HETEROCYCLES VIA ORTHO-LITHIATED BENZAMIDES

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Ortho-lithiated N,N-diethyl benzamides, readily generated by treatment of the corresponding amides with sec-BuLi or t-BuLi in THF or Et_2O/TMEDA at -78°, are important new synthons (d_3-reagents) for the regiospecific construction of highly substituted aromatic derivatives which are difficult to obtain by classical (usually electrophilic substitution) chemistry (Scheme 1). This paper will demonstrate the utility of ortho-lithiated benzamides for the synthesis of contiguously substituted aromatics, phthalide and isochroman-1,3-dione heterocycles, phthalideisoquinoline alkaloids, anthraquinone natural products, polycyclic anthraquinones and corresponding PAH's, heterocyclic benzoquinones, and ellipticine alkaloids.

The term directed metalation is defined as the deprotonation of an sp^2-carbon α to a heteroatom-containing substituent on an aromatic or olefinic substrate. In this context, ortho metalation refers specifically to aromatic substrates (Fig. 1). The ortho directing group Z 1) anchors the strong base (invariably an alkyllithium reagent) by coordination, 2) provides an inductive electron-withdrawing effect in the deprotonation step, and 3) stabilizes the ortho metalated intermediate by chelation. Systems in which the Z group bears acidic hydrogen require

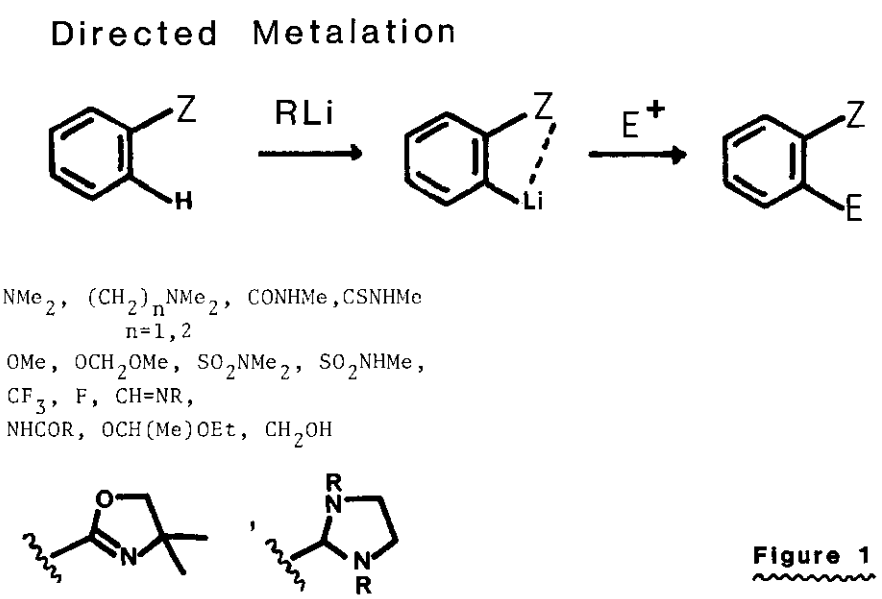


Figure 1

two equivalents of base and, by necessity, lead to dimetalated species. Gilman[1], and subsequently Hauser[2], in extensive pioneering efforts, laid the groundwork in this area and defined many of the groups which promote ortho metalation. The industrial development[3] of organolithium bases such as sec-BuLi and t-BuLi has provided a strong impetus for the exploitation and advancement of the original discoveries.

In recent years, the list of groups which promote ortho metalation has grown considerably (Fig. 1) and the early findings have been modernized and significantly extended.[4] For example, Hauser's metalated secondary benzamides have been vigorously applied to the synthesis of heterocycles[5] and natural products,[6] secondary thioamides have been successfully tested,[7] the methylenemethoxy ether group has received considerable attention,[8,9] and has served as a model for the development of the analogous OCH(Me)OEt moiety,[9] and even the methyleneoxy anion has been shown to be a moderately efficient ortho metalation director.[10] The criteria for a group Z to be effective in ortho metalation are 1) it must be resistant to nucleophilic attack by the RLi reagent, and 2) it must contain at least one heteroatom which can coordinate with the incipient ortho metal atom in a 4-, 5- (most favorable) or 6-membered intermediate. Nucleophilic attack can be minimized by using sterically demanding (e.g. $CONEt_2$) and charge deactivated (e.g. $CO\bar{N}R$) Z groups.

In Seebach's terminology, ortho metalated species behave as d_3 reagents.[11] In synthesis, this translates into the potential for placing carbon substituents, with and without functionality for further modification, into positions normally

Directed Metalation

Relative Ortho-Directing Priorities

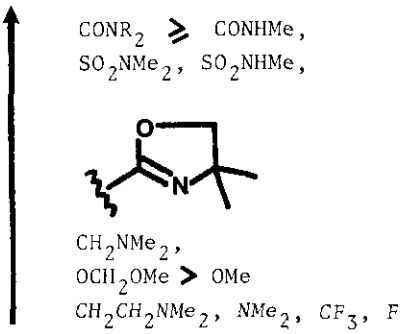


Figure 2

not accessible by classical aromatic electrophilic substitution chemistry. The synthesis of contiguously tri- and tetra-substituted aromatics, particularly difficult by classical methodology,[12] becomes a feasible, short range project by directed metalation strategy.

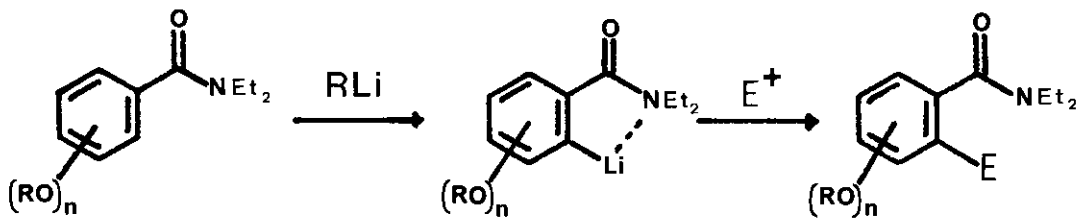
The relative directing ability of various groups will depend upon their inductive, resonance, and coordinating properties.[4] This question has only recently been addressed (Fig. 2).[13] The qualitative priorities shown, established by competitive inter- or intra-molecular experiments,[13] are highly dependent on the type of experiment as well as on the solvent and temperature used for the generation of the metalated intermediate. Thus, perhaps not surprisingly, disagreement exists on the order of priorities: the tertiary amide appears to be better or equal to the 2-oxazolino group, the secondary amide is on par with the tertiary amide, and the secondary and tertiary sulfonamides seem to promote ortho metalation as readily as the tertiary amides. The synergistic effect of two groups to promote metalation in between them has not been systematically studied;[14] numerous recent examples attest to the value of this concept for regioselective aromatic substitution. The determination of the survival rate of groups on an aromatic ring which are not involved in the directed metalation reaction also requires comprehensive study. The problem of kinetic vs thermodynamic ortho metalation in competitive situations has also not been carefully addressed.

Our work in directed metalation chemistry was triggered by the observations of Beak and Brown who showed that N,N-diethylbenzamides (but not the corresponding dimethylamides) are smoothly ortho metalated.[15] We shall show that the resulting ortho metalated benzamides are useful synthons for 1) the construction of highly substituted benzene derivatives and from these, phthalides and isochroman-1,3-diones; 2) the total synthesis of phthalideisoquinoline(benzylisoquinoline group) and ellipticine alkaloids; 3) the total synthesis of anthraquinone natural and unnatural products and, from the latter, 4) the construction of polycyclic aromatic hydrocarbons (PAH's). These synthetic fragments have the common theme of the diethylcarboxamide group as an excellent promotor of ortho metalation.

Synthesis of Highly Substituted Aromatics

In connection with a problem in alkaloid synthesis, we first investigated the directed metalation of a series of methoxy- and dimethoxy-N,N-diethylbenzamides 1 which are all easily prepared by standard procedures from commercially available

acids (Scheme 1).[16] We found that a variety of contiguously tri- and tetra-substituted benzenes 2 can be prepared (Table 1) most of which are accessible only by multistep sequences if traditional approaches are used. The general conditions for this reaction as routinely carried out in our laboratories involve the generation of the ortho-lithiated species using sec-BuLi or, less frequently, t-BuLi in THF solution in the presence of TMEDA at -78° C. In reactions with aromatic aldehydes, Et_2O is used to advantage as a solvent. Following the addition of the electrophile, also at -78° C, the mixture is allowed to warm to room temperature and processed in a standard manner.



