The Directed *ortho* Metalation — Cross-Coupling Symbiosis in Heteroaromatic Synthesis

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Thirty years after its discovery by Gilman and Wittig, the Directed *ortho* Metalation (D*o*M) reaction continues to march in synthetically useful paths. To offer evidence for this statement, this lecture review describes a new and general cumyl Directed Metalation Group (DMG) (Schemes 2-6) and a phosphine oxide DMG (Schemes 7 and 8). Aryl-aryl cross-coupling chemistry is highlighted by polymer support Suzuki-Miyaura (Schemes 10 and 11) and an aryl *O*-carbamate-Grignard of value in the construction of naphthalenes (Scheme 12) and indoles (Scheme 13) and, for the latter class of compounds, in the generation of 4,5-quinodimethane intermediates (Scheme 14) for the synthesis of corresponding annelated derivatives (Scheme 15). The marriage of D*o*M with the Negishi cross-coupling reaction is demonstrated in general (Scheme 16). The concept of Directed remote Metalation (DreM) (Schemes 17 and 19) is applied to the synthesis of dibenzopyranones (Scheme 18), xanthones (Scheme 21), acridones, dibenzoazepinones, and oxindoles (Scheme 20). In this context, a carbanionic *N*-to-*ortho*-C *t*-Boc migration leading to anthranilate esters is also achieved (Scheme 20). For provision of diaryl ethers, diaryl sulfides, and diaryl amines, a new copper catalyst is introduced into the venerable Ullmann reaction (Scheme 22) and its extension by D*o*M, and cross-coupling chemistry is indicated (Scheme 23). A recently evolving link to D*o*M, the Grubbs metathesis process is manifested in the total synthesis of two natural products (Schemes 25 and 26) and has anticipated use more broadly in heterocyclic synthesis (Scheme 27).

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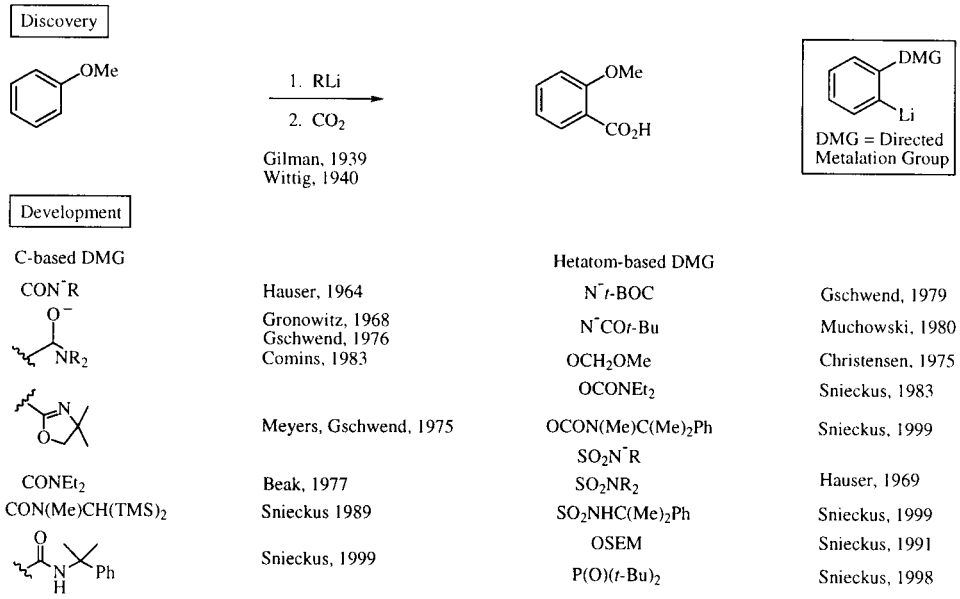
Already in the seventh decade since the independent discovery by Gilman and Wittig, the Directed *ortho* Metalation (D*o*M) reaction (Scheme 1) continues to thrive in fundamental concepts and in the suggestion of inventive avenues for the regiospecific construction of polysubstituted aromatics and heteroaromatics [1]. The trail-blazing systematic investigations of Hauser and his students in the early 1960's presented amide and sulfonamide Directed Metalation Groups (DMGs) but the full impact of D*o*M in synthesis was realized only by the subsequent contributions of Beak, Christensen, Comins, Gschwend, Meyers, and Muchowski, who designed and developed a variety of carbon- and heteroatom-based DMGs. The heterocyclic D*o*M (Het D*o*M) reaction evolved equally rapidly but continues to offer challenges both in derivation of compatible DMGs and efficient application in these more sensitive, coordination-prone, and, in cases of pyridines and related π-deficient heterocycles, electrophilic systems [2]. In our laboratories, synthetically useful chemistry [3,4] evolved from Beak's tertiary amide and our *O*-carbamate DMGs while the potential of the OSEM group remains incompletely explored [5].

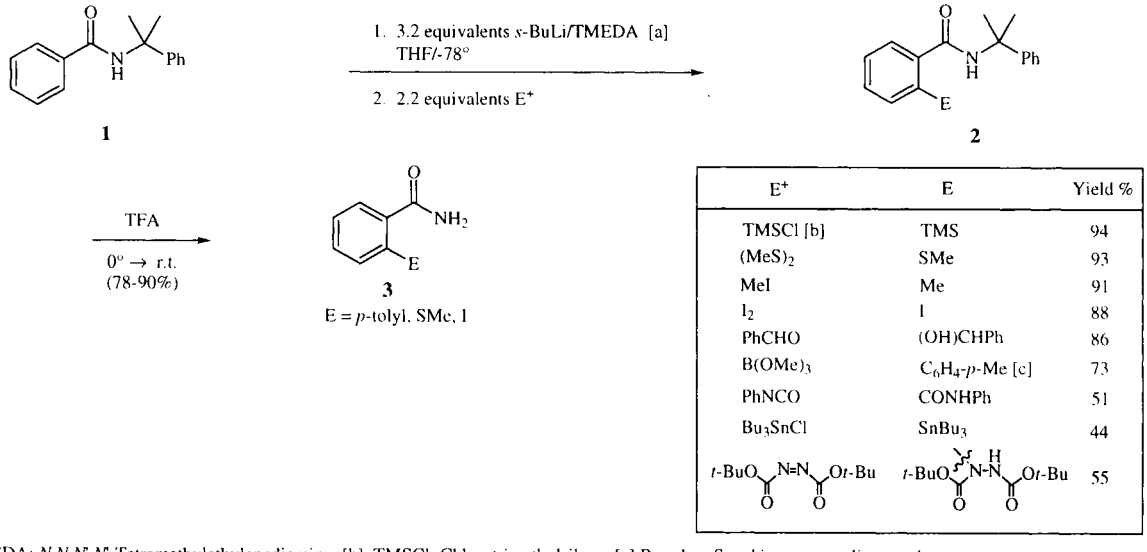
Scheme 1



Directed *ortho* Metalation (D*o*M) Chemistry. The Evolution of the Directed Metalation Groups (DMGs): CONHCumyl, SO_2NHCumyl, OCON(R)Cumyl, and P(O)(*t*-Bu)$_2$.

Although introduction of *ortho* functional groups with potential for anchimerically assisted amide hydrolysis, the recalcitrant nature of this DMG compromised application, especially in systems bearing fragile functionality or chiral centers [1]. Following the appraisal of the unrelated report by Carpino [6] of the striking lability of *N*-cumyl group to mild acid, the *N*-cumyl benzamide **1** was metalated under standard (but excess) *s*-BuLi/TMEDA conditions. As gleaned from Scheme 2, the viability of the *N*-cumyl DMG was established by reaction with a variety of electrophiles, including boron which, after Suzuki-Miyaura cross-coupling, led to a biaryl *N*-cumyl amide product [7]. Brief treatment with trifluoroacetic acid (TFA) under mild conditions afforded primary amide **3** whose further manipulation to carboxylic acids and other functional groups is well established. The synthetic utility was further illustrated by the transformation **1** → **4** (Scheme 3) whose conversion by a D*o*M-electrophile quench sequence afforded **5** and thence the phthalimides **6**. Survival of sensitive functionality in this overall route (*e.g.* **6**, E = TMS) bodes well for the use of this methodology for preparation of 4-substituted phthalimides which have been classically obtained by nonregioselective and harsh electrophilic substitution-based reactions (*e.g.* **7** → **8**).

