH derivatives (section VIII.D.3). Significant improvement in yields is observed when the second metalation is carried out with excess *sec*-BuLi (entry 2) or by the metal–halogen exchange[186] (entries 5–15 and 18) processes. The latter is of course dependent upon the convenient availability of the *o*-bromoaldehyde precursor. Using the non metal–halogen exchange tactic, methoxy-substituted benzaldehydes give modest yields of products

TABLE 29. Synthesis of PAH Quinones and PAH via Phthalides[a]

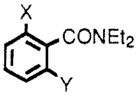
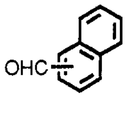
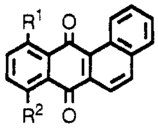
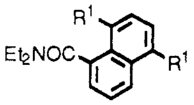
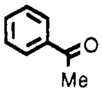
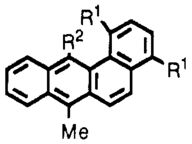
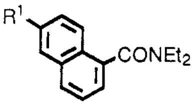
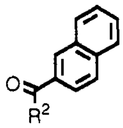
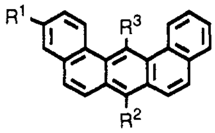
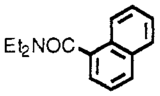
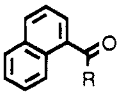
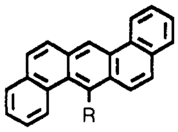
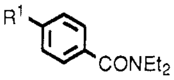
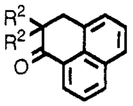
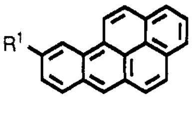
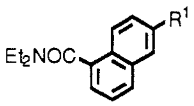
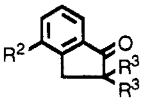
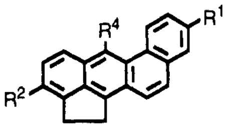
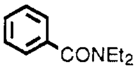
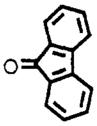
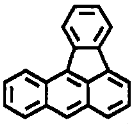
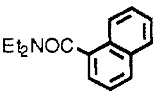
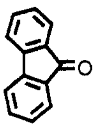
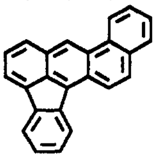
Entry	Aromatic Amide	ArCHO or ArCOAr	Product	Yield, % Overall	Ref
					
1	X = Y = Br	1-CHO	R^1 = Br, R^2 = H	22	127,171
2	X = Y = Br	2-CHO	R^1 = H, R^2 = Br	33	127,171
3	X = CH(TMS)$_2$, Y = H	2-CHO	R^1 = Me, R^2 = H	31	164
4	X = CH(TMS)$_2$, Y = H	2-CHO	R^1 = H, R^2 = Me	43	164
					
5	R^1 = H		R^1 = R^2 = H	54	176
6	R^1 = OMe		R^1 = OMe, R^2 = Me	31	177
					
7	R^1 = H	R^2 = H	R^1 = R^2 = R^3 = H	52	176
8	R^1 = H	R^2 = Me	R^1 = R^2 = H, R^3 = Me	55	176
9	R^1 = OMe	R^2 = H	R^1 = OH, R^2 = R^3 = H	51	178
10	R^1 = OMe	R^2 = H	R^1 = OH, R^2 = R^3 = Me	18	178
					
11		R = H	R = H	50	176
12		R = Me	R = Me	35	176
					
13	R^1 = H	R^2 = H	R^1 = H	15	176
14	R^1 = H	R^2 = D	R^1 = H	35	176
15	R^1 = t-Bu	R^2 = H	R^1 = t-Bu	34	179
					
16	R^1 = H	R^2 = Me, R^3 = H	R^2 = Me, R^1 = R^4 = H	23	176
17	R^1 = H	R^2 = Me, R^3 = D	R^2 = Me, R^1 = R^4 = H	40	176
18	R^1 = H	R^2 = Me, R^3 = D	R^1 = H, R^2 = R^4 = Me	36	180
19	R^1 = H	R^2 = H, R^3 = D	R^1 = R^2 = R^4 = H	25	180
20	R^1 = OMe	R^2 = H, R^3 = D	R^1 = OH, R^2 = R^4 = H	17	181
21	R^1 = OMe	R^2 = H, R^3 = D	R^1 = OH, R^2 = H, R^4 = Me	22	181
22				22	182
23				21	182

TABLE 29 (Continued)

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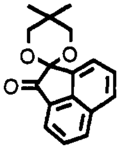
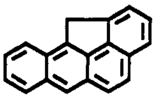
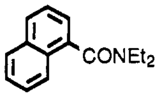
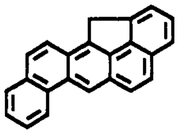
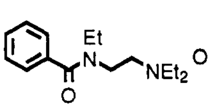
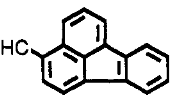
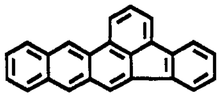
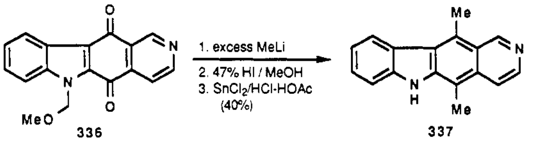
24				18	183
25				37	183
26				31	184

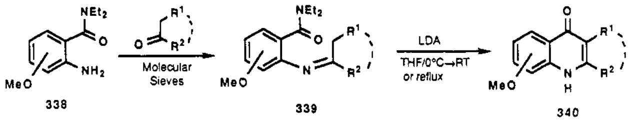
[a] All metalations were carried out under *sec*-BuLi/TMEDA/THF/-78 °C conditions.

SCHEME 74



336 337

SCHEME 75



338 339 340

(entries 2 and 3), while methyl groups are poorly tolerated (entry 4). *N,N*-Diethyl-1-naphthamide is a useful reactant (entries 16–18) but the corresponding 2-naphthamide is a poor partner (entry 19), most likely due to nucleophilic addition of the alkyllithium.[88] The preferred formation of a linear anthraquinone using a naphth-2-carbaldehyde by a DoM process is clearly improved by incorporating a metal–halogen exchange step (entry 14).

Coupling of aromatic or heteroaromatic amides with heterocyclic aldehydes provides access to a variety of heterocyclic quinones, some of which are new and others of which have been previously prepared only by tedious and inefficient routes (entries 21–34). Although furancarbaldehyde (entry 22), thiophenecarbaldehyde (entries 21 and 23–26), and indolecarbaldehyde (entries 32–37) give useful yields of products, pyridinecarbaldehyde (entries 27–30)[187] is a poor coupling partner, undoubtedly due to competing nucleophilic attack by alkyllithium in the second metalation step. A similar explanation may be responsible for the low yields of azaellipticine quinones from reactions with a pyrrolopyridinecarbaldehyde (entries 38–44).[188] A one-pot assemblage of the ellipticine alkaloid skeleton (entries 35–37) allows the achievement of a very short synthesis of the alkaloid itself, **336** → **337** (Scheme 74).[87] Standard *sec*-BuLi/TMEDA metalation of *N,N*-diethylbenzamide followed by warming to room temperature also affords anthraquinone (74%).[87] This potentially general reaction, which presumably proceeds via an ortho-lithiated benzophenone intermediate, has been effected under LDA conditions to prepare a symmetrical dipyridoquinone (entry 31).[189]

5. *Intramolecular Epoxycyclialkylation*

Although intermolecular condensation of ortho-lithiated *N,N*-diethylbenzamides with epoxides fails,[86] the corresponding intramolecular process may be achieved stereoselectively and has some generality (Table 31).[191] This reaction, for which the Parham metal–halogen exchange analogue exists,[25] leads via 5-exo-tet modes to dihydrobenzofurans in acceptable yields (entries 1–4 and 6 and 7). Steric impedance to cyclization is observed in β-substituted epoxide (entry 5), although the formation of the requisite anion was confirmed by TMSCl quench. Bis(epoxycyclialkylation) (entry 8) cannot be achieved, and corresponding 6-exo-tet ring closure (entry 9) proceeds in lower yield.

E. Ortho Carboxylation and Acylation

Although DoM-mediated ortho carboxylation of benzamides and *O*-aryl carbamates proceeds well (Table 6, e.g., entries 58, 78, and 85; Table 12, entries 8 and 31), acylation with acid chlorides or esters is, with one exception (diethyl oxalate, Table 6, entries 86 and 97), not a useful synthetic process.[190] The demonstration of smooth acylation of metalated pyridinecarboxamides using *N,N*-dimethylbenzamides (Table 8, entries 14–18) suggests that the use of these electrophiles for the corresponding benzamides should be explored. The viability of introduction of a new DMG by carbamoylation using $ClCONEt_2$ has been amply documented (Schemes 25 and 26).