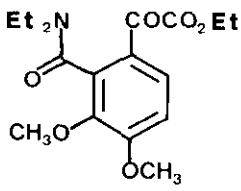
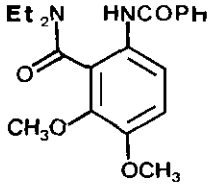
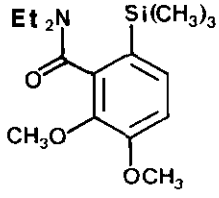
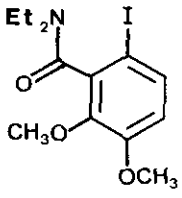
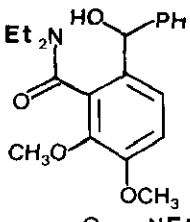
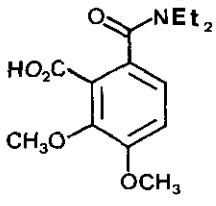
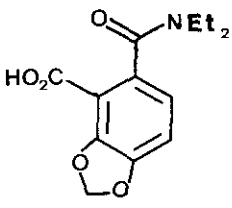
1 2

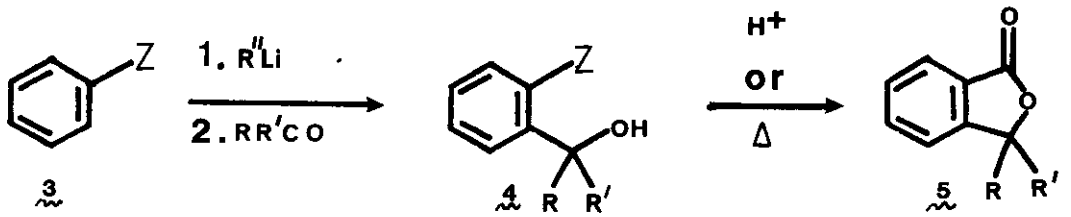
Scheme 1

Synthesis of Phthalides

Hauser first showed that dimetalated species of secondary benzamides 3a can be condensed with benzophenone and other ketones to give amide alcohols 4 which upon thermolysis readily undergo cyclization to the phthalides 5[2] (Scheme 2). Additional examples of this type of sequence have been provided by Baldwin[17] and by Raphael.[18] Recently, Fitt and Gschwend invoked the corresponding thioamide 3b to achieve the same result[7] and Meyer and Seebach, as part of an in depth study, showed that the successive metalation and carbonation of benzyl alcohols (3c) also serves as a route to phthalides 5.[10] That N,N-diethylbenzamides 4d are similarly useful in reactions with carbonyl compounds was first demonstrated by Beak and Brown.[15] We found that reaction of 4d with benzaldehydes followed by acid-catalyzed cyclization or with DMF followed by $NaBH_4$ reduction and cyclization leads to phthalides 5 in excellent yield.[16,19] Using the latter sequence, short syntheses of the isomeric phthalides 7 and 9, of demonstrated utility in anthraquinone and anthracyclinone synthesis, and phthalide carboxylic acids 11, useful in alkaloid synthesis, have been effected in our laboratory starting with readily available benzamides 6, 8 and 10 (Scheme 3).[16] An alternate route to 9 from

TABLE 1

Electrophile	Product	Yield %
$(CO_2Et)_2$		88
PhNCO		71
$(CH_3)_3SiCl$		65
I_2		70
PhCHO		75
CO_2		71
CO_2		89



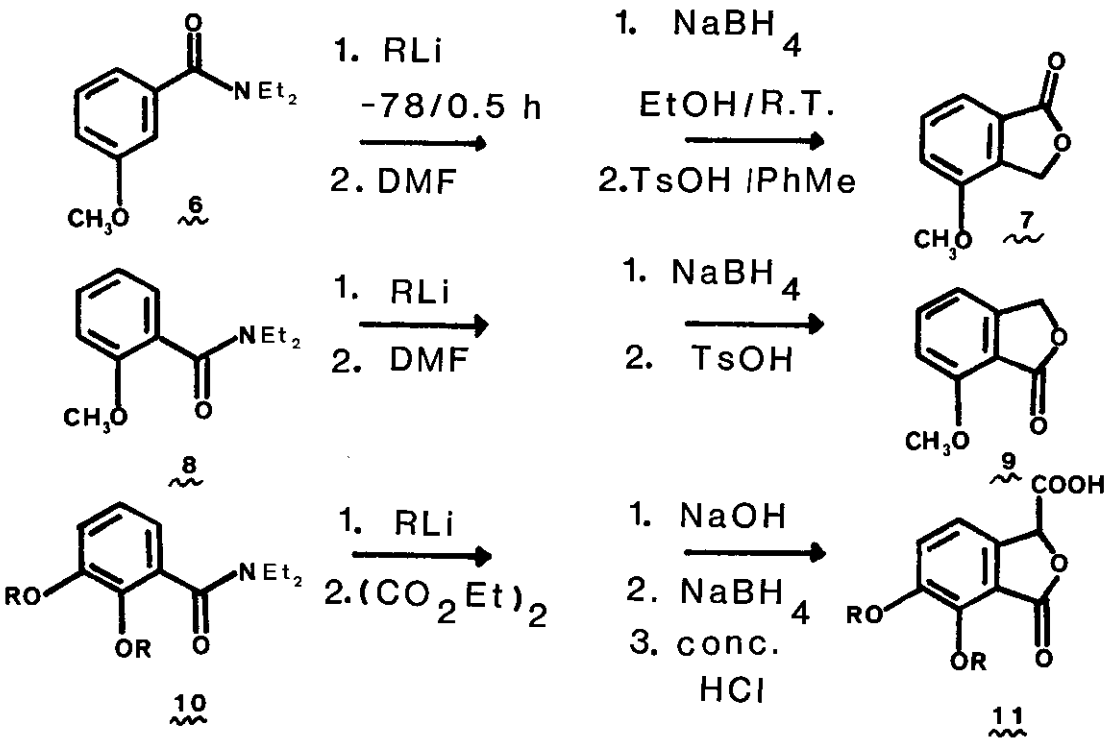
3 4 5

Z = a: CONHR; b: CSNHR; c: CH_2OH; d: $CONEt_2$

Scheme 2

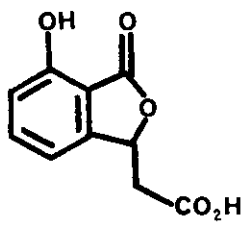
metalated m-methoxybenzyl alcohol, first reported by Uemura,[20] has been improved by Trost.[21] However, this route is inefficient for the synthesis of 3-substituted phthalides.[10,20]

In search of application for the phthalide synthesis, we noted that there exists a small and not rapidly growing number of natural products which exhibit

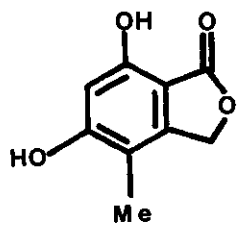


Scheme 3

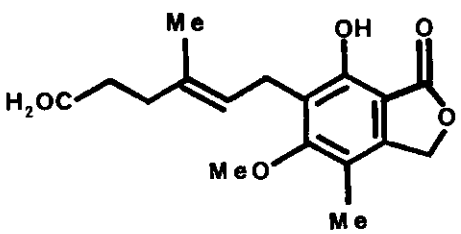
highly substituted phthalide structures (Fig. 3).[22] Three of these are fungal metabolites, and the remaining one, shihunine, is an alkaloid which has recently been synthesized from ortho lithiated benzoate generated by a metal-halogen exchange reaction.[23] We achieved a simple synthesis of iso-ochracinic acid, a product of the parasitic fungus Alternaria kikuchiana which is responsible for black spot disease on Japanese pears (Scheme 4). Formylation of the o-anisamide



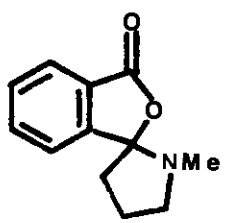
Iso-ochracinic acid
Alternaria kikuchiana



Unnamed
Aspergillus flavus

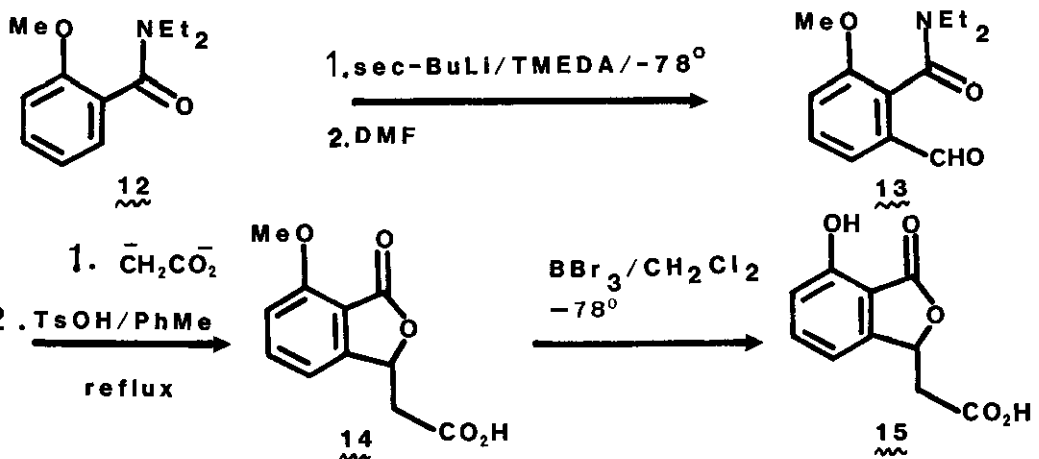


Mycophenol ic acid
Penicillium spp.



Shihunine
Dendrobium spp.