Scheme 2



1

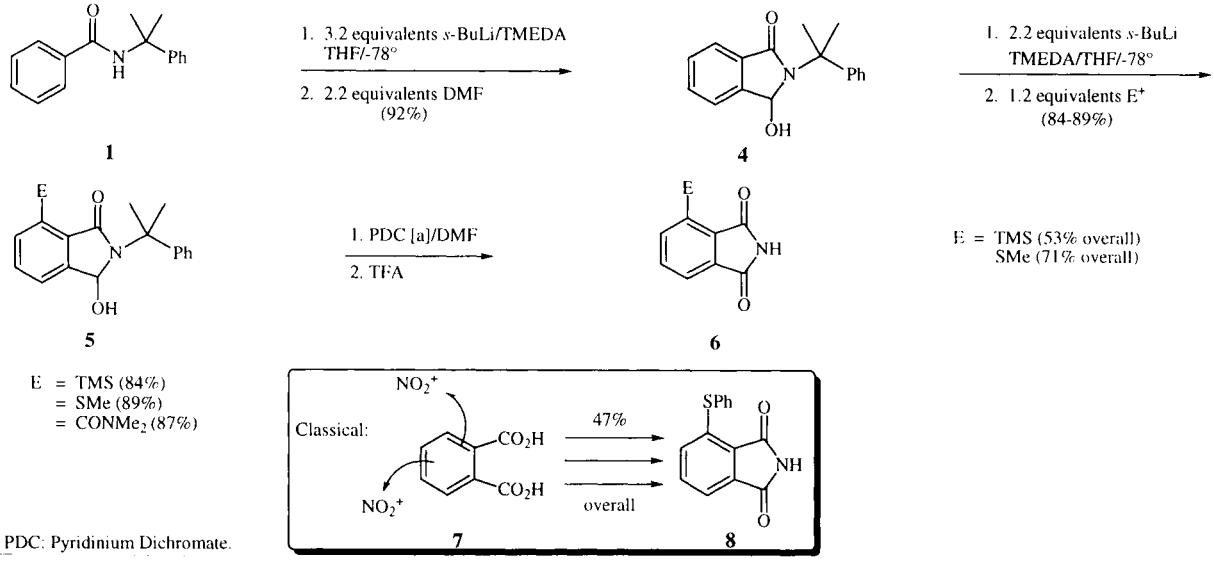
2

3

E^+	E	Yield %
TMSCl [b]	TMS	94
$(MeS)_2$	SMe	93
MeI	Me	91
I_2	I	88
PhCHO	(OH)CHPh	86
$B(OMe)_3$	C_6H_4-*p*-Me [c]	73
PhNCO	CONHPh	51
Bu_3SnCl	$SnBu_3$	44
t-BuO(C=O)N=N(C=O)O*t*-Bu	*t*-BuO(C=O)N(H)-N(H)(C=O)O*t*-Bu	55

[a] TMEDA: *N,N,N',N'*-Tetramethylethylenediamine; [b] TMSCl: Chlorotrimethylsilane; [c] Based on Suzuki cross-coupling result.

Scheme 3



1

4

5

6

7

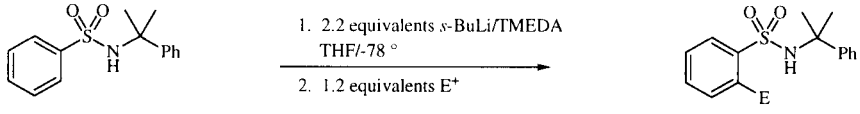
8

[a] PDC: Pyridinium Dichromate.

The analogous benzenesulfonamide **9** (Scheme 4) was metalated under identical, albeit nonexcess base, conditions to furnish *ortho*-substituted products **10** in mainly excellent yields. The conversion **9** → **12**, E = CHO (Scheme 5), parallel to the benzamide study (Scheme 3), led to an equilibrium mixture of hydroxyphthalide **13** and open-chain aldehyde (as judged by nmr) whose further oxidation gave the corresponding product **15**. On the other hand, the benzophenone quench product **13**, E = $Ph_2C(OH)$ afforded, after brief trifluoroacetic acid treatment, the saccharin **11** derivative.

These encouraging results invited attempts to effect *Do*M chemistry on the tertiary aryl *N*-cumyl *O*-carbamate **18** with the goal of overcoming hydrolytic and other manipulative difficulties of the original *N,N*-diethyl *O*-carbamate DMG (box) [4]. In the event, metalation-electrophile quench and, significantly, anionic *ortho* Fries rearrangement results, **16** and **17** respectively, were observed. The facile further manipulation of **16** and **17** by trifluoroacetic acid and trifluoroethanol (TFE) treatment to *ortho*-substituted phenol **19** and salicylamide **20**, respectively, were smoothly realized. From **19**, smooth reversal of the standard phenol-isocyanate condensation using sodium hydroxide (NaOH) led to **21**. As in the benzamide series (Scheme 3), the retention of sensitive trimethylsilyl (TMS) functionality is noteworthy.

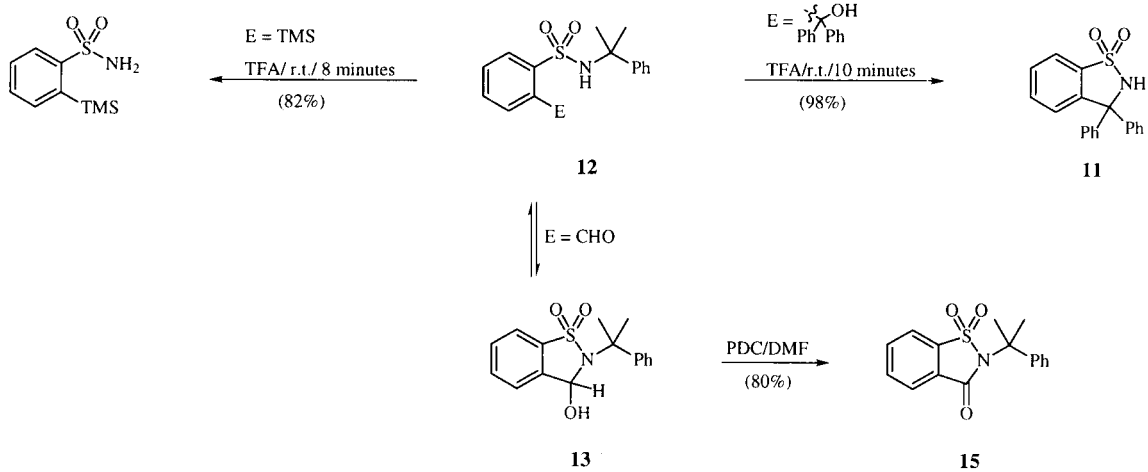
Scheme 4



9 **10**

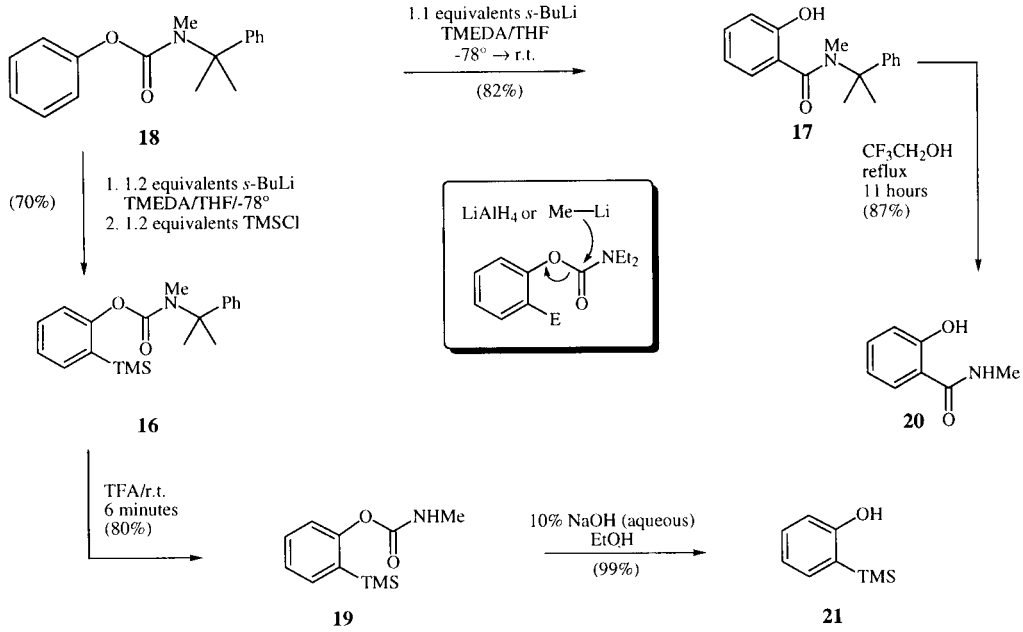
E^+	E	Yield %
PhCOPh	$C(OH)Ph_2$	95
$(MeS)_2$	SMe	92
I_2	I	88
DMF	CHO	87
$ClCONMe_2$	$CONMe_2$	79
TMSCl	TMS	60