XI. Synthetic Consequences of o-Heteroatom Introduction

A. *o*-Amino

1. *Quinolones*

The availability of anthranilamides **338** (Scheme 75) by the $TsN_3/NaBH_4$ method (Table 6, entries 27, 36, 45, 52, 60, 66, 73, 106, 146, and 147) and the demonstration of the electrophilic character of the $CONEt_2$ group (Scheme 41) led to the development of a new

TABLE 30. Synthesis of Anthraquinones by the Tandem DoM Reaction

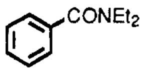
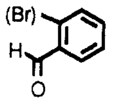
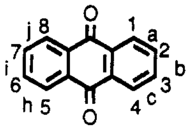
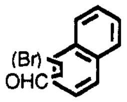
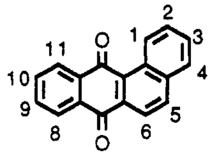
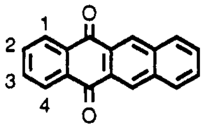
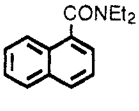
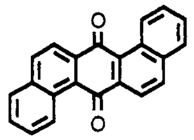
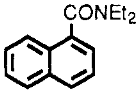
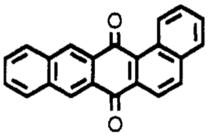
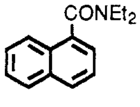
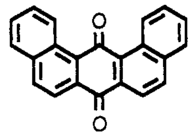
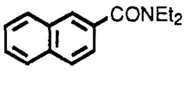
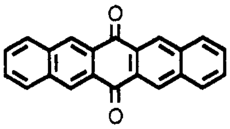
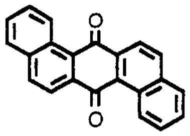
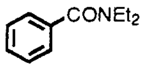
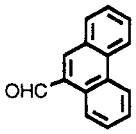
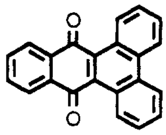
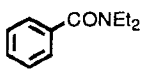
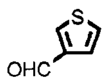
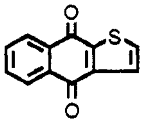
Entry	Amide	Aldehyde	Product	Yield, % Cond^a A	B	C	Ref
							
1	no subst	no subst	no subst	43			87
2	no subst	2-OMe	1-OMe	10	55		87,123
3	no subst	4-OMe	2-OMe	28			87
4	no subst	4-Me	2-Me	15	15	65^b	87, 123,185
5	3,4-$(OMe)_2$	no subst	1,2-$(OMe)_2$			70	185
6	5-OMe, 2-OMOM	no subst	1-OMe, 4-OMOM			66	185
7	2-TMS, 3,4-$(OMe)_2$	no subst	1-TMS, 2,3-$(OMe)_2$			58	185
8	3-OMe	3,4-OCH_2O	1-OMe, 6,7-OCH_2O-			70	185
9	3,4-$(OMe)_2$	3,4-OCH_2O	1,2-$(OMe)_2$, 6,7-OCH_2O-			68	185
10	4-$CONEt_2$	3,4-OCH_2O	2-$CONEt_2$, 6,7-OCH_2O-			60	185
							
11	no subst	1-CHO	no subst	49	53	75	87,123,185
12	4-OMe	1-CHO, 2-Br	9-OMe			73	185
13	2-$CONEt_2$	1-CHO, 2-Br	11-$CONEt_2$			50	185
							
14	no subst	2-CHO	no subst	39^c		61	87,185
15	4-OMe	2-CHO	3-OMe			70	185
16		1-CHO		10			87
17		2-CHO		10			87
18		1-Br, 2-CHO				62	185
19		2-CHO		2			87
				2			
20				41			87
21				35			87

TABLE 30 (Continued)

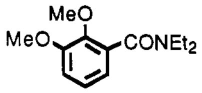
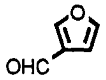
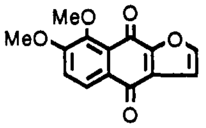
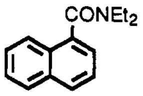
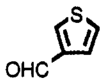
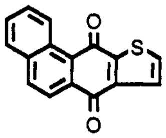
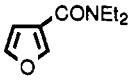
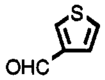
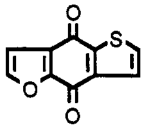
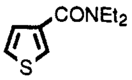
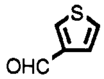
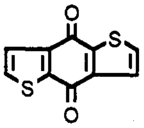
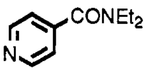
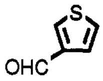
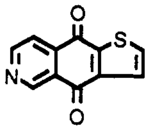
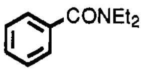
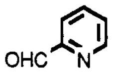
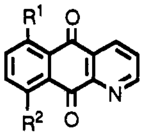
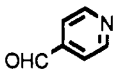
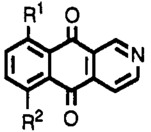
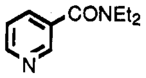
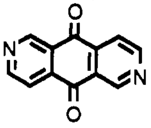
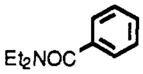
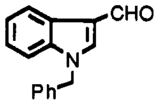
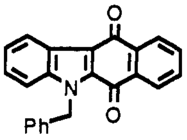
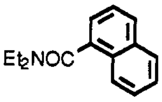
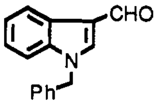
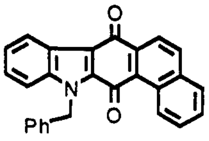
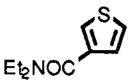
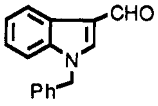
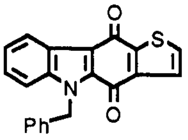
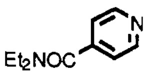
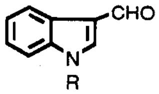
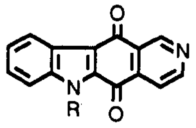
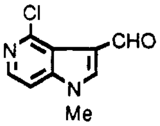
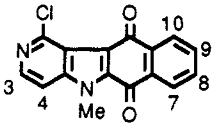
Entry	Amide	Aldehyde	Product	Yield, %			Ref
				Cond^a A	B	C	
22				15			169
23				37			87
24				24			87
25				77			87
26				20			87
							
27	2-OMe		R^1 = OMe, R^2 = H	-			187
28	3-OMe		R^1 = H, R^2 = OMe	-			187
							
29	2-OMe		R^1 = OMe, R^2 = H	10			187
30	3-OMe		R^1 = H, R^2 = OMe	-			187
31				90^d			189
32				44			87
33				20			87
34				67			87
							
35		R = CH_2OMe		26			87
36		R = Me		76			87
37		R = CH_2Ph		40			87

TABLE 30 (Continued)

Entry	Amide	Aldehyde	Product	Yield, % Cond^a A	B	C	Ref
							
38	no subst		no subst	4 (9)^e			188
39	4-OMe		9-OMe	4 (6)^e			188
40	3-OMe		10-OMe	12 (36)^e			188
41	2,5-(OMe)2		7,10-(OMe)2	20^e			188
42	3,4,5-(OMe)3		8,9,10-(OMe)3	40^e			188
43	3,5-(OMe)2		8,10-(OMe)2	57^e			188
44	2-OMe		7-OMe	9^e			188

[a] Conditions A: (1) equiv *sec*-BuLi/TMEDA/THF/−78 °C/1 h; (2) ArCHO; (3) 1 equiv *sec*-BuLi/TMEDA/1 h; (4) → room temperature (5) H$^+$. Conditions B: Same as conditions A except for step 3, in which 4 equiv *sec*-BuLi/TMEDA was used, and step 5, CrO_3/HOAc. Conditions C: Same as conditions A; (2) ArCHO; (3) *t*-BuLi; (4) → room temperature; (5) H_2O/O_2. [b] From reaction of $4\text{-MeC}_6H_4CONEt_2$ with 2-BrC_6H_4CHO. [c] Benz[*a*]anthracene-7,12-dione (5%) was also isolated. [d] Conditions: 3 equiv of LDA in THF–HMPA/−78 °C. The corresponding isonicotinamide also gave the same product in unspecified yield. [e] Two equivalents of the diethylbenzamide was used.

general method for the regiospecific construction of 4-quinolones **340**.[192] Thus compounds **338** were readily converted into imines **339**, which, without purification, were treated with LDA to afford 4-quinolones **340**. As gleaned from Table 32, 2-substituted (entries 1–5), annelated (entry 7), and condensed (entry 10) products have been obtained in good to excellent yield. Unsymmetrical imines undergo cyclization from the less sterically hindered incipient azaallyl anion (entries 2, 3, and 6). The formation of methoxy-substituted quinolones (entries 8 and 9) by this mild modification of the von Niementowski reaction is of particular synthetic significance.

