Pure & Appl. Chem., Vol. 62, No. 10, pp. 2047–2056, 1990.
Printed in Great Britain.

The directed ortho metalation reaction. Methodology, applications, synthetic links, and a non-aromatic ramification

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Abstract - Three themes in context of Directed *ortho* Metalation (DoM) chemistry are developed: the use of the OSEM directed metalation group to achieve regiospecific synthesis of substituted benzene, naphthalene, and pyridine derivatives (**Schemes 2-5**); a tandem one-pot DoM - metal halogen exchange route to prepare diverse anthraquinones (**Scheme 7**) including antitumor ellipticine alkaloids (**Scheme 8**); a DoM - cross coupling link to attain *m*-terphenyl and biaryl amides which lead, by remote metalation, to condensed (**Schemes 10, 11**), simple (**Scheme 12**), and naturally occurring (**Scheme 13**) fluorenones. A diversion to α-metalated enol carbamates (**Scheme 15**) which provide new avenues to a myriad of acyl anion synthons (**Schemes 16-20**) is also described.

INTRODUCTION

Recent efforts in our laboratories have been concerned with the evolution and reinforcement of the Directed *ortho* Metalation (DoM) reaction as an important strategy for the regiospecific synthesis of aromatic and heteroaromatic compounds.[1] Presented herein are selected current topics in areas of methodology (OSEM, a new directed metalation group), application (a tandem DoM-metal halogen exchange route to anthraquinones), links to cross coupling (remote metalation route to fluorenones), and a foray into non-aromatic metalation (α-metalated enol carbamates).

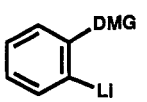
THE OSEM DIRECTED METALATION GROUP. REGIOSPECIFIC ROUTES TO SUBSTITUTED AROMATICS AND PYRIDINES

The continuing search for oxygen-based directed metalation groups (DMGs) **1** (**Scheme 1**) is driven by requirements of selectivity and mild deprotection methods. To supplement and improve the currently used DMGs,[2] we have investigated the OSEM moiety.[3] Metalation of the *p*-tolyl OSEM derivative **2** (**Scheme 2**) with *n*-BuLi at room temperature followed by quench with a variety of electrophiles, affords substituted products **3** in good to excellent yields with the exception of enolizable aldehydes and ketones; allylation is carried out via *in situ* lithium-copper exchange. Deprotection to *ortho* substituted phenols **4** may be achieved in high yield under mild TBAF conditions.

Smooth regioselective *ortho* rather than methyl deprotonation occurs in the 2,4-dimethylphenyl OSEM case **5** (**Scheme 3**) as evidenced by products **6** obtained from reactions with selected electrophiles. In contrast to the 2-OSEM derivative which gives regiorandom 1- and 3-metalation,[3] 1-OSEM naphthalene (**7**) undergoes regiospecific 2-metalation as attested from the products **8** formed. To demonstrate that the OSEM DMG is effective in pyridine metalation chemistry, the 3-pyridyl system **9** (**Scheme 4**) was

subjected to *t*-BuLi conditions (avoidance of pyridine ring nucleophilic attack); subsequent quench with electrophiles gave 4-substituted products **10** in good yields. Moreover, under the same conditions, the 4-TMS derivative of **10** leads, after PhCHO quench, to the carbinol **11**. Under mild TBAF conditions, **11** undergoes selective desilylation to give **12**, thus completing a silicon protection route[4] to 2-substituted 3-pyridinols which offers, in principle, a new synthetic method for diverse higher substituted 3-pyridinols **13**.

Scheme 1

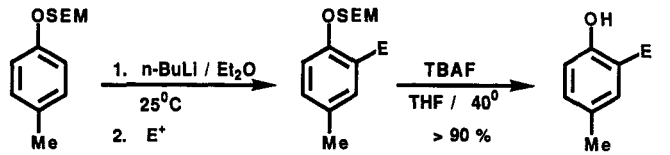


1

DMG (Directed Metalation Group)
= OMe, OMOM, $OCONEt_2$, OTHP,
$OP(O)(NMe_2)_2$

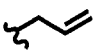
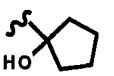
Scheme 2