Scheme 5



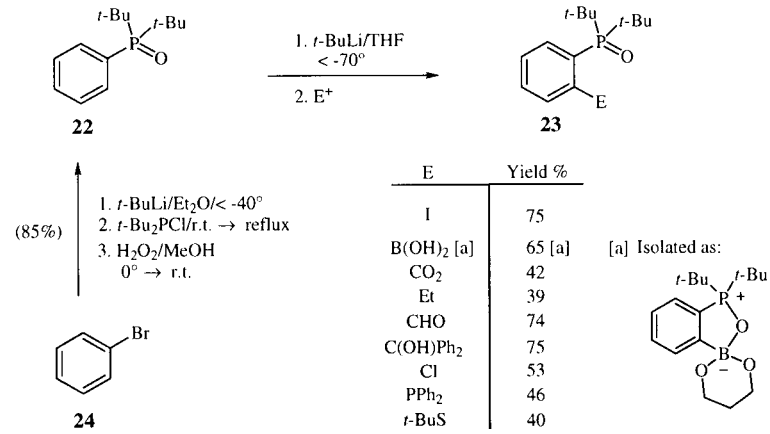
12 **11** **13** **15**

Scheme 6

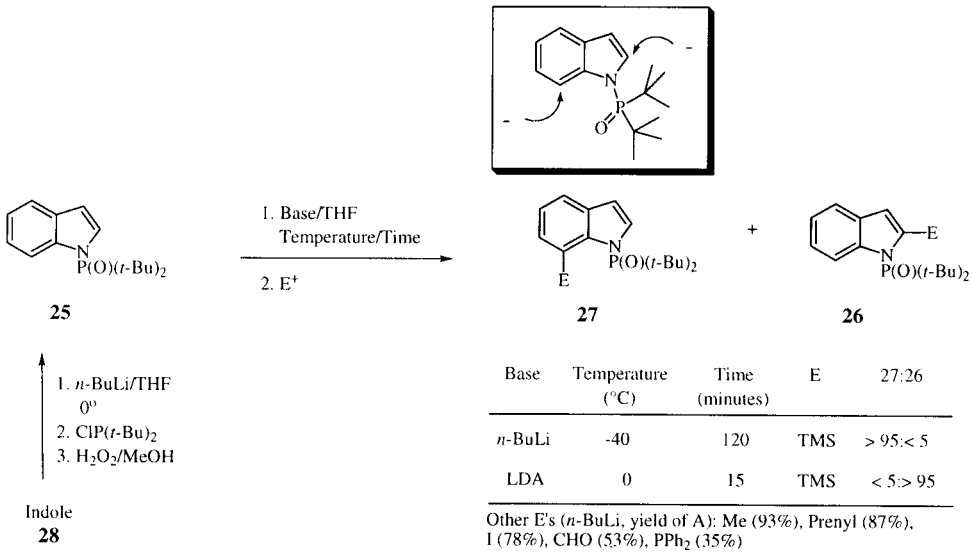


The surge of activity in the area of enantioselective organometallic catalysis using phosphorus-based ligands [8] provided the stimulus to improve currently available P-DMGs [9]. Thus, the di-*t*-butyl phosphine oxide system **22** (Scheme 7), prepared by the Shaw procedure from bromobenzene (**24**), underwent smooth deprotonation and electrophile quench to give a variety of 1,2-disubstituted aryl phosphorus systems **23**, including iodo, sulfur, (differentiated) phosphorus, and boron (unusually bonded P-B heterocyclic) derivatives. Application of this P-DMG to indoles has allowed, as a function of conditions, regiospecific C_2- (**26**) or C_7- (**27**) functionalization (box) of the substrate **25**, readily derived from indole (**28**) (Scheme 8) [10]. These results may be rationalized by kinetic and thermodynamic effects respectively and, in view of the introduction of the C_7 prenyl group, may be useful in indole-terpenoid natural product synthesis.

Scheme 7



Scheme 8



Base	Temperature (°C)	Time (minutes)	E	27:26
n-BuLi	-40	120	TMS	> 95:< 5
LDA	0	15	TMS	< 5:> 95

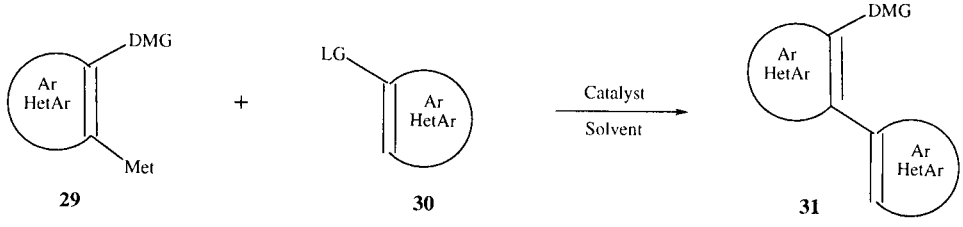
Other E's (*n*-BuLi, yield of A): Me (93%), Prenyl (87%), I (78%), CHO (53%), PPh_2 (35%)

The Directed *ortho* Metalation — Cross-Coupling Connection. $ArB(OH)_2$-ArX and ArMgX-Aryl *O*-Carbamate Cross-Coupling Regimens Including Solid Support Methods.

The synthetic chemist's armamentarium for sp^2-sp^2 C-C bond formation has been revolutionized by the discoveries, over 25 years ago, of transition metal catalyzed processes which, in the context of aromatic substrates, allows facile access to various combinations of biaryls and heterobiaryls, **29** + **30** → **31** (Scheme 9) [1,11]. Using a variety of DMGs depicted in Scheme 9, we have concentrated on the Suzuki-Miyaura and Corriu-Kumada-Tamao processes, expanding these processes to include OTf [12] and $OCONEt_2$/$SCONEt_2$ [13,14] leaving groups (LGs), respectively.

In recent work, a solid support-based Suzuki-Miyaura process has been formulated which takes advantage of D*o*M-derived boron derivatives [15]. Thus, cross-coupling of the Merrifield resin embodying a bromobenzene-acetal Leznoff linker **32** with the *ortho*-*N*-Boc phenylboronic acid **33** under standard conditions directly afforded, after hydrolysis, phenanthridine (**35**) in high yield and purity. Alternatively, coupling of **32** with the corresponding *O*-carbamate boronic acid **34** similarly furnished the biaryl **37** which, upon a two-step reduction oxidation process, provided the dibenzopyranone **36**. These regimens may be adapted to the preparation of small libraries (bookshelves) of the final phenanthridine and dibenzopyranone heterocycles. Further libraries of heterobiaryls (**41**, **42**, **43**, Scheme 11) are rapidly available by the general solid support Suzuki-Miyaura reaction, *e.g.*, **38** → **39** → **40**.

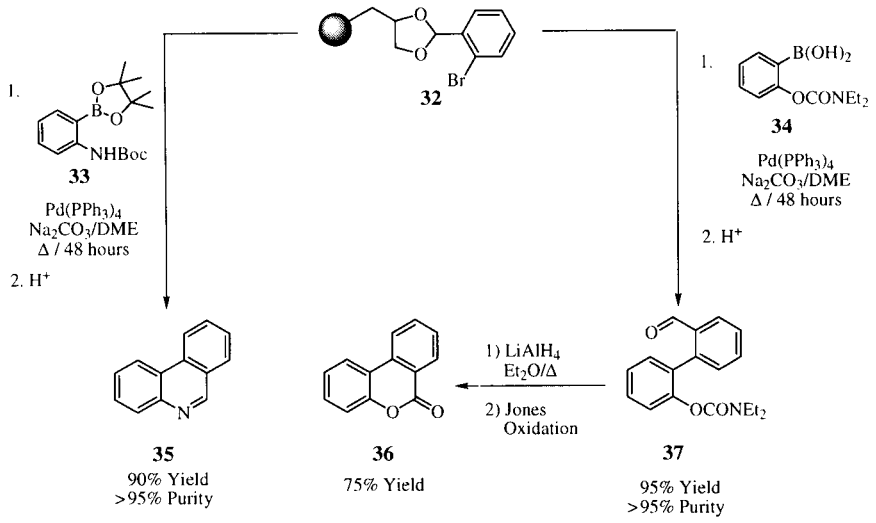
Scheme 9



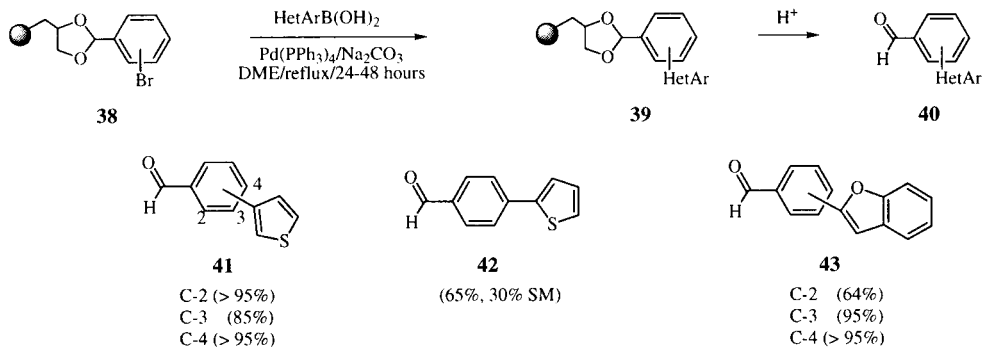
Met	LG	Catalyst	Name of Reaction
$B(OR)_2$	I > Br > OTf	Pd	Suzuki-Miyaura
MgX	OTf > $OCONEt_2$, $SCONEt_2$	Ni	Corriu-Kumada-Tamao
ZnX	Hal, OTf	Ni	Negishi
SnR_3	Hal, OTf	Pd	Stille