Figure 3

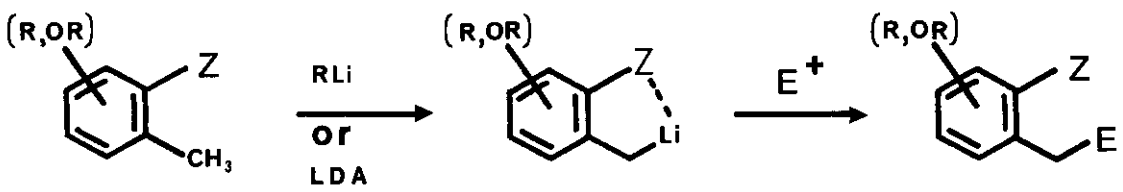


Scheme 4

12 with DMF proceeds quantitatively to give 13 which upon treatment with acetic acid dianion followed by TsOH affords the phthalide 14. Boron tribromide demethylation proceeds in modest yield to give iso-ochracinic acid (15) (40% overall yield). The previous synthesis of this natural product involved a non-regioselective, low yield Wittig reaction on 3-methoxyphthalic anhydride.[24] During the preparation of the present paper, Trost reported the synthesis of 15 (44% overall yield) using carbonation of metalated m-methoxybenzyl alcohol as the key step.[21]

Synthesis of Phthalideisoquinoline Alkaloids

Alkyl substituents ortho to certain directed metalation groups Z (16) are activated by resonance to deprotonation by bases weaker than the alkyllithium reagents (e.g., LDA) (Scheme 5). The resulting chelated benzylic anions 17 may be attacked by electrophiles to give compounds 18 in an overall synthetically useful process of carbon chain extension. Of particular advantage are those ortho-alkylated derivatives which arise by the directed metalation regimen themselves, e.g., Z=CONHR,[25] CSNHR,[7] 2-oxazolino.[26] The finding by Creger that o-toluic acid undergoes this process[27] has been especially exploited by F.M. Hauser in the synthesis of napthalenes and napthalene lactone lignan natural products.[28]

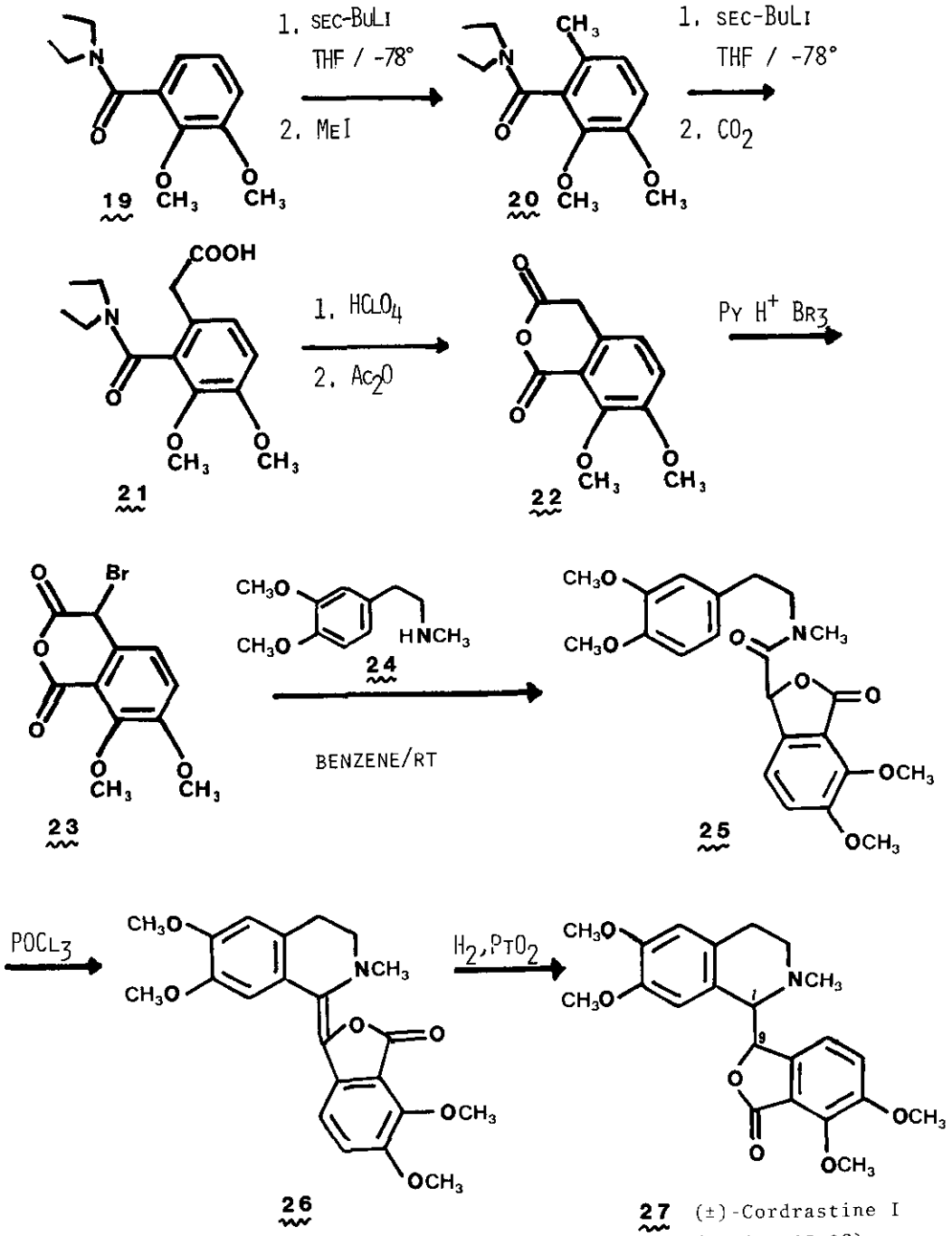


16 17 18

Z = CO_2H, CO_2R, CONHR, $CONR_2$, CSNHR, CH_2NMe_2, 2-Oxazolino

Scheme 5

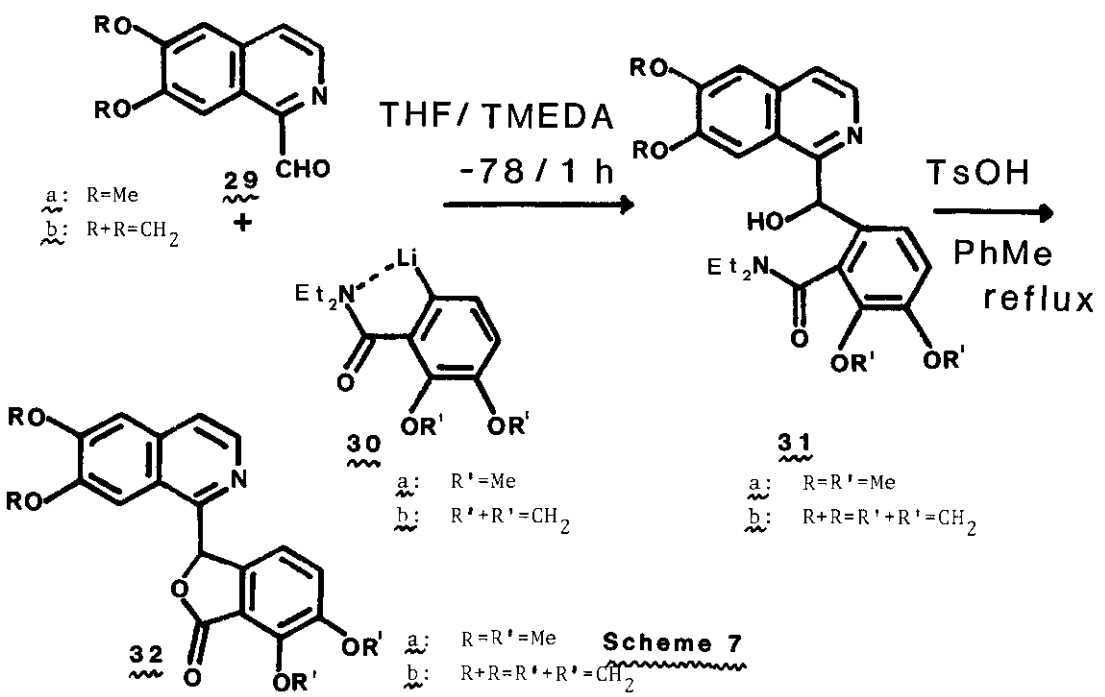
In planning a highly convergent assemblage of the phthalideisoquinoline alkaloid skeleton, we required the bromoisochroman-1,3-dione 23 (Scheme 6). A classical synthesis of the penultimate precursor 22, proceeding in 9 steps and 28% overall yield was carried out in our laboratory with less than overwhelming enthusiasm.[29] Simplification and abbreviation was achieved by the directed metalation strategy starting with the benzamide derivative 19.[29] Metalation of 19 followed by treatment with methyl iodide afforded the toluamide 20 in quantitative


1. sec-BuLi
THF / -78°
2. MeI
1. sec-BuLi
THF / -78°
2. CO2
19
20
1. HClO4
2. Ac2O
Py H+ Br3
21
22
24
BENZENE/RT
23
25
POCl3
H2, PtO2
26
27 (±)-Cordrastine I (1R,9R; 1S,9S)
28 (±)-Cordrastine II (1R,9S; 1S,9R)

Scheme 6

yield. Metalation of 20 resulted in the formation of a deep purple solution of the o-toluoyl anion which upon quenching with dry carbon dioxide gave the homophthalic acid amide 21 (71% yield). The conversion of 19 into 21 may be carried out in a one-pot operation with only minor loss in efficacy. Acidic hydrolysis followed by acetic anhydride cyclization gave 22. This abbreviated and simplified synthesis of 22 proceeds in 46% overall yield. Bromination give the unstable bromoanhydride 23 which upon treatment with the phenethylamine 24 produced the rearranged amide phthalide 25. The utility of such compounds for the synthesis of phthalideisoquinoline alkaloids has been known since the time of Perkin and Robinson. Their availability by this and another directed metalation route[30] assures synthetic accessibility to most members of the phthalideisoquinoline alkaloid group. Bischler-Napieralski cyclization of 25 gave the orange-yellow dehydrophthalideisoquinoline 26 which upon catalytic hydrogenation provided the diasteriomeric alkaloids cordrastine I (27) and cordrastine II (28) thereby completing the total synthesis.