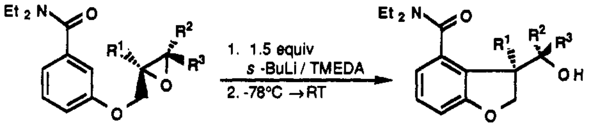
2. Acridones

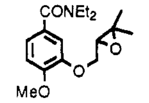
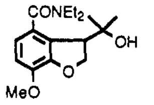
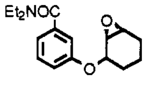
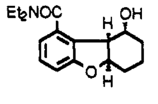
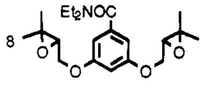
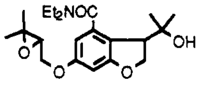
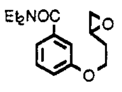
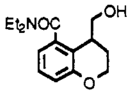
The demonstration of oxidative coupling of ortho-lithiated benzamides with anilido cuprates to form *N*-arylanthranilamides (Table 6, entries 1, 3–5, 8, 10, 17, 18, and 35) served as the basis for the general regiospecific synthesis of acridones (Table 33).[193] A variety of methoxy-substituted N–H and N–Me acridones have been prepared from *N*,*N*-dimethyl- or *N*,*N*-diethylamide precursors, mainly under vigorous heptafluorobutyric acid conditions. Naturally occurring acridones have been synthesized (entries 1, 7, and 8) in yields that compare favorably with those obtained by classical Ullmann- or benzyne-based[194] protocols.

B. *o*-Thiol and *o*-Selenol

The conveniently prepared thiosalicylamides (Table 6, entries 48, 53, 63, and 68) undergo lithium isopropylcyclohexylamide (LICA)-mediated condensation with benzynes, derived in situ from halobenzenes, to form thioxanthan-9-ones (Table 34).[195] All four isomeric monomethoxy thioxanthenones (entries 1, 3, 5, and 7) as well as some dimethoxy (entries 2, 4, 6, 8) and trimethoxy (entry 9) derivatives are obtained by taking advantage of the regioselective benzamide DoM reaction and the polarization effect of the OMe group in directing the cycloaddition. The 2-, 3-, and 4-methoxy regioisomers cannot be prepared from the corresponding condensation of methyl thiosalicylate owing to the unfavorable OMe polarization effect in the requisite benzyne intermediates. Entry 10 illustrates an interesting albeit low-yield case of this type of heteroannelation using a thiosalicylate.

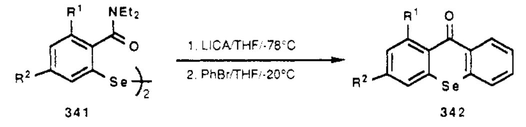
TABLE 31. Tertiary Amide DoM-Induced Epoxycyclialkylation[191]



Entry	Epoxide R^1	R^2	R^3	Product R^1	R^2	R^3	Yield, %
1	H	H	H	H	H	H	67
2	H	Me	H	H	Me	H	60
3	H	Ph	H	H	Ph	H	64
4	H	Me	Me	H	Me	Me	68
5	Me	H	H	Me	H	H	0
6							53
7							65
8							38^a
9							32

[a] Three equivalents of *sec*-BuLi/TMEDA was required.

SCHEME 76

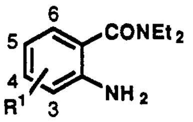
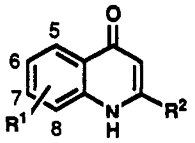
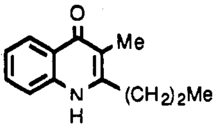
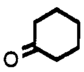
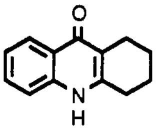
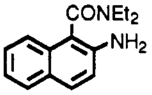
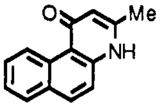


341 342

a: R^1 = R^2 = H (40%); **b**: R^1 = H, R^2 = OMe (22%); **c**: R^1 = OMe, R^2 = H (42%).

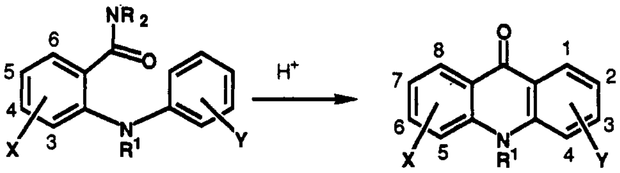
By an analogous process, several relatively unknown selenoxanthen-9-ones **342** (Scheme 76) have been pre-

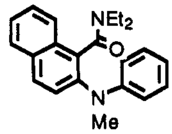
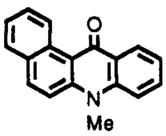
TABLE 32. Synthesis of 4-Quinolone Derivatives from Anthranilamides[192]

Entry		Ketone	Conditions[a]		Yield, %
1	$R^1 = H$	MeCOMe	A	$R^1 = H, R^2 = Me$	55 (45)[b]
2	$R^1 = H$	MeCOEt	A	$R^1 = H, R^2 = Et$	95
3	$R^1 = H$	$MeCO(CH_2)_4Me$	A	$R^1 = H, R^2 = (CH_2)_4Me$	93
4	$R^1 = H$	MeCOPh	A	$R^1 = H, R^2 = Ph$	70
5	$R^1 = H$	$MeCOCO_2Et$	A	$R^1 = H, R^2 = CO_2Et$	64
6	$R^1 = H$	$MeCH_2CO(CH_2)_2Me$	A		58
7	$R^1 = H$		B		70
8	$R^1 = 3\text{-}OMe$	MeCOMe	A	$R^1 = 8\text{-}OMe, R^2 = Me$	95
9	$R^1 = 6\text{-}OMe$	MeCOMe	C	$R^1 = 5\text{-}OMe, R^2 = Me$	73
10		MeCOMe	B		84

[a] Conditions A: 0 °C → room temperature, 8–12 h. Conditions B: reflux, 8–12 h. Conditions C: reflux, 3 h. [b] Yield using the *N,N*-dimethylanthranilamide.

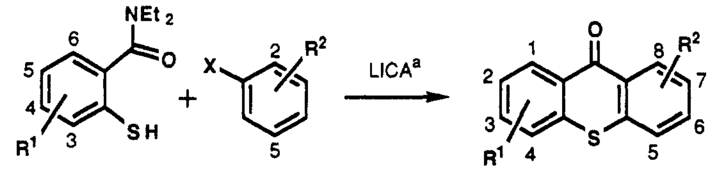
TABLE 33. Synthesis of Acridones from *N*-Phenylanthranilamides



Entry	Anthranilamide				Conditions[a]	Acridone			Yield, %	Ref
	R	R^1	X	Y		R^1	X	Y		
1	Et	Me	H	H	A	Me	H	H	32	193
2	Et	H	H	2'-OMe	B	H	H	4-OMe	58	193
3	Et	H	6-OMe	H	B	H	8-OMe	H	80	193
4	Me	Me	6-OMe	H	B	Me	8-OMe	H	95	193
5	Me	H	6-OMe	3'-OMe	B	H	8-OMe	3-OMe	95	193
6	Me	Me	3-OMe	H	B	Me	5-OMe	H	25	193
7	Me	Me	4,6-$(OMe)_2$	H	C	Me	6,8-$(OMe)_2$	H	79	193
8	Me	Me	4,5-OCH_2O, 6-OMe	H	D	Me	6,7-OCH_2O, 8-OMe	H	61	193
9	Et	H	6-Me	H	B	H	8-Me	H	50	130
10					B				85	193

[a] Conditions A: $POCl_3$/PhMe/reflux/10 h. Conditions B: heptaflurobutyric acid/reflux/24–27 h. Conditions C: CF_3CO_2H/reflux/60 h. Conditions D: HCO_2H/reflux/60 h.

