FMC

Winter 2000

LITHIUM LINK™

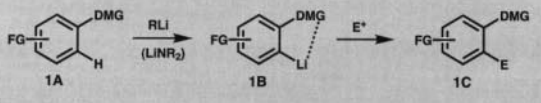
Linking DoM/DreM With Other Technologies

Introduction

The DoM methodology offers a powerful method for the regiospecific construction of polysubstituted aromatics. *ortho*-Lithiation of substrates (1A) bearing heteroatom-based DMGs generates reactive organolithiums (1B) that may be treated with a host of electrophiles, E^+, to afford *ortho*-substituted derivatives (Fig. 1). Here, the FG compatibility for substrates (1A) employed are defined. In Fig. 2, various substitution patterns that may be achieved by sequential and "walk-around-the-ring" DoM, which invariably complement

Fig. 1

Why DoM it? Scope and Tolerance



DMGs	E^+	FG Compatibility	
		Yes	No
C (all oxid states) O N P S F I, Br, Cl (HetDoM only)	C^+ (all oxid states) ^+OH $^+NH_2$, ^+NHR, $^+NR_2$ $^+PR_3$ ^+SH, $^+S(O)_nR$, $^+SO_2NR_2$ $^+SiR_3$, $^+GeR_3$ ^+SeR, ^+TeR ^+I, ^+Br, ^+Cl, ^+F	SiR_3 (GeR_3) Cl, F other DMGs	I, Br ➤ MHEx CO_2R, CN, CHO, COR CH_2R (but SiR_3 PG)

Snieckus, V. *J.Heterocyclic Chem.* **2000**, *37*, 1.

FROM THE EDITOR

The FMC Lithium Division is pleased to bring to you the 13th *Lithium Link* issue. This feature article is a condensed version of a lecture presented by a good friend and promoter of organolithiums, Professor Victor Snieckus of Queen's University in Kingston, Ontario. Without the help of several people, this would not have been possible. Please see pages 11 & 12 for more about the authors, acknowledgements, and availability of a full version, which is a transcription of the lecture.

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ABBREVIATIONS

Am	$C(=O)NEt_2$
Ar	Aryl or Aromatic
B	Strong Base
CIPE	Complex Induced Proximity Effect
DHB	Dihydroxybiphenyl
DMF	Dimethylformamide
DMG	Directed Metalation Group
DoM	Directed *ortho* metalation
DreM	Directed remote metalation
E^+	Electrophile
FC	Friedel-Crafts
FG	Functional Group
HetAr	Heteroaromatic
LA	Lewis Acid
LAH	$LiAlH_4$
LG	Leaving Group
Nu^-	Nucleophile
OMOM	Methoxymethyl ether
PDC	Pyridinium Dichromate
PG	Protecting Group
PPA	Polyphosphoric Acid
rt	Room Temperature
TF_2O	Triflic anhydride (also TFAA)
TFA	Trifluoroacetic acid
Xcoupl	Cross Coupling

Fig.2

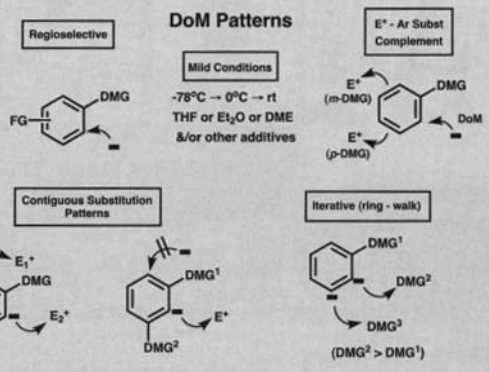


Fig.3

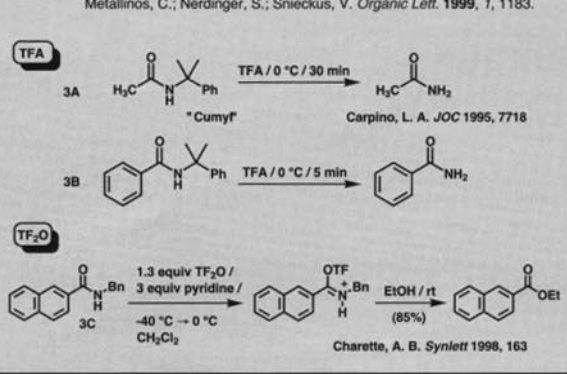


Fig.4

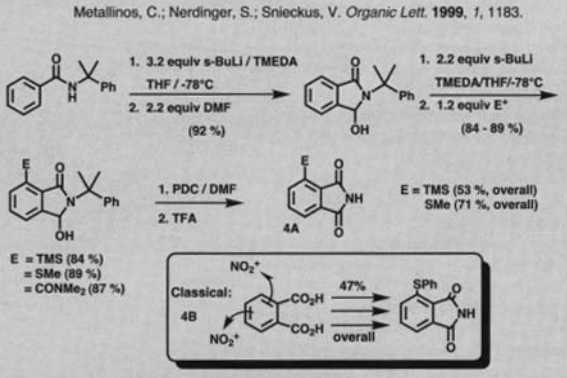
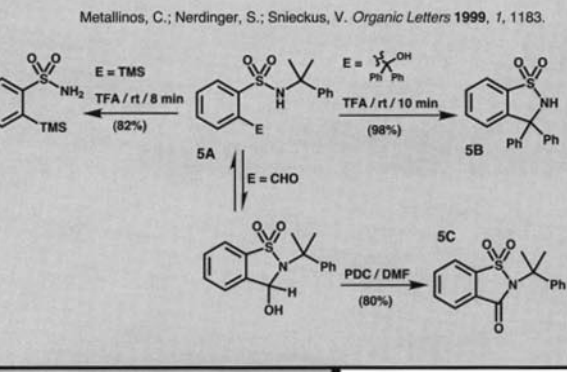


Fig.5



classical electrophilic substitution are shown. The increasing understanding of mechanistic aspects of the DoM reaction suggests that new DMGs and reaction conditions (i.e., temperature and medium effects) will be developed in the near future. This will lead to prediction of conditions and more rapid optimization of useful synthetic processes.

New Benzamide and O-Carbamate DMGs

Recently, the problematic hydrolysis of secondary and tertiary amide DMGs subsequent to effective DoM chemistry was overcome by the development of the cumyl DMG. This was uncovered by the recognition (Fig. 3) that TFA hydrolysis of N-cumylbenzamide (3B) is faster than that of the corresponding acetamide (3A) and that triflic anhydride/pyridine conditions will convert an N-benzylamide into an ester (3C). The synthetic utility of the N-cumylbenzamide is amply illustrated by the efficient preparation of *ortho*-substituted imides (4A, Fig. 4), which rivals the classical electrophilic substitititution approach (4B).

The analogous DoM chemistry of N-cumyl benzenesulfonamides (5A, Fig. 5), allows the construction of unusually substituted saccharins such as 5B and 5C.

Perhaps most significantly, the cumyl group was incorporated into a new O-carbamate DMG (6A). The original N,N-diethyl O-carbamate (6B), developed by Sibi in 1983 required rigorous RLi or LAH conditions for cleavage. 6A behaved analogously but with the advantage of cleavage to products (6C and 6D), which may maintain sensitive FGs.

DoM - Xcoupl Links

In the last two decades, the Suzuki-Miyaura, Kumada-Tamao-Corriu, Negishi, and Stille Xcoupl reactions have emerged as major synthetic protocols for sp^2-sp^2 bond formation (Fig. 7). The availability of fine chemical substrates and catalysts is fueling application of these reactions on the industrial scale. Based on current literature perusal, the Suzuki-Miyaura reaction appears to be the mode of preference for the preparation of pharmaceuticals containing the biaryl motif (Fig. 8). The observation that Cs_2CO_3 is an advantageous base for the Suzuki-Miyaura process may be rationalized by the demonstration

Fig.6 Metallinos, C.; Nerdinger, S.; Snieckus, V. *Organic Lett.* **1999**, *1*, 1183.

