Directed Lithiation of Aromatic Tertiary Amides: An Evolving Synthetic Methodology for Polysubstituted Aromatics

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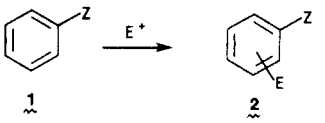
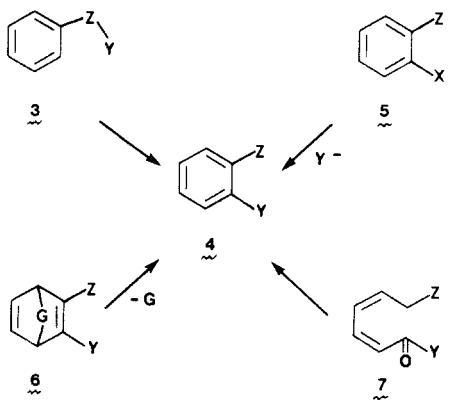
The efficient and regiospecific preparation of polysubstituted aromatic compounds is one of the classic problems of synthetic chemistry. The most common approach involves electrophilic substitution (1 → 2)



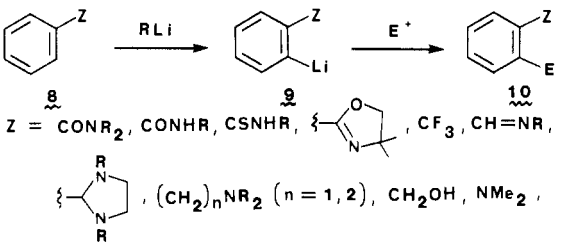
which usually is effected under harsh conditions and often does not proceed with the desired positional specificity.[1] The preparation of 1,2-disubstituted aromatics (2, Z,E ortho) thus can become a demanding undertaking, requiring either the separation of isomers, several step diversions involving protecting groups,[2] or the use of substituents that provide ortho specificity by chelation.[3]

A number of alternative methods have been developed for the regiospecific syntheses of 1,2-disubstituted aromatic molecules. Sigmatropic rearrangements of the (*n*,3) type (3 → 4) can be advantageous in cases where



one substituent is a heteroatom.[1,4-6] If appropriate precursors are available, nucleophilic aromatic substitution (5 → 4) is useful. For successful reaction, X must be a good leaving group and Z must be strongly electron withdrawing.[7] The $S_{RN}1$ reaction also allows the preparation of 4 from 5 with different restrictions on Z, but this sequence similarly depends on the availability of appropriately substituted systems.[8] Formally

Scheme I



related reactions involving σ- and π-transition-metal complexes are at a promising but early state of development.[9,10]

The conversion of 6 to 4 represents an approach from nonaromatic precursors in which the formation of 6 by a cycloaddition is followed by thermal extrusion of stable fragments.[11] Alternatively, the formation of 4

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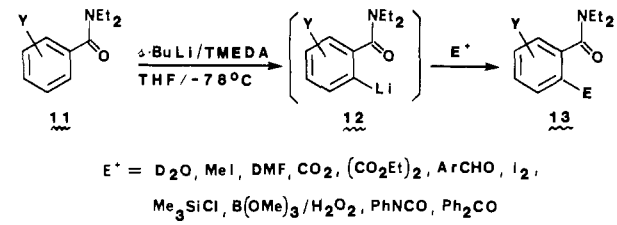
via a carbanionic cyclization of 7 or its equivalent is a widely recognized if unsystematized approach to polysubstituted aromatics.[12]

The independent discovery by Gilman and Bebb and by Wittig and Fuhrman that the methoxy group of anisole directs lithiation to an ortho position initiated the systematic investigation of directed metalations.[13,14] Further work, primarily by Gilman and by Hauser but with many contributions from other groups, expanded the scope of directing substituents to include thioethers, amines, halogens, alcohols, sulfonamides, and secondary amides.[15,16] The ortho metalation–electrophilic substitution sequence has become recognized today as an efficient route for the regiospecific synthesis of a wide variety of polysubstituted aromatic compounds. The sequence is illustrated for the preparation of 1,2-disubstituted aromatics by the conversion of 8 to 10 (Scheme I).[15]

Until a few years ago, functional groups that were regarded as useful for directed metalation were those that would be expected to be inert toward the organolithium base required for the metalation. The recent reports that the oxazoline[17] and tertiary amide[18] functions can serve as ortho metalation directors and retain their structural integrity provides a significant extension of this approach. In this Account, we summarize work that demonstrates that the tertiary amide takes priority in directing ortho lithiation over other substituents and that the lithiated intermediates can be used advantageously in repetitive and tandem metalation sequences. The convenient preparation and subsequent transformations of aromatic tertiary amides suggest that this group is frequently the best choice in a directed metalation strategy. The studies reviewed herein, along with those summarized in the Account by Parham and Bradsher[19] on lithiated aromatics obtained by metal–halogen exchange, provide the basis for the rational regiospecific synthesis of a wide variety of polysubstituted aromatic and heteroaromatic systems.