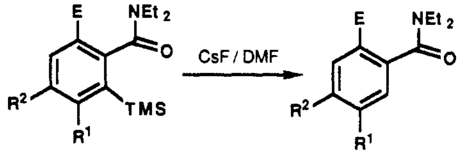
TABLE 34. Synthesis of Thioxanthan-9-ones from Thiosalicylamides[195]

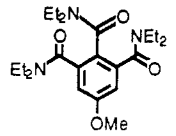


Entry	Thiosalicylamide R^1	Halobenzene X	Halobenzene R^2	Thioxanthanone R^1	Thioxanthanone R^2	Yield, %
1	3-OMe	Br	H	4-OMe	H	60
2	3-OMe	Br	2-OMe	4-OMe	8-OMe	37
3	4-OMe	Br	H	3-OMe	H	90
4	4-OMe	Br	2-OMe	3-OMe	8-OMe	45
5	5-OMe	Br	H	2-OMe	H	50
6	5-OMe	Br	2-OMe	2-OMe	8-OMe	38
7	6-OMe	Br	H	1-OMe	H	65
8	6-OMe	Br	2-OMe	1-OMe	8-OMe	61
9	6-OMe	Cl	2,5-$(MeO)_2$	1-OMe	5,8-$(MeO)_2$	65
10	Methylthiosalicylate	Br	2-$CONEt_2$	1-$CONEt_2$	H	22

[a] Conditions: (1) 1 equiv of thiosalicylamide/3 equiv of lithium isopropylcyclohexylamide (LICA)/THF/−78 °C; (2) → −20 °C/2 equiv of halobenzene/THF; (3) → room temperature.

TABLE 35. Silicon Protection Route to Polysubstituted Benzamides[130]



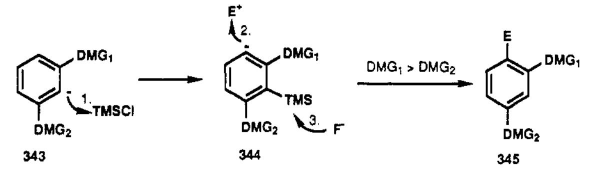
Entry	Product R^1	Product R^2	Product E	Yield, %
1	OMe	H	Me	85
2	OMe	H	CHO	76
3	OMe	H	$CONEt_2$	73
4	OMe	H	SMe	82
5	OMe	H	I	93
6	OMe	OMe	D	65
7	OMe	OMe	Me	87
8	Cl	H	D	90
9	Cl	H	CHO	80
10	F	H	D	95
11	F	H	Me	90
12				75

pared from the corresponding diselenides **341** (Table 6, entries 24, 54, and 64).[195]

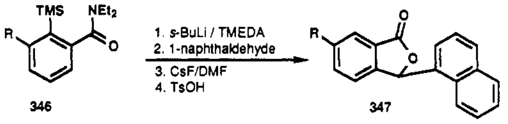
C. *o*-Silyl

1. Protection of Aromatic Preferred Metalation Sites

SCHEME 77



SCHEME 78



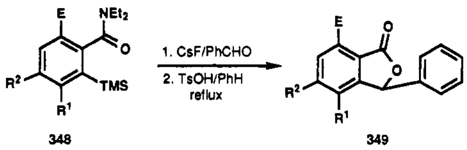
a: R = Cl (32%); b: R = F (40%)

The cooperative effects of 1,3-interrelated DMGs (Table 3) allow conceptualization of silicon protection (**343**, Scheme 77) of the in between site in order to achieve further DoM reactions (**344**, DMG_1 more powerful than DMG_2) and, eventually, deprotection as a general three-step procedure to diverse polysubstituted aromatics **345**. Such a sequence has been achieved for the ortho-silylated *m*-methoxy- (Table 35, entries 1–7), *m*-chloro- (entries 8 and 9), and *m*-fluorobenzamides (entries 10 and 11) and briefly explored in the synthesis of chloro and fluorophthalides, **346** → **347** (Scheme 78).[130] The former illustrates mainly the preparation of 1,3,5-functionalized systems at different oxidation states, while the latter sequence indicates potential for the preparation of specifically substituted PAH (section VIII.D.3).

2. Fluoride- and Electrophile-Induced Ipso Desilylation

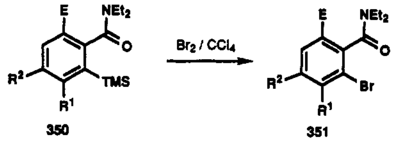
ortho-Silylated benzamides may also be used in fluoride-mediated condensation with aromatic aldehydes to give, after acid treatment, modest yields of phthalides, **348** → **349** (Scheme 79).[130] Although as yet insufficiently investigated in terms of substituent effects, this mild carbodesilylation process accommodates groups that, owing to preferential metalation or potential benzyne formation (e.g., **348c**) would not be

SCHEME 79

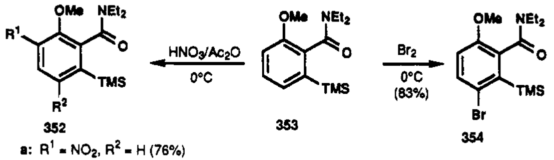


a: E = R^1 = R^2 = H (48%); b: E = H, R^1 = R^2 = OMe (49%);
c: E = Me, R^1 = Cl, R^2 = H (45%)

SCHEME 80



a: E = Me, R^1 = R^2 = H (89%); b: E = Me, R^1 = Cl, R^2 = H (81%);
c: E = H, R^1 = R^2 = OMe (67%); d: E = Me, R^1 = R^2 = OMe (95%)



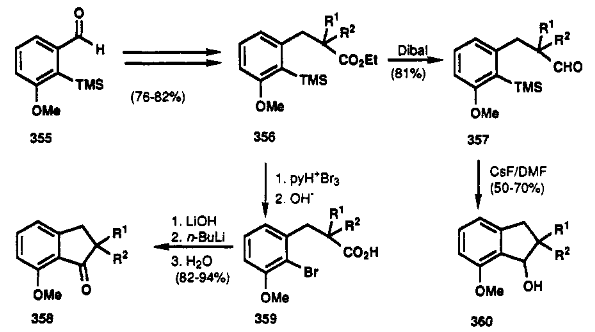
a: R^1 = NO_2, R^2 = H (76%)
b: R^1 = H, R^2 = NO_2 (19%)

tolerated by the strongly basic DoM conditions, thus precluding the synthesis of analogous products by the latter method (compare Schemes 62 and 82).

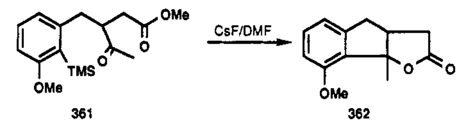
Ipso bromodesilylation of ortho-silylated benzamides using bromine leads to *o*-bromobenzamides, **350** → **351** (Scheme 80).[130] Although well-known and mechanistically documented, this electrophilic reaction of arylsilanes has enjoyed limited synthetic application in spite of the promise of achieving substitution patterns that constitute far from trivial problems in classical electrophilic aromatic substitution. 2,6-Bis ipso bromodesilylations of benzamides (Scheme 22) and carbamates[196] have also been reported. While as yet undefined in scope, interesting limitations that may also be of synthetic value are seen from comparison of these results with transformations **353** into **352** and **354**. The high-yield formation of **354** is indicative of the overriding directing effect of the methoxy group[130] while the generation of **352a** and **352b** favoring the former product[197] suggests a steric effect of TMS to the larger nitronium electrophile.

Intramolecular versions of the fluoride-mediated carbodesilylation processes provide regiospecific routes to 7-methoxyindanol derivatives (**360a–c**, Scheme 81).[103] Benzaldehyde **355**, obtained in three steps from the corresponding amide (Scheme 11), was converted by standard procedures involving Wittig chemistry and reduction via **356a–c** into **357a–c**. Cyclization using CsF afforded modest yields of 7-methoxy-1-indanols **360a–c**. Under similar conditions, a more complex case, the keto ester **361**, was transformed into the lactone **362**.[198] These cases illustrate a mild methodology that overrides the textbook example of normal Friedel–Crafts reactivity and suggest broader utility for carbo- and heteroannelation. As a complementary method, the bromo acids **359**, readily accessible from **356** by ipso bromodesilylation, have been converted[103] in somewhat higher overall yields into the 7-methoxy-1-indanones **358** by the metal–halogen exchange initiated Parham cycliacylation reaction.[186]