DMG = $CONEt_2$, $OCONEt_2$, OMOM, NH*t*-Boc, SO_2t-Bu

Scheme 10



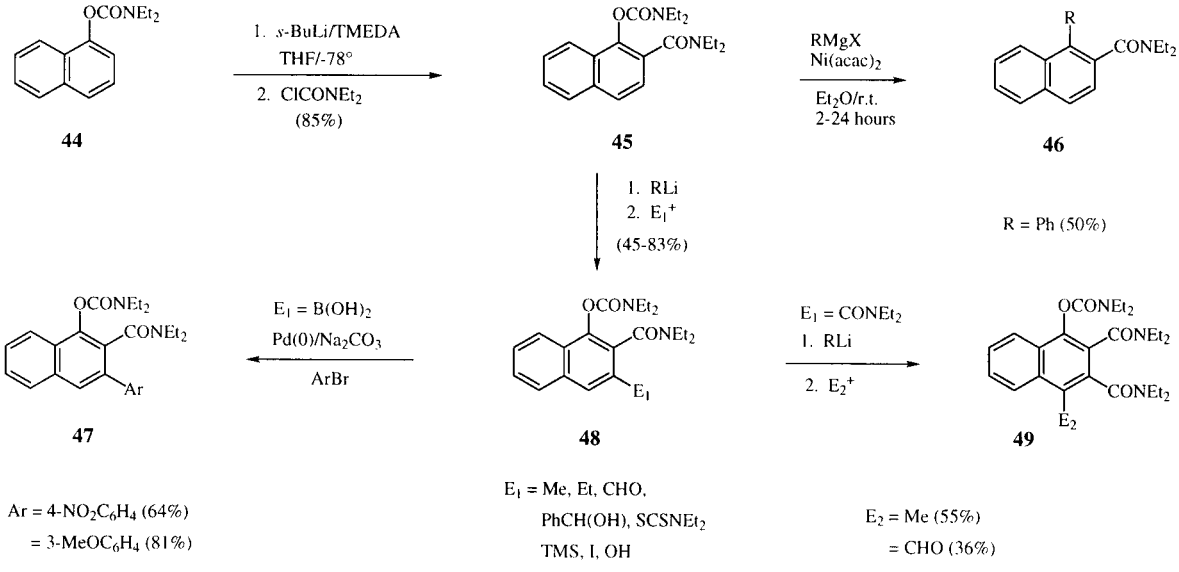
Scheme 11

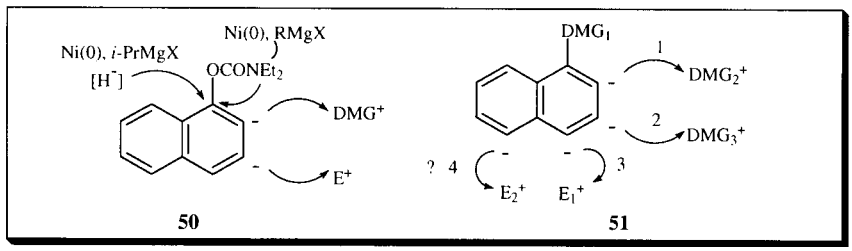


Extensions of the new Ni-catalyzed ArMgX + $ArOCONEt_2$ cross-coupling reaction [14] have included development of methods for naphthalenes (Scheme 12) and indoles (Scheme 13). In the former, tactics for the preparation of compounds which are not conveniently or regiospecifically accessible by classical (electrophilic substitution) routes have been devised, **44** → **45** → **46** [13]. In recent work [14], further metalation-electrophile quench has led to tri-substituted naphthalenes **48** which, for **48,** E = $B(OH)_2$, has provided functionalized biaryls **47** by Suzuki-Miyaura cross-coupling. Alternatively, for **48**, E = $CONEt_2$, an additional D*o*M has provided contiguously tetra-substituted naphthalenes **49**. Thus, latent DMG (**50**) and walk-around-the-ring D*o*M (**51**), principles of potential broader utility, have been demonstrated. D*o*M-Grignard cross-coupling reactions of aryl *O*-carbamates [13] have been adapted to indoles leading to methods of regiospecific functionalization of the benzene moiety which, to the best of our knowledge, have not been tested for this class of heterocycles. In early work [16], the indole 5-*O*-carbamate **53**, Z = H, conveniently available on a 20 g scale by the Leimgruber-Batcho method, was shown to serve for regioselective carbon or heteroatom functionalization at the C_4-position (**52**) → **53**. Further investigation [17] has demonstrated interesting C_6-regioselectivity in D*o*M processes applied to 3-substituted indoles, **52**, Z = Me, TMS, $(CH_2)_nOH$, n = 1,2, CH_2CH_2NHBoc → **54**. The *O*-carbamate-Grignard reagent cross-coupling was first achieved for the prototype indole **53**, E = Z = H providing C_5-carbon functionalized systems **55**, of potential value in melatonin-serotonin analogue synthesis. As a further application of this

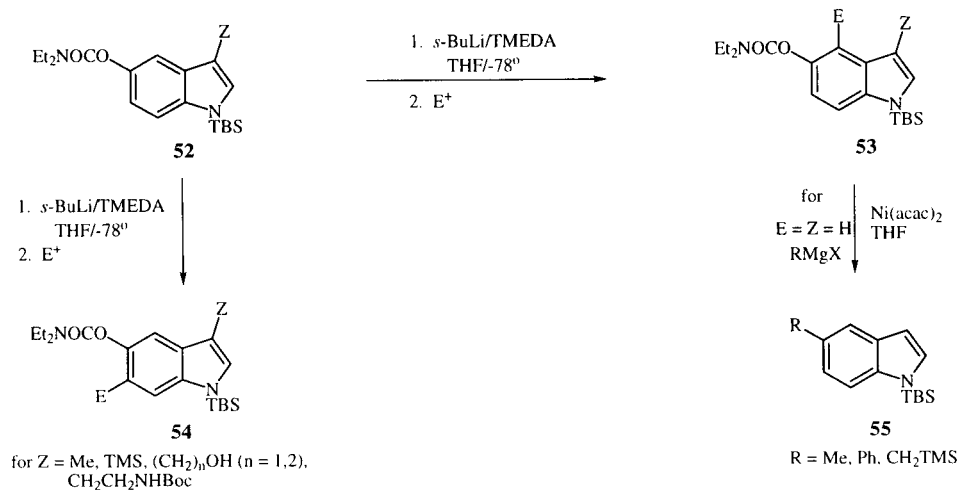
new methodology, a route to the generation of reactive 4,5-quinodimethine (QDM) in the indole series was investigated (Schemes 14 and 15) [18]. Metalation and carbamoylation of the Leimgruber-Batcho intermediate **52** (Z = H) led to the amide **55**, which upon cross-coupling with (trimethylsilylmethyl)magnesium chloride ($TMSCH_2MgCl$) and more than a catalytic amount of nickel(II) acetylacetonate ($Ni(acac)_2$), afforded the benzyl silane **56**. Reduction and workup with the useful Rochelle salt method afforded amine **57** which, upon quaternization and *N*-TBS for *N*-Boc protecting group exchange, furnished **58**. Attempts to use the *N*-TBS intermediate corresponding to **58** in the Saegusa-Ito reaction in the presence of acrylate ester (Scheme 15) resulted in complication due to *N*-desilylation and Michael addition of the dienophile. Interestingly, treatment of quaternary ammonium salt from **57** with one equivalent of cesium fluoride (CsF) in the presence of $(Boc)_2O$ does not trigger *o*-QDM formation. Subjection of **58** (Scheme 15) to tetrabutylammonium fluoride (TBAF) or *excess* cesium fluoride in the presence of excess dienophile leads, *via* the *o*-QDM intermediate **59**, to adducts **60-63** in useful to excellent yields. In this manner, 4,5-cyclohexyl (**60**), -benz (**61**), and new-heterocyclic (**62**, **63**) annulated indoles have been prepared. This work constitutes the first generation of a 4,5-QDM **69** in the indole series.