Scheme II



Ortho Lithiation of Tertiary Benzamides

The directing ability of the tertiary amide was unrecognized in early work because nucleophilic addition occurred in the cases studied. For example, Hauser showed that *N,N*-dimethylbenzamides undergo nucleophilic attack by *n*-butyllithium to give aryl butyl ketones in high yields.[20] Gschwend and co-workers have nicely demonstrated that the lithiated carbinol amine group formed by the addition of RLi to the carbonyl carbon of *N,N*-dimethyl-*p*-chlorobenzamides may be used to direct in situ ortho metalation.[21] Although the highly hindered base lithium 2,2,6,6-tetramethylpiperidide was found to ortho metalate *N,N*-diethylbenzamide, the major product was *N,N*-diethyl-*o*-benzoylbenzamide arising from addition of the deprotonated species to unmetalated amide.[22] This result did show that ortho metalation of a tertiary benzamide was possible with bulky *N*-substituents and hindered bases and set the stage for later developments.

The reaction of *N,N*-diethylbenzamide (11, Y = H) with *sec*-butyllithium (*sec*-BuLi) in $Me_2NCH_2CH2NMe_2$(TMEDA) in tetrahydrofuran (THF) at −78 °C was shown to provide the synthetically useful orthometalated tertiary benzamide species 12, Y = H (Scheme II).[18] The utility of 12 was demonstrated by its reaction with alkyl halide and carbonyl electrophiles; subsequently, more highly substituted lithiated *N,N*-diethylbenzamides were shown to undergo reaction with these and other electrophiles as depicted in Scheme II.[23,24a] Recent studies reporting the formation of 14,[25,26a] 15,[25] 16,[25,27a] 17,[27] 18,[27] and 19[25] by lithiation indicate that the tertiary amide is useful in directing ortho lithiation in condensed aromatic and heterocyclic systems. The formation of 16 – 18 is no-

(12) Harris, T. M.; Harris, C. M. *Tetrahedron*, **1977**, *33*, 2159. Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. Chan, T.-H.; Brownbridge, P. *Ibid.* **1980**, *102*, 3534. Hauser, F. M.; Pogany, S. A. *Synthesis*, **1980**, *814*.

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(14) For a review of the early work, see: Gilman, H.; Morton, J. W. *Org. React.* (N.Y.) **1954**, *8*, 258.

(15) For an excellent review, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (N.Y.) **1979**, *26*, 1. For recent selected work on groups effective in directed metalation not considered in this Account, see: (b) CH_2NMe_2: Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. S. *Tetrahedron Lett.* **1981**, 2797. (c) CH_2O^-: Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *118*, 1304. $Cr(CO)_3$ complex: Uemura, M.; Nishikawa, N.; Hayashi, Y. *Tetrahedron Lett.* **1980**, 2069. (d) $CH(OMe)_2$: Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Ibid.* **1979**, 4921. (e) imidazolidine: Harris, T. D.; Roth, G. P. *J. Org. Chem.* **1979**, *44*, 2004. (f) ^-NCOR: Fuhrer, W.; Gschwend, H. W. *Ibid.*, **1979**, *44*, 1133. Muchowski, J. M.; Venuti, M. C. *Ibid.* **1980**, *45*, 4798. (g) OMe: Ng, G. P.; Dawson, C. R. *Ibid.*, **1978**, *43*, 3205. Achenback, H.; Kohl, W.; Kunze, B. *Chem. Ber.* **1979**, *112*, 1841. (h) OCH_2OMe and related groups: Kraus, G. A.; Pezzanite, J. O. *J. Org. Chem.* **1979**, *44*, 2480. Narasimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis*, **1979**, 906. Barton, D. L.; Conrad, P. C.; Fuchs P. L. *Tetrahedron Lett.* **1980**, 1811. Townsend, C. A.; Bloom, L. M. *Ibid.* **1981**, 3923. (i) SR: Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257. Reich, H. J.; Chow, F.; Shah, S. K. *Ibid.* **1979**, *101*, 6683. (j) F: Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968**, *11*, 814. Ladd, D. L.; Weinstock, J. *J. Org. Chem.* **1981**, *46*, 203. Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Kruse, H.; Walker, J. C.; Geyer, H. M. III., *J. Med. Chem.* **1981**, *24*, 74.

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(19) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, preceding paper in this issue.

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(22) Beak, P.; Brubaker, G. R.; Farney, R. *J. Am. Chem. Soc.* **1976**, *98*, 3621.

(23) DeSilva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099.

(24) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (b) Iwao, M.; Snieckus, V., unpublished results.

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(26) (a) Jacobs, S. A.; Harvey, R. G. *Tetrahedron Lett.* **1981**, 1093. However, alkoxynaphthalene tertiary amides undergo nonregioselective metalation: (b) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

(27) (a) Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwrak, A. *Tetrahedron Lett.* **1980**, 4739. Dimetalated secondary 2-pyridinecarboxamides also show synthetic potential: (b) Katritzky, A. R.; Rahimi-Rastoo, S.; Ponkshe, N. K., *Synthesis* **1981**, 127. On the other hand, oxazolinylpyridines undergo competitive nucleophilic addition and ortho metalation: (c) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133. Hauck, A. E.; Giam, C.-S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2070 and references therein.