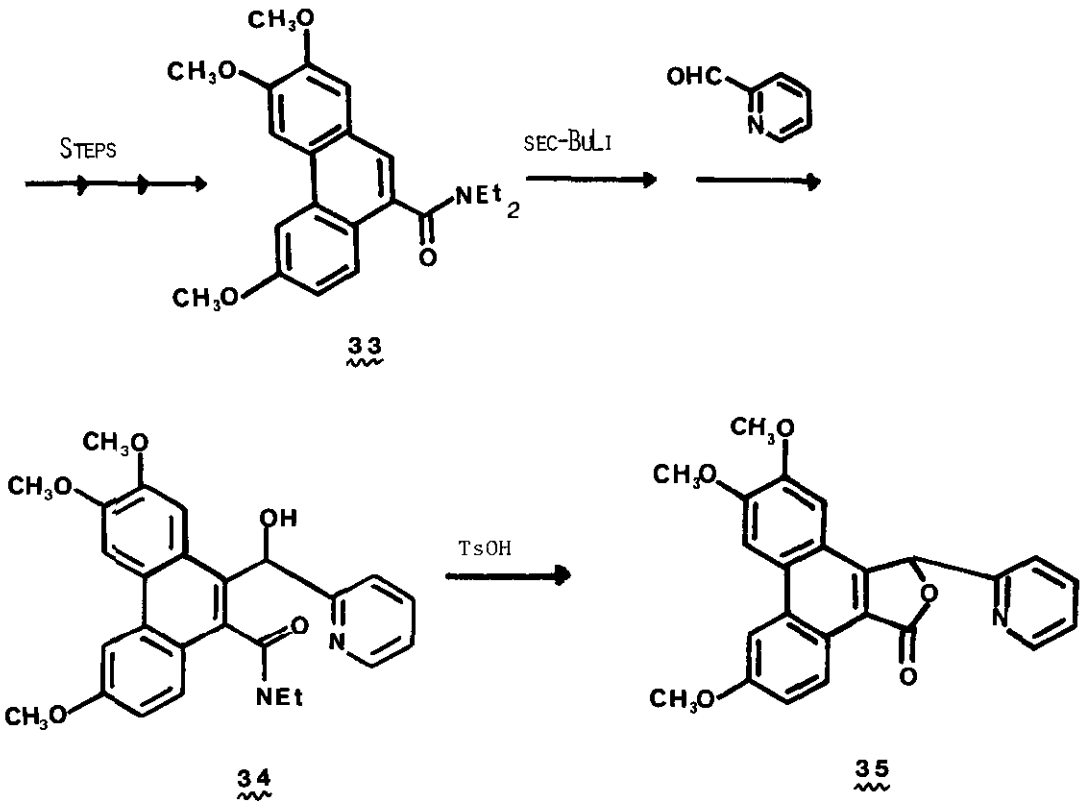
An alternate highly convergent approach to the phthalideisoquinoline alkaloids (Scheme 7)[31] was based on the facile condensation of ortho-lithiated benzamides with aromatic aldehydes[16] and the large rate enhancement in the anchimerically-assisted hydrolysis of ortho methylenehydroxybenzamides to phthalides.[32] Thus,



Scheme 7

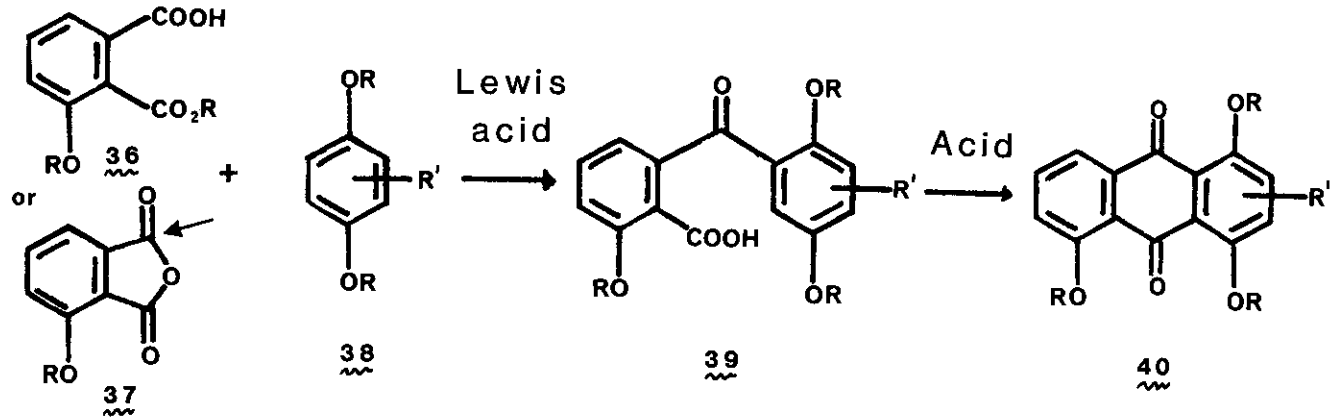
treatment of the readily but not so efficiently available isoquinoline aldehyde 29a with the ortho-lithiated species 30a preferably in ether solution gave compound 31a. This compound was found to be extractable from acidic solution! This interesting property, presumably the result of strong hydroxyl to isoquinoline nitrogen H-bonding, provided the answer to the initial low yields of the reaction which we observed and reaffirmed a basic credo of the synthetic organic chemist: success depends not on how many reactions you run but on how you work them up. When 31a was subjected to cyclization with TsOH, the phthalide 32a was obtained in high yield. Since 32a has been converted into the cordrastines 27 and 28,[33] this completed an alternate formal synthesis of these natural products. Phthalide 32b has been prepared by the analogous sequence 29b + 30b → 31b → 32b.[34]

We have recently applied the directed metalation reaction to the polycyclic aromatic amide 33 (Scheme 8)[35] in a projected approach to the antitumor quinolizidine alkaloids.[36] Successive metalation and condensation with pyridine 2-aldehyde

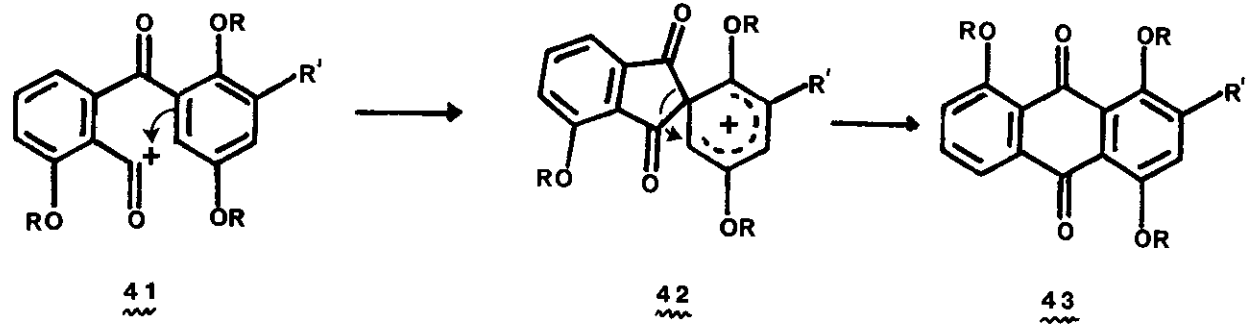


Scheme 8

Classical Synthesis of Anthraquinones



Hayashi Rearrangement



Scheme 9

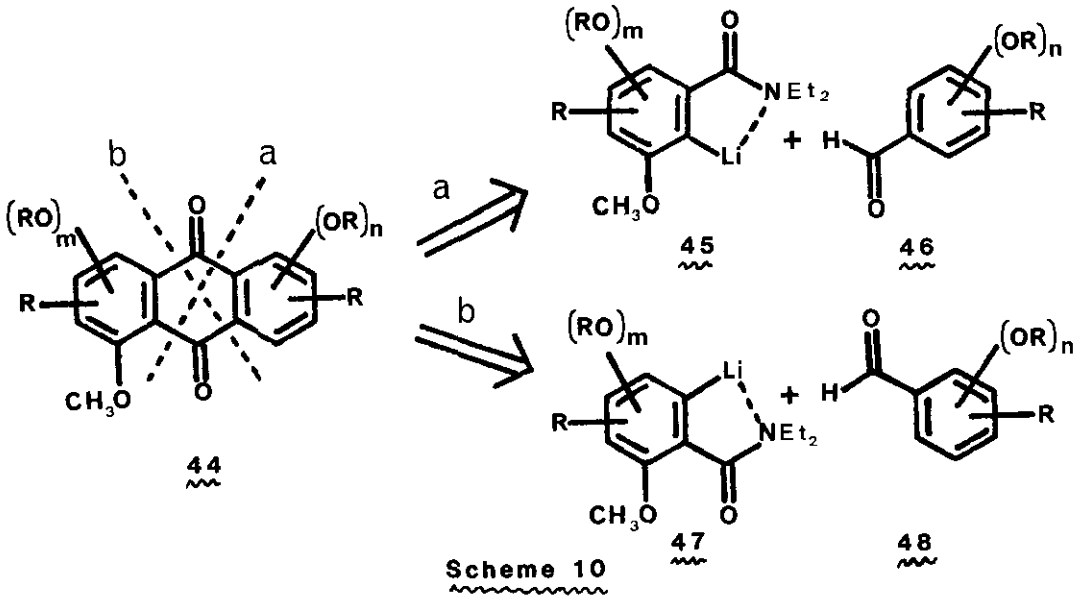
gave the amide alcohol 34 whose properties were annoyingly similar to those of compound 31. Acid-catalyzed cyclization of 34 gave the phthalide 35.