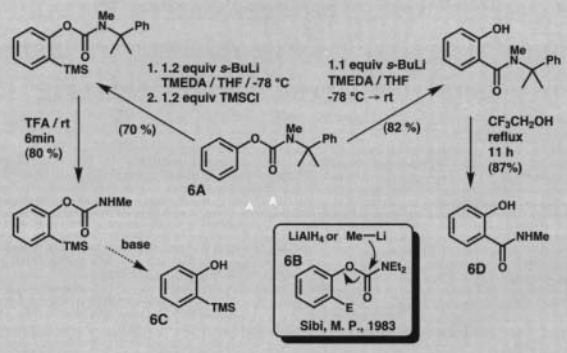
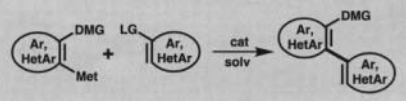


Fig.7

The DoM - Cross Coupling Nexus

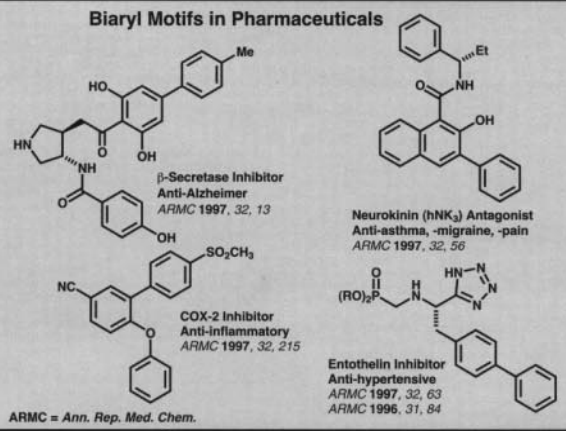


Met	LG	cat	Xcoupl
$B(OH)_2$	I > Br > OTf	Pd	Suzuki-Miyaura
MgX	OTf > $OCONEt_2$, $SCONEt_2$	Ni	Kumada-Tamao-Corriu
ZnX	hal, OTf	Ni	Negishi
SnR_3	hal, OTf	Pd	Stille

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

Snieckus, V. *J. Heterocyclic Chem.* **2000**, *37*, 1.

Fig.8 **Biaryl Motifs in Pharmaceuticals**



ARMC = *Ann. Rep. Med. Chem.*

Fig.9 M. Campbell, Ph.D. thesis, University of Waterloo, 1996.

Effect of Base on the Suzuki Cross Coupling. A ^{11}B NMR Study of the Base Effect

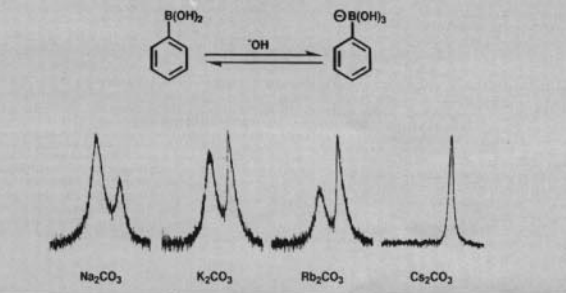


Fig.10 Nerdinger, S.; Kendall, C.; Marchhart, R.; Riebel, P.; Johnson, M.; Yin, C.; Eltis, L.; Snieckus, V. *J. Chem. Soc. Chem. Commun.* **1999**, 2259.

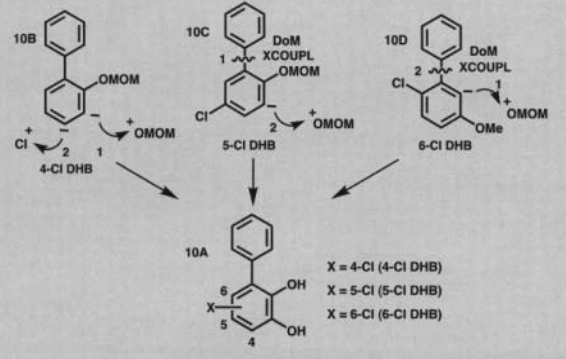
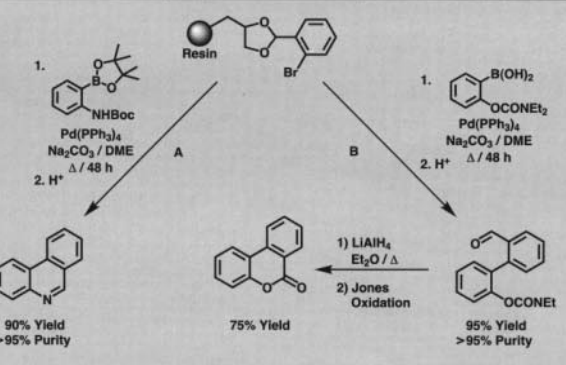


Fig.11



Chamoin, S.; Houldsworth, S.; Krusse, C.G.; Iwema Bakker, W.; Snieckus, V. *Tetrahedron Lett.* **1998**, 4179.

Fig. 12

Quesnelle, C. Ph.D. thesis, University of Waterloo, 1996.

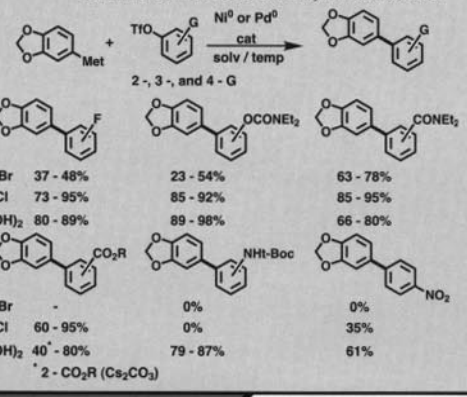


Fig. 13

Griffen, E.J.; Roe, D.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484.

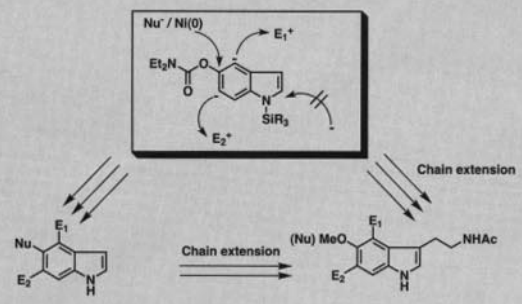
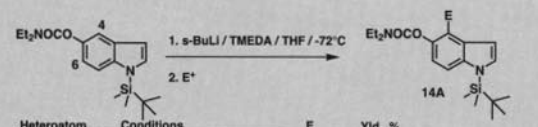


Fig. 14

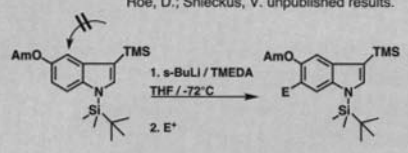
Griffen, E.J.; Roe, D.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484.



Heteroatom	Conditions	E	Yld, %
NH_2^+	1. TsN_3 2. EDTA 3. Pd / C / H_2 4. Ac_2O / Et_3N	NHAc	47
OH^+	tBuOOLi; Ac_2O / py	OAc	25
	TMSOOTMS; Ac_2O / py	OAc	32 (54% recd sm)
	1. $MgBr_2$ 2.	OAc	59 (33% recd sm)
	3. AcOH 4. Ac_2O / Et_3N		
Cl^+	Cl_3CCCl_3	Cl	44
I^+	I_2	I	89
$^tBuS^+$	$^tBuSSO_2Ph$	S^tBu	77

Fig. 15

Roe, D.; Snieckus, V. unpublished results.



E+	E	yld, %
DMF	CHO	90
$ClCO_2Et$	CO_2Et	42
I_2	I	75
p-$MeC_6H_4SO_2S^tBu$	S^tBu	68
TMSCl	TMS	67

of the high equilibrium concentration of the borate, the active species in the Xcoupl reaction (Fig. 9). Fig. 10 illustrates the preparation of three different chlorinated dihydroxybiphenyls by DoM "walk-around-the-ring" methodology, DoM/Xcoupl, and/or chlorination. The Xcoupl tactic also may be carried out on solid support and linked to solution-phase DoM to afford heterobiaryls (Fig. 11). Comparison of solution DoM-Xcoupl efficacies of three named Xcoupl reactions shows that the Suzuki-Miyaura method leads, in general, to highest overall yields (Fig. 12).

Indole Indulgence

New DoM and Xcoupl methods for the preparation of C_4-to-C_8 substituted tryptamines, systems of considerable biological interest, used the key indole 1-silyl-5-O-diethyl carbamate as starting material (Fig. 13). As illustrated with heteroatom electrophiles, DoM reactions gave moderate to good yields of C_4-substituted products (14A, Fig. 14). C_6-functionalization of the N-TBS was possible if C_4 is remotely protected by a C_3-TMS (Fig. 15). The steric effect of a C_3-substitutent is further demonstrated in DoM chemistry of a tryptamine 5-O-carbamate (Fig. 16).

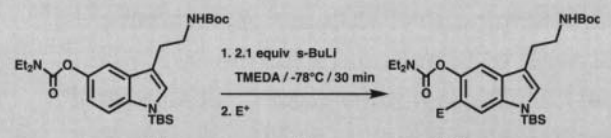
DreM: Beyond ortho *Metalation*

DreM of biaryl amides and O-carbamates, a reaction based on CIPE but undoubtedly assisted by other factors, leads to new products as the inherent DMG becomes the intra-electrophile to yield cyclizations and migrations (Fig. 17). DreM and Friedel-Crafts strategies are complementary in providing regioisomers from the same

substrate (Fig. 18). With C-silyl protection, a biaryl O-carbamate, prepared by DoM-Xcoupl, undergoes an anionic remote Fries rearrangement thereby providing a new regiospecific route to dibenzo[b,d]pyran-6-ones (19A, Fig. 19). Coumestans and their S-analogues (20A) result from such DreM reactions followed by refluxing HOAc treatment (Fig. 20). Prior kinetic C_2 silyl protection (with LDA/TMSCl) overcomes formation of intermolecular condensation products and gives additional O- and S- coumestan analogues (Fig. 21).

