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The directed *ortho* metalation–transition metal–catalyzed reaction symbiosis in heteroaromatic synthesis*

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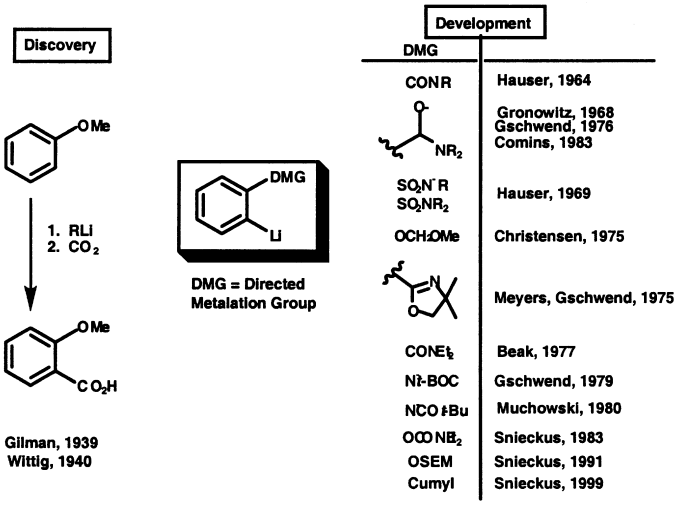
Abstract: New developments from our laboratories in Directed *ortho* (D*o*M) and remote (DreM) metalation reactions are presented and connections to transition metal catalyzed cross coupling and olefin metathesis processes are described.

As it heads into its seventh decade since the Gilman and Wittig discovery, the Directed *ortho* metalation (D*o*M) reaction (Scheme 1) [1] is increasingly poised to the challenges and opportunities in synthetic aromatic chemistry. In the quest to develop new amide-based Directed Metalation Groups (DMGs), we have recently discovered that secondary *N*-cumyl benzamide **1** (Scheme 2) undergoes smooth deprotonation—electrophile quench providing a general route to products **2** which, in contrast to previously developed amide DMGs [1,2] are rapidly hydrolyzed to primary amides **3** which, in turn, are readily manipulated to other useful functionality [3]. Similarly, the corresponding benzenesulfonamide **4** is converted to *ortho*-substituted products **5** (Scheme 3). Most significantly, the tertiary cumyl aryl *O*-carbamate **8** is transformed to *ortho*-TMS derivative **6** and undergoes the anionic Fries rearrangement to **7** in useful yields (Scheme 4). The facile further TFA- and TFE-mediated hydrolysis to **10** (*via* **9**) and **11,** respectively, opens avenues for mild synthesis and manipulation of phenol and salicylamide derivatives which offer advantage over the previous reactions of the corresponding diethyl carbamate **11**.



Scheme 1 Directed *ortho* metalation: the new aromatic chemistry.

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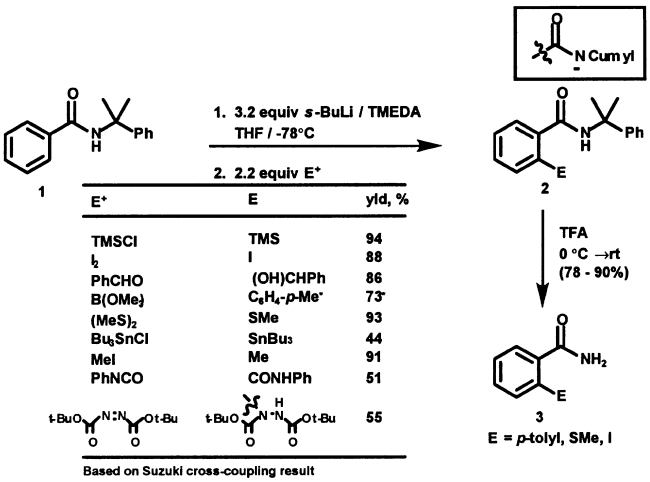
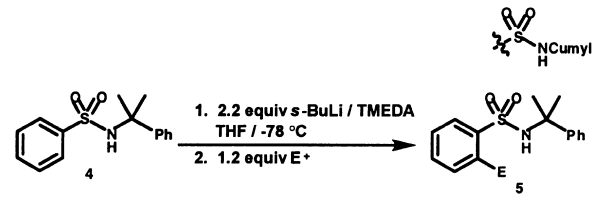