Synthesis of Anthraquinone Natural Products

Anthraquinones have a fascinating history as natural products derived from plants[37] and insects[38] and as important dye substances.[39] The recent renaissance in anthraquinone synthesis is due, in large part, to the discovery of clinically useful antitumor activity in the related anthracyclinone derivatives.[40] The classical approach to anthraquinones involves Friedel-Crafts coupling of phthalic acids 36 or the corresponding anhydrides 37 with phenols or phenol ethers 38 (Scheme 9). For unsymmetrically oxygenated systems, this approach initially provides at least two regioisomeric o-benzoylbenzoic acids 39. Moreover, it carried the potential of a *Hayashi rearrangement*, 41→42→43 *via equilibrating* o-benzoyl benzoyl cation intermediates (41) in the second Friedel-Crafts step 39→40. Overall, this route is therefore inefficient and potentially ambiguous.[41]

Retrosynthetic analysis of the anthraquinone nucleus (44) based on the directed metalation tactic allows four modes of dissection based on initial coupling of two oxygenated, appropriately substituted benzamide 45, 47 and benzaldehyde 46, 48 starting materials (Scheme 10). Of these, the disconnections a and b shown focus

Directed Metalation Route to Anthraquinones

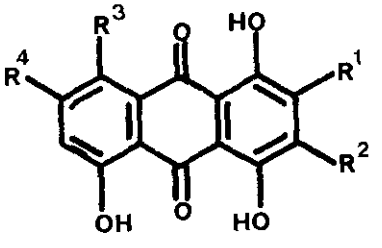


Scheme 10

on the correct positioning of the C-4 methoxy substituent in the target anthraquinone and the regiospecific formation of the new C-C bond. This process, once completed, forces the subsequent Friedel-Crafts central ring closure to proceed regiospecifically. The choice between the a and b modes is dictated by the relative accessibility of the benzamide and benzaldehyde precursors.

Based on these considerations, we have synthesized a number of anthraquinone natural products (Fig. 4).[19] Our general approach is illustrated by the synthesis of erythroglaucin and catenarin (Scheme 11). Lithiation of 3,5-dimethoxybenzamide

Naturally Occurring Anthraquinones Synthesized by Directed Metalation Route



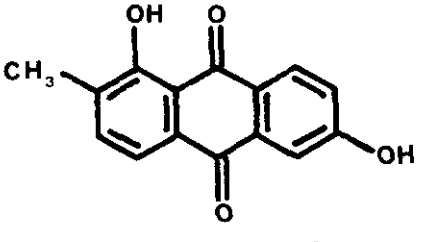
R^1 = Me, R^2 = R^3 = R^4 = H Islandicin

R = R^3 = R^4 = H, R^2 = Me Digitopurpone

R^1 = Me, R^2 = R^3 = H, R^4 = OMe Erythroglaucin

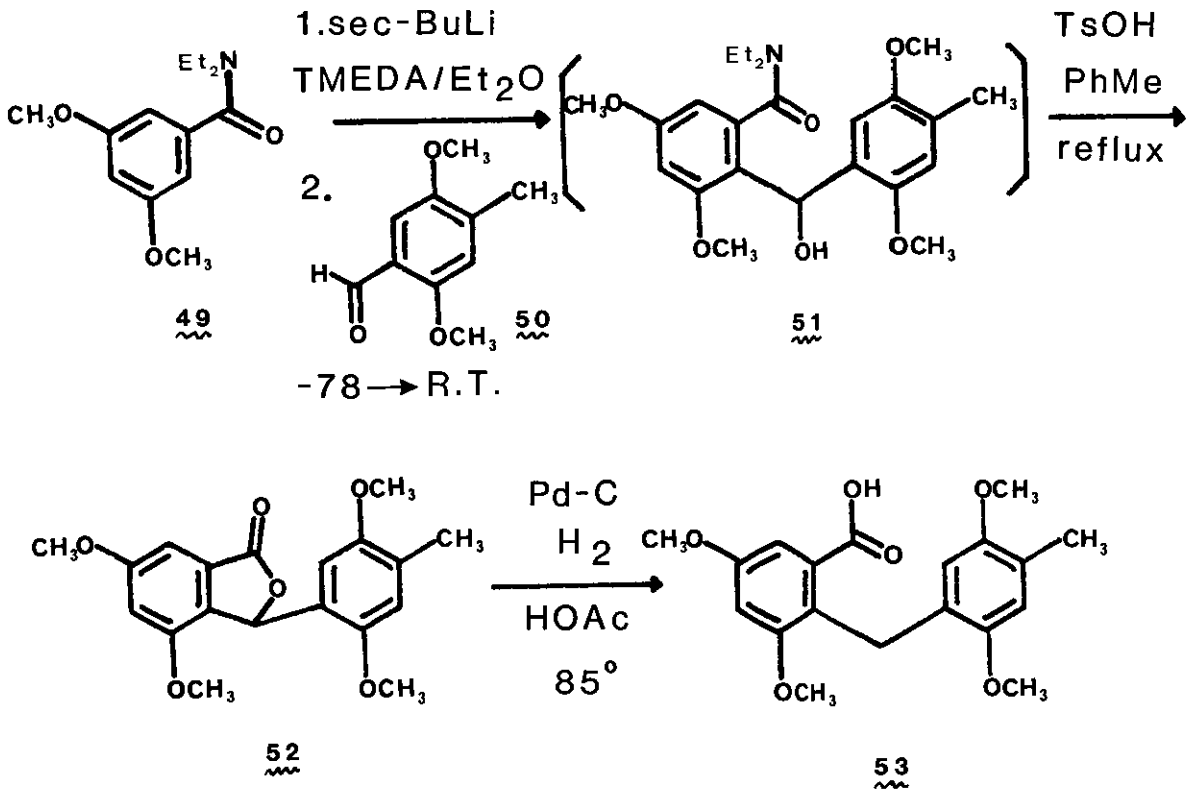
R^1 = Me, R^2 = R^3 = H, R^4 = OH Catenarin