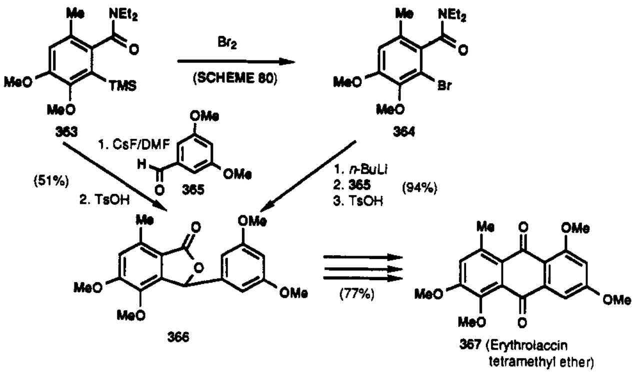
SCHEME 81



a: R^1 = R^2 = H; b: R^1 = H, R^2 = Me; c: R^1 = R^2 = Me



SCHEME 82

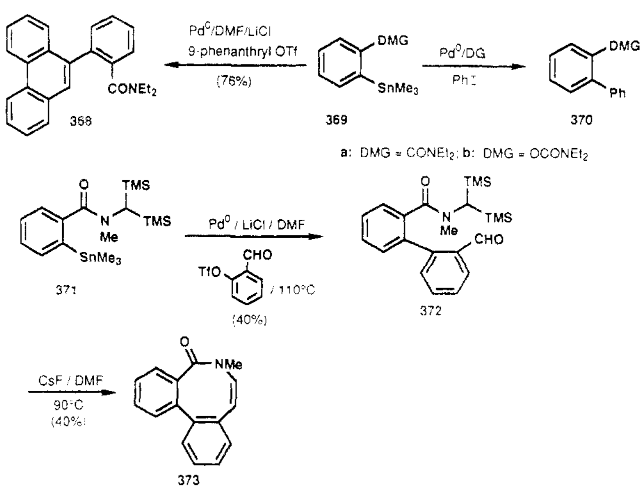


Both silicon protection and ipso bromodesilylation serve as guiding principles in the synthesis of erythrolaccin tetramethyl ether (**367**) (Scheme 82).[164] Thus treatment of **363** with the benzaldehyde **365** in the presence of CsF followed by TsOH cyclization gave the phthalide **366** in modest yield. On the other hand, by taking advantage of extremely fast alkyllithium-induced metal–halogen exchange compared to *o*-tolyl methyl deprotonation, the bromobenzamide **364** provided, after condensation with **365** and acid treatment, **366** in almost quantitative yield. Unexceptional steps led to **367** in 65% overall yield, thus completing the most efficient synthesis of this penultimate precursor of the naturally occurring anthraquinone.

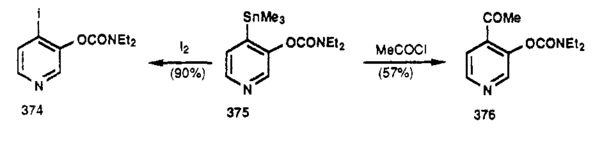
D. *o*-Stannyl

ortho-Stannylated benzamides and *O*-aryl carbamates, readily obtained by DoM processes (e.g., Table 6, entries 25 and 140; Table 14, entry 10), represent synthetic connections to the excellent Stille transition-metal-catalyzed cross-coupling regimen.[199] Thus **369a** (Scheme 83) has been converted into **368** and **370a** using aryl triflate[200] and bromide[158] coupling partners, respectively; similarly, **369b** gave **370b**.[158] As a further link, the biphenyl **372**, obtained from the *o*-stannyl α,α-disilyl amide **371** by cross coupling, has been transformed in modest yield into the dibenzazocinone **373** using an intramolecular Peterson olefination.[104] The known fast rate of electrophile-induced ipso destannylation of arylstannanes has been adapted in the regiospecific iodination (**374**) and acylation (**376**) of the

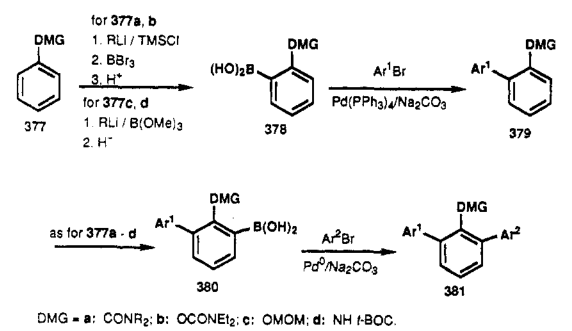
SCHEME 83



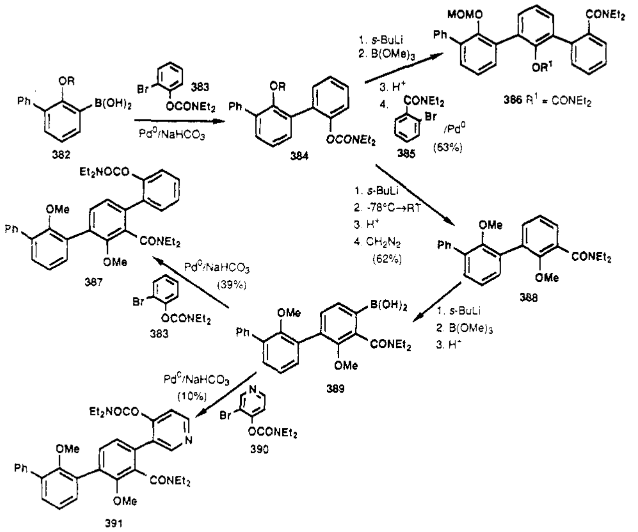
SCHEME 84



SCHEME 85



SCHEME 86



tin *O*-pyridyl carbamate **375** (Scheme 84).[108] Generalization of such synthetically useful processes for amide, carbamate, and other DMGs may be anticipated.

E. *o*-Boronic Acid

1. Cross-Coupling Methodology

The ready availability of ortho-DMG arylboronic acids either by metalation–boronation or by metalation–silylation–ipso borodesilylation sequences, **377** → **378** (Scheme 85) provides a synthetic link to the Suzuki cross-coupling protocol.[201] Although the boronic acids **378a–d** may be characterized as their diethanolamine adducts, they are normally coupled directly as crude foams with aryl bromides under Pd^0 catalysis, in one of several different solvent systems, to afford a variety of biaryls with carbon- and heteroatom-DMGs **379** in high yields.[202,203] Furthermore, iteration of this process via the biarylboronic acids **380** allows access to similarly functionalized *m*-terphenyls **381**.[203]

In the context of tertiary amide **377a** and carbamate **377b** arylboronic acids, procured by either indicated tactic, this sequence has considerable scope for the synthesis of unsymmetrical biaryls and heterobiaryls (Table 36). Thus a variety of biphenyl-2-carboxamides with methyl (entries 2–5 and 10), methoxy (entries 6–8), carboxamido (entries 4 and 9), and chloro (entry 5) substituents have been obtained. Steric hindrance appears not to be a major factor for the formation of 2,2′-disubstituted systems (entries 2–6 and 8) unless one of the ortho groups is exceedingly bulky in the aryl bromide coupling component (entry 9). Of the number of methoxy-substituted boronic acids that participate in this reaction (entries 19–26), those leading to the formation of a 2,2′,6′-trisubstituted system (entry 22), a differentiated oxygenated derivative (entry 25), and others derived by inversion of the boronic acid (non-DoM origin) and bromo functions in the coupling partners (entries 24 and 27) may be of specific synthetic value. Furthermore, unsymmetrical phenyl–naphthyl (entries 11 and 12), phenyl–9-phenanthryl (entry 13), and phenyl–heteroaryl (entries 14–17) systems are accessible in high yields. A solitary case of coupling with benzyl bromide has been recorded (entry 18), but allyl and vinyl bromides have not yielded the expected products.[202]

Although requiring further investigation in scope, coupling reactions of phenyl *O*-carbamates provide products in lower yields (entries 28 and 29) perhaps due to competing hydrolysis under the mild base-catalyzed conditions.

Benzamide 2-aryl-6-boronic acids (**380**, Scheme 85), prepared by identical metalation–boronation sequences, undergo efficient cross coupling with substituted phenyl (Table 36, entries 30, 31, 33, and 34), naphthyl (entries 32, 35, and 36), and phenanthryl (entry 37) bromides to give diverse amide *m*-terphenyls. The observed good to excellent yields of these products suggest that aryl steric hindrance effects, clearly evident in the twisted orientation of the 1,2,3-substituents (X-ray structure of entry 32),[204] are not detrimental to the cross-coupling process. Similarly, high yields of carbamate *m*-terphenyls are obtained (entries 38–40), which also suggest that, in comparison to the formation of the corresponding biaryl systems (entries 28 and 29), carbamate hydrolysis under the basic reaction conditions is sterically impeded.