Fig. 16

Roe, D.; Snieckus, V. unpublished results.



E^+	E	yld, %
MeI	Me	69
EtI	Et	83
DMF	CHO	69
TMSCl	TMS	65
t-BuSSO$_2$-p-tol	St-Bu	70
I_2	I	47

DoM-DreM-Xcoupl links also lead to azacoumestans and isoazacoumestans, which are less convenient to prepare via other routes (Fig. 22). Sequential amide and O-carbamate DreMs on substrates with proper protection (PG_1 and PG_2), allow the synthesis of uncommon fluorenones, a strategy that portrays a carbonyl dication equivalency (Fig. 23). An intermediate (24A, Fig. 24) for prekinamycin (Fig. 25) was prepared via a key O-carbamate DreM step with prior DoM silylation to avoid the anionic Fries rearrangement. Following O-methylation, 24A, when subjected to an LDA-promoted DreM followed by de-silylation, yields 25A, which concludes the formal total synthesis of prekinamycin and kinobscurinone (Fig. 25).

Fig. 17

Snieckus, V. *J. Heterocyclic Chem.* **2000**, *37*, 1.

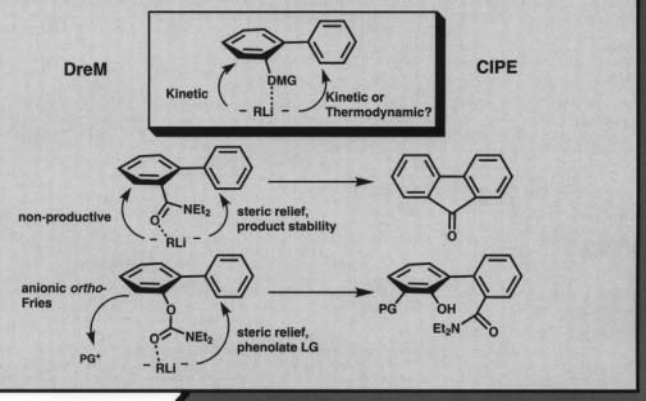
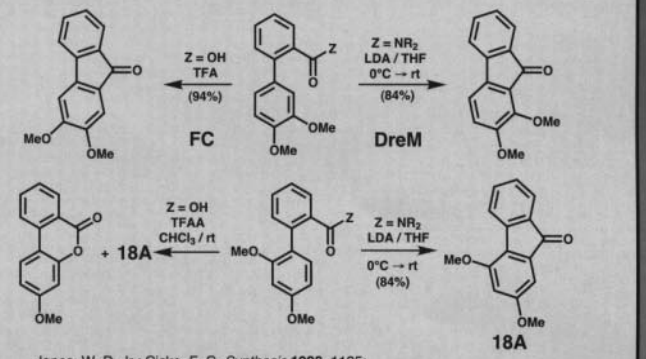


Fig. 18



Jones, W. D. Jr.; Ciske, F. C. *Synthesis* **1998**, 1195;
Jones, W. D. Jr.; Ciske, F. C. *J. Org. Chem.* **1996**, *61*, 3920
Sharp, M. J.; M. Sc. thesis, University of Waterloo, **1986.**

Fig. 19

Snieckus, V. *J. Heterocyclic Chem.* **2000**, *37*, 1.

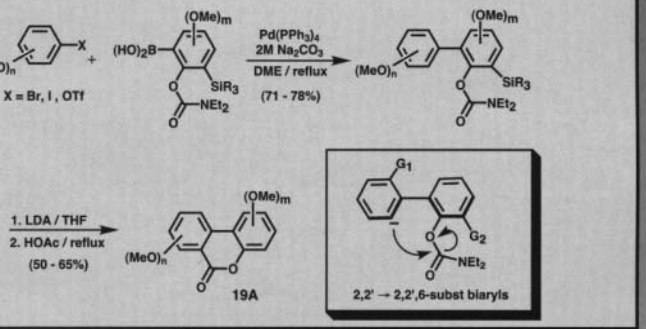
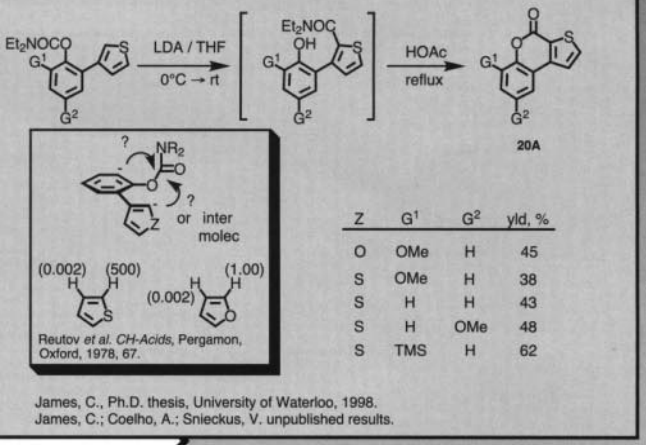


Fig. 20



Z	G^1	G^2	yld, %
O	OMe	H	45
S	OMe	H	38
S	H	H	43
S	H	OMe	48
S	TMS	H	62

James, C., Ph.D. thesis, University of Waterloo, 1998.
James, C.; Coelho, A.; Snieckus, V. unpublished results.

Fig.21

James, C., Ph.D. thesis, University of Waterloo, 1998.
James, C.; Coelho, A.; Snieckus, V. unpublished results.

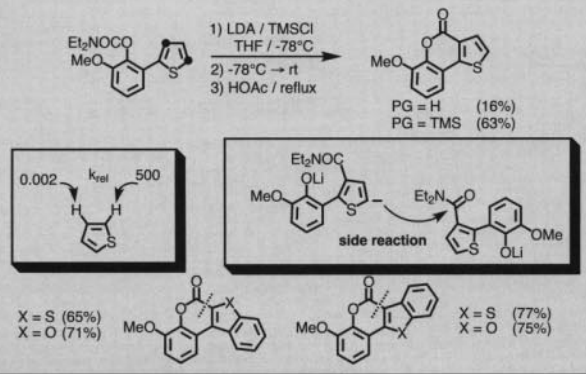


Fig.22

James, C., Ph.D. thesis, University of Waterloo, 1998.
James, C.; Coelho, A.; Snieckus, V. unpublished results.

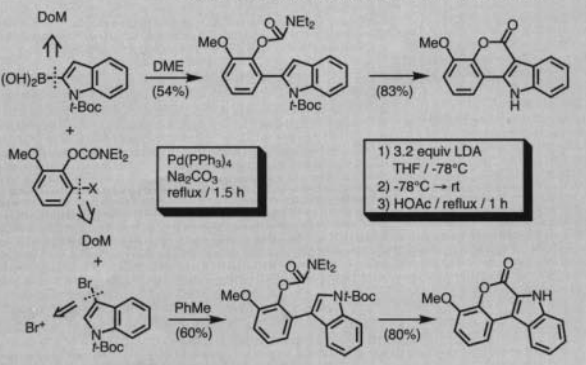
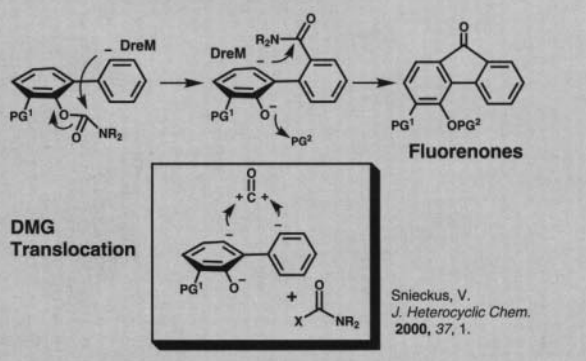


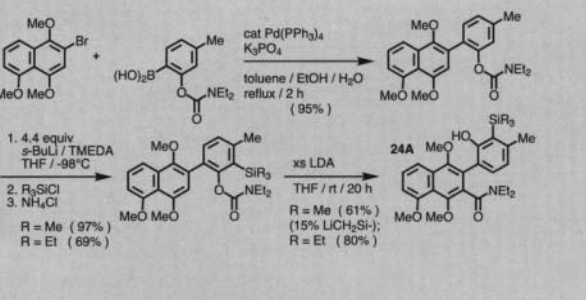
Fig.23



Snieckus, V.
J. Heterocyclic Chem.
2000, *37,* 1.