R^1 = Me, R^2 = R^4 = H, R^3 = OH Cynodontin

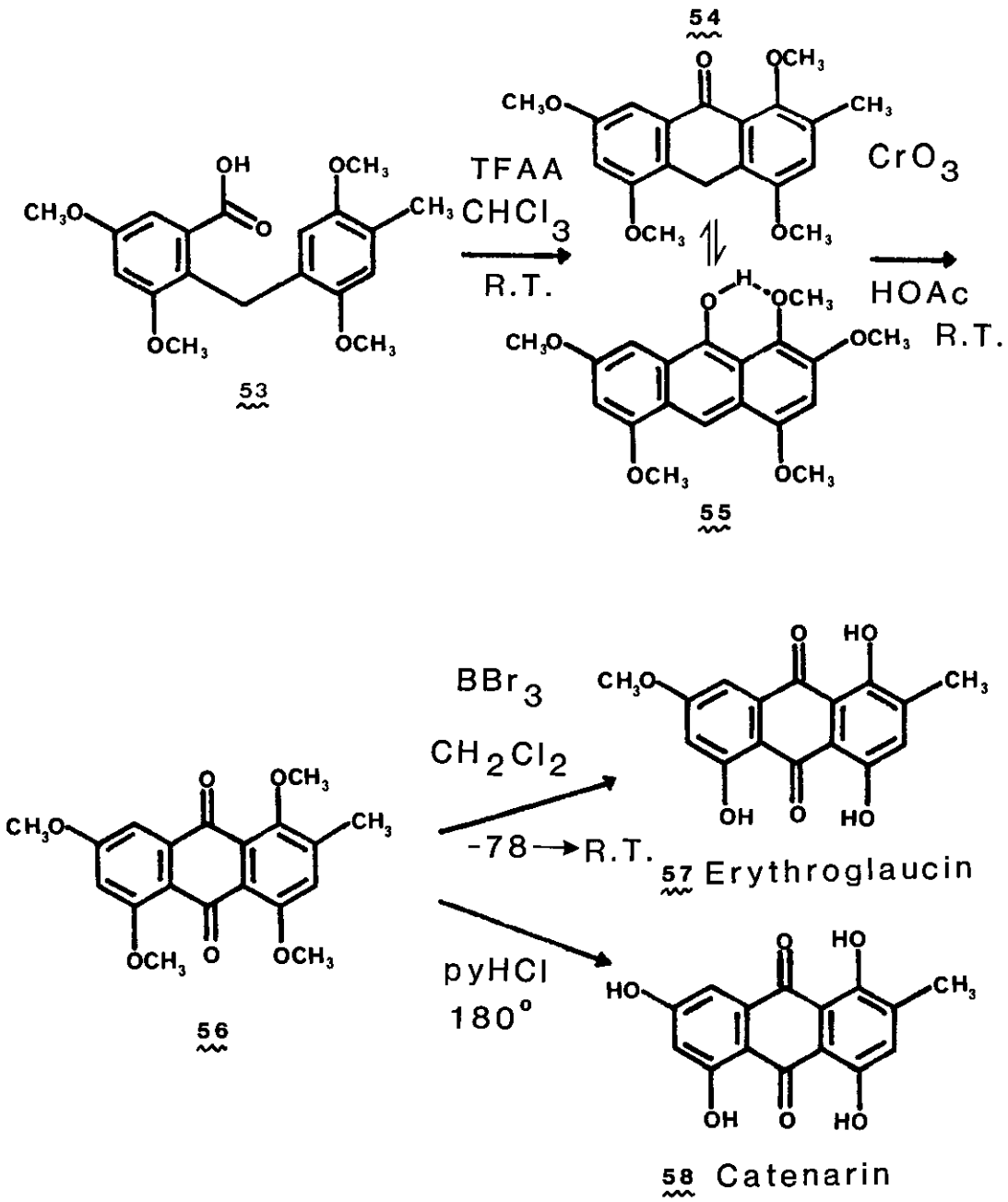


Soranjidiol

Figure 4


1.sec-BuLi
TMEDA/Et2O
2.
-78 → R.T.
TsOH
PhMe
reflux
Pd-C
H2
HOAc
85°
49
50
51
52
53

Scheme 11

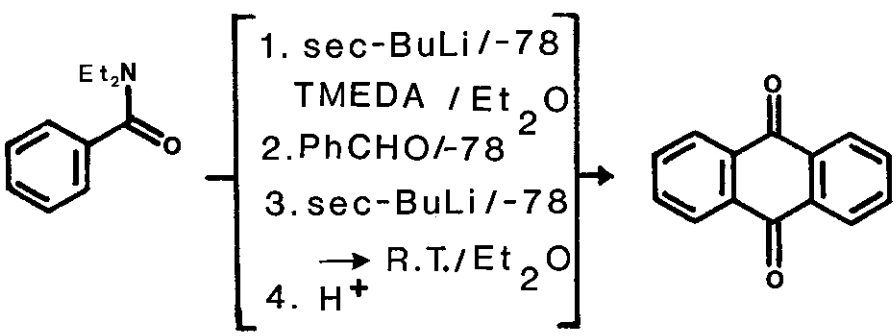


Scheme 11 (concluded)

(49) followed by quenching with 2,5-dimethoxy-p-tolualdehyde (50) gave the alcohol amide 51 which, without isolation, was treated with TsOH to give the phthalide 52. Hydrogenolysis under standard pressure in acetic acid furnished the benzylbenzoic acid 53. This compound, unlike the corresponding benzoylbenzoic acid which is deactivated to Friedel-Crafts cyclization and, under vigorous conditions, undergoes the Hayashi rearrangement, was smoothly converted by trifluoroacetic anhydride at room temperature into the anthrone 54. Compound exists in concentration dependent tautomeric equilibrium with the anthracenol 55 as evidenced by NMR studies. Typifying a well-known behavior of anthrones, 54 suffered aerial oxidation upon standing to the anthraquinone 56. This conversion was more reproducibly carried out by chromium trioxide oxidation. To complete the syntheses, selective demethylation of 56 with BBr_3 yielded erythroglaucin (57) while vigorous treatment with pyridium hydrochloride delivered catenarin (58). The successful syntheses of naturally occurring anthraquinones (Fig. 4) by short (6 steps) and efficient (20-30% overall yield) routes from readily available amide and benzaldehyde derivatives demonstrates the generality and versatility of the directed metalation approach. Worthy of note is the toleration of methyl groups both in the benzamide (e.g. for soranjidiol) and benzaldehyde (50 used in 5 of the 6 syntheses) components in the metalation and condensation reactions respectively.

Synthesis of Polycyclic Anthraquinones and Polycyclic Aromatic Hydrocarbons (PAH's)

While engaged in the synthesis of anthraquinone natural products, we treated N,N-diethylbenzamide by the sequence shown in Scheme 12 and observed the formation



Scheme 12

of anthraquinone in 44% yield.[42] Pasteur's dictum (chance favors the prepared mind)[43] is personally validated in that I had executed, as an undergraduate student, Fieser's preparation of anthraquinone and therefore I was in the position to quickly recognize the insoluble and rock-stable nature of the compound which precipitated from the reaction outlined in Scheme 12. The requirement for benzaldehyde in this reaction could be demonstrated; when it was excluded, only trace amounts of anthraquinone were obtained (most likely by dimerization of ortho-lithiated benzamide). Furthermore, substituted benzaldehydes were shown to participate in the reaction (Fig. 5). Alkyl and alkoxy benzaldehydes undergo the reaction in poorer yields presumably owing to competitive proton exchange and directed metalation respectively. 1-Naphthaldehyde, 2-napthaldehyde, and 9-phenanthraldehyde afforded polycyclic anthraquinones in yields comparable to the parent reaction.

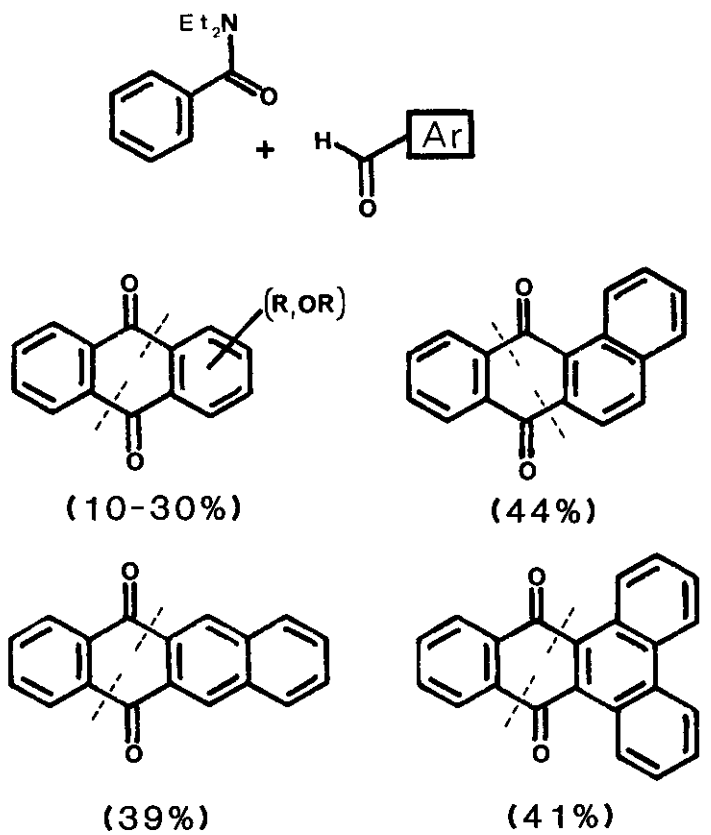
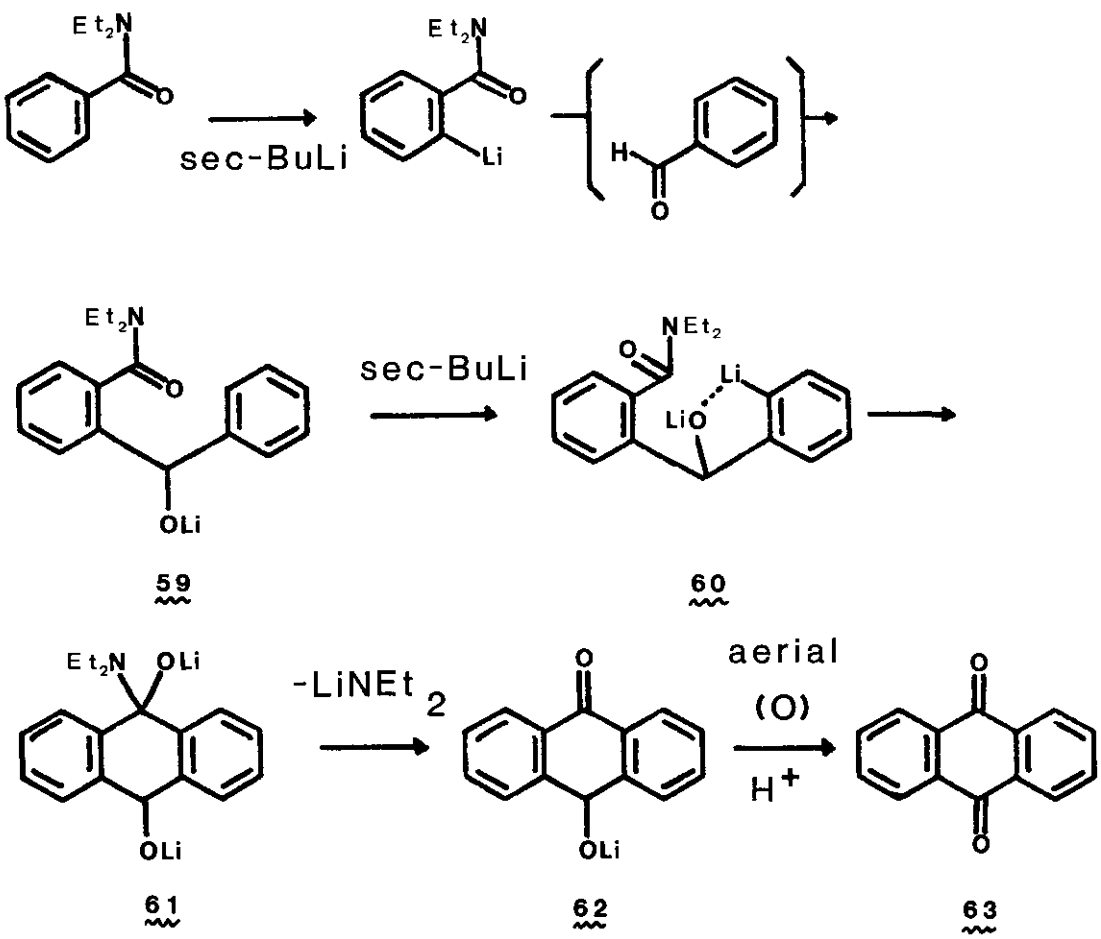
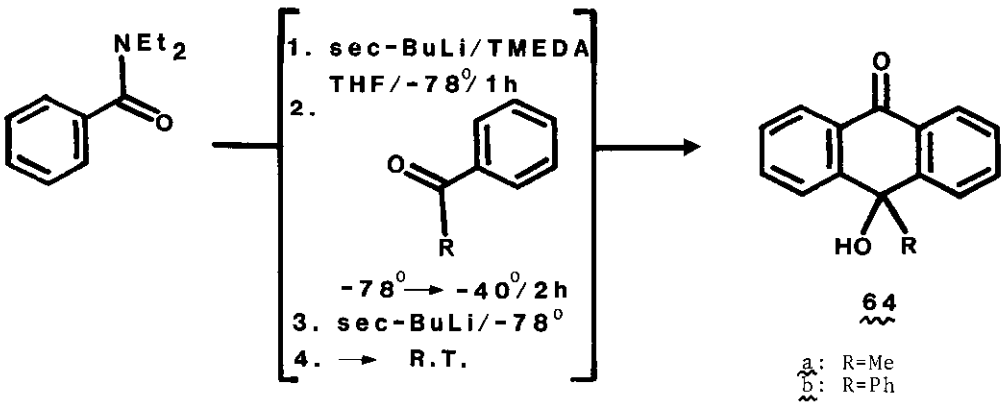