The OSEM Group : A Well Known PG is a Useful DMG



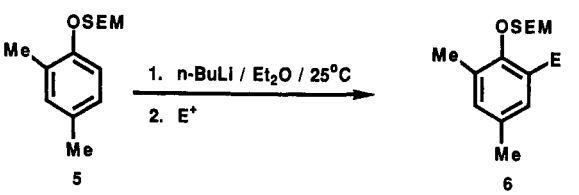
2 3 4

SEM ≡ $CH_2OCH_2CH_2SiMe_3$

E = $SiMe_3$ (85%), Me (82%), CHO (76%), COPh (70%), CH(OH)Ph (80%),
CH(OH)i-Pr (52%),  (CuBr, 76%),  (57%).

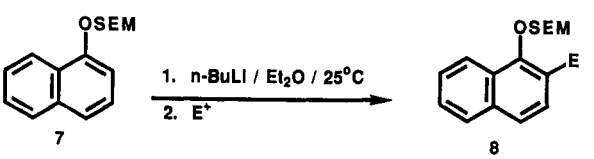
Scheme 3

The OSEM DMG : ortho-Cresol and Naphthalene Cases



5 6

E = Me (78%), $CH(OH)C_6H_4$-OMe-p (70%)

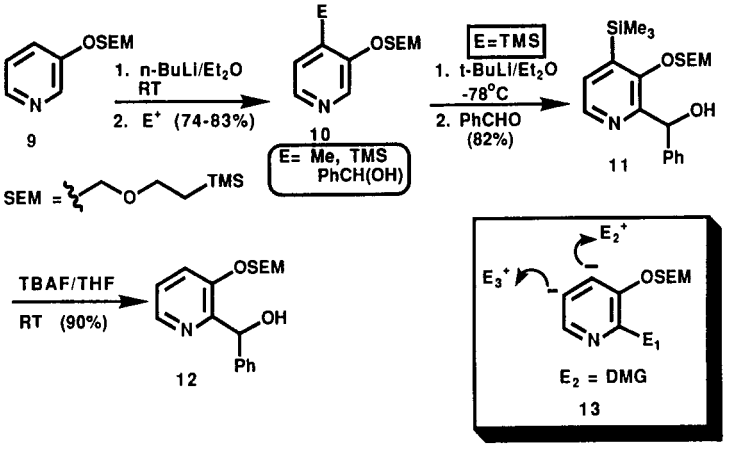


7 8

E = Me (82%), CH(OH)i-Pr (45%)

Scheme 4

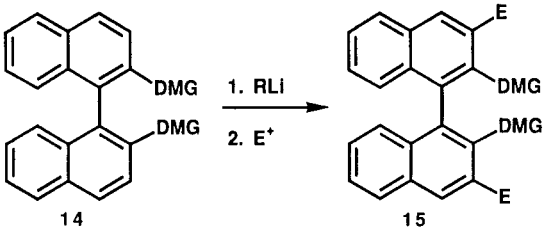
The OSEM DMG in Pyridine Metalation. Silicon Protection Route to 2-Substituted 3-Pyridinols

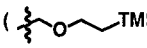


The increasing use of 1,1′-binaphthols as reagents and catalysts in organic chemistry[5] prompted a DoM study of these compounds with oxygen-based DMGs, including the OSEM group (**Scheme 5**).[6] Deprotonation of OMOM, $OCONEt_2$, and OSEM systems **14** using **2** equiv of RLi reagent under appropriate conditions followed by electrophile quench yields 2,2′-disubstituted products **15** in modest to excellent yields. In view of the mild deprotection conditions, OSEM may be the DMG of choice for the synthesis of useful new binaphthols. Monoanion generation from **14** is also feasible leading to 2-substituted derivatives.[6]

Scheme 5

Directed *ortho* Metalation of (±) - 2,2'-Binaphthol Derivatives. Dianions



DMG = OMOM, $OCONEt_2$, OSEM ()

E = D, Me, TMS, SPh, Cl, I

DMG	Conditions	Yield, %
OMOM	t-BuLi / HMPA* / THF /-78°C	43 - 92
$OCONEt_2$	s-BuLi / TMEDA / THF /-78°C	60 - 98
OSEM	n-BuLi / Et_2O / RT	57 - 96