E^+	E	yld, %
TMSCl	TMS	94
I_2	I	88
PhCHO	(OH)CHPh	86
B(OMe)$_3$	C_6H_4-*p*-Me	73
$(MeS)_2$	SMe	93
Bu_3SnCl	$SnBu_3$	44
MeI	Me	91
PhNCO	CONHPh	51
t-BuO, N=N, Ot-Bu; O, O	t-BuO, H, N-N, Ot-Bu; O, O	55

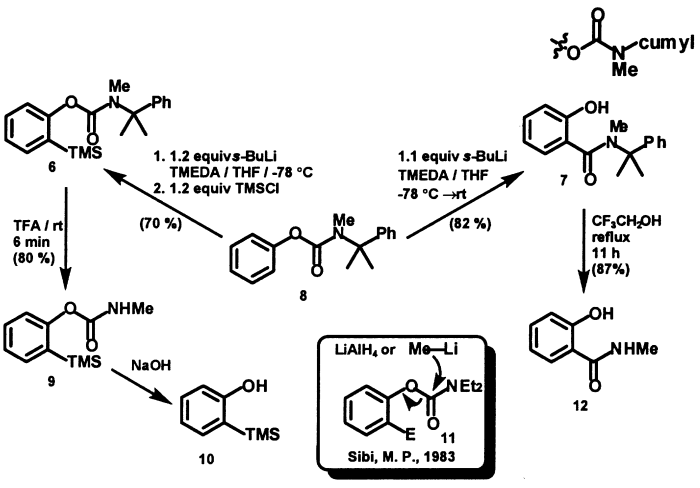
Scheme 2 Evolution of a new amide DMG.



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

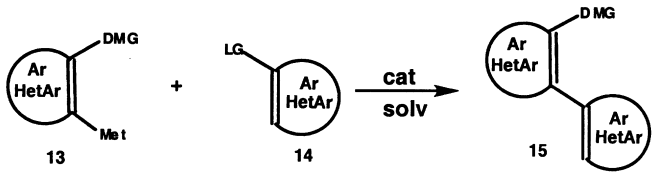
Metallinos, C.; Ang, P. J. A. (1999)

Scheme 3 Evolution of a new sulfonamide DMG.



Scheme 4 Evolution of a new carbamate DMG.

In the last two decades, transition metal-catalyzed cross coupling reactions have had a specific impact in the synthetic chemist's approach to the aryl–aryl bond forming process [4]. Work in our group has been focussed on the D*o*M-cross coupling link, **13** → **14** → **15** (Scheme 5) especially in the Suzuki-Miyaura, Corriu-Kumada-Tamao, and Negishi reactions. Aside from extensive studies in solution phase chemistry, [1,2] we have effected solid support Suzuki–Miyaura cross coupling reactions. Of these, the Leznoff acetal linked system **16** (Scheme 6) undergoes coupling with boronic acids **17** and **18** derived from D*o*M chemistry. These reactions allow cyclization modes leading, respectively, to phenanthridines **19** and dibenzopyranones **20** (via **21**) in high yields and purities [5]. The discovery of the Grignard–aryl *O*-carbamate cross coupling process [6] has prompted systematic studies, including the development of a regiospecific route to polysubstituted naphthalenes (Scheme 7). Thus, metalation–carbamoylation of **22** leads to **23** which, upon a second metalation–electrophile quench, produces a variety of 1,2,3-trisubstituted naphthalenes **25** [7]. In the appropriate case, **25** undergoes smooth Suzuki-Miyaura cross coupling to give biaryls **24** and, upon further metalation–quench, leads to tetra-substituted naphthalenes **26**. The overall concept (**27**) provides walk-around-the-ring D*o*M chemistry that may allow also an answer to the peri-metalation question. In an application of the new Grignard-carbamate cross coupling which is connected to the Saegusa-Ito *ortho*-quinodimethane generation method (Scheme 8), compound **28** undergoes exclusive C-4 deprotonation and, upon electrophile quench, provides **29** [8]. Cross coupling with a commercial Grignard reagent affords **30**, demonstrating a new mode for functionalization of the important indole C-5 position. Reduction, quaternization, and a protecting group switch (necessary to avoid complications at the N-TBS in the subsequent reaction) leads to **32**, which, upon fluoride treatment (Scheme 9) and dienophile trap gives, *via* the reactive species **33**, cycloadducts **34**–**37**. The D*o*M-cross coupling marriage is also effectively illustrated in the organozinc **38**–aryl triflate **39** union (Scheme 10) to give products **40** exemplified in various DMG flavors [9].