Iterative application of the DoM boronation–cross coupling process has led to the assemblage of highly functionalized *m*-tetraphenyls and mixed *m*- and *p*-tetraphenyls (Scheme 86).[205] Thus cross coupling of the biphenylboronic acid **382** with the *o*-bromophenyl

TABLE 36. Cross-Coupling of Benzamide and *O*-Aryl Carbamate *o*-Boronic Acids with Aryl Bromides

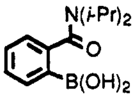
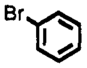
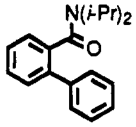
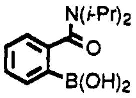
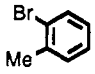
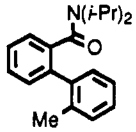
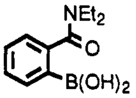
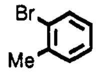
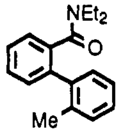
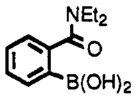
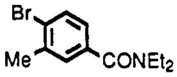
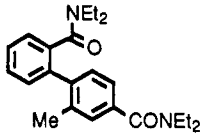
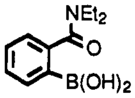
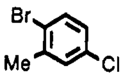
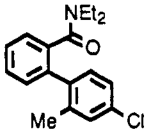
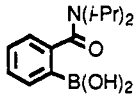
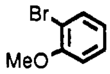
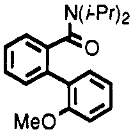
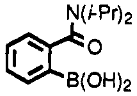
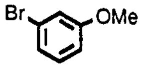
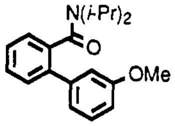
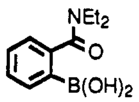
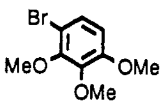
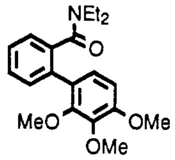
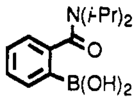
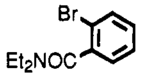
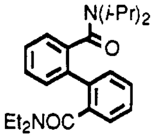
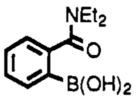
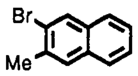
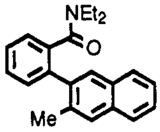
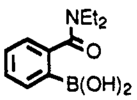
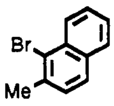
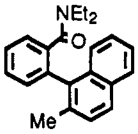
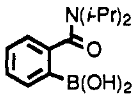
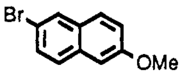
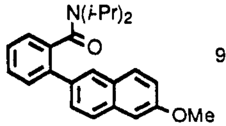
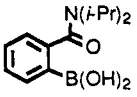
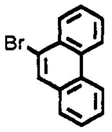
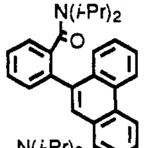
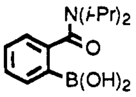
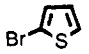
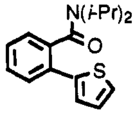
Entry	Boronic Acid	Aryl Bromide	Product	Yield, %	Ref
1				82	202
2				81	200
3				87	200
4				77	200,208
5				85	200,208
6				85	202
7				71	206,209
8				73	206,207
9				44	202
10				79	200,208
11				25	200,208
12				95	202
13				89	209
14				92	202

TABLE 36 (Continued)

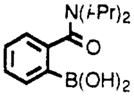
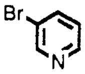
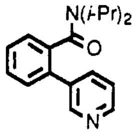
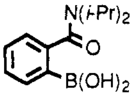
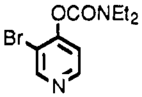
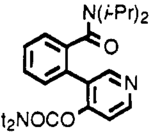
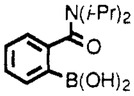
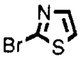
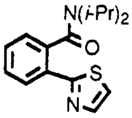
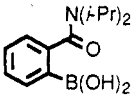
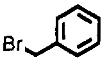
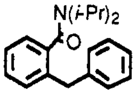
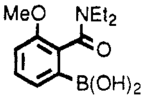
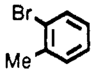
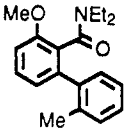
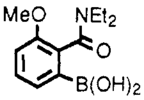
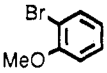
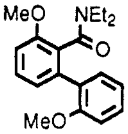
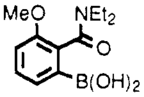
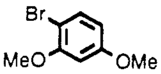
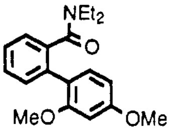
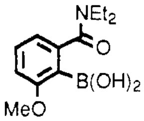
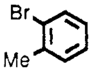
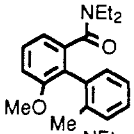
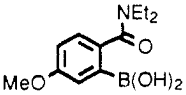
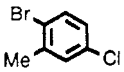
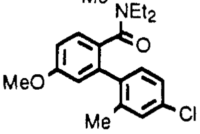
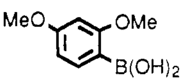
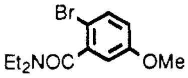
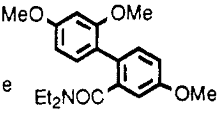
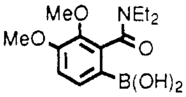
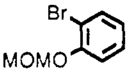
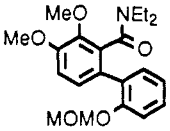
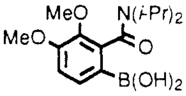
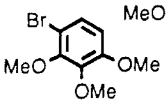
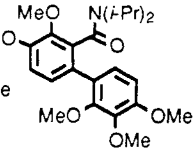
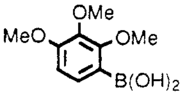
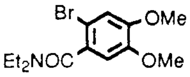
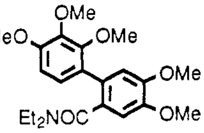
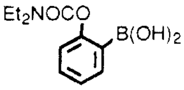
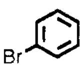
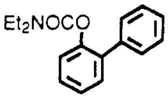
Entry	Boronic Acid	Aryl Bromide	Product	Yield, %	Ref
15				90	202
16				80	202
17				87	202
18				83	202
19				85	200,208
20				64	206
21				88	207
22				23	200,208
23				98	200,208
24				76	207
25				75	207
26				74	207
27				77	207
28				52	203

TABLE 36 (Continued)

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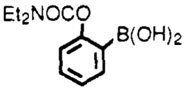
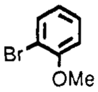
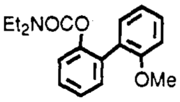
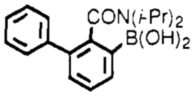
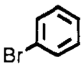
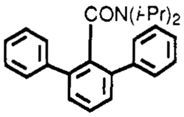
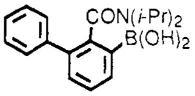
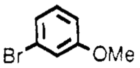
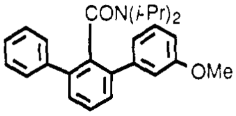
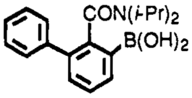
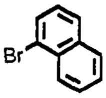
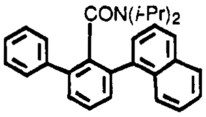
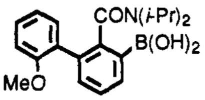
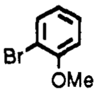
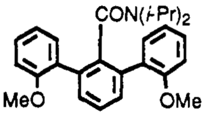
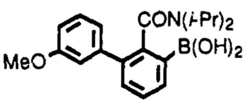
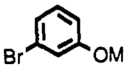
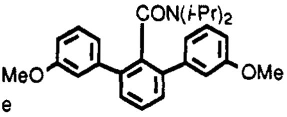
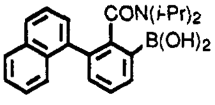
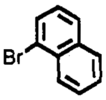
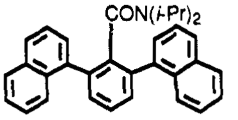
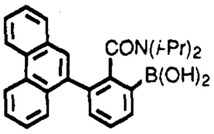
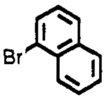
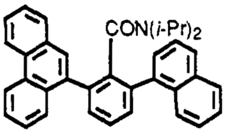
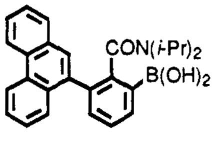
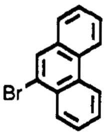
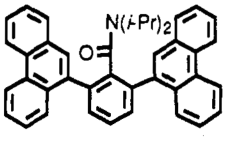
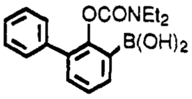
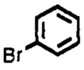
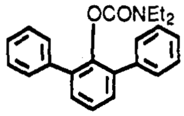
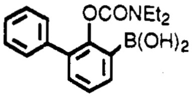
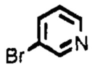
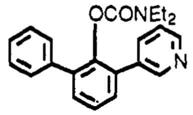
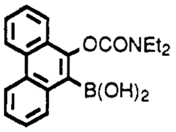
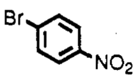
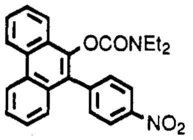
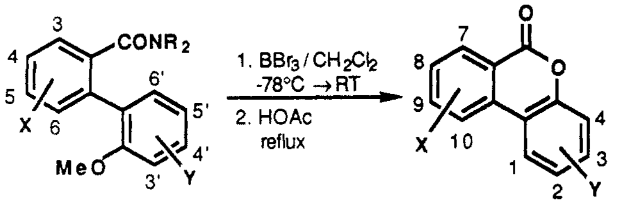
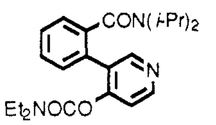
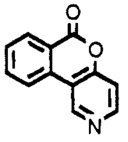
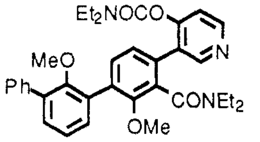
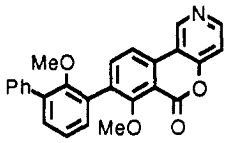
29				40-55	202,203
30				91	203
31				85	209
32				84	203
33				80	209
34				83	209
35				84	209
36				81	209
37				78	209
38				87	203
39				75	203
40				80	200