Fig.24

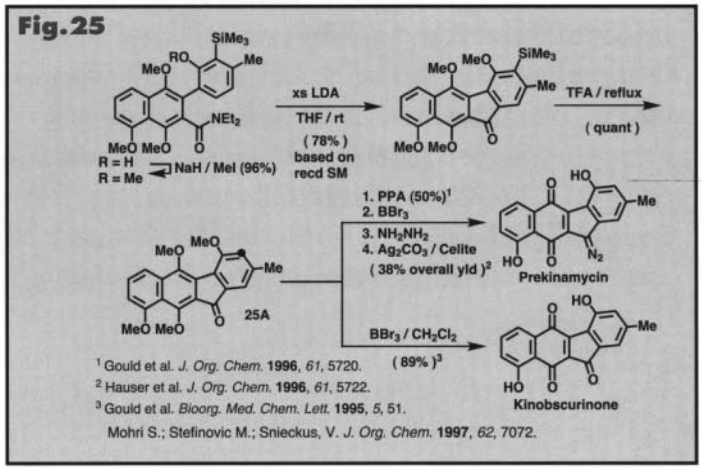
Mohri S.; Stefinovic M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072.



Phenanthrols (26B) are available by a double DreM of O-carbamates with/without phenol protection during the second DreM, which involves a lateral methyl deprotonation (26A, Fig. 26). This and the previous sequence (Fig. 23) constitute amide translocation processes. The LDA-mediated, one-step synthesis of an unusually substituted oxygenated phenanthrene (27B from 27A) illustrates the power of this methodology (Fig. 27). Fig. 28 summarizes the DreM consequences for biaryls, DMG = $CONEt_2$, $OCONEt_2$, and asks what the prognosis will be for biaryls bridged by X = O, NR, $S(O)_n$, n = 0, 1, 2 heteroatoms. The Snieckus lab started on this path by a serendipitous discovery of the synthesis of DMG-bearing diaryl sulfones (29A) using Honeywell International's (formerly Allied Signal) NFSI reagent, a good F^+ electrophile whose use, in general, led to the expected products (29B).

ortho-Tertiary amide diaryl sulfones (29A = 30A) also inexpensively prepared via DoM (Fig. 30), when treated with LDA, lead to thioxanthen-9-one 10,10-dioxides (30B). This reaction constitutes a heterocyclic case of an anionic Friedel-Crafts equivalent. Similarly, analogous O-carbamates (31A) regiospecifically afford functional derivatives (31B) by a combined FC-remote anionic Fries process (Fig. 31). In another general reaction with FC complementarity, xanthen-9-ones result from DreM on diaryl ethers (Fig. 32)

Fig.25



[1] Gould et al. *J. Org. Chem.* **1996**, *61*, 5720.
[2] Hauser et al. *J. Org. Chem.* **1996**, *61*, 5722.
[3] Gould et al. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 51.

Mohri S.; Stefinovic M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072.

and this type of reaction is feasible without phenol protection (Fig. 33). Taking the lead from the Buchwald laboratories, the Ar-X-Ar DreM precursors were prepared by a $CuPF_6$-mediated Ullmann reaction (Fig. 34). Di-biarylethers and mixed biaryl biaryl ethers are available via DoM-Ullmann and DoM-Negishi Xcoupl links (Fig. 35). Diaryl amines (36A) originally made in the Snieckus labs by cuprate-lithiated benzamide coupling are now also conveniently prepared by adaptation/modification of Buchwald-Hartwig Xcoupl methods (Fig. 36). Results of DreM reaction on such systems (Fig. 37) are a function of N-substituent, base, and presence of a lateral methyl group. Thus 37A, G = CO_2t-Bu and G = Me, leads via cyclization and N-anionic *ortho* Fries rearrangement to an acridone and an anthranilate respectively, while 37B affords either oxindole or dibenzazepinone systems.

Fig.26

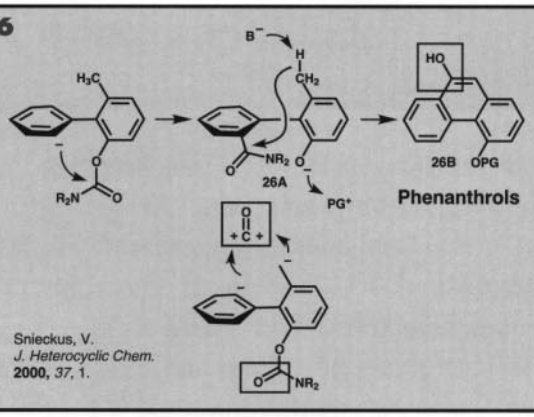


Fig.27

Wang, X.; Snieckus, V. unpublished results.

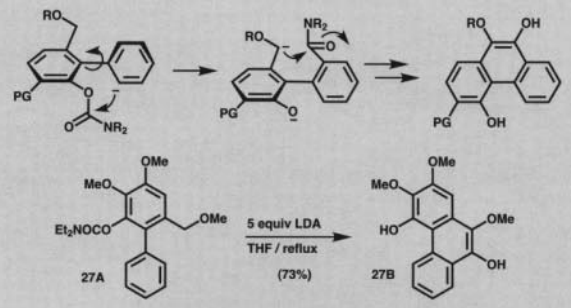
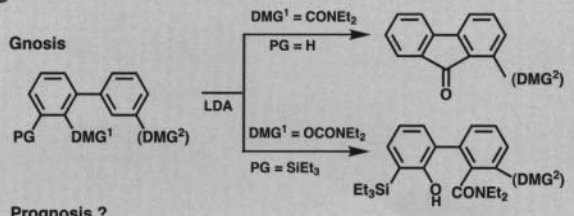
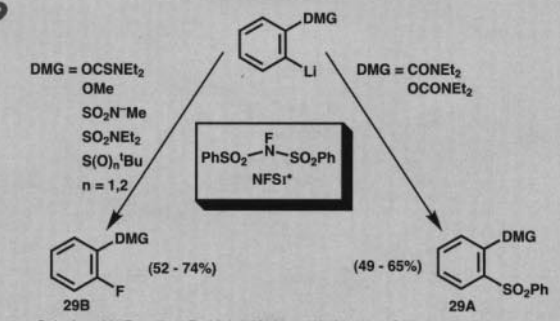


Fig.28



Snieckus, V. *J. Heterocyclic Chem.* **2000,** *37,* 1.

Fig.29



Snieckus, V.; Beaulieu, F.; Mohri, K.; Han, W.; Murphy, C.K.; Davis, F.A. *Tetrahedron Lett.* **1994,** *35,* 3465.

*Honeywell International - Pharmaceutical Fine Chemicals

Fig.30

Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994,** *59,* 6508.

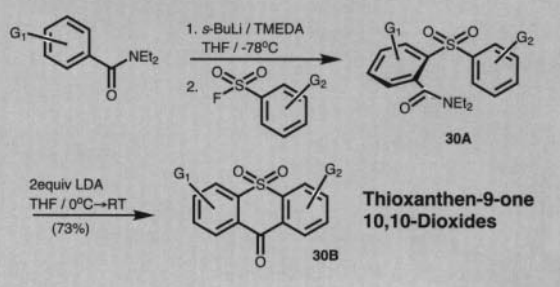


Fig.31

Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508.

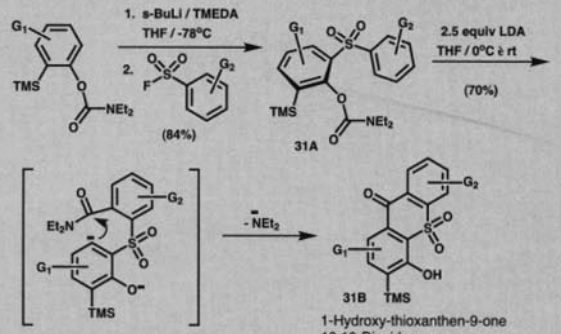
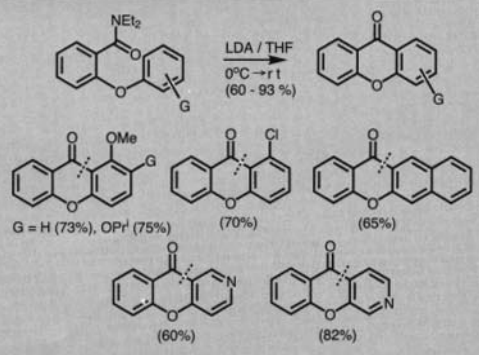


Fig.32



Familoni, O.B.; Ionica, I.; Bower, J.; Snieckus, V. *Synlett* **1997**, *9*, 1081.

Fig.33

Familoni, O.B.; Ionica, I.; Bower, J.; Snieckus, V. *Synlett* **1997**, *9*, 1081.