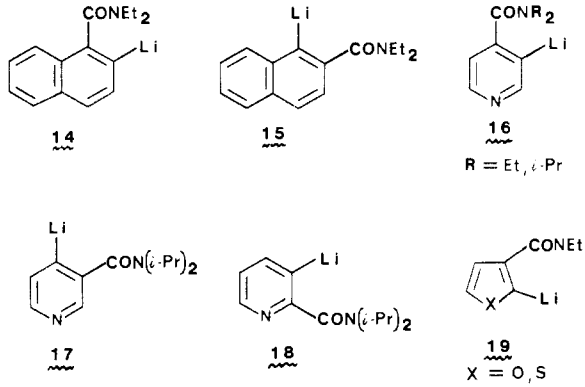


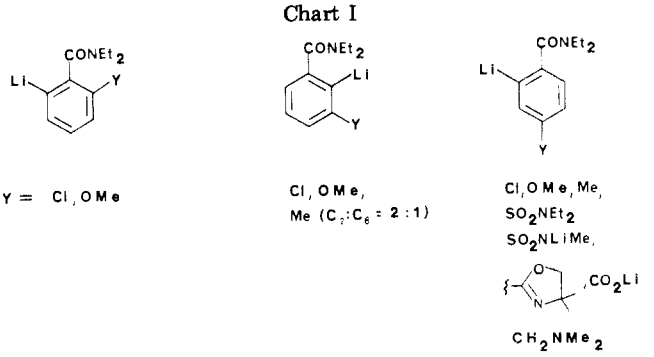
table in view of the susceptibility of the pyridine nucleus toward nucleophilic addition.[27c]

The choice of the reactants and metalation conditions can be crucial. Thus, treatment of *N,N*-dimethylbenzamide with *sec*-BuLi/TMEDA leads to *sec*-butyl phenyl ketone and *N,N*-dimethyl-*o*-benzoylbenzamide.[24] If a solution of **12** is allowed to warm to room temperature, anthraquinone is obtained.[28] However, the smooth ortho metalations of *N,N*-diisopropylbenzamide with *n*-BuLi[24a] and of *N,N*-dimethyl-*o*-methoxybenzamide with *sec*-BuLi imply that each case may require some investigation in order to define optimum conditions.

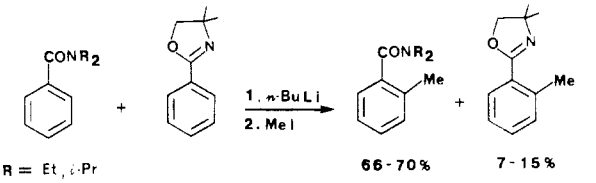
Comparison of Tertiary Amide with Other Directing Groups

Information about the relative directing abilities of different groups has been gained by studies of intra- and intermolecular competitions.[15a,24a,29,30] The intramolecular competitions, represented in Chart I by the structure of the intermediate species in a lithiation–deuteration sequence, tested the tertiary amide against the deactivating methyl and carboxylate, the weakly directing chloro, the moderately directing methoxy, and the strongly directing [(dimethylamino)methyl], oxazolinyl, and sulfamoyl groups. As judged by the site of deuteration, the tertiary amide appears to be the best director of ortho metalation with *sec*-BuLi/TMEDA in THF at −78 °C. The *m*-chloro and *m*-methoxy substituents cooperate with the tertiary amide to direct lithiation between the two groups. A *m*-methyl substituent is less influential, as 6- and 2-deuterio derivations are obtained in a 2:1 ratio. while both *p*- and *o*-methyl groups might be expected to provide resonance-stabilized benzylic anions, it is only the latter which gives benzylic lithiation under the prescribed conditions. The resulting *o*-toluamide anions and their analogues are useful synthetic intermediates (vide infra). Recent work shows that *N,N*-diethyl-2-ethylbenzamide also undergoes benzylic metalation but that *N,N*-diethyl-2-isopropylbenzamide metalates at the 6-position.[30] Corroboration of the tertiary amide as a more effective ortho director that the oxazoline group comes from the intermolecular competition experiments of Myers and Lutomski in which they allowed the two groups to compete for *n*-BuLi and determined the site of metalation by quenching with methyl iodide (Scheme III).[31]

Chart I

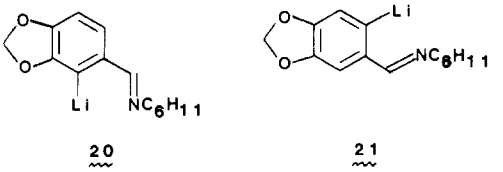


Scheme III



Indirect comparisons also support the superiority of the tertiary amide. Thus, treatment of *N,N*-diethyl-3,5-dimethoxybenzamide with *n*-BuLi in THF leads to metalation at C-2 adjacent to the amide, while under the same conditions (3,5-dimethoxyphenyl)oxazoline is metalated predominantly between the two methoxy groups.[32] The ratio of C-4 to C-2 metalation in the latter case varies from 78:22 to 93:7 as a function of organolithium base or solvent, a result which suggests caution in interpretation.[33]