Scheme 12

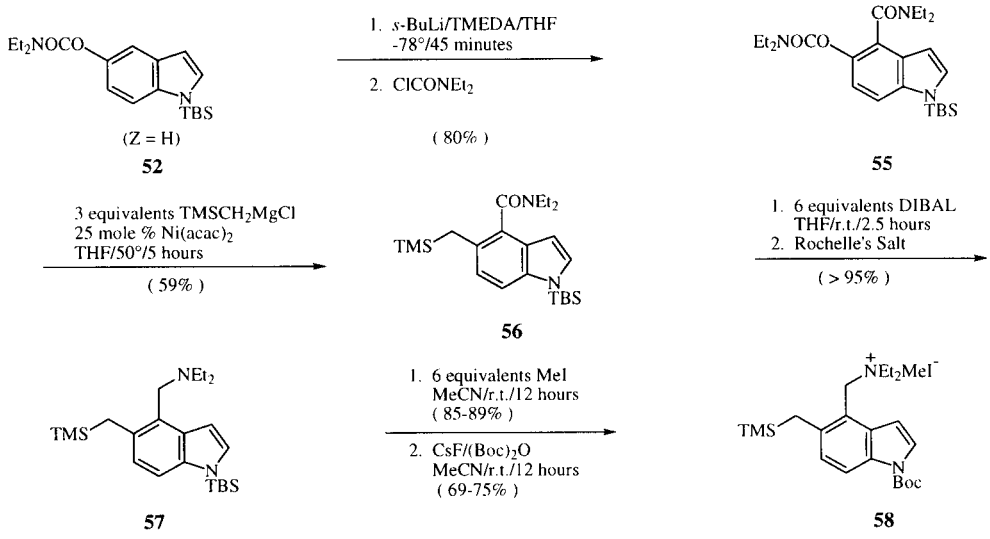




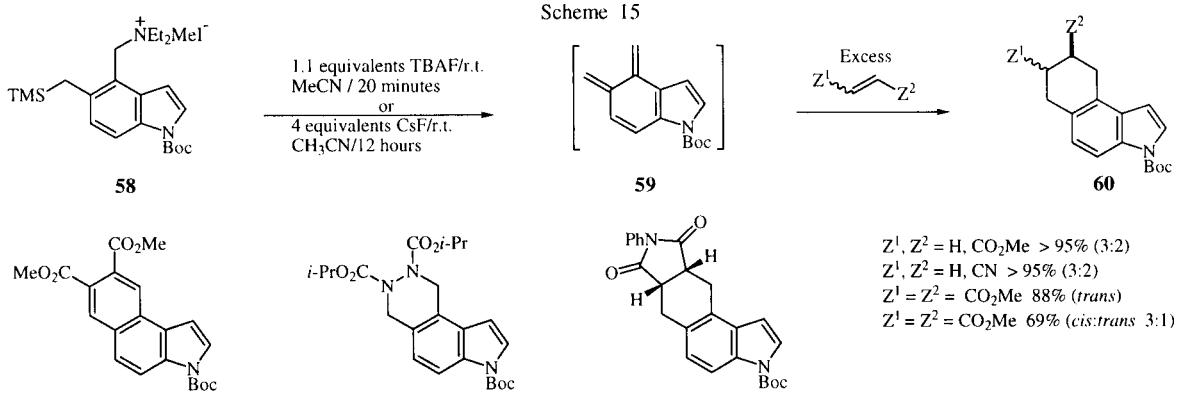
Scheme 13



Scheme 14



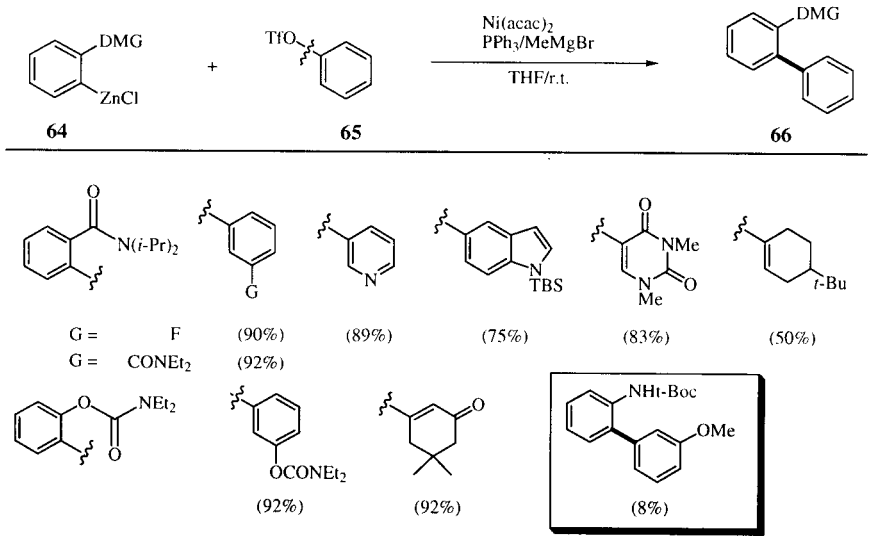
Scheme 15



In a systematic and extensive study, we have also demonstrated the utility of the DoM-Negishi cross-coupling connection for biaryl and heterobiaryl synthesis using aryl triflate partners (**64** + **65** → **66**, Scheme 16) [19]. As gleaned from Scheme 15, a number of heterocyclic triflates are readily coupled providing succinct access to new substances usually not available by previous methodology. An inefficient reaction is observed for a coupling of an *ortho*-zinc *N*-Boc aniline (box) presumably due to considerable stability of the zinc complex.

and 2-carboxamido-2'-hydroxybiaryls **62** [23]. Although azafluorenones are available by these processes whose regioselectivity complements Friedel-Crafts reactivity by virtue of DMG effects [22], more interesting is the sequence of remote anionic Fries rearrangement, → **69** which provides advantageous routes to dibenzopyranones (Scheme 18) [24]. Thus, Suzuki-Miyaura coupling of 2-boronic acid substituted *O*-aryl carbamates **70** with diverse aryl halides or triflates **71** affords the biaryls **72** which, provided that 3-alkoxy or silyl protection is pre-

Scheme 16

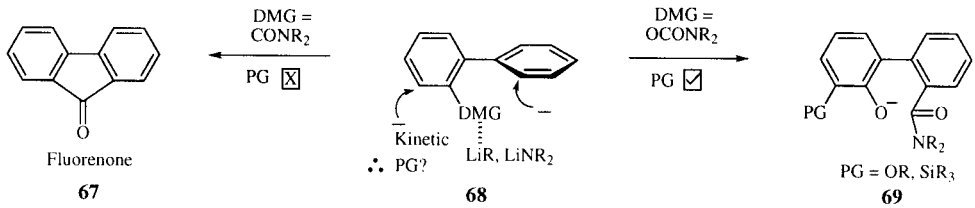


The Directed Remote Metalation (DreM) as an Anionic Friedel-Crafts Equivalent for Regioselective Construction of Diverse Heterocycles.

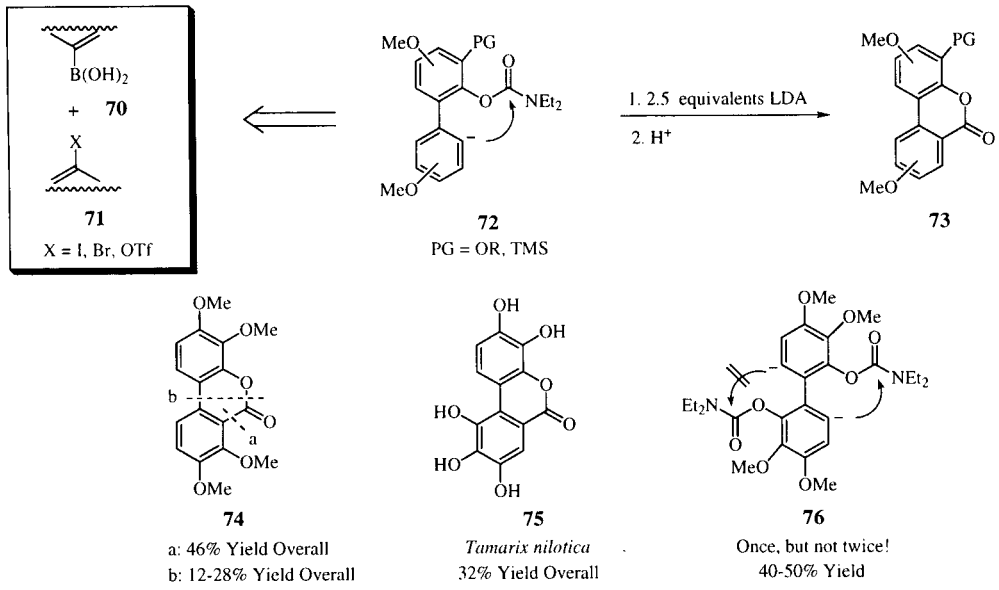
The Complex-Induced Proximity Effect (CIPE) concept advanced by Beak and Meyers [20] and Klumpp [21] concerning the deprotonation of nonthermodynamically acidic sites by initial coordination phenomena was applied to biaryl 2-amides and 2-*O*-carbamates **68** leading, respectively, without and with protection, to fluorenones **67** [22]

sent to avoid the anionic *ortho* Fries rearrangement, undergo the LDA-mediated remote Fries migration to give, after acid treatment, the dibenzopyranoes **73**. The advantage of this protocol (**74**, path a) compared to direct cross-coupling (**74**, path b) for the preparation of dibenzopyranones and the synthesis of a natural product (**75**) was demonstrated. Unfortunately, double remote anionic Fries rearrangement has not been successful to date (**76**). Application to the synthesis of the defucogilvocarcin antitumor antibiotics has also been achieved [25].

Scheme 17

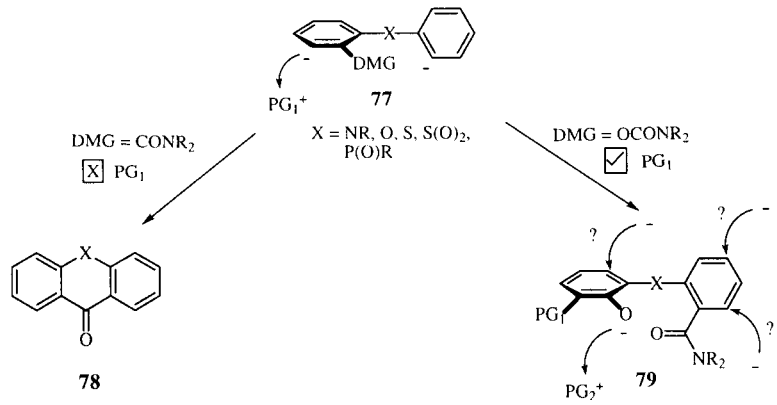


Scheme 18



As a logical small step, the CIPE concept which contributed to the above findings leading to the synthesis of fluorenones and dibenzopyranones (Scheme 17) was tested on the heteroatom bridged systems **77** (Scheme 19). In the event, for the X heteroatoms shown, systems **77**, DMG = $CONR_2$, without protection (PG_1), led to tricyclics **78** while derivatives **77**, DMG = $OCONR_2$, with protection (PG_1 = OR, SiR_3), furnished the carbamoyl migrated products **79** [26]. Thus, acridones (**78**, X = NR) [26a], xanthones (**78**, X = O) [26b], thioxanthone dioxides (**71**, X = SO_2) [26c], and dibenzophosphorinones (**78**, X = P(O)Ar) [26d] are efficiently available by this methodology from the respective heteroatom-bridged biaryls **77**. The carbamoyl ring-to-ring transfer, **77** → **79** has been explored successfully only with the X = SO_2, and P(O)Ar systems leading, in each case, two sequential anionic reactions from the intermediate **79** to substituted thioxanthone dioxides [26c] and dibenzophosphorinones [26d], respectively. The potential for further metalation of systems **79**, after appropriate phenol protection (PG_2), as raised by the question marks has also not been addressed.