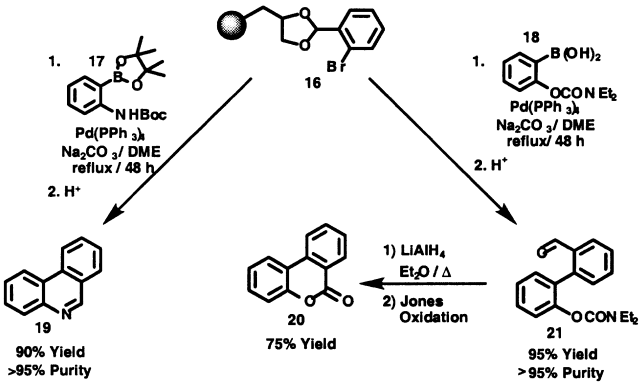


Met	LG	cat	
$B(OR)_2$	I > Br > OTf	Pd	Suzuki-Miyaura
MgX	OTf > $OCONEt_2$ $SCONEt_2$	Ni	Corriu-Kumada-Tamao
ZnX	hal, OTf	Ni	Negishi
SnR_3	hal, OTf	Pd	Stille

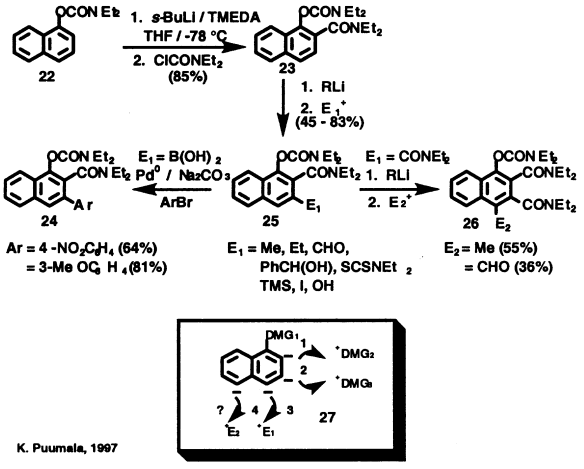
DMG = $CONEt_2$, $OCONEt_2$, OMOM, NH*t*-Boc, SO_2*t*-Bu

Scheme 5 The D*o*M–cross coupling nexus.

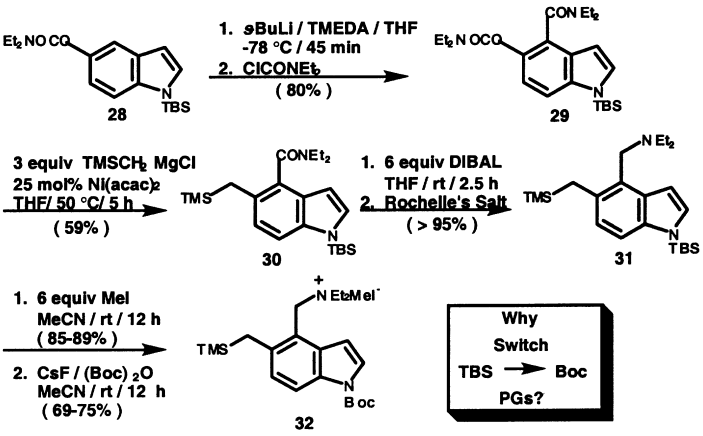
The salient Complex-Induced Proximity Effect (CIPE) concepts of Beak & Meyers [10] and Klumpp [11] led, as a direct consequence, to the establishment of Directed remote Metalation (DreM)-induced reactions, **42** → **41** and **43**, and **45** → **44** (Scheme 11) [1,2], While the fluorenone (**41**) forming reaction has been extensively developed for methodology and total synthesis [12], emphasis has been placed more recently on the remote anionic Fries rearrangement (**42** → **43**), the tolyl DreM (**45** → **44**), and the yet to be fully evaluated competition, **45** → **46** or **47**. Thus, coupling of D*o*M-derived boronic acids (**48**) (Scheme 12) with halides or triflates (**49**) affords biaryls **50** which, upon LDA treatment followed by acid-catalyzed cyclization lead to products **51**, in overall routes which are higher yielding than the more sterically demanding direct cross coupling (**52**), furnish natural products (**53**), and, as yet, cannot be forced to double migration modes (**54**) [13]. Among other natural product synthesis applications, the naphthobenzopyrone **55** (Scheme 13), obtained by *O*-carbamate DreM, was readily transformed, *via* Stille product **56** into defucogilvocarcin V **57** [14]. In these processes, the effective use of the carbamate moiety as a carbonyl dication equivalent is demonstrated. As a foray into the synthetic potential of the



Scheme 6 Solid support links to D*o*M. Generation of heterocycles.