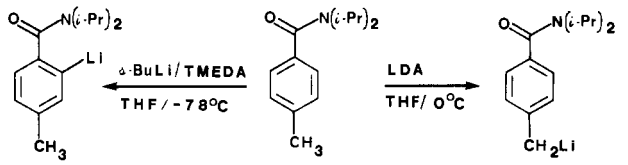
The fundamental kinetic and thermodynamic information that is needed for understanding the order of directing effects is lacking. While equilibration between lithiated species has been shown to be slow with respect to trapping at −78 °C,[30,32] an obligatory condition if reliable deductions about lithiations are to be drawn from yields of deuterated and methylated products (vide supra), relative thermodynamic stabilities have been determined in only a few cases. A study by Ziegler and Fowler established that the 2-lithio species **20** is



produced both by direct lithiation at −78 °C and by allowing the 6-lithio isomer **21**, obtained by metal–halogen exchange, to warm to room temperature.[34a] Furthermore, dimeric 2-lithioanisole has been shown to be more stable than the dimeric 3- and 4-lithioanisoles, a result which parallels the course of lithiation.[34b]

(28) DeSilva, S. O.; Snieckus, V., unpublished results.
(29) Slocum, D. W.; Sugarman, D. I. *Adv. Chem. Ser.* **1974**, *130*, 2227. Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.
(30) Beak, P.; Tse, A.; Hawkins, J.; Chen, C.-W.; Mills, S. *Tetrahedron* **1982**, in press.
(31) Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464.
(32) Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, 3335.
(33) There are some inconsistencies between the intramolecular and intermolecular competitions. Intermolecular competitions show that oxazoline > $CONR^-$ at −45 °C in THF/HMPT, while in intramolecular rivalries, the order $CONR^- \simeq CONR_2$ > oxazoline is observed at −78 °C in THF.[24a,31] In intramolecular competition the order is $CONR^-$ > $CONR_2$ by 5:1 while in intermolecular competition the order is $CONR_2$ > $CONR^-$ by 10:1.[30] Small energy differences appear to be involved and further work will be needed to resolve these inconsistencies.
(34) (a) Ziegler, F. F.; Fowler, K. W.; *J. Org. Chem.*, **1976**, *41*, 1564. See also ref 15b and references therein. (b) Beak, P.; Siegel, B. *J. Am. Chem. Soc.* **1976**, *96*, 6803.

Scheme IV

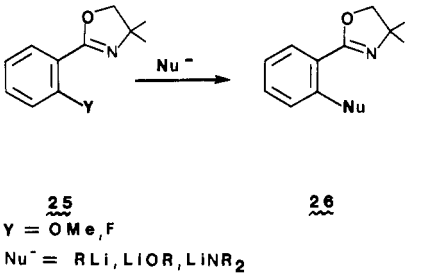


A consistent, if provisional, explanation of the dominant directing effect of the tertiary amide can be based on the assumption that a complex is formed between lithium and the amide group. Thus kinetic control could be rationalized by assuming that this initial complex delivers the base intramolecularly to the ortho position. The results of the competitions would then reflect the superiority of the amide as the site for preferential complexation of the lithium reagent. The formation of *o*-toluamide but not *p*-toluamide anions is consistent with the concept of intramolecular delivery of the base to an acidic proton. This effect can also be used to rationalize the relative directing effects of secondary and tertiary amides.[30] Complexation and inductive effects are generally used to rationalize directed metalations.[15a] The inductive effect of the amide would also be increased by amide–lithium complexation. Thermodynamic control would be explained by invoking a stabilizing action between the lithium and the carbonyl of the amide in the ortho-lithiated species.

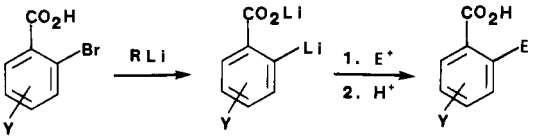
However, the congruence of kinetic and thermodynamic effects suggested by the above rationale may not be general. For example (Scheme IV), the *p*-toluamide **22** undergoes ortho lithiation with *sec*-BuLi/TMEDA at −78 °C to give **23** but with lithium diisopropylamide (LDA) benzylic lithiation yields **24**.[24a] A plausible explanation is that **23** is formed under kinetic control while **24** results from thermodynamic control.[35] Alternatively, the formation of an RLi–TMEDA complex may be responsible for the observed behavior. The effects of aggregation, ion association, solvation, complexation, and temperature on the regiospecificity of directed lithiation need to be determined to clarify the structure–stability relationships for ortholithiated species.

Although the tertiary amide has the highest priority for directing lithiations, there are situations where other groups may be preferred. The discovery by Puterbaugh and Hauser that the secondary amide acts as an ortho director, attributed in part to deactivation toward addition by initial deprotonation, has been extensively used for synthetic purposes.[15,36,37] The disadvantages

Scheme V



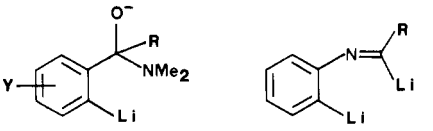
Scheme VI



of the secondary amide, in our experience, result from the insolubility and reduced reactivity of the dilithiated species, and from electrophilic substitution on nitrogen. On the other hand, the principal disadvantage of the tertiary amide, resistance to hydrolysis, appears to be less serious for the secondary amide.