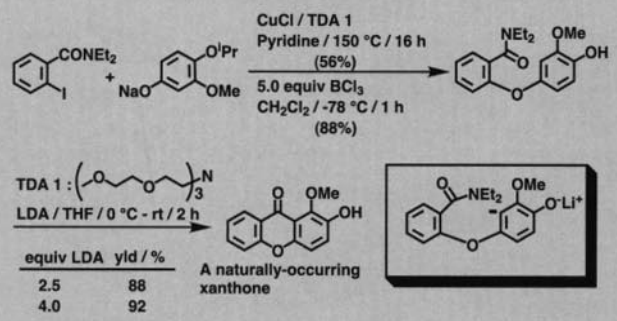
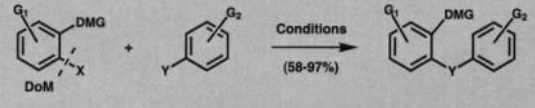


Fig.34

Kalinin, A.V.; Bower, J.F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 298

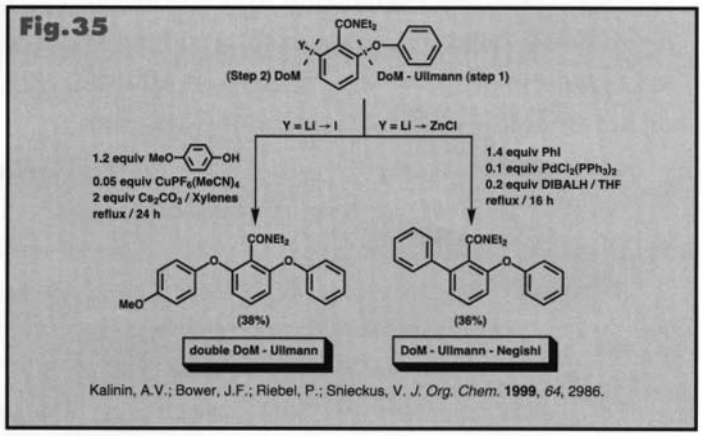


X	DMG	Y	G_2
Br, I	CONHEt	OH	H, Me
Cl	$CONEt_2$	SH	2,6-diMe
	SO_2NHEt	NH_2 (slow)	OMe, F
	SO_2NEt_2	CH_2NH_2	CO_2H, $CONEt_2$

- Conditions : 1.2-1.5 equiv ArY / 0.05 equiv $CuPF_6(MeCN)_4$ / 2 equiv Cs_2CO_3 Tol or Xyl / reflux / 19-30 h / c 0.5 M
- Rates : $CuPF_6(MeCN)_4$ > CuI, Cu_2O
- $CuPF_6(MeCN)_4$ air-stable vs $CuOTf(PhH)_{0.5}$

The N to *ortho*-C migration has been generalized for DMG[1] = CO_2t-Bu and extended to DMG[1] = $CONEt_2$ (Fig. 38). Some of these LDA-mediated DreM reactions have been generalized for the regiospecific synthesis of dibenz[b,f]azepinenes (AZ) or acridones (AC) (Fig. 39). The lateral metalation process for dibenzazepines has also been generalized for X = SO_2, O, and P(O)R (Fig. 40) allowing non-FC approaches to such systems, e.g. as established by the original work of Manske.

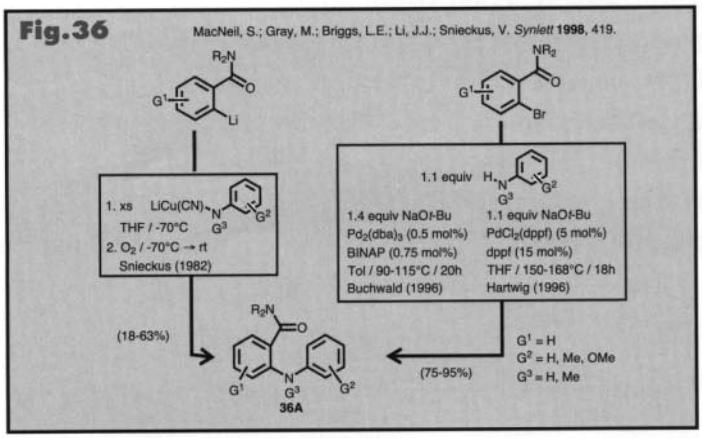
Fig.35



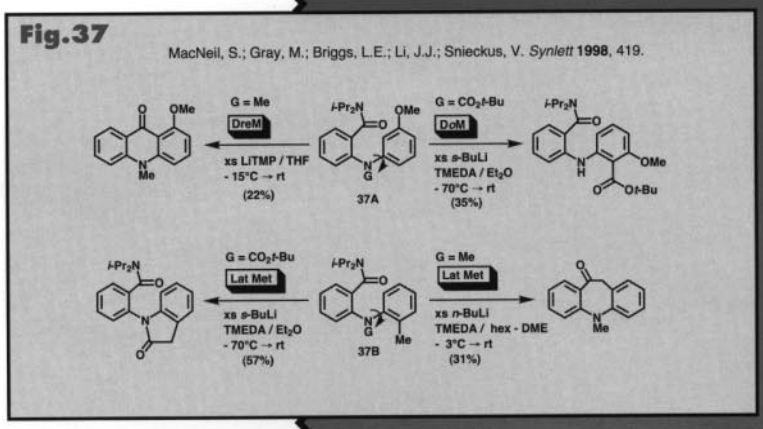
Kalinin, A.V.; Bower, J.F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.

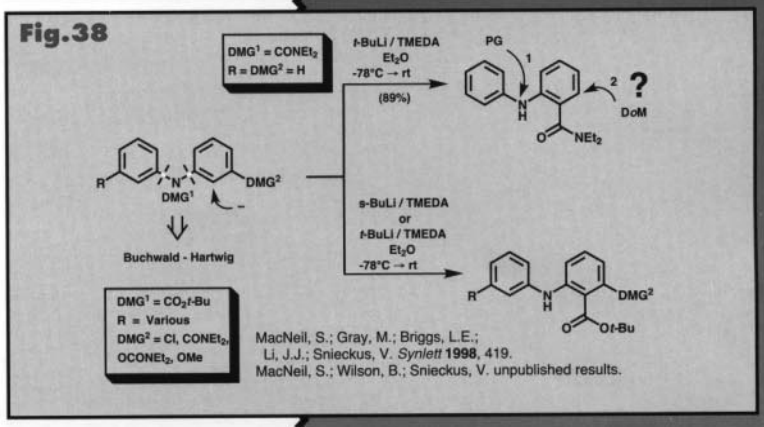
A Synthetic Litany to DoM, DreM, Xcoupl

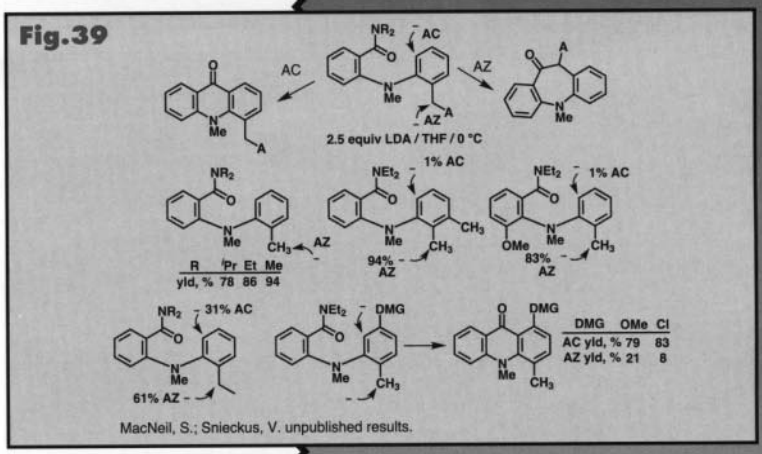
The synthesis of plicadin (Fig. 41) was chosen to demonstrate the utility of DoM, DreM, and Xcoupl reactions. In Fig. 42, two retrosynthetic approaches, rich in DoM, DreM, and Xcoupl but also other (Sonogashira, Castro-Stephens) reactions, begin with a common starting material (42A) prepared by DoM (Fig. 45), DMG = $OCONEt_2$ and not available via FC chemistry (42B). From this work, general synthetic methods emerged:



(a) A new synthesis of 4-OH benzopyran-2-ones (43A, Fig. 43) using the DoM-Negishi Xcoupl-Baker Venkataraman (see box) was established, which is applicable to benzopyranones unavailable by FC and Lewis acid-induced Fries rearrangement, and also provides interesting FC complementarity for the synthesis of aryl ketones (Fig. 44).