Figure 5

A reasonable mechanism for the reaction outlined in Scheme 12 is depicted in Scheme 13. The expected initial condensation product 59, suffers metalation directed by the alkoxy group to give the dianion 60. Such ortho-metalated species of benzyl alcohol have received credence from the recent work of Seebach.[10] Intermediate 60 in turn undergoes cyclization to the tetrahedral intermediate 61 which, by expulsion of $LiEt_2$, gives the hydroxyanthrone 62. The latter undergoes aerial oxidation, also a well precedented step, to give anthraquinone 63. Support for the key step 59→60 of this tandem metalation mechanism

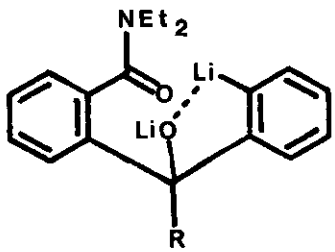


Scheme 13



64

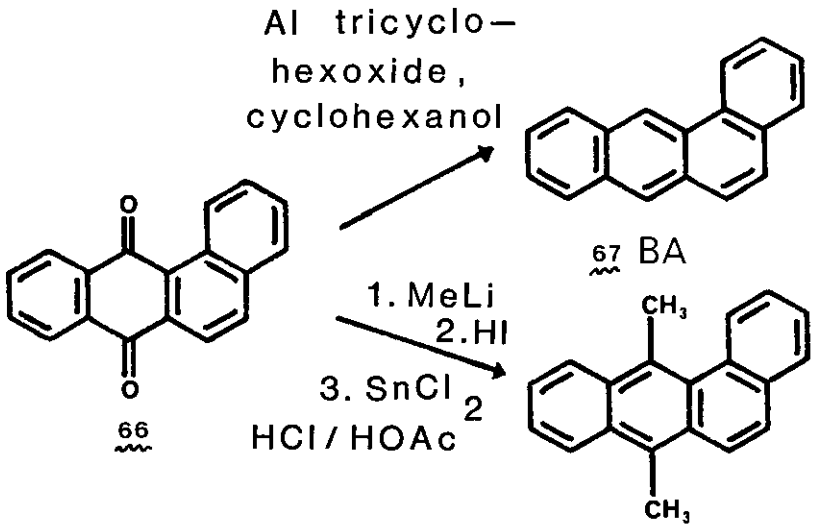
a: R=Me
b: R=Ph



R = Me,Ph

65

Scheme 14



66

67 BA

68 DMBA

Scheme 15

was derived from the reaction of N,N-diethylbenzamide with acetophenone and benzophenone under identical reaction conditions (Scheme 14).[42] The formation of the hydroxyanthrones 64a and 64b is consistent with the involvement of the proposed intermediate 65 in the overall reaction.

Anthraquinones are easily converted into the corresponding aromatic hydrocarbons. For example, the synthesis of benz[a]anthracene (66) and 7,12-dimethylbenz[a]anthracene (67) may be achieved in high yield from the anthraquinone 68, (Scheme 15) thus providing a short route to these carcinogenic PAH's.[42]

The one-step synthesis of anthraquinones is less successful for α- and β-naphthamides and more highly condensed aromatic amides (Fig. 6). Since the major products are phthalides with only minor amounts of anthraquinones being obtained, it appears that the reaction fails at the second metalation step (59→60, Scheme 13). Nevertheless, the phthalides are also useful precursors to PAH derivatives. Our knowledge concerning the directed metalation capabilities of the $CONEt_2$ group in more highly condensed aromatic is currently limited. More successful is the combination of certain heterocyclic aldehydes with benzamides and naphthamides, a reaction which allows access in one step to some bizarre heterocyclic benzoquinones (Figure 7). As the last possible variation, combination of heterocyclic aldehydes with heterocyclic amides provides some new and unusual diheterocyclic benzoquinones (Fig. 8).

In the formation of thiopheno- and furano-benzoquinones (Figs. 7 and 8), advantage is gained from the inherently high kinetic acidity of the 2-hydrogen in the thiophen and furan rings. On the other hand, the formation of the thiopheno-pyrido benzoquinone (Fig. 8) must proceed via 3-metalated pyridine 4-carboxamides. To test the efficacy of this step, we metalated three isonicotinamides under the standard conditions and quenched the resulting species with D_2O (Scheme 16).[42] The results show that the N,N-diisopropyl and N-phenyl isonicotinamides incorporate deuterium almost quantitatively whereas the diethyl analogue is less efficient. Unfortunately, tandem metalation reaction with benzaldehyde on the former two compounds did not produce benzoquinone products. These results, presumably due to hindrance (N,N-diisopropyl) and deactivation (N-phenyl) in the formation of the tetrahedral intermediate (61, Scheme 13) forced us to use the N,N-diethyl isonicotinamide for these reactions.