Meyers and co-workers showed that the oxazoline group is particularly useful in activating nucleophilic displacement of *o*-methoxy or *o*-fluoro groups (**25** → **26**, Scheme V).[38] This discovery led to efficient syntheses of a variety of benzo-fused ring systems.[38,39] The oxazoline may also be advantageous in that N-alkylation of the ortho-substituted system may facilitate hydrolysis.

Sequences in which nucleophilic addition of the RLi reagent to dimethylamides or isonitriles precedes ortho lithiation to give **27** or **28**, respectively, are useful for



the synthesis of ortho-substituted ketones[21] and anilines,[40] respectively. The isonitrile together with the $^{-}NCO_2R^{15f}$ and $^{-}NCOR^{15f}$ functions provide pathways to anthranilic acid derivatives, which have also been obtained by the reaction of an ortholithiated *N,N*-diethylbenzamide with azidomethyl phenyl sulfide.[41] Finally, the metal–halogen exchange regimen systematically developed by Parham, Bradsher, and co-workers (Scheme VI)[19] provides a synthetic equivalent of the ortholithiated benzamide. Since the metal–halogen exchange is usually fast, this approach is very useful for the preparation of aromatic systems bearing reactive functional groups, providing that the requisite-bromobenzoic acids are available.

(35) This comparison is not intended to imply that **23** is formed as an intermediate in the reaction with LDA. Exclusive benzylic metalation is reported in a similar lithiation of acetal groups which are para to an oxazoline. Meyers, A. I.; Campbell, A. L. *Tetrahedron Lett.*, **1979**, 4155.

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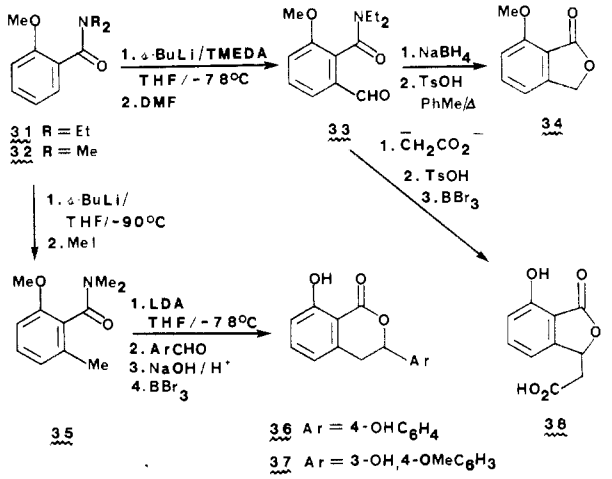
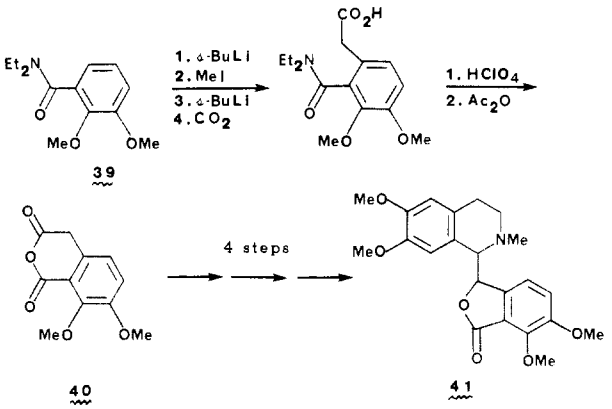
Scheme VII

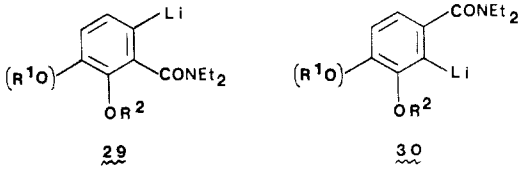


Scheme VIII



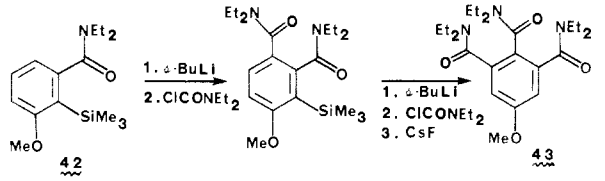
Lithiated Tertiary Aromatic Amides in Synthesis

The synthetic advantages of the tertiary amide have been demonstrated in a number of syntheses. The tri- and tetrasubstituted lithiated intermediates **29** and **30**



are generated in a few steps from commercially available benzoic acids.[23] Introduction of carbon electrophiles followed by benzylic substitutions gives systems which are particularly difficult to prepare by classical methodology. Thus, the synthesis of the phthalide **34** (Scheme VII) may be achieved[23] in three steps and 73% overall yield from **31**, in contrast to the multistep, low-yield sequences using traditional appraoches.[42] Furthermore, two-carbon chain extension of **33** results in a simple pathway to isoochracinic acid **38**.[43] The conversion of **32** to the *o*-toluamide **35** followed by preferential deprotonation at the *o*-methyl group provides an alternate, synthetically useful chain extension procedure.[44] Thus, hydrangenol (**36**) and the sweetening agent, phyllodulcin (**37**), are obtained by one-pot sequences. On the other hand (Scheme VIII) sequential methylation and carbonation of **39** lead, after hydrolysis and cyclization, to the isochroman-1,3-dione **40**, a key intermediate in a convergent assemblage of the phthalide isoquinoline alkaloids **41**.[46]

Scheme IX



The facile introduction and removal of the $SiMe_3$ group by directed metalation and protodesilylation[47] provide methodology to block metalation at the more reactive site in a *m*-anisamide **42** (Scheme IX). This approach, explored but briefly to date,[48] shows promise for the preparation of polysubstituted aromatics **43**.