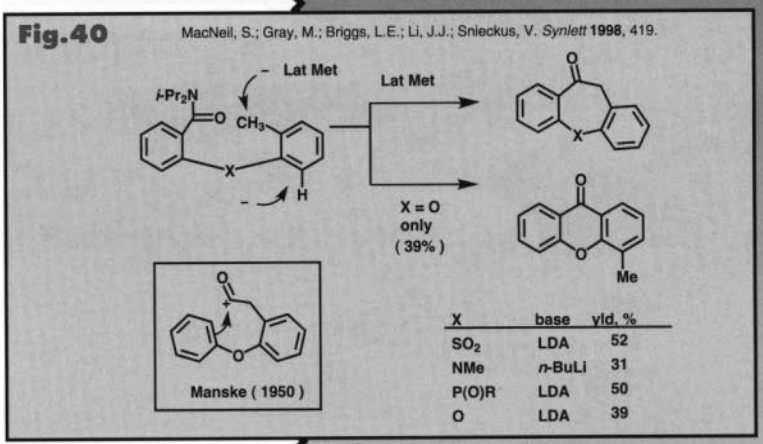
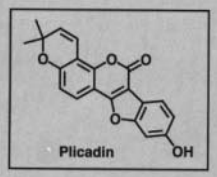


Fig.41



- Natural Source: Leguminosae Family the *Psoralea plicata plant*
- Isolation: Malik *et al. Phytochemistry* 1991, *30*, 2800.
- Coumestans: antiestrogenic antibacterial antifungal phytoalexin activity

Fig.42

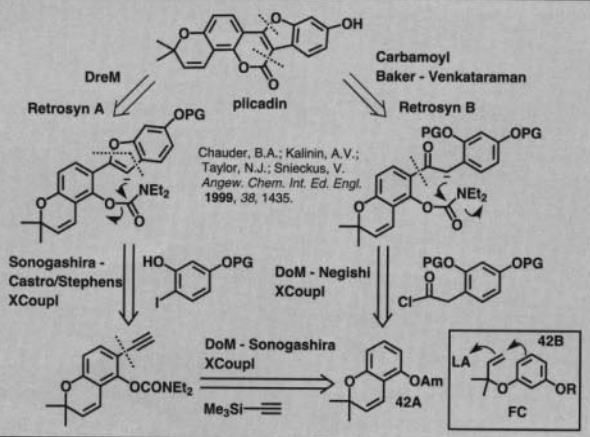
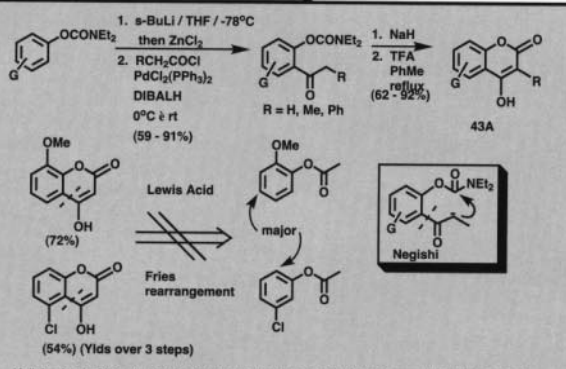
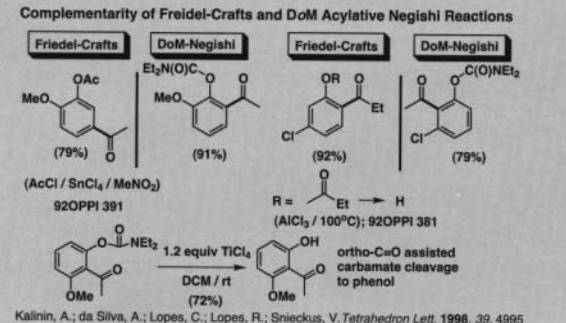


Fig.43



Kalinin, A.; da Silva, A.; Lopes, C.; Lopes, R.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995.

Fig.44



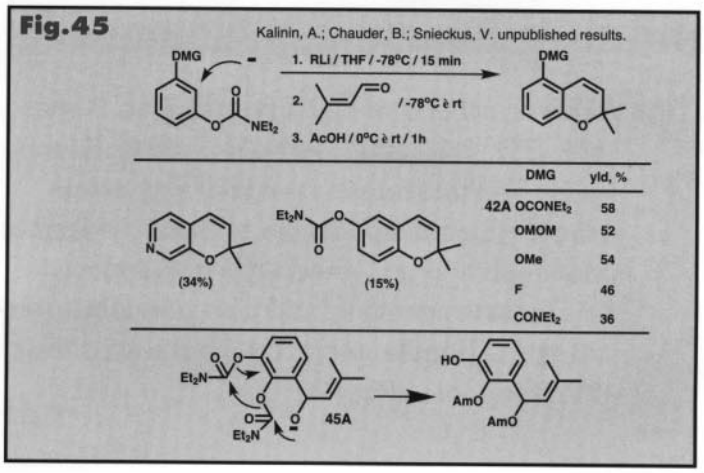
Kalinin, A.; da Silva, A.; Lopes, C.; Lopes, R.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995
Kalinin, A.; Snieckus, V. unpublished results.

(b) A one-pot regiospecific synthesis of chromenes was achieved (Fig. 45), which has a sidelight of domino O to O carbamoyl migration (45A). The FC-DreM complementarity for chromenes is reinforced (Fig. 46) for the synthesis of C-5 and C-7 $OCONEt_2$ chromenes and recent work (Fig. 46) indicates exciting new extensions for E = TMS (46A), where the "question mark" has been positively answered.

DoM - Olefin Metathesis Link

The rapidly expanding utility of the olefin metathesis reaction stimulated the Snieckus group to establish DoM connections (Fig. 47). Thus, using DoM as a take-off point, a dihydrobenzoazocinone (48A, Fig. 48), a macrocyclic sulfonamide (49A, Fig. 49) and, in an as yet sparsely investigated yne-ene Grubbs reaction, the benzothiazepine (50A, Fig. 50) have been obtained.

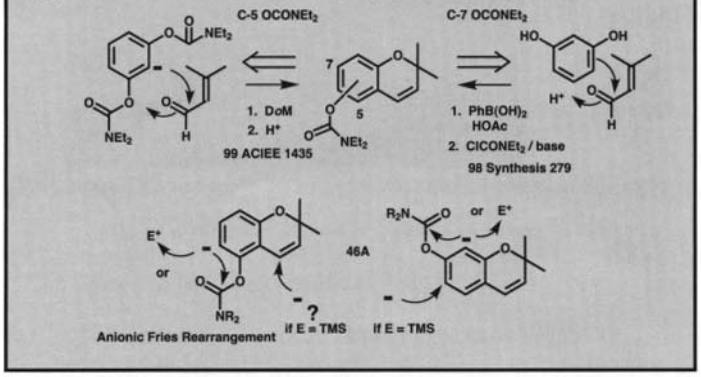
Fig.45



Conclusion

The power of DoM and DreM, in conjunction with Xcoupl, for the construction of contiguously substituted aromatics, biaryls, and condensed aromatic and heterocyclic systems is amplified by the complementarity of the metalation methods to classical electrophilic substitution (especially FC) chemistry. Further synergy is realized by using DoM and DreM in tandem with other transition metal catalyzed processes and, most recently, with olefin metathesis. The emerging use of these strategies in the industrial sector is ample testimony of their practical value.

Fig.46 Chauder, B.; Snieckus, V. unpublished results.



About the Feature Article

This condensed feature article summarizes a seminar presented by Professor Victor Snieckus in December 1999 at FMC Lithium Division's R&D facility in Bessemer City, North Carolina. Most of the technical slides presented at that time are included in this condensed version as figures (Fig.). The full version of the seminar is available by E-mail as a .pdf file. The file basically contains the same figures, but the text is a transcription of Professor Snieckus' lecture.

The presentation is an overview of recent work from the Snieckus laboratories, as well as from other germane laboratories. The presentation demonstrates the complementarity and synergy of DoM and DreM with both classical and modern methodologies and reagents. It is hoped that this feature article will prove to be an important resource for you, our readers.

Fig.47 Stefinovic, M.; Snieckus, V. *J.Org. Chem.* **1998**, *63*, 2808-2809.

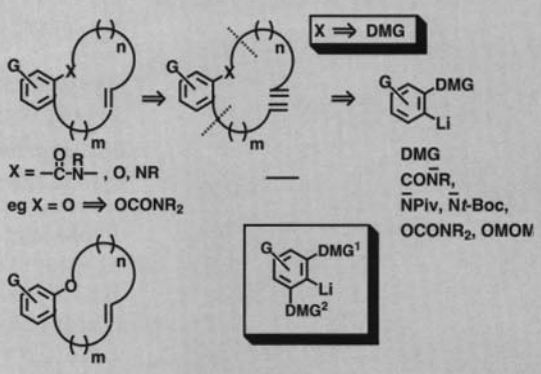


Fig.48 Lane, C.; Snieckus, V. *Synlett* **2000**, in press.