carbamate **383** gave the expected product **384**, R = MOM (31%), and, surprisingly, the phenol **384**, R = H (41%). With **384**, R = MOM, a second sequence of metalation, boronation, and cross coupling with **385** led to the *m*-tetraphenyl **386**. Alternatively, anionic ortho-Fries rearrangement (section V.A) on **384**, R = MOM, followed by acid hydrolysis and etherification of the intermediate diphenol gave the *m*-terphenol **388**, which now reveals a site for para cross coupling. Metalation–boronation gave the boronic acid **389**, which served a pivotal position for cross coupling with bromo carbamates **383** and **390** to afford, in low yields, the tetraphenyl **387** and the azapyridotetraphenyl **391**, respectively.

The connection between the DoM and the Suzuki cross-coupling reactions provides an entry into highly functionalized biaryls, *m*-teraryls, and tetraaryls whose generality, scope, and regioselectivity allow anticipation

TABLE 37. Synthesis of Dibenzo[*b*,*d*]pyran-6-ones



Entry	Biaryl Amide			Dibenzopyrone		Yield, %	Ref
	R	X	Y	X	Y		
1	*i*-Pr	H	H	H	H	89	202
2	Et	3-OMe	H	7-OH	H	79	206
3[a]	Et	3,4-(OMe)$_2$	H	7,8-(OH)$_2$	H	82[b]	207
4	*i*-Pr	H	3',4'-(OMe)$_2$	H	3,4-(OH)$_2$	71	207
5	Et	3-OMe	4'-OMe	7-OH	3-OH	62	207
6	Et	4-OMe	4'-OMe	8-OH	3-OH	47	207
7	*i*-Pr	3,4-(OMe)$_2$	3'4'-(OMe)$_2$	7,8-(OH)$_2$	3,4-(OH)$_2$	70	207
8	Et	4,5-(OMe)$_2$	3'4'-(OMe)$_2$	8,9-(OH)$_2$	3,4-(OH)$_2$	75	207
9						92[c]	202
10						c	205

[a] The 2'-OMOM derivative was used. [b] The order of reactions with BBr$_3$ and HOAc was inverted. [c] Obtained under 2 N HCl/reflux conditions.

of broad application for the synthesis of polyaryls with interesting properties.

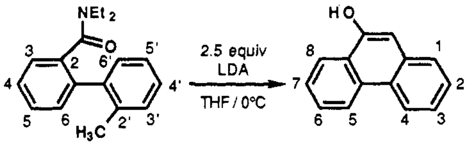
2. Dibenzopyrones

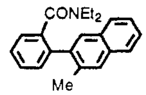
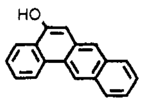
The simple two-step conversion of 2-methoxy-2'-carboxamidobiphenyls, efficiently obtained by the cross-coupling tactic (Table 36), into dibenzopyranones (Table 37) constitutes a new general synthesis of this class of heterocycles.[202,205-207] Good to excellent yields of highly oxygenated dibenzopyrones (entries 1–8) have been obtained, including two heterocyclic analogues (entries 9 and 10).

3. Phenanthrols and Phenanthrenes

The conversion of 2-methyl-2'-carboxamidobiphenyls into 9-phenanthrols (Table 38) defines a further exploitation of the DoM–cross coupling connection.[200] This high-yield process, based on the vinylogous thermodynamic acidity of the 2-methyl hydrogens, shows good versatility for the regiospecific preparation of methoxy (entries 2, 5, and 6), carboxamido (entry 3), and chloro (entries 4 and 6) phenanthrols but fails for nitro derivatives (entries 7 and 8), presumably because of the incompatability of nitro aromatics and LDA. Peri-substituted (entry 5) and condensed (entry 9) phenanthrols have also been obtained. Access to the parent hydrocarbons via triflate intermediates, **392** → **393** (Scheme 87),[200,208] provides additional scope to this method which is favorably competitive with the classical Pschorr, Ullmann, and the more recent Mallory phenanthrene methodologies.

TABLE 38. Synthesis of 9-Phenanthrols from Biaryls[200]



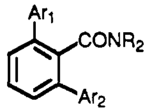
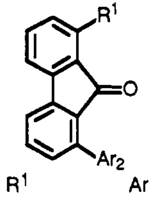
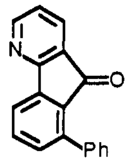
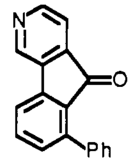
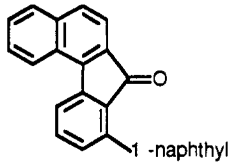
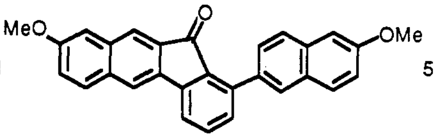
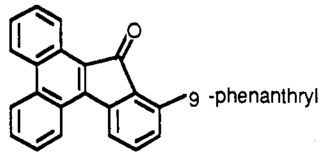
Entry	Biaryl	Phenanthrol	Yield, %
1	no subst	no subst	92 (98)[a]
2	3-OMe	8-OMe	92
3	4'-CONEt$_2$	2-CONEt$_2$	78
4	4'-Cl	2-Cl	96
5	6-OMe	5-OMe	92
6	5-OMe, 4'-Cl	6-OMe, 2-Cl	93
7	4'-NO$_2$	-	NR
8	5'-NO$_2$	-	NR
9			90

[a] Yield using the corresponding diisopropylamide.

4. Remote Metalation to Fluorenones

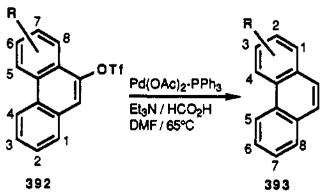
Examination of the X-ray crystallographic structure of a *m*-terphenyl (Table 36, entry 32)[204] and consider-

TABLE 39. Synthesis of Fluorenones by Remote Metalation[206,208,209]

Entry	m-Terphenyl		Fluorenone		Yield, %
					
	Ar_1	Ar_2	R^1	Ar_2	
1	Ph	Ph	H	Ph	$65^{a,b,c}$, $84^{b,d}$
2	$3\text{-}MeOC_6H_4$	Ph	OMe	Ph	$45^{a,b}$
3	$3\text{-}MeOC_6H_4$	$3\text{-}MeOC_6H_4$	OMe	$3\text{-}MeOC_6H_4$	$42^{a,b}$
4	2-pyridyl	Ph			$46^{a,c}$
5	3-pyridyl	Ph			$55^{a,c}$
6	1-Naphthyl	1-Naphthyl			48a,b
7	2-(6-OMe)naphthyl	2-(6-OMe)naphthyl			$53^{a,b}$
8	9-phenanthryl	9-phenanthryl			$34^{a,b}$

[a] Yield from the diisopropylamide. [b] t-BuLi/THF/0 °C → room temperature conditions. [c] LDA/THF/0 °C → room temperature conditions. [d] Yield from the the diethylamide.