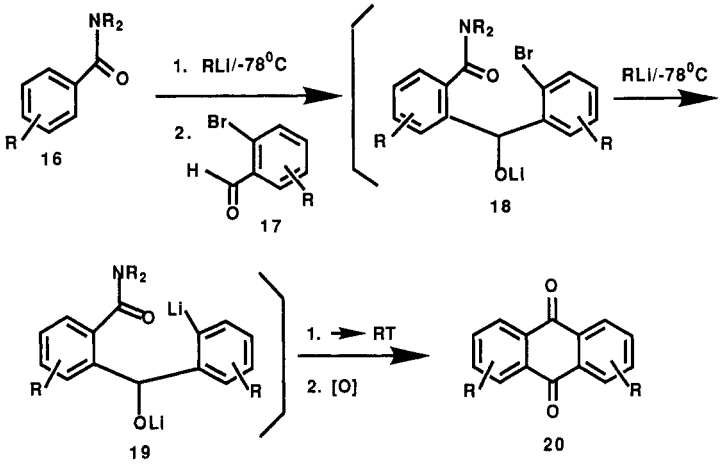
* Omitted for E = TMS

TANDEM DIRECTED ORTHO METALATION–METAL HALOGEN EXCHANGE REACTIONS. REGIOSPECIFIC CONSTRUCTION OF ANTHRAQUINONES

The aspiration to improve the yields of our previously reported tandem DoM process to anthraquinones[7] led to the development of a one-pot tandem DoM-metal halogen exchange method (**Scheme 6**).[8] Thus metalation of benzamide substrates **16** followed by reaction with easily prepared *ortho*-bromo benzaldehydes **17** affords intermediates **18** which, when subjected to a further equiv of RLi, undergo metal-halogen exchange to give species **19**. Warming to room temperature to promote cyclization followed by aerial oxidation of the intermediate hydroxyanthrones give anthraquinones **20**. A range of substituted simple and condensed anthraquinones **21-25** (**Scheme 7**)[8] are available by this new regiospecific method in yields which comfortably surpass those obtained by the earlier tandem DoM procedure.[7]