The condensation of ortholithiated benzamides with aromatic aldehydes constitutes a highly convergent synthetic operation and also provides an intramolecular hydroxyl group that induces amide hydrolysis by anchimeric assistance. Illustrative of such procedures is the construction of the phenanthroindolizidine (**45**) and phenanthroquinolizidine (**46**) alkaloids by ortho lithiation of the phenanthrene amide **44** followed by coupling with pyridine and pyrrole aldehydes (Scheme X).[49] The alkaloid **41** has also been prepared by a similar route.[46a] This approach also provides versatile methodology for the regiospecific synthesis of naturally occurring anthraquinones.[50] The six-step preparation of soranjidiol in 21% overall yield (Scheme XI) is exemplary. Reaction of the lithiated *o*-anisamide **47** with *m*-tolualdehyde results in the alcohol amide **48** which, without isolation, is treated with *p*-toluenesulfonic acid (TsOH) to give the phthalide **49**. Compound **49** is converted into the naturally occurring anthraquinone **50** by an efficient four-step sequence. This protocol, which is general and circumvents problems of regioselectivity and ambiguity associated with the classical Friedel–Crafts method, has been used for the synthesis of numerous anthraquinone natural products.[50] Kende and co-workers have nicely adapted this strategy in highly convergent routes to several antitumor anthracyclinones using dilithiated secondary benzamides.[51]

In situ metalation of the alkoxy amide intermediates results in the direct formation of anthraquinones in a

(42) Blair, J.; Brown, J. J.; Newbold, G. T. *J. Chem. Soc.* **1955**, 708. It is similarly instructive to compare the synthesis of the isomeric 4-methoxyphthalide by directed metalation (ref 23, 26b) and classical (Houbion, J. A.; Miles, J. A.; Paton, J. A. *Org. Prep. Proced. Int.* **1979**, *11*, 27) methodologies.

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(44) Other *o*-toluoyl systems, not necessarily all derived by directed metalation, are similarly useful; see ref 15a, 37, and: Ito, Y.; Kobayashi, Y.; Saegusa, T. *Chem. Lett.* **1980**, 1563. Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1980**, 206. Hauser, F. M.; Rhee, R. P.; Prasanna, S. *Synthesis* **1980**, 72, Kraus, G. A. *J. Org. Chem.* **1981**, 46, 201 and references therein.

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(47) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.

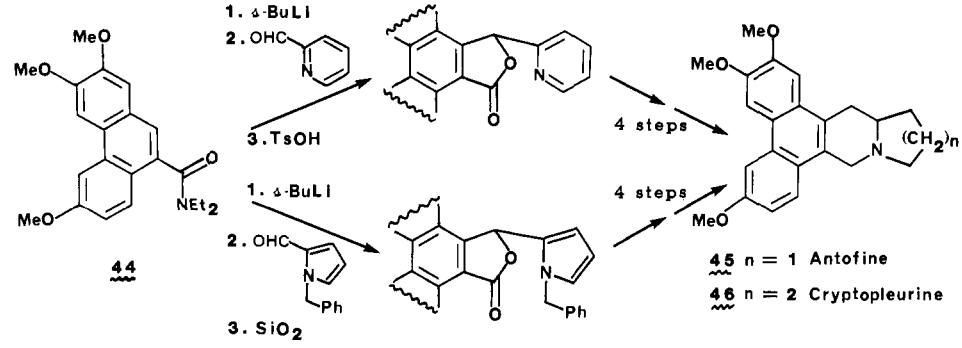
(48) Reed, J. N.; Mills, R. J.; Snieckus, V. unpublished results.

(49) Iwao, M.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron Lett.* **1981**, 2349.

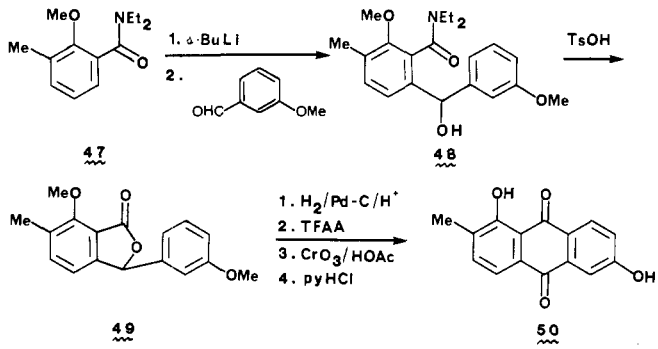
(50) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

(51) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799. Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247.