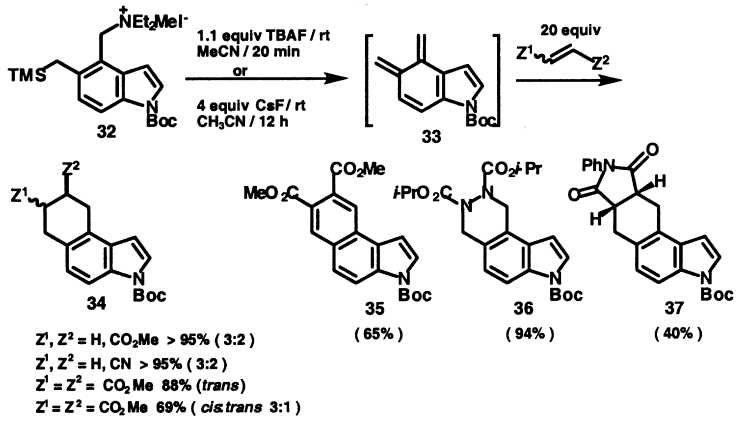
Scheme 7 Combined D*o*M-XCOUPL strategies for polysubstitued aromatics. Naphthalenes as a case study.



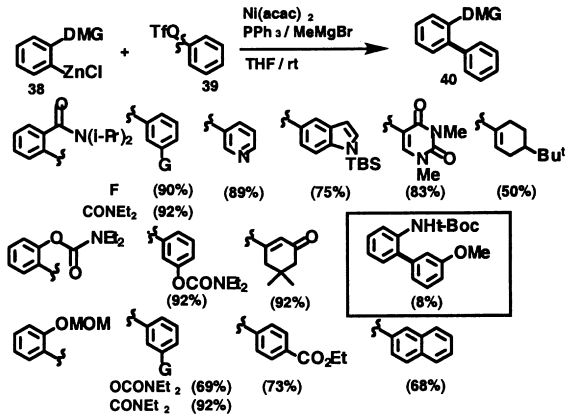
Scheme 8 D*o*M, X-coupling and indole-4,5-QMDs. Saegusa–Ito precursor.

competition between aryl vs. tolyl C-H deprotonation, **45** → **46** or **47** (Scheme 11), the conversion **58** → **59** (Scheme 14) has been effected [15].

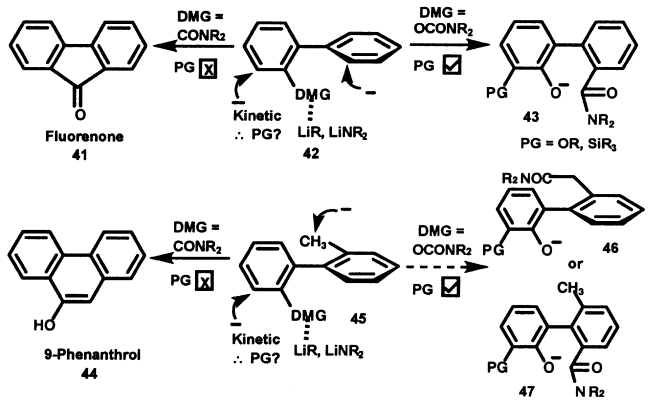
The question of the title of Scheme 15 has been answered for most of the heteroatoms X in the **60** → **61** and **62** conversions [16]. Work to answer question marks in **62** is in progress. In the specific diaryl ether structural entity, the general synthesis of xanthones has triggered application to the synthesis of several



Scheme 9 Cycloaddition of *N*-boc-indole-4,5-QDMs with dienophiles. Route to benz[e]indoles.