Scheme 19

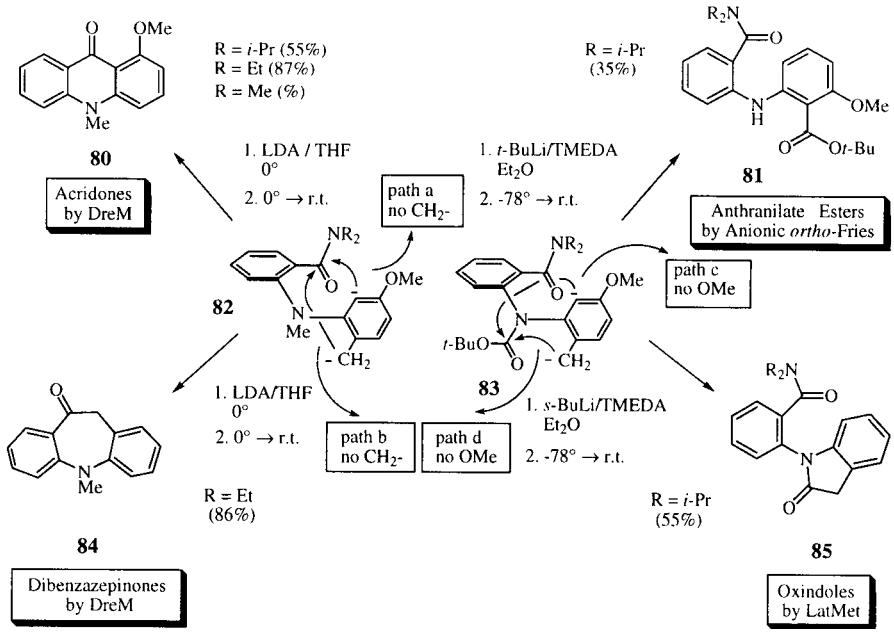


In the *N*-heteroatom bridged biaryl series, **77**, X = NR, DMG = $CONR_2$ (Scheme 19), available by the highly useful Pd-catalyzed coupling protocols developed by Buchwald and Hartwig [28], further studies have led to findings which broaden the scope of aromatic carbanion chemistry for the construction of *N*-heterocycles. Thus, the new regiospecific acridone synthesis **82** → **path a** → **80** (Scheme 20) proceeds in increasingly higher yields as a function of decreasing alkyl group size of the amides [29], and follows regiospecificity according to the DMG = OMe advantage. A series of acridones have been thus prepared, including a precursor to acronycine, an antitumor alkaloid isolated from the *Rutaceae* family [26a]. Incorporation of a methyl group in the nonamide ring led, somewhat surprisingly, to the conversion **82** → **path b** → **84**, thus establishing a new route to dibenzazepinones which are classically available by the Friedel-Crafts process [26a]. This reaction may be also achieved on prototype systems which afford dibenzooxepinones [26b], dibenzothiopenone dioxidies [26c], and dibenzphosphorinones [26d].

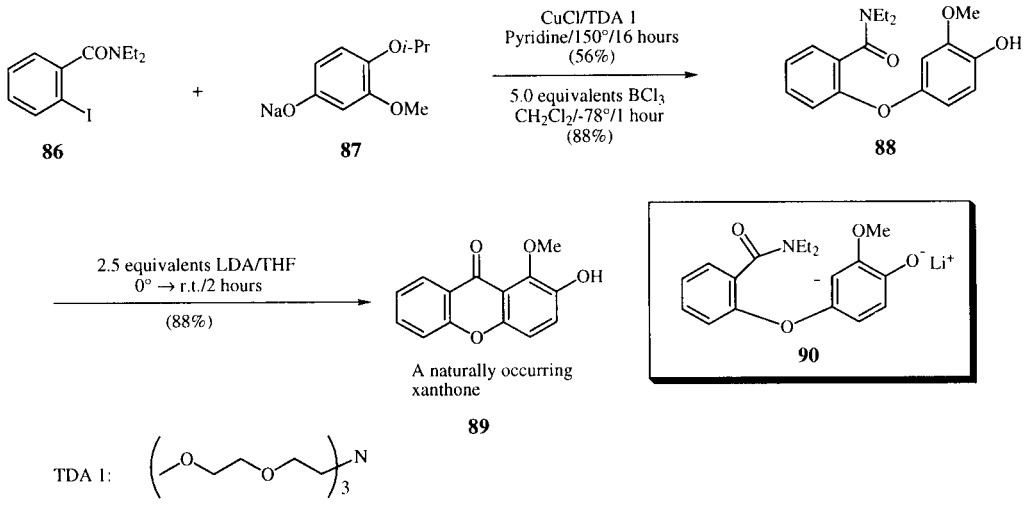
In an attempt to enhance aryl C-H metalation reactivity, the *N*-Boc diarylamine **83** was prepared. *t*-BuLi/TMEDA Metalation led to a regiospecific *N*-to-C Boc migration, **83** → **path c** → **81**. This constitutes an *N*-anionic Fries rearrangement analogous to the previously observed aryl *O*-carbamate migration (Scheme 6) and may provide a new general route to *N*-aryl anthranilate esters **81**, well known building blocks for *N*-heterocycles [26a]. As a further variation, the presence of the acidic methyl group hydrogens in **83** leads to another path, that of lateral metalation-cyclization, to afford oxindole derivatives, **83** → **path d** → **85** [26a]. The convenient availability of the starting materials **82** and **83** and the rich anionic chemistry described invites generalization and expansion [27].

The *O*-heteroatom-bridged series **77**, X = O, DMG = $CONR_2$ (Scheme 19) provided a general route to xanthones **78**, X = O, including some complex and simple (Scheme 21) natural products [26b]. Thus, in case of the latter result, Ullmann coupling of the iodobenzamide **86** with phenoxide **87** using tris[2-(2-methoxyethoxy)ethyl]-amine (TDA 1), a Cu chelating agent, followed by chemoselective deisopropylation, afforded the diaryl ether **88** in modest yield. Treatment with excess LDA directly furnished, presumably *via* a dianionic species **90**, the naturally occurring xanthone **89** in excellent yield. The displeasure with the harsh conditions of the classical Ullmann and the recent report by Buchwald concerning an improved CuOTf-catalyzed Ullmann process [28], provided the incentive to contribute to this area. $CuPF_6$, used extensively in Rh-carbenoid generation reactions, was found to serve well when used with the obligatory Cs_2CO_3 [28a], in the Ullman coupling of *ortho*-halo secondary and tertiary benzamides and sulfonamides **91** with salts of phenols, thiophenols, anilines, and benzylamine **92** to give products **93** (Scheme 22) [29]. While the qualitative rates of the $CuPF_6$-catalyzed process are faster than for CuI and Cu_2O and the new catalyst has advantage over the air-sensitive CuOTf, the conditions for the reaction are still demanding thus placing restraint on the view that Ar-O-Ar bond formation is a solved synthetic problem [30].

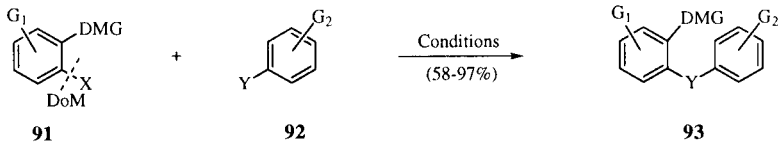
Scheme 20



Scheme 21



Scheme 22



X	DMG	Y	G_2	
Br, I	CONHEt	OH	H, Me	
Cl	$CONEt_2$	SH	2,6-diMe	⇐
	SO_2NHEt	NH_2 (slow)	OMe, F	
	SO_2NEt_2	CH_2NH_2	CO_2H, $CONEt_2$	

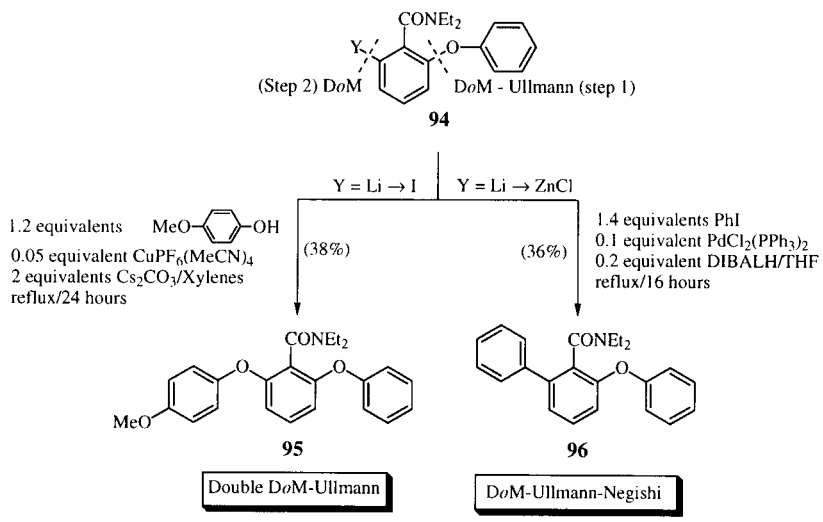
Conditions : 1.2-1.5 equivalents ArY/0.05 equivalent $CuPF_6(MeCN)_4$/ - 2 equivalents Cs_2CO_3 Tol or Xyl/reflux/19-30 hours/c 0.5 *M*

The efficient availability of diaryl ethers by the new $CuPF_6$ Ullmann variant (Scheme 22) prompted simple connections to D*o*M-Ullmann and D*o*M-Negishi processes for the formation of diaryl-diaryl diether and aryl-aryl-diarylether frameworks (Scheme 23) [29] which have potential interest as subunits in vancomycin and related substances [31].