SCHEME 87



392

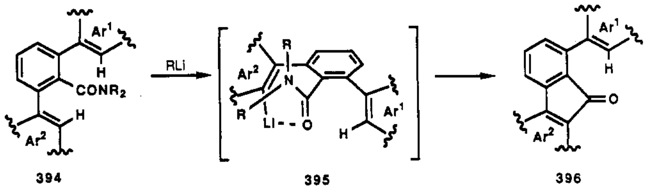
a: R = H
b: R = 2-Cl
c: R = 5-OMe
d: R = 8-OMe

393

a: R = H (67%)
b: R = 2-Cl (68%)
c: R = 4-OMe (93%)
d: R = 1-OMe (97%)

ation of the role of complex induced proximity effects in amide reactions[65] led to the discovery of a remote metalation-induced synthesis of fluorenone derivatives, **394** → **395** → **396** (Scheme 88).[206,208,209] The regioselectivity of this process (**395**) will be dependent in part, upon the relative acidities of the remote hydrogens in the Ar^1 and Ar^2 moieties. On the basis of preliminary observations (Table 39), rapid regiospecific access to a variety of substituted (entries 1–3), heterocyclic (entries 4 and 5), and condensed (entries 6–8) fluorenones from readily available *m*-terphenyls (Table 36, entries 30–37) is feasible and generalization is anticipated.

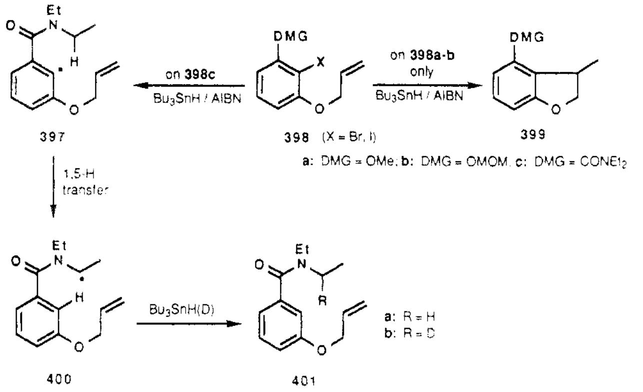
SCHEME 88



X. DoM of Benzamides and Free Radical Chemistry

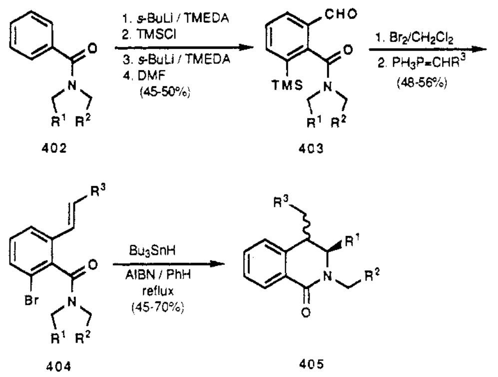
Although a variety of OMe- and OMOM-substituted bromoaryl allyl ethers **398a,b** (Scheme 89), available by the DoM reaction, undergo smooth radical-induced ring closure to give a series of benzene annelated furans **399**,[210] including aflatoxin synthons,[211] the corresponding carboxamide **398c** suffers dehalogenation to **401a** in high yield. A tin deuteride mediated experiment on

SCHEME 89



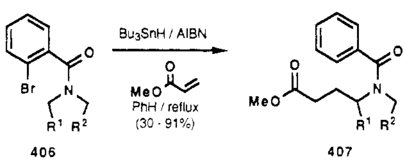
a: DMG = OMe; b: DMG = OMOM. c: DMG = $CONEt_2$

SCHEME 90



a: $R^1 = R^2 = Me, R^3 = H$; b: $R^1 = R^2 = Me, R^3 = Ph$; c: $R^1 = R^2 = Me, R^3 = CO_2Et$;
d: $R^1 + R^2 = (CH_2)_2, R^3 = H$; e: $R^1 + R^2 = (CH_2)_3, R^3 = H$; f: $R^1 = R^2 = R^3 = H$.

SCHEME 91



a: $R^1 = R^2 = H$; b: $R^1 = R^2 = Me$; c: $R^1 + R^2 = (CH_2)_2$;
d: $R^1 = R^2 = (CH_2)_3$; e: $R^1 = H, R^2 = Ph$; f: $R^1 = TMS, R^2 = H$.

398c gave **401b** (>95% d_1 content), thus implicating the formation of an α-amidoyl radical via a 1,5-hydrogen atom transfer process, **397** → **400**, which supersedes the normally rapid 5-exo-trig ring closure. On the basis of this observation, a new method for heteroannelation to an aromatic ring has been developed (Scheme 90).[212] Thus application of the tin hydride method to compounds **404a–f**, available from **402** by a sequence of DoM (**402** → **403**), ipso halodesilylation, and standard Wittig procedures (**403** → **404**), led to diastereomeric mixtures of dihydroisoquinolone derivatives **405a–f** in modest to good yields. The success of this reaction is dependent upon rapid 1,5-hydrogen atom transfer and 6-exo-trig ring closure relative to ring–CO bond rotation of the incipient α-amidoyl radical and bimolecular quench by tin hydride. Intermolecular interception of the α-amidoyl radical by electron-deficient alkenes has also been demonstrated, **406** → **407** (Scheme 91). These early results suggest the development of a new class of intra- and intermolecular carbon–carbon bond-forming reactions, connected to DoM chemistry, which proceed via radical intermediates generated by 1,5-hydrogen atom transfer processes at normally unreactive sites.

XI. Concluding Remarks

Discovered 50 years ago by Gilman[19] and Wittig,[20] the DoM reaction began its rise to prominence by the systematic studies of Hauser and his school in the late 1950s.[22,29f] Early mechanistic studies[39,52,56,58] provided additional stimulus. The accelerating pace of application became evident only after alkyllithiums reached commercial status as a result of necessity in the industrially important anionic polymerization.[26] The timely review by Gschwend and Rodriguez[27] in 1979 stimulated synthetic chemists to fresh conceptualization in aromatic chemistry from the surprisingly large and, to that time, scattered body of accumulated knowledge on DoM processes.

In the past decade, the promise of the DoM reaction has been realized in significant and diverse applications in academic and industrial laboratories on micro- and macroscale operations. Although the reaction may be ripe for inclusion into undergraduate texts, the current limited mechanistic understanding[62] and continuing accumulation of new DMGs (Table 1) with their inherent new synthetic vistas forces the admission that the DoM process is still in a highly evolutionary stage. Mechanistic[62] and structural[36,37] insight into organolithiums and their reactions will allow the formulation of new, industrially more convenient, conditions for the DoM reaction, the discovery of new DMGs, and the further rational design of new synthetic pathways in aromatic chemistry.

The above comments are pertinent to the areas of benzamide and *O*-aryl carbamate DoM reactions. While amide metalations have been significantly exploited in synthesis, corresponding carbamate reactions are at early stages of development. The limited results in DoM reactions of heterocyclic systems may be ameliorated by the development of new compatible base/electrophile combinations. Consideration of amides and carbamates in combination and with other DMGs raises a multitude of retrosynthetic combinations and permutations invariably of considerable, and, at times, unique, value for the preparation of polysubstituted aromatics. The use of amide DMGs in electrophilic reaction modes subsequent to DoM chemistry has been barely initiated. The anionic ortho-Fries rearrangement of the carbamate DMG not only provides migratory functionalization methods for aromatics but also opens new doors for further DoM reaction of the migrated amide. The generation of dianionic species of both DMGs invites the development of new concepts in aromatic ring functionalization. The establishment of connections between the amide or carbamate DoM process and other modern synthetic methods, illustrated by cross coupling and free radical reactions, will continue to enhance the power of the methodology.

The complex induced proximity effect concept[65] will undoubtedly play a role in the further general development of DoM chemistry. Early indications in its value are evident in remote metalation of biaryl (Table 39) and annulene amides.[213] In a general context of amide and carbamate DMGs, this effect may stimulate the discovery of new metalation processes that would create a greater interplay between aliphatic and aromatic areas of chemistry. This path would naturally lead to the next evolutionary stage of the DoM reaction as a tool for organic synthesis. For, as in any scientific endeavor, "le dernier mot n'est certainement pas encore dit et l'avenir nous réservera encore bien des surprises".[214]

XII. Acknowledgments

I heartily thank all students whose joy in discovery, dedication, insight, and skillful experimentation over the past decade has provided the harvest of results on the benzamide and carbamate DoM chemistry. I dedicate this article to those who have been, those who are here, and those who will come. Our work has been supported by NSERC Canada, Merck Frosst, Imperial Oil, and the Ministry of Environment (Ontario) to whom I am grateful.

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