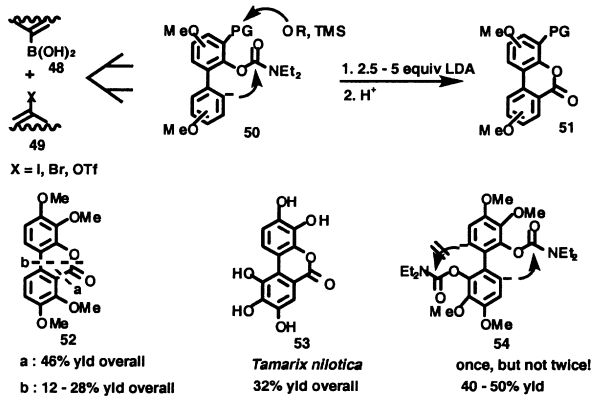


Scheme 10 D*o*M-cross coupling connections. ArZnX + ArOTf partners.

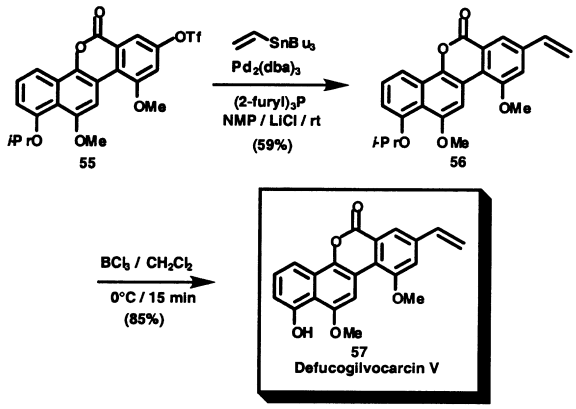


Scheme 11 DreM concepts inspired by CIPE. Condensed aromatics.

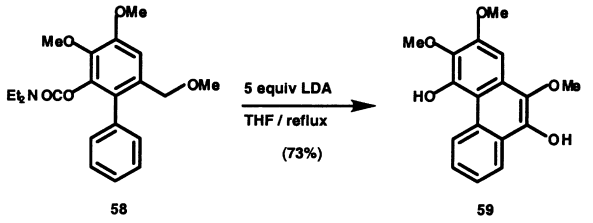
natural products including **66** (Scheme 16), derived by application of an Ullmann, **63** + **64** → **65**, using a Cu-solubilizing ligand (TDA 1) and a DreM (→ **66**) which does not require phenol protection (**67**) [17]. Taking the lead from the Buchwald laboratories, this work also led to the finding of a $CuPF_6$-mediated Ullmann for D*o*M-derived *ortho*-halo (*including Cl*) amides and sulfonamides **68** (Scheme 17) with (mainly) phenols and thiophenols **69** to give products **70** of value for further D*o*M, DreM, and cross coupling chemistry, some of which has been demonstrated [18].



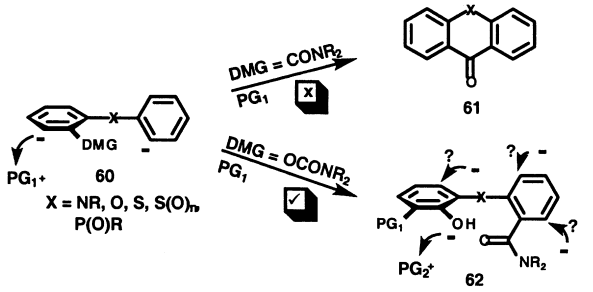
Scheme 12 Biaryl O-carbamate anionic remote fries equivalent. Regiospecific route to dibenzo-[b,d]pyran-6-ones.



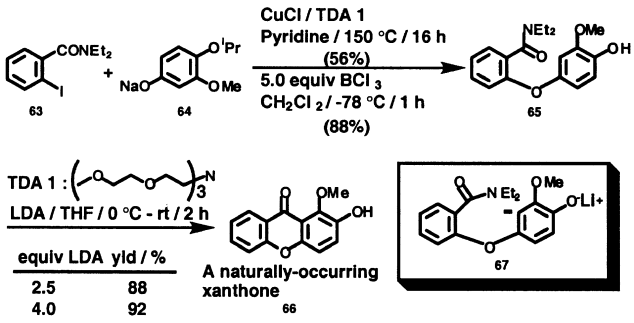
Scheme 13 Vinyl group introduction. Completion of the total synthesis of defucogilvocarcin V.