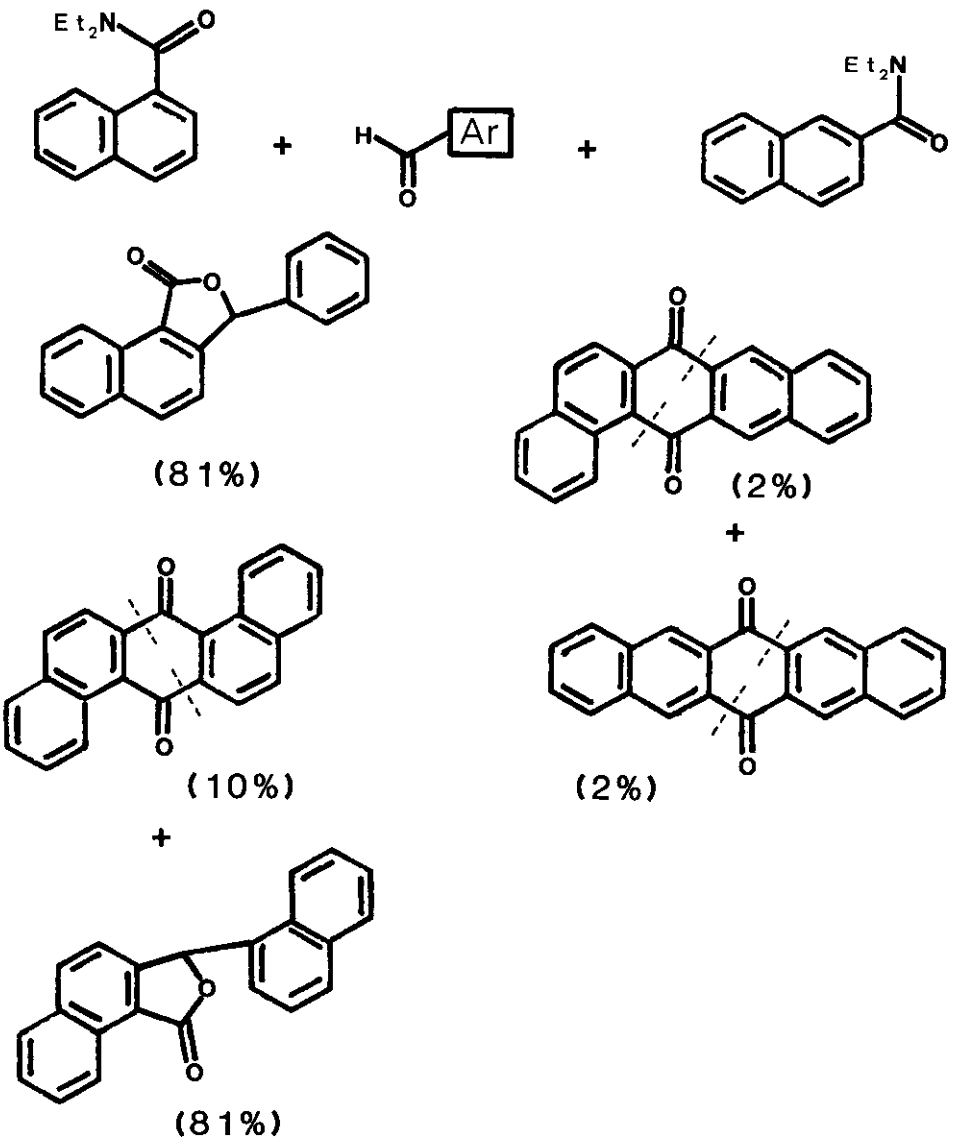
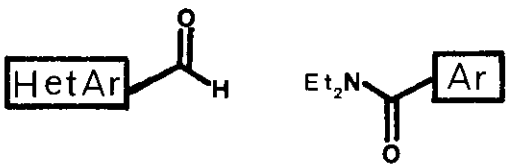
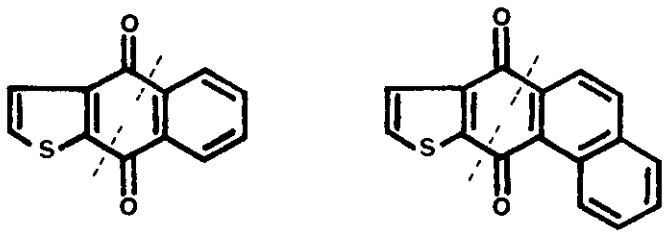
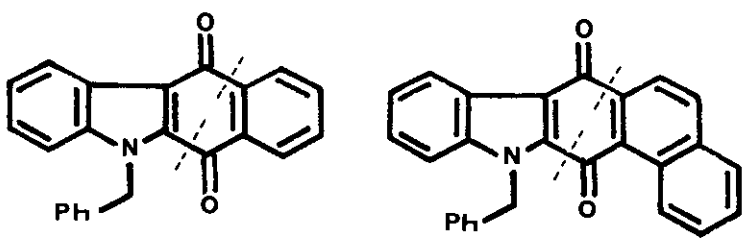


Figure 6



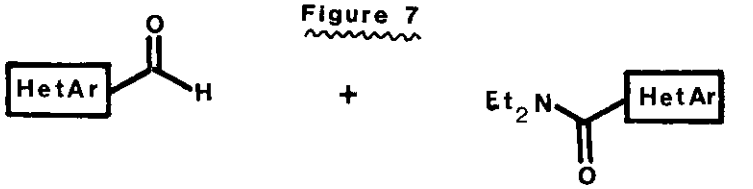


(35%) (37%)

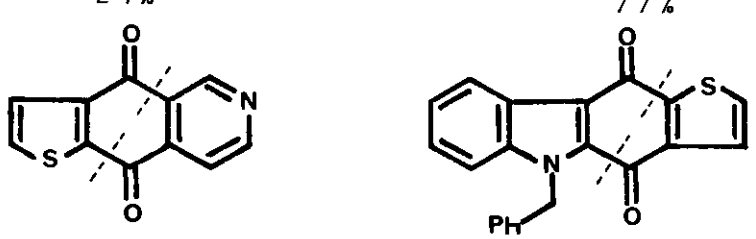


(44%) (20%)

Figure 7

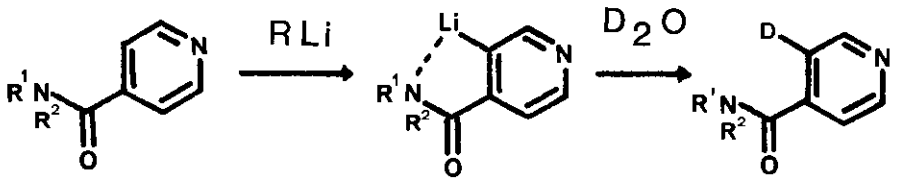


24% 77%



20% 67%

Figure 8

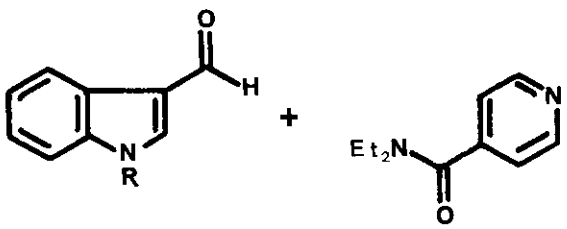


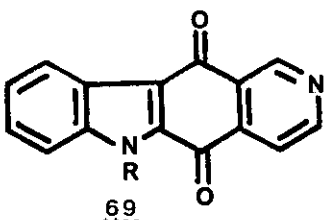
R^1	R^2	% D
Et	Et	55
i-Pr	i-Pr	95
Ph	H	100

Scheme 16

Synthesis of Ellipticine Alkaloids

The efficient incorporation of an indole 3-aldehyde into the indolo thiopheno benzoquinone (Fig. 8) and the isonicotinamide deuteration experiments (Scheme 16) suggested that the linear benzoquinones 69 (Scheme 17) representing the ellipticine alkaloid skeleton could be prepared by the tandem directed metalation route. In the event,[42] the reaction proceeded to give the desired derivatives 69 in yields which are inversely proportional to the utility of the R protective group. The indolopyridobenzoquinones 69 were then transformed in a three-step sequence without purification of intermediates into the pyridocarbazoles 70 (Scheme 18). As expected from the potent reductive-acidic conditions used, the methylenemethoxy derivative 69, R=CH_2OMe gave ellipticine (70, R=H) directly. This short synthesis of the antitumor ellipticine alkaloids furnished the compounds to neutralize the effects of the PAH's obtained earlier (Scheme 15) so that work in our laboratory could continue!

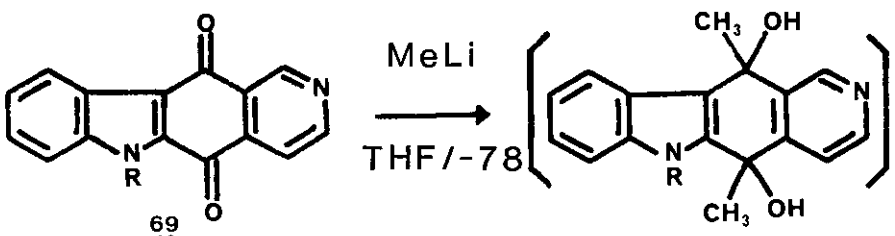




69

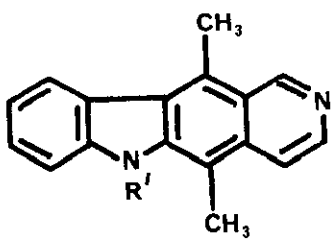
R	%
Me	76
CH_2Ph	44
CH_2OMe	26

Scheme 17



69

1.47% HI
2.HOAc / HCl
$SnCl_2$



70

R	R′	Yield, %
Me	Me	62
CH_2Ph	CH_2Ph	40
CH_2OMe	H	40

Scheme 18

Conclusion

Directed metalation of aromatic substrates is an important strategy for the regiospecific synthesis of highly substituted and condensed aromatics, heterocycles, and several classes of natural products. We have shown that ortho-metalated benzamides are useful synthons for the preparation of contiguously tri- and tetra-substituted benzene derivatives (Table 1), phthalides (Schemes 2 and 4), isochroman-1,3-diones (Scheme 6), phthalideisoquinoline alkaloids (Schemes 6 and 7), anthraquinone natural products (Scheme 11 and Fig. 4), polycyclic anthraquinones (Figs. 5 and 6), heterocyclic benzoquinones (Figs. 7 and 8, Scheme 17), PAH's (Scheme 15), and ellipticine alkaloids (Scheme 18).

The chemical genealogies of the diverse ortho metalated aromatic species developed recently (Fig. 1) may be traced to the original contributions of Hauser, Gilman, Wittig and, of course, Grignard among many others. Wittig discovered phenyllithium and, in recent years, called it his Wünschelrute (divining rod). This quality appears to have been transcribed into many of the ortho metalated aromatics including, on the basis of our experience, the N,N-diethylbenzamides.

Future efforts in the area of directed metalation chemistry will provide new groups which promote ortho metalation, establish priorities among them, determine kinetic and thermodynamic control parameters in their generation and, undoubtedly, find new applications in organic synthesis.

Acknowledgement

The work described in this review originating from our laboratories has been carried out by Dr. I. Ahmad, Roland Billedeau, Dr. S. Osmund de Silva, Dr. Borje Egestad, Doug Kuntz, Dr. D. Rajapakse, J. Norman Reed and Dr. M. Watanabe. In their hands, the directed metalation technique nurtured and developed as an important synthetic method. I am very grateful for their dedicated and patient efforts.

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