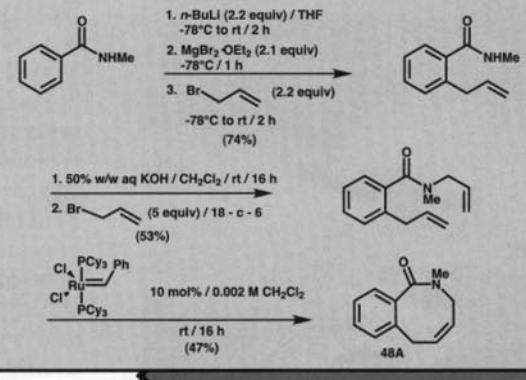
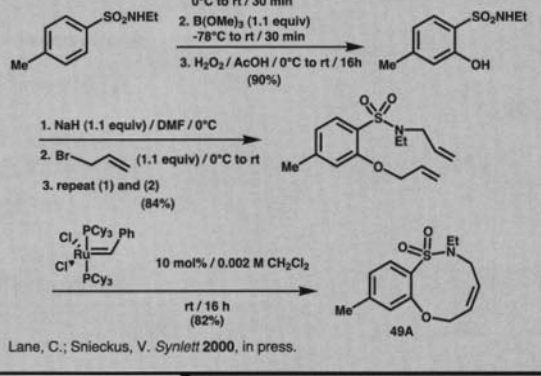
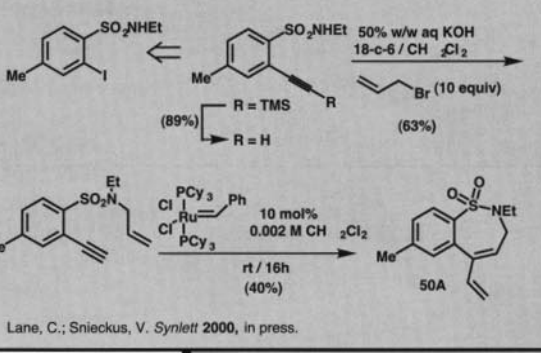


Fig.49



Lane, C.; Snieckus, V. *Synlett* **2000**, in press.

Fig.50



Lane, C.; Snieckus, V. *Synlett* **2000**, in press.

About the Authors
Professor Victor Snieckus and Andrew Larkin

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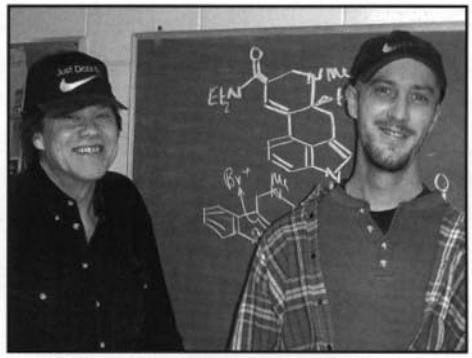
Professor Victor Snieckus holds the Bader Chair in Organic Chemistry at Queen's University, Department of Chemistry in Kingston, Canada, KL7 3N6. He was born in Lithuania, grew up in a displaced-person camp in Germany, and migrated to Canada in 1948. Aside from his DoM, DreM and Xcoupl activities, Professor Snieckus is an editor of the *Canadian Journal of Chemistry* and *Synlett* and enjoys teaching, which also encompasses industrial short courses.

In 1999, Professor Snieckus was inaugurated into the Lithuanian Academy of Sciences. He currently serves as an organizer for an eclectic chemical and cultural meeting on synthesis in Lithuania (see http://web.chem.queensu.ca/dupont/index.htm). In addition, he is vice president/chemical research of CIDtech Research Inc. in Cambridge, Ontario. Professor Snieckus enjoys languages, still plays some hockey (low-contact), and wishes he could play a soprano saxophone and beat t'Li' in Ping-Pong (or to aficionados of the game, Table-Tennis).



Prof. Victor Snieckus **Andrew Larkin**
(Suspiciously missing from this photo is t'Li'.)

Andrew Larkin

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Andrew Larkin obtained a bachelor of science degree from Acadia University in Wolfville, Nova Scotia, in 1991. After several years as an analytical chemist, he enrolled at Queen's University, where he is nearing completion of his master of science degree with Victor Snieckus. Larkin's research project is the total synthesis of ergot alkaloids.

Acknowledgements

The editor of *Lithium Link* wishes to acknowledge the assistance of the following: Sandie Leach, administrative assistant to Professor Victor Snieckus; Denise Odems, Kim Rathman and JoAnn Trull, transcribers of the audio tape of the two-hour lecture; Peter Rhyne, Barringer & Associates Ltd. production manager; and Lila Gladden, proofreader par excellence. Without their responsive cooperation, the condensed and full versions of this feature article could not have been completed in time to meet various deadlines. The editor thanks these individuals and the authors for their assistance.

Past Feature Articles

From Previous 'Lithium Link' Newsletters:

- "Applications of Lithium Metal in Organic Synthesis" (Fall 1999). Professor Karl Dieter of Clemson University.
- "Uses of Dibutylmagnesium (DBM) in Synthesis" (Winter 1999).
- "Preparation of Alkene Derivatives via Organolithium Intermediates" (Fall 1996). Dr. Cheryl P. Kordik and Dr. Allen B. Reitz of R.W. Johnson.
- "Preparation of Alkynyl Derivatives via Organolithium Methodologies" (Winter 1995). Professor Mukund Sibi of North Dakota State University.
- "The Structure and Reactivity of Organolithium Reagents" (Summer 1995). Professor Craig Ogle of University of North Carolina at Charlotte.
- "Titration Methods for Commercial Organolithium Compounds" (Winter 1994). Dr. Conrad W. Kamienski of FMC Lithium Division.
- "Metal-Halogen Exchange Involving Aliphatic Substrates Using Organolithiums" (Spring 1994). Professor William Bailey of University of Connecticut.
- "Metal-Halogen Exchange of Aryl and Heteroaryl Ring Systems Using Alkyllithiums" (Winter 1993). Professor Don Slocum of University of Western Kentucky.
- "Ring and Lateral Metalation of Heteroaryl Substrates Using Strong Base Systems" (Spring 1993).
- "Ring and Lateral Metalation of Aryl Substrates Using Strong Base Systems" (Spring 1992, photocopy only).
- "Chirals and Carbanions" (Winter 1991).
- "Focus on *t*-Butyldimethylchlorosilane (TBSCl)" (Spring 1991, photocopy only).

MEETINGS TO BE ATTENDED BY FMC IN 2000

- **February 14-17, INFORMEX, New Orleans, Louisiana**
- **March 8-10, 1st Florida Heterocyclic Conference, University of Florida, Gainesville, Florida, organized by ARKAT and Scientific Update**
- **March 26-30, ACS National Meeting, San Francisco, California**
- **April 6-9, Annual C&FGR, Sandhills, North Carolina**
- **June 2, HOPE Symposium, Holland, Michigan**
- **June 14-15, ChemSpec Europe 2000, Lyons, France**
- **June 26-29, BOS 2000, Vilnius University, Lithuania**
- **July 1-5, ICOS-13, IUPAC, Warsaw, Poland**
- **July 9-13, Gordon Research Conf., Organic Reactions & Processes, Roger Williams University, Bristol, Rhode Island**
- **August 20-24, ACS National Meeting, Washington, DC**
- **October 12-13, MPPCC, Abbott, North Chicago**
- **November 7-9, CPhI, Milano, Italy**

R&D and Manufacturing Capability Improvements To Meet Our Increasing Customer Needs

- **New Kilo Lab in R&D** (3Q, 2000)

Equipment	Alkyl-lithiums	Alkoxides	PFI's/Als	Non-cGMP Intermediates
Hastalloy Rxn Sys-2x10 gal.	X	X	X	X
Glass Rxn Sys-2x22 liter				X
Filtration + Mud Quenching (Hastalloy Filter)	X		X	
Filtration (Glass Filter)		X		X
Distillation	X		X	X
WFE or Rotovap Concentration	X		X	X
Hot Oil, 135°C	X	X	X	X
Cold Oil, -40°C	X	X	X	X
Drying		X		X
Solids Handling		X		X
Vacuum				X
Air-sensitive Manipulations	X	X	X	X
GC/HPLC	X	X	X	X

- **Engineering Research Laboratory**

Numerical Tools

- Dynamic simulation of reaction/separation processes.
- Continuous process simulation.
- Dynamics of venting processes and other safety problems.
- Modeling accidental release dispersions (OSHA, EPA-RMP).
- Computer-aided molecular/mixture design.
- Prediction of thermochemical and potential hazards.
- Modeling and prediction of physical and thermodynamic equilibrium (VLE) properties of pure compounds and mixtures.
- Modeling of reactivity and thermal properties via electronic theory (*ab initio* methods).