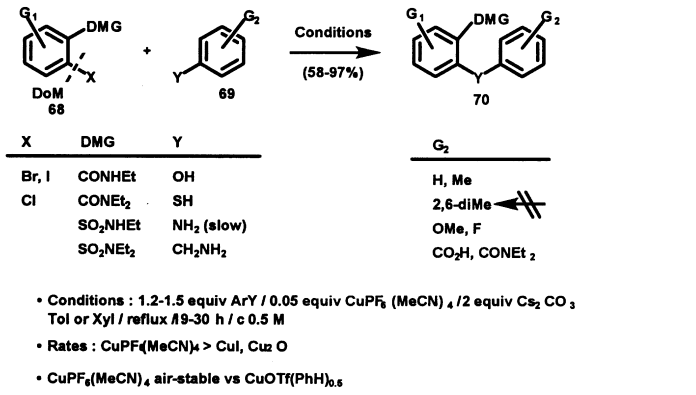
Scheme 14 Sequential remote metalation reactions.



Scheme 15 Heteroatom-bridges biaryl remote D*o*M?

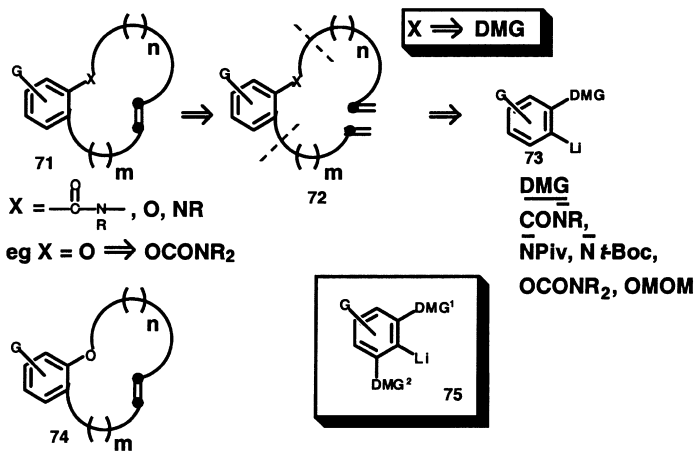


Scheme 16 Anionic Friedel–Crafts approach to xanthones without phenol protection.

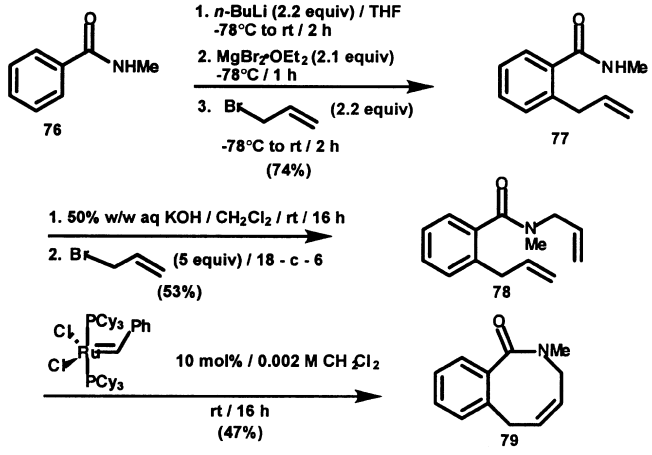


Scheme 17 D*o*M–Ullmann connection. A CuPF6 variant.

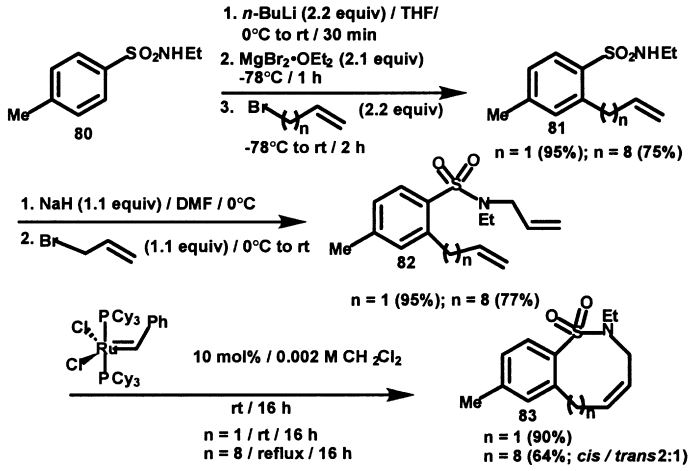
The explosive arrival of the Grubbs olefin ring-closing metathesis on the synthetic scene invited a contribution of a D*o*M connection (Scheme 18). Grubbs-envisaged retrosynthetic analysis of aromatic, ring-annelated targets **71** → **72** cascades to simple *ortho*-lithiated species **73** with diverse DMG potential to be either directly or, with modification, incorporated into **71** and extension to synergistic effects of double-DMG containing substrates **75**. Initial work led to the synthesis of benzene-ring annelated macrocyclic ethers **74**, including two natural products [19]. Most recently, prototype syntheses of 8-membered lactam (**76** → **77** → **78** → **79**, Scheme 19), macrocyclic sulfonamide (**80** → **81** → **82** → **83**, Scheme 20), and thiazepines with (realized) potential for Diels–Alder chemistry (**84** → **85** → **86** → **87**, Scheme 21) have been realized [20].