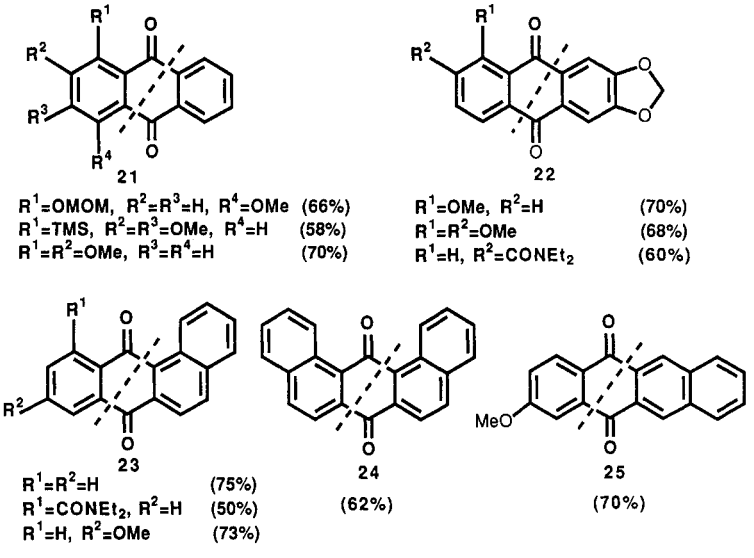
Scheme 6

ANTHRAQUINONES BY TANDEM DIRECTED METALATION-METAL HALOGEN EXCHANGE



Scheme 7

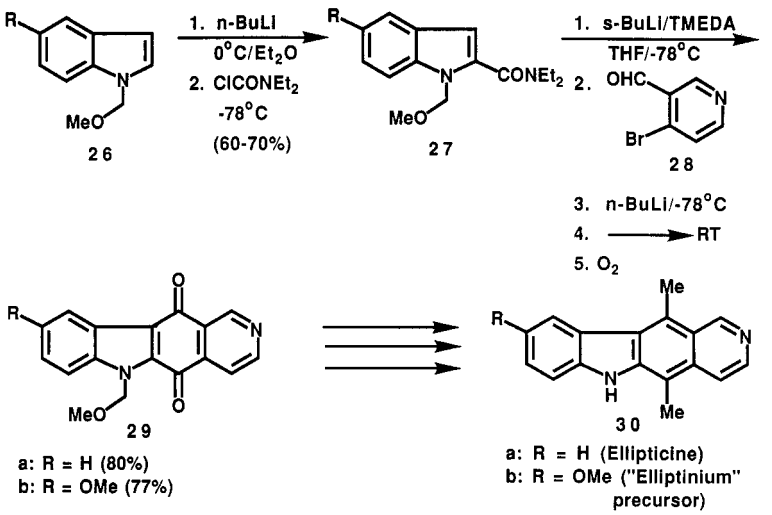
Anthraquinones by Tandem Directed Metalation-Metal Halogen Exchange. Illustrative Examples



A similar goal, to improve the previously reported[7] tandem DoM synthesis of the clinically useful antitumor ellipticine alkaloids,[9] led to the development of routes to ellipticine quinone (**30a**) and elliptinium precursor (**30b**) (**Scheme 8**).[10] Using N-DMG activation, the indoles **26** were metalated and carbamoylated to give derivatives **27**. When subjected to the one-pot tandem DoM-metal halogen exchange regimen with the bromopyridine aldehyde **28** (itself prepared by a DoM tactic), compounds **27** furnished the quinones **29** in good yields. The conversion of **29a** into antitumor agent **30a** has been previously achieved[7] while that of **29b** into **30b** is in hand.[10]

Scheme 8

Tandem Directed *ortho* Metalation-Metal-Halogen Exchange Route to Antitumor Ellipticine Alkaloids and Analogues

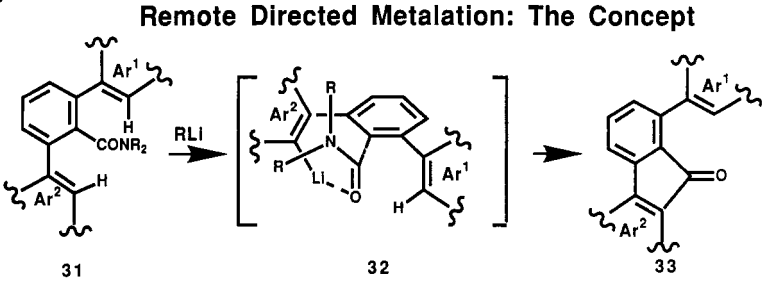


DIRECTED ORTHO METALATION – CROSS COUPLING LINKS. SYNTHESIS OF CONDENSED AND NATURALLY OCCURRING FLUORENONES BY REMOTE METALATION

Contemplation of the x-ray structure of N,N-diisopropyl 2-phenyl-6[1′-naphthyl]benzamide[11] in conjunction with the Complex Induced Proximity Effect concept,[12] led to the hypothesis that remote aromatic metalation of **31** (**Scheme 9**) could be achieved. Thus depending on relative Ar_1/Ar_2 hydrogen acidities, exposure of **31** to strong base may lead, via species **32**, to cyclized products **33**. Exploratory experiments with 2,6-diphenyl benzamides **34** (**Scheme 10**) showed that *t*-BuLi or LDA deprotonation led rapidly to the fluoreone **35** in yields which varied as a function of base and N-substitution.[11] Attempts to intercept the remote metalation species have been unsuccessful. In order to generalize this process, a range of 2,6-disubstituted benzamides (*m*-terphenyls) were prepared and subjected to identical conditions to give the condensed and hetero analogues **35-40** (**Scheme 11**) in yields not greatly surpassing 50%. Methoxy substituents in unsymmetrical cases directs the regioselective cyclization (**35**) while the formation of azafluorenone **37** is driven by the known higher pyridine C-4 hydrogen acidity.