Experimental Tools

- Reaction calorimeter (RC-1) (2 L).
- CRC-90 microcalorimeter (3μW detection).
- Hazard calorimeter (VSP2, RSST).
- High-pressure reactor to 5000 psi, with *in-situ* FTIR capability to 2000 psi, compressor to 10000 psi.
- *In situ* FTIR probe.
- Camile (data acquisition and control).

- **Specialty Organics (SO) Capabilities (for non-butyllithium products)**

Plant Equipment

- 2x1000-gallon reactor trains.
- Reactor train includes, at a minimum, agitated feed mix tank, jacketed and agitated reactor, reflux condenser, multiple Nutsche product filters and product receiver.
- Each vessel in the train is at least 1000-gallon capacity.
- Reactor process equipment is primarily stainless steel.
- Bulk solid addition to the reactor or a feed mix tank.
- Refrigerated or heated Isopar heat-transfer media for reactor jackets, condensers and product storage.
- Extensive storage, handling, packaging facilities.
- Access to low temperature chilling and product filter/dryers.
- High degree of process control and instrumentation.
- Lithium metal dispersion capability.
- Quenching capability for reactive materials using water, chloride brines or acid.
- State-of-the-art safety systems including emergency-relief containment.
- All permits in place for process flare, organic/aqueous liquid-waste disposal, hazardous waste.

Processing Experience

- Butyllithium-processing experience from 40 years of production including four worldwide sites.
- THF is primary solvent in existing product lines.
- All reactions currently handled are exothermic including quench. Heat of reactions up to 700 kilojoules/gm-mole.
- Present products are non-cGMP pharmaceutical reagents including alkyllithiums, organomagnesiums, alkoxides and amides.
- Experience in analogous chemistry. Also lithiation of substrates with strong bases followed by electrophile addition.

Product Lists

COMMERCIAL PRODUCTS

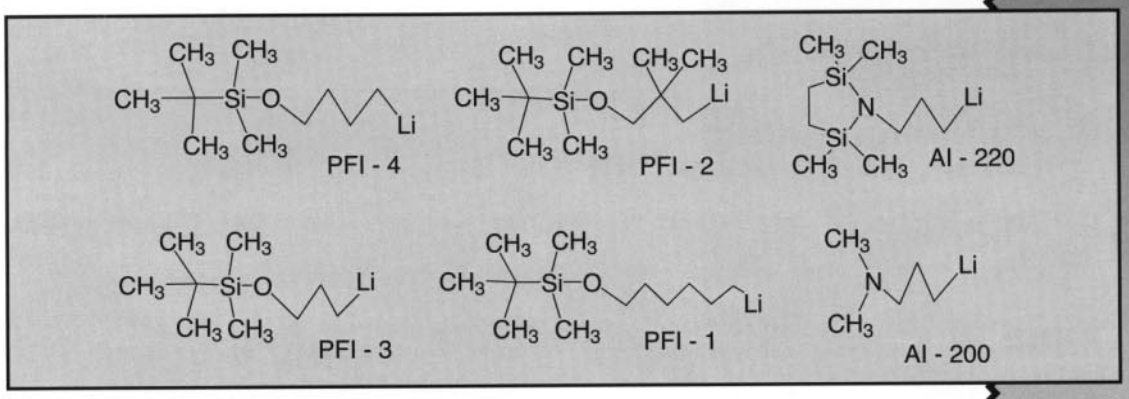
***n*-Butyllithium (NBL),** (15, 24, and 86 wt%) in hydrocarbon solvents
***n*-Butyllithium (NBL),** 2.2M (17 wt%) in toluene
***sec*-Butyllithium (SBL),** (12 wt%) in cyclohexane, or heptane
Lithium diisopropylamide (LDA-9505), 2M (26 wt%), **nonpyrophoric**
Lithium diisopropylamide (LDA-EB), 2M (26 wt%) in THF/ethylbenzene, **nonpyrophoric**
Lithium hexamethyldisilazide (LHS), 1.3M (25 wt%) in THF, **nonpyrophoric**
Methyllithium (MeLi-9307), 1.1M (3 wt%) in THF/cumene, **nonpyrophoric**
Lithium *t*-butoxide (LTB), 2M (18 wt%) in THF, $LiOC(CH_3)_3$
Lithium methoxide (LM), 2.2M (10 wt%) in methanol, $LiOCH_3$
Lithium amide ($LiNH_2$), solid
***t*-Butyldimethylsilyl chloride (TBSCl),** solid 98%, $(CH_3)_3CSi(CH_3)_2Cl$ (distributor)
Dibutylmagnesium (DBM), 0.7M (14 wt%) in heptane or hexane

RESEARCH PRODUCTS

t*-Butyllithium (TBL),** 1.8M in heptane, **safer than in pentane
***n*-Hexyllithium (NHL),** 2.8M (35 wt%) in hexane, $CH_3CH_2H_2CH_2CH_2Li$*
2-Ethylhexyllithium (EHL), 2M in heptane, $CH_3CH_2CH_2CH_2CH(Et)CH_2Li$
***n*-Octyllithium (NOL),** 2M in heptane, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2Li$
Phenyllithium (PhLi), 1.7M (17 wt%) in di-*n*-butylether, **nonpyrophoric***
Thienyllithium (TLT), 1.5 to 2M in THF/heptane, **nonpyrophoric**
Lithium isopropoxide (LIPH), 3.3M (30 wt%) in heptane, $LiOCH(CH_3)_2$
Lithium *t*-butoxide (LTBC), 1M (10 wt%) in cyclohexane, $LiOC(CH_3)_3$
Lithium *t*-butoxide (LTBS), solid >97%, $LiOC(CH_3)_3$
***t*-Butyldiphenylsilyl chloride (BPS),** liquid 97%, $(CH_3)_3CSiPh_2Cl$
***t*-Butyltrichlorosilane (BTC),** waxy solid 97%, $(CH_3)_3CSiCl_3$
Di-*t*-butyldichlorosilane (BDC), liquid 97% $[(CH_3)_3C]_2SiCl_2$
Di-*t*-butylsilane (DTBS), bp 128°C, 98% $(t\text{-Butyl})_2SiH_2$
***t*-Butyldimethylsilyl chloride (TBSCl),** 3M (50 wt%) in toluene

**Becomes a commercial product by mid-2000*

All the following PFIs are 15 wt% in cyclohexane:
6-(*t*-Butyldimethylsilyloxy)-1-hexyllithium (PFI-1)
3-(*t*-Butyldimethylsilyloxy)-2,2-dimethyl-1-propyllithium (PFI-2)
3-(*t*-Butyldimethylsilyloxy)-1-propyllithium (PFI-3)
4-(*t*-Butyldimethylsilyloxy)-4-butyllithium (PFI-4)



For other organometallics and/or formulations, please contact those listed on page 1 in the "From the Editor" section.

Customer Support

Bottles for Laboratory Use
We offer our organometallic solutions in 500 mL containers. Prices depend on type and availability.

Consultations and Presentations
Our chemists and engineers are available for customer visits and confidential consultations aimed at specific customer needs. Also available are presentations ranging from general reviews of the utility of our products in organic synthesis to safety, storage and handling procedures. We would be glad to present a seminar, "Optimization of Reactions Involving Organolithiums," at your location.

Capabilities
Please see "R&D and Manufacturing Capability Improvements" on page 14.

Literature
"Organometallics in Organic Synthesis" is a comprehensive brochure (1992) including extensive utility references as well as a complete description of our organometallic products. Our brochure, "Butyllithium: Guidelines For Safe Handling," is a must for customers considering handling butyllithium that is contained in cylinders. Also ask about our video on the safe handling of butyllithium.

Web Site
In September 1999, the first phase of our new Web page was launched at *http://www.fmclithium.com*. Subsequent upgrades will include access to past *Lithium Links*, both condensed and full articles, in addition to new and standard product information. The trend will be to put more on the Web and less in the mail and thus save a few trees (see Mailing List Update).

Toll-free Phone Number
If you want to reach us by phone, use **1-888-LITHIUM**

FMC LITHIUMLINK Winter 2000

Lithium Division
449 North Cox Road
Gastonia, NC 28054

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What's Inside?

Mailing List Update:

To help reduce the cost of mailing *Lithium Link,* we are continually updating our mailing list. Although many customers have helped us by updating their subscriber lists, we still need your help in making our list current. You can let us know of changes and deletions in either of the following ways:

1) Simply detach mailing label(s) of nonexistent readers or nondelivered newletters, attach to correspondence card inside the newsletter and mail the card.

2) Contact us at *terry_rathman@fmc.com* with the necessary information.

Please keep your eyes open for those noncirculating issues, and thanks for your assistance and cooperation.