The D*o*M-Metathesis Connection.

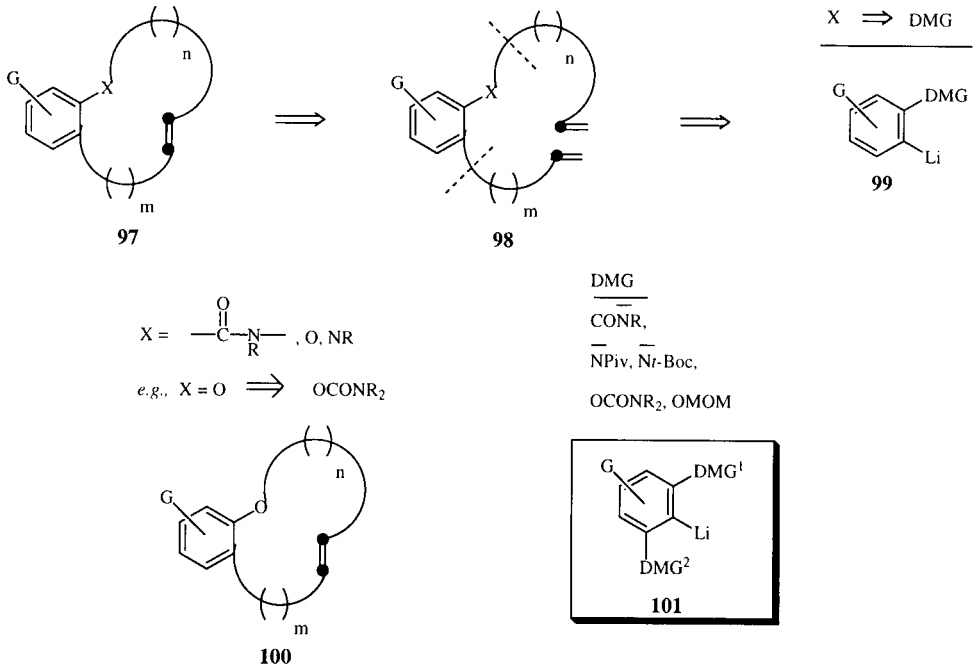
In the most recent foray, work in our laboratories has aimed to connect D*o*M with the Ring-Closing Metathesis (RCM) reaction which has gained rapid acceptance by synthetic practitioners for ring formation, especially for medium- and large-membered rings [32]. Retrosynthesis of ring annulation to aromatic rings **97** (Scheme 24) by metathesis readily cascades *via* **98** to DMG-bearing aromatics **99** which can also encompass systems **101** that may be more difficult to access by conventional means. First efforts led to the preparation of aromatics with annulated ethers **100**, n + m = 7-15 and included the total synthesis of two natural products (Schemes 25 and 26) [33]. The first synthesis of calmodulin inhibitor, radulanin A

Scheme 23

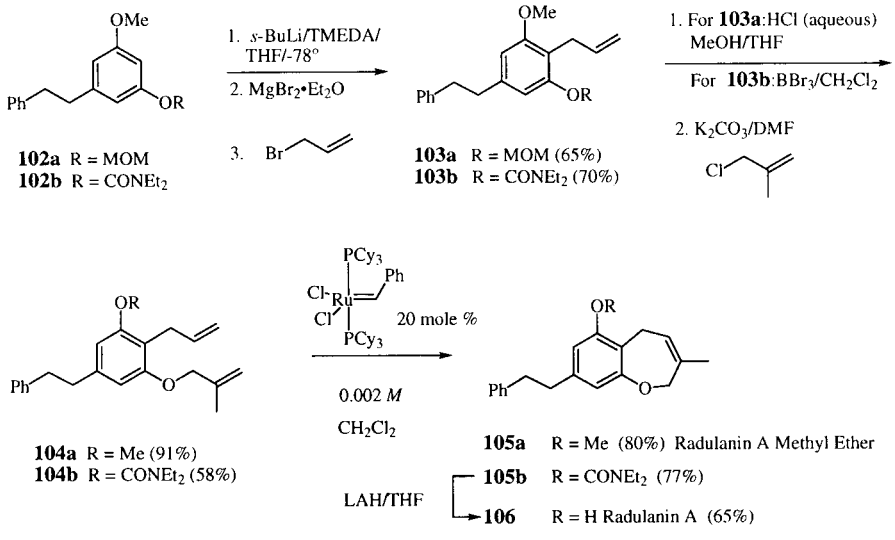


(**106**) was initiated from **103a**, readily available from **102a**. Subjection to D*o*M-transmetalation-allylation gave **103a** which, upon acid-catalyzed cleavage and *O*-allylation, furnished the diallylated product **104a**. Although Grubbs metathesis conditions (20 mole % Ru-based catalyst) afforded radulanin A methyl ether (**105a**), its demethylation was severely compromised by the presence of the cyclic allylic ether. Thus, the approach was retailored starting from the *O*-carbamate **102b** which, following the identical sequence to that used for **102a** (→ **102b** → **103b** → **104b**) afforded the benzoxepine **105b**. Lithium aluminum hydride (LAH) reduction completed the synthesis of radularin A (**106**) in 11 steps and 14% overall yield.

Scheme 24



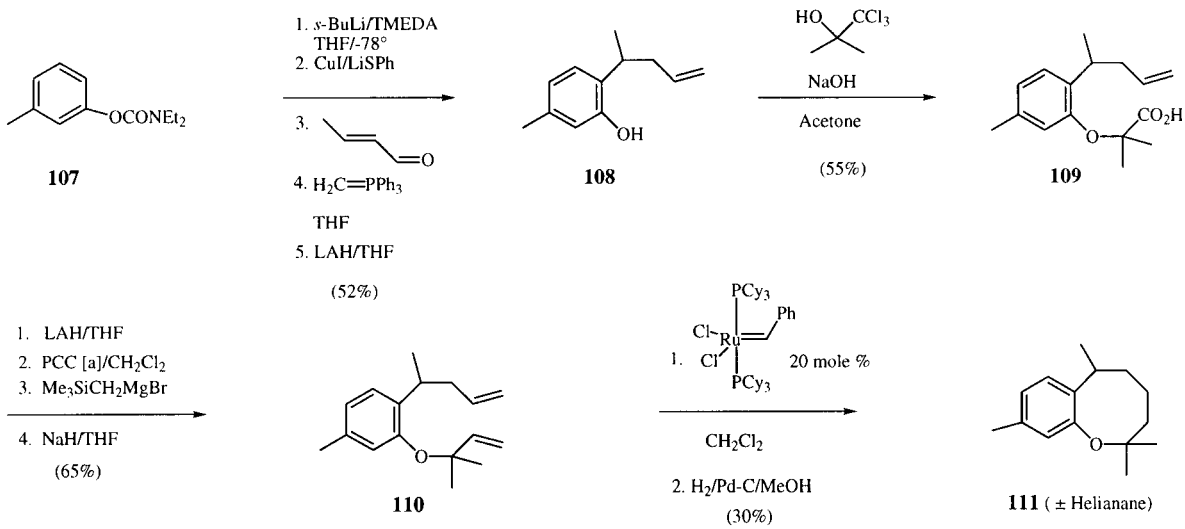
Scheme 25



The synthesis of the racemic natural product, helianine (**111**) commenced from *m*-cresol *O*-carbamate **107** which was subjected to regiospecific lithiation-transmetalation to the corresponding cuprate, and Michael addition, followed by Wittig reaction and reductive decarbamoylation, to furnish the phenol **108** in acceptable yield. The interesting Barhellini reaction was adapted to convert **108** into the *gem*-dimethyl carboxylic acid **109**. The desired metathesis precursor **110** was obtained in a three-step sequence involving a Petereson olefination. Ru-mediated metathesis as for radularin A followed by hydrogenation gave (+/-)-helianine (**111**) (9 steps, 6% overall yield).