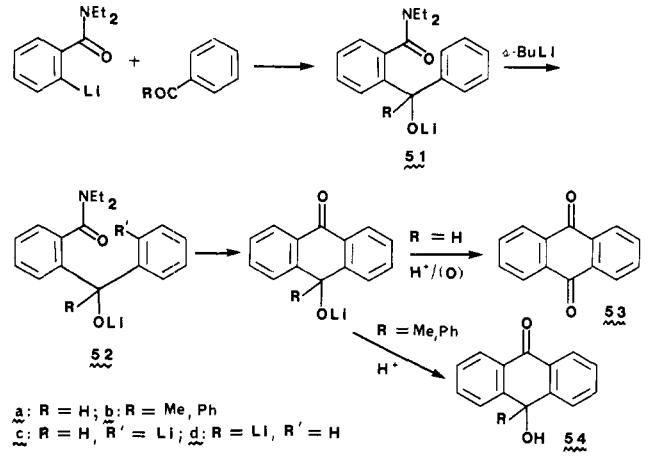
Scheme X



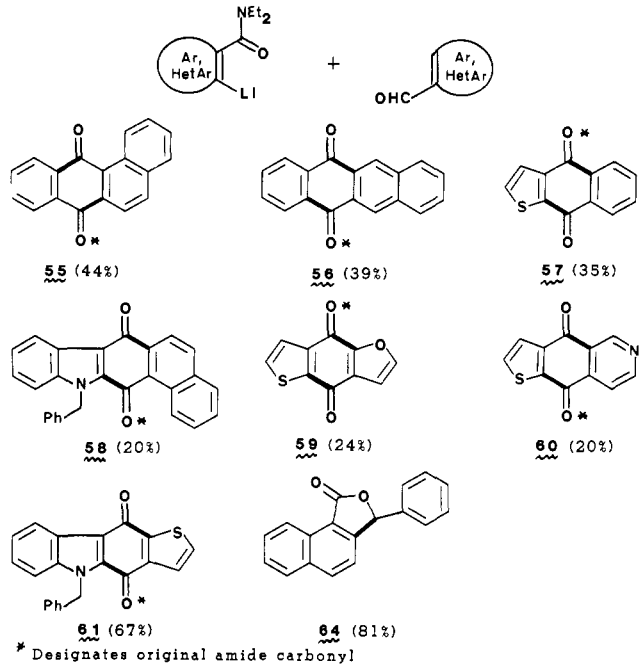
Scheme XI



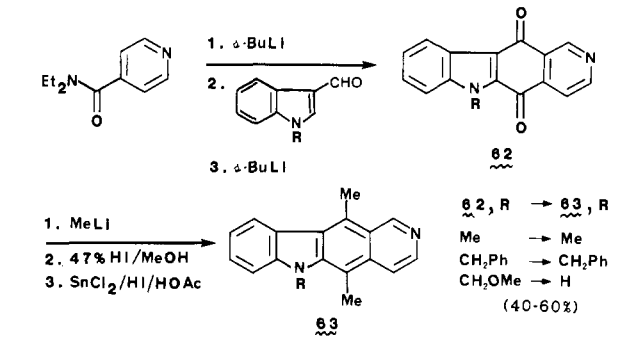
Scheme XII



Scheme XIII



Scheme XIV

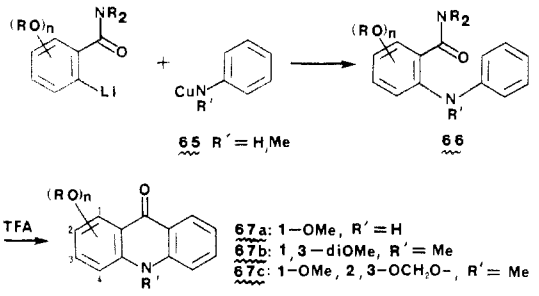


tandem sequence as illustrated by the conversion of **12** to **53** (Scheme XII).[25] The synthetic utility of this one-pot tandem metalation route is demonstrated by the preparation of a variety of carbocyclic and heterocyclic anthraquinones **55–61** (Scheme XIII).[25] The separate use of indole-3-carboxaldehyde and pyridine-4-carboxamide precursors in the tandem metalation reaction formed the basis for the one-pot synthesis of linear benzoquinones representing the skeleton of the antitumor ellipticine alkaloids **62** (Scheme XIV).[25] A three-step sequence, without purification of intermediates, was used to transform compounds **62** into the pyridocarbazoles **63**. The methoxymethyl derivative **62** ($R = CH_2OMe$) gave ellipticine **63** (R = H) directly under the forcing reductive–acidic conditions. Application of similar reductive conditions allows the conversion of other condensed anthraquinones into the corresponding polycyclic aromatic hydrocarbons, e.g., **55** into the carcinogenic benz[*a*]anthracene and 7,12-dimethylbenz[*a*]anthracene, with minimum handling of potentially hazardous compounds.[25,26a]

That the cyclization of **51a** could involve the ortho-lithiated intermediate **52c** was favored on the basis of the formation of **54b** when acetophenone and benzophenone were used as electrophiles. Similar species could be favored in the syntheses of **57** and **59–61** by the high kinetic acidities at the 2-position in the respective heterocyclic rings. On the other hand, cyclization via **52d**, a species analogous to the *o*-toluamide anion and benzophenone dianion, is also possible.[52]

(52) The use of 4 equiv of sec.-BuLi for the metalation of **52a** increases the yields of anthraquinones and possible suggests the involvement of higher order lithiated species (Doadt, E. G.; Snieckus, V., unpublished results).