Scheme 9

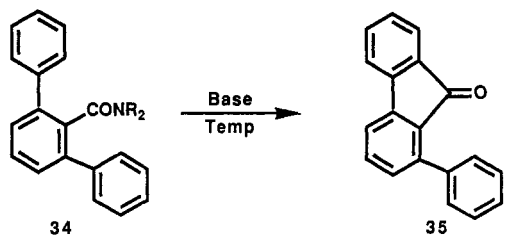
Remote Directed Metalation: The Concept



Whereas *t*-BuLi conditions on diphenyl amides **41** (**Scheme 12**) did not lead to any cyclization, LDA metalation under thermodynamic conditions resulted in clean conversions into the nonaryl substituted fluorenones **42**.[11] With this result in hand, a synthetic route to the orchid natural product dengibsinin (**47**)[13] could be conceptualized and was achieved (**Scheme 13**).[11] Suzuki cross coupling of the borate ester **43**, prepared by DoM chemistry, with the iodobenzene **44** under modified conditions[14] afforded the biphenyl **45**. Application of the remote metalation conditions provided the fluorenone **46** which upon selective deisopropylation with BCl_3 led to the natural product **47**.

Scheme 10

Remote Directed Aryl Metalation

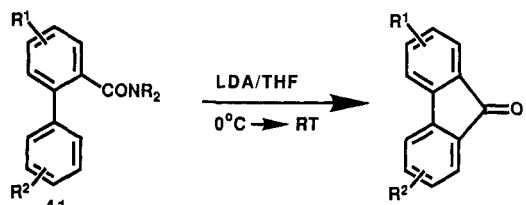


34 35

R	Base	Yield %	Temp
Et	t-BuLi	84	0°C → RT
i-Pr	t-BuLi	66	0°C → RT
i-Pr	LDA	65	0°C → RT
i-Pr	t-BuLi/t-BuOK	13	-78°C → RT

Scheme 12

Remote Directed Metalation-Cyclization of Biphenyl Carboxamides



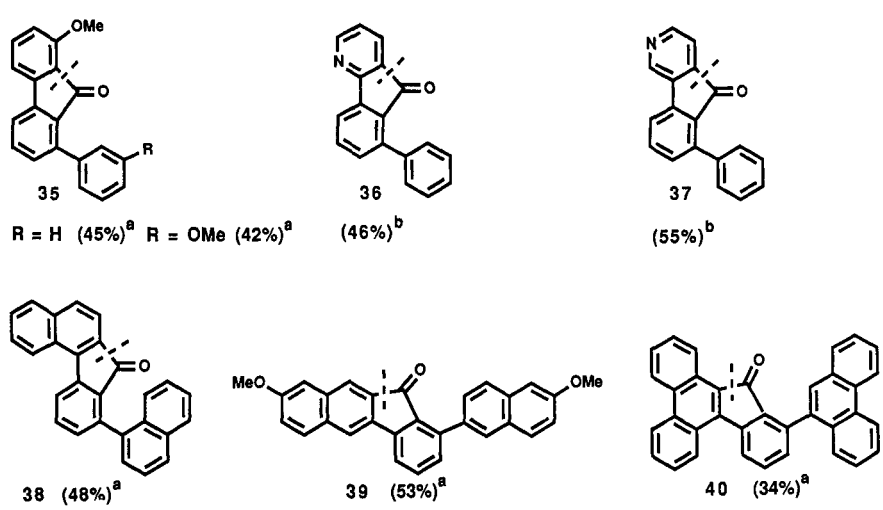
41 42

R = Et, i-Pr

R^1, R^2 = H, $(OMe)_n$, TMS

Scheme 11

Substituted and Condensed Fluorenones by Remote Aryl Metalation



35 36 37

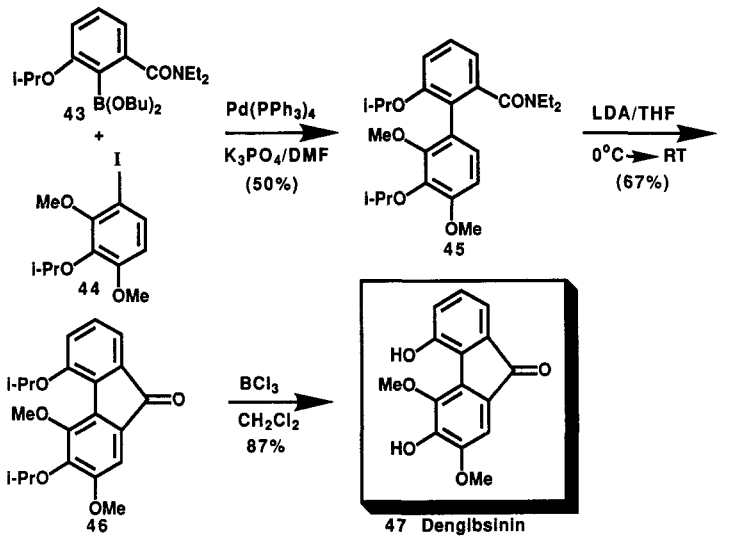
R = H (45%)[a] R = OMe (42%)[a] (46%)[b] (55%)[b]