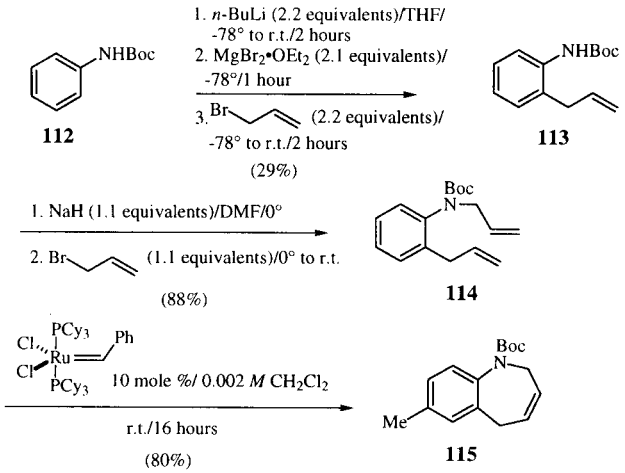
Current work in our group is testing the scope of the DoM-metathesis connection for heterocyclic construction. A recent result offers a new method for the synthesis of benzazepine derivatives (Scheme 27) [34]. Thus, DoM-transmetalation-allylation of *N*-Boc aniline (**112**) led to **113** which, upon *N*-allylation and Grubbs metathesis, provided **115** in the shown but as yet unoptimized yield. Other heterocyclic ring annulations of this type are in hand [34].

Scheme 26



[a] PCC: Pyridinium Chlorochromate.

Scheme 27



Concluding Remarks.

Our work in the D*o*M field began over twenty years ago at the University of Waterloo. Since 1998, with a transition to Queen's University (350 km = 219 miles), we are continuing to uncover reactions and find new directions and connections of synthetic interest and value. The present report attests to the undenied continuing evolution of the D*o*M method by demonstrating *inter alia*:

- New and general cumyl (Schemes 2-6) and P(O)(*t*-Bu)$_2$ (Schemes 7 and 8) DMGs;
- Advantages of the Suzuki-Miyaura cross-coupling reaction (Scheme 9) including on solid support (Schemes 10 and 11);
- Promising development of a Grignard-aryl *O*-carbamate cross-coupling reaction (Scheme 12) with implications, when also linked to D*o*M, for construction of unusually substituted naphthalenes (Scheme 12) and indoles (Scheme 13);
- General DreM processes for biaryl amides and *O*-carbamates (Scheme 17) and their application to dibenzopyranone (Scheme 18), acridone, xanthone, thioxanthone, dibenzphosphorinone (Scheme 19) and dibenzazepinone and oxindole (Scheme 20) synthesis;
- A new anionic *N*-to-*ortho*-C Fries rearrangement (Scheme 20) analogous to the *O*-to-*ortho*-C reaction constituting a potentially useful route to substituted anthranilic acid derivatives; and
- A synthetic bridge between D*o*M and the Grubbs methathesis reaction which allows heterocyclic annelation of diverse ring sizes (Schemes 24), the synthesis of natural products (Schemes 25 and 26), and appears to offer still broader application (Scheme 27).

Acknowledgements.

The above summary of recent efforts is a Waterloo-Queen's contribution due to an in-transit, lively, and dedicated group of students who make going to the lab each day an exciting prospect. We are grateful to NSERC Canada for support of our synthetic programs *via* the Industrial Research Chair (to 1998) and Research Grant programs.

REFERENCES AND NOTES

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[†] We dedicate this lecture review to the memory of Dr. Raymond N. Castle for his vision in founding the International Society for Heterocyclic Chemistry, his relentless promotion of the discipline, and his personal and enthusiastic support of heterocyclic chemists throughout the world. His typically eloquent introduction of VS in Vienna is firmly embedded in my memory.

[1] V. Snieckus, *Chem. Rev.*, **90**, 879 (1990).

[2] N. Ple, A. Turck, E. Fiquet and G. Queguiner, *J. Heterocyclic Chem.*, **28**, 283 (1991).

[3] S. O. de Silva, J. N. Reed, R. J. Billedeau, X. Wang, D. J. Norris and V. Snieckus, *Tetrahedron*, **48**, 4863 (1992).

[4] M. P. Sibi and V. Snieckus, *J. Org. Chem.*, **48**, 1935 (1983).

[5] S. Sengupta and V. Snieckus, *Tetrahedron Letters*, **31**, 4267 (1990).

[6] L. A. Carpino, H. Chao, S. Ghassemi, E. M. E. Mansour, C. Riemer, R. Warrass, D. Sadat-Aalaee, G. A. Truran, H. Imazumi, A. El-Faham, D. Ionescu, M. Ismail, T. L. Kowaleski, C. H. Han, H. Wenschuh, M. Beyermann, M. Bienert, H. Shroff, F. Albericio, S. A. Triolo, N. A. Sole and S. A. Kates, *J. Org. Chem.*, **60**, 7718 (1995).

[7] C. Metallinos, S. Nerdinger and V. Snieckus, *Organic Letters*, **1**, 1183 (1999).

[8a] M. Trost, D. L. Van Vranken, *Chem. Rev.*, **96**, 395 (1996); [b] M. Shibasaki, C. D. J. Boden and A. Kojima, *Tertahedron*, **53**, 7371 (1997); [c] K. Kitayama, Y. Uozumi and T. Hayashi, *Tetrahedron: Assymetry*, **4**, 2419 (1993); [d] T. Ohkuma, H. Ooka, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, **117**, 10417 (1995).

[9] M. Gray, B. J. Chapell, J. Felding, N. J. Taylor and V. Snieckus, *Synlett*, 422 (1998).

[10] B. Chapell and V. Snieckus, unpublished results.

[11a] A. Godard, J. C. Rovera, F. Marsais, N. Ple, G. Queguiner, *Tetrahedron*, **48**, 4123 (1992); [b] F. Trecourt, M. Mallet, O. Mongin, B. Gervais and G. Queguiner, *Tetrahedron*, **49**, 8373 (1993) and references cited therein.

[12] J.-m. Fu and V. Snieckus, *Tetrahedron Letters*, **31**, 1665 (1990).

[13] S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle and V. Snieckus, *J. Org. Chem.*, **57**, 4066 (1992).

[14a] F. Beaulieu, Ph.D. Thesis, University of Waterloo (1994); [b] K. Puumala, M.Sc. Thesis, University of Waterloo (1997).

[15] S. Chamoin, S. Houldsworth, C. G. Kruse, W. I. Bakker and V. Snieckus, *Tetrahedron Letters*, **39**, 4179 (1998).

[16] E. J. Griffen, D. G. Roe and V. Snieckus, *J. Org. Chem.*, **60**, 1484 (1995).

[17] D. Roe and V. Snieckus, unpublished results.

[18] A. C. Kinsman and V. Snieckus, *Tetrahedron Letters*, **40**, 2453 (1998).

[19a] C. Quesnelle, W. Familoni and V. Snieckus, *Synlett*, 349 (1994); [b] C. Quesnelle, Ph.D. Thesis, University of Waterloo (1996).

[20] P. Beak and A. I. Meyers, *Acc. Chem. Res.*, **6**, 356 (1986).

[21] G. W. Klumpp, *Rec. Trav. Chim. Pays-Bas*, **105**, 1 (1986).

[22] J.-m. Fu, B.-p. Zhao, M. J. Sharp and V. Snieckus, *J. Org. Chem.*, **56**, 1683 (1991).

[23] W. Wang and V. Snieckus, *J. Org. Chem.*, **57**, 424 (1992).

[24a] B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, P. D. Josephy and V. Snieckus, *J. Org. Chem.*, **56**, 3763 (1991); [b] A. Coelho, C. James and V. Snieckus, unpublished results.

[25a] C. A. James and V. Snieckus, *Tetrahedron Letters*, **38**, 8149 (1997); [b] C. A. James, Ph.D. Thesis, University of Waterloo (1992).

[26a] S. L. MacNeil, M. Gray, L. E. Briggs, J. J. Li and V. Snieckus, *Synlett*, 419 (1998); [b] J. Bower, O. B. Familoni, I. Ionica and V. Snieckus, *Synlett*, 1081 (1997); [c] F. Beaulieu and V. Snieckus, *J. Org. Chem.*, **59**, 6508 (1994); [d] M. Gray, B. J. Chapell, N. J. Taylor and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, **35**, 1558 (1996).

[27] S. L. MacNeil, B. Wilson and V. Snieckus, unpublished results.

[28a] J.-F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 10539 (1997); For reviews on new C-N and C-O bond forming cross-coupling reactions, see B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **576**, 125 (1999); J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, **31**, 805 (1998); J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, **37**, 2047 (1998); J. F. Hartwig, *Synlett*, 329 (1997).

[29] A. V. Kalinin, J. F. Bower, P. Riebel and V. Snieckus, *J. Org. Chem.*, **64**, 2986 (1999).

[30] F. Thiel, *Angew. Chem. Int. Ed. Engl.*, **38**, 2345 (1999).

[31a] K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes and T. Bando, *Angew. Chem. Int. Ed. Engl.*, **38**, 240 (1999); [b] D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow and J. L. Katz, *Angew. Chem. Int. Ed. Engl.*, **37**, 2700 (1998); [c] D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, O. Loiseleur and S. L. Castle, *J. Am. Chem. Soc.*, **121**, 3226 (1999).

[32a] R. H. Grubbs and S. Chang, *Tetrahedron*, **54**, 4413 (1998); [b] S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 371 (1998); [c] B. A. Chauder, *Synlett*, 267 (1999).

[33] M. Stefinovic and V. Snieckus, *J. Org. Chem.*, **63**, 2808 (1997).

[34] C. Lane and V. Snieckus, unpublished results.