Scheme XV



Tandem metalation of α- and β-naphthamides leads largely to phthalide products, e.g., **64**, suggesting ineffectiveness of the second metalation step. Nonetheless, the phthalides are useful intermediates for conversion into quinone products by conventional methods.[26a,50]

Ortholithiated benzamides are also useful for the preparation of acridones as illustrated by the formation of **67** (Scheme XV).[53] The copper coupling reaction, based on the work of Yamamoto,[54] is very sensitive to the purity of the cuprous chloride used in the preparation of the copper anilides **65** from the corresponding lithiated species and appears to be more seriously inhibited by steric effects than reactions of ortholithiated benzamides with other electrophiles. Since direct Friedel-Crafts cyclizations of **66** to **67** can be achieved, the overall sequence provides ready access to unusually substituted acridones, including acridone alkaloids, e.g., evoxanthine **67c**.

Concluding Remarks

The tertiary amide, together with secondary amide, thioamide, and oxazoline structures, offer a flexible range of ortho metalation directing groups for application in synthetic endeavors. Advantages of the tertiary amide include ease of preparation, priority over other directors with *sec*-BuLi/TMEDA at -78° in THF, utility in polysubstituted aromatic systems, and resistance to nucleophilic attack. Indeed, its principal disadvantage is resistance to hydrolysis.

The present Account demonstrates the use of the readily available alkoxybenzamides in lithiation-substitution sequences for the regiospecific synthesis of a variety of polysubstituted aromatics. The amide facilitates further manipulation of the introduced electrophiles to allow ortho carbon chain extension and cyclization to carbocyclic and heterocyclic systems including a variety of natural products. The use of ortholithiated tertiary benzamides in tandem metalation sequences is a particularly efficient approach to the synthesis of carbocyclic and heterocyclic benzoquinones.

The development of ortholithiated tertiary amides is part of a generally renewed interest in directed metalations.[15] Promising developments have been forthcoming, and new approaches and applications can be anticipated.[55]

The work in Urbana was carried out not only by those named in the references but also with the advice and encouragement of many co-workers. P.B. is grateful for their efforts and to the National Institutes of Health and the National Science Foundation for support. The work at the Guelph-Waterloo Centre is due to a dedicated international group of co-workers who ignored cultural and political differences for the common goal of directed metalation chemistry. V.S. is grateful for their skillful efforts and to the Natural Sciences and Engineering Research Council of Canada for support.

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(55) For recent examples, see lithiations of (arene)chromium tricarbonyl complexes: Semmelhack, M. F.; Bisha, J.; Czarny, M. *J. Am. Chem. Soc.*, **1979**, *101*, 768. Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2560. Fukui, M.; Ikeda, T.; Oishi, T. *Tetrahedron Lett.* **1982**, 1605. The use of ortholithiated sulfonic acids for the regiospecific synthesis of meta-substituted benzenes: Figuly, G. D.; Martin, J. C. *J. Org. Chem.* **1980**, *45*, 3728. Lithiation of aminopyridines: Tamura, Y.; Fujita, M.; Chen, L.-C.; Inoue, M.; Kita, Y. *Ibid.* **1981**, *46*, 3564.

Some Theoretical Aspects of Organic Photochemistry

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Until 1960 organic photochemistry was only an occasionally studied field. This stemmed partly from the feeling that photochemical reactions were random and unpredictable. It was often stated that reactions occurred by virtue of the high energy imparted to reacting molecules by light photons absorbed. In 1960, the author[1-6] suggested that despite the high energy of excited states, these molecules did not react indiscriminately but, rather, transformed themselves by continuous electron redistribution, seeking out low-energy pathways and avoiding high-energy routes. Controlled by the same forces as ground-state reacting species, the energy

Howard E. Zimmerman is a native of Connecticut. He received his B.S. and Ph.D. degrees from Yale in 1950 and 1953. After a Lilly N.R.C. Postdoctoral Fellowship at Harvard spent with R. B. Woodward, he served on the Northwestern University faculty from 1954 to 1960 when he moved to the University of Wisconsin. He has held the Arthur C. Cope chair there since 1975. He received the James Flack Norris Award in Physical Organic Chemistry in 1976 and the Halpern Award for Photochemistry in 1979. He was elected to the National Academy of Sciences in 1980. His research interests include the synthesis of unusual organic molecules, reaction mechanisms, mechanistic and exploratory organic photochemistry, and theoretical organic chemistry. His 1966 work on the Möbius-Hückel differentiation of pericyclic transition states provides an alternative to symmetry based determination of allowedness and forbiddeness.

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(2) Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1961**, *83*, 4486-4487.
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(4) Zimmerman, H. E. *Adv. Photochem.* **1963**, *1*, 183-208.
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