38 (48%)[a] 39 (53%)[a] 40 (34%)[a]

Base : [a] t-BuLi, [b] LDA

Scheme 13

Total Synthesis of Dengibsinin

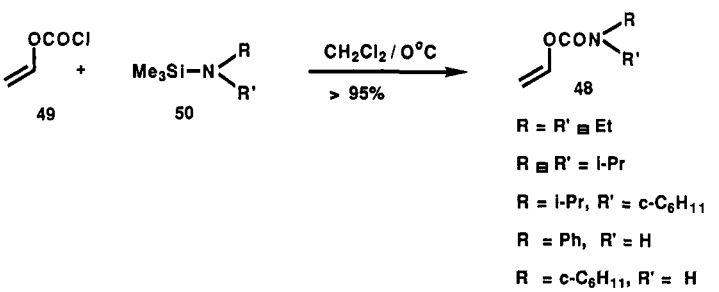


α-METALATED TERTIARY ENOL CARBAMATES. A NEW ACYL ANION EQUIVALENT

As a contribution to the area of the synthetically useful α-metalated α-heteroatom substituted species[15] and perhaps as a rational departure from our interest in aryl O-carbamate metalation chemistry,[1] we undertook a metalation study of tertiary enol carbamates.[16] Secondary and tertiary carbamates **48** (**Scheme 14**) representing a class of relatively unknown compounds,[17] were prepared in nearly quantitative yields by a direct, potentially general approach, involving treatment of commercial vinyl

Scheme 14

A General Preparative Route to Enol Carbamates

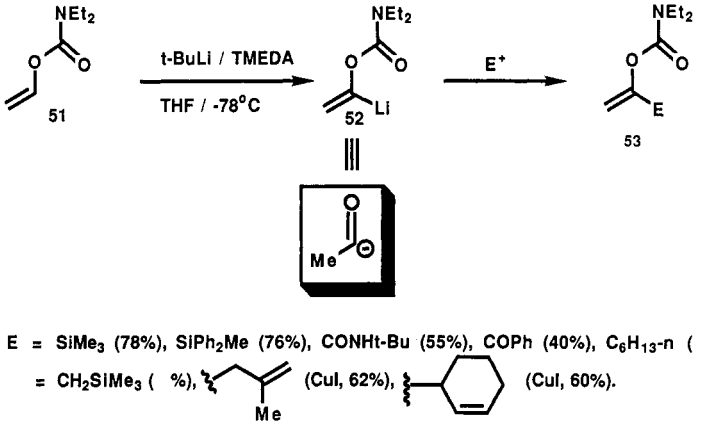


chloroformate (**49**) with appropriate silylamides **50**. Metalation of enol carbamate **51** (**Scheme 15**) under standard *t*-BuLi/TMEDA or, more recently, *sec*-BuLi/TMEDA conditions led smoothly to the α-lithiated species **52** which was trapped by a variety of electrophiles to give products **53** in good yields. Aside from the normal electrophiles, $ClCH_2TMS$, allylic halides (CuX), and tosyl halides are persuaded to react giving potentially valuable products. Reaction of the α-lithio species **52** followed by condensation with

cyclohexene oxide (BF_3,Et_2O) and butadiene epoxide (CuCN) leads to equally interesting compounds **54** and **55** respectively (**Scheme 16**). Furthermore, $ZnBr_2$ transmetalation of the α-lithio enol carbamate **52** (**Scheme 17**) followed by Pd(O)-catalyzed cross coupling with aryl and vinyl bromides affords products **56a** and **56b**. The formation of **56a** represents a new equivalent of Friedel-Crafts acylation.