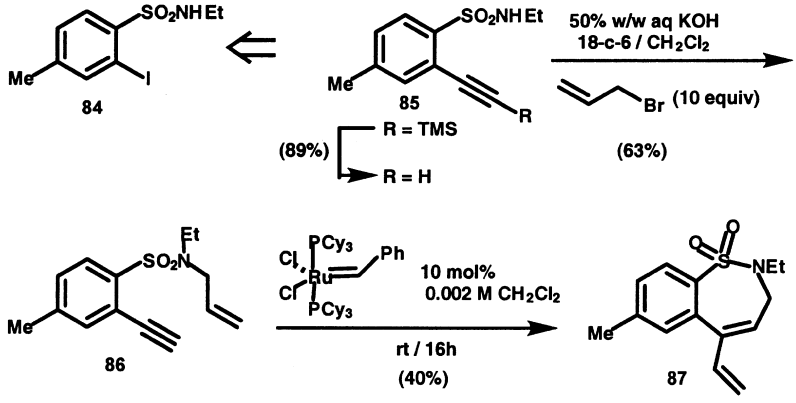
Scheme 18 Synthetic potential of D*o*M–olefin metathesis links.



Scheme 19 D*o*M–Grubbs metathesis connection: synthesis of dihydrobenzoazocinones.



Scheme 20 D*o*M–Grubbs metathesis connection: synthesis of macrocyclic sulfonamides.



Scheme 21 D*o*M–Yne-ene Grubbs metathesis connection: synthesis of benzothiazepines.

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REFERENCES

1 V. Snieckus. *Chem. Rev.* **90**, 879–933 (1990).

2 C. Chatgilialoglu, V. Snieckus. In *Chemical Synthesis Gnosis to Prognosis; NATO ASI Series E. Applied Sciences*, Vol. 320 p. 191. Kluwer Academic Publishers, Netherlands (1994).

3 S. Nerdinger, C. Metalllinos, V. Snieckus. *Organic Lett.* (1999), submitted.

4 F. Diederich, P. J. Stang, eds. *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH, Weinheim (1998).

5 S. Chamoin, S. Houldsworth, C. G. Kruse, W. Iwema Bakker, V. Snieckus. *Tetrahedron Lett.* **39**, 4179–4182 (1998).

6 S. Sengupta, V. Snieckus, *J. Org. Chem.* **55**, 5680–5683 (1990).

7 K. Puumala. MSc Thesis, University of Waterloo, Canada (1997).

8 A. C. Kinsman, V. Snieckus. *Tetrahedron Lett.* **40**, 2453–2456 (1999).

9 C. Quesnelle, W. Familoni, V. Snieckus. *Synlett* **349–350** (1994); C. Quesnelle. PhD Thesis, University of Waterloo, Canada (1996).

10 P. Beak, A. Meyers. *Acc. Chem. Res.* **6**, 356–363 (1986).

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

12 S. Mohri, M. Stefinovic, V. Snieckus, *J. Org. Chem.* **62**, 7072–7073 (1997).

13 A. Coelho, V. Snieckus. Unpublished results.

14 C. James, V. Snieckus. *Tetrahedron Lett.* **38**, 8149–8152 (1997); C. James. PhD Thesis, University of Waterloo (1998).

15 X. Wang. PhD Thesis, University of Waterloo (1992).

16 S. MacNeil, M. Gray, L. E. Briggs, J. J. Li, V. Snieckus. *Synlett.* 419–421 (1998), and references cited therein.

17 O. B. Familoni, I. Ionica, V. Snieckus. *Synlett.* 1081–1084 (1997).

18 A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **64**, 2986–2988 (1999).

19 M. Stefinovic, V. Snieckus, *J. Org. Chem.* **63**, 2808–2809 (1997).

20 C. Lane, V. Snieckus. Unpublished results.