Scheme 15

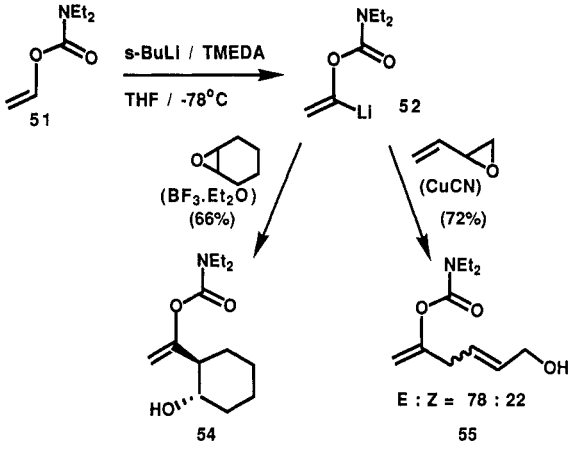
α–Metalation of Tertiary Enol Carbamates: An Acyl Anion Synthon



E = $SiMe_3$ (78%), $SiPh_2Me$ (76%), CONHt-Bu (55%), COPh (40%), C_6H_{13}-n (%)
= CH_2SiMe_3 (%), (CuI, 62%), (CuI, 60%).

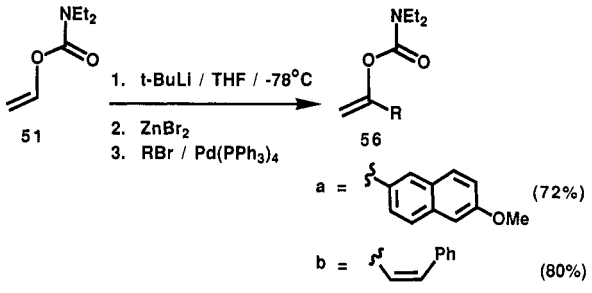
Scheme 16

α-Lithio Enol Carbamates: Reactions with Epoxides



Scheme 17

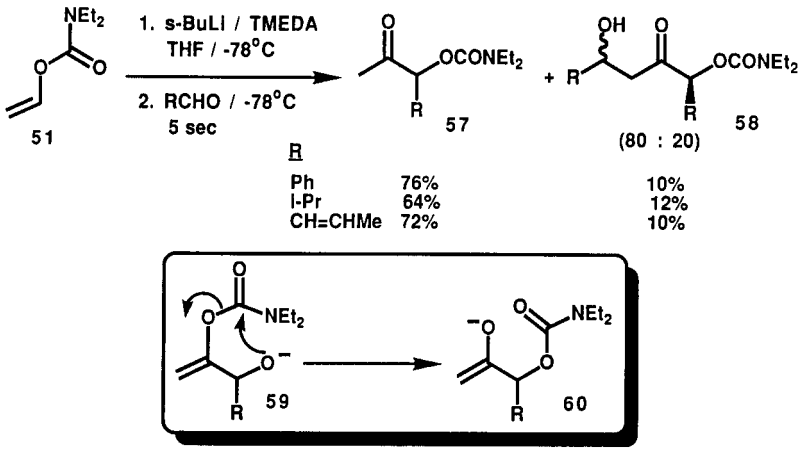
Pd-Catalyzed Cross Coupling Reactions of α-Metalated Enol Carbamates



In a markedly different reaction from that observed for other α-heteroatom vinylmetallics,[15] metalation-condensation of **51** (**Scheme 18**) with aliphatic and aromatic aldehydes affords, under strict conditions of short reaction times (5 *sec* at -78 °C), products **57** (major) and **58** (minor). A mechanistic rationalization for these results involves rapid carbamoyl transfer, **59** → **60** to give, after protonation, **57** and further condensation of **60** with aldehyde to yield **58**. Compounds **58**, constituting *umpolung cum* normal reactivity products, were obtained with good diastereoselectivity, a feature of potential general utility in aldol chemistry. In analogous fashion, metalation-condensation of **51** (**Scheme 19**) with excess of ketone electrophiles gave acyloin carbamates **61** in good isolated yields, the cases **62-64** being representative. To further expand the scope of anionic enol carbamate chemistry, metalation-condensation with an imine (**Scheme 20**) leads to a new synthesis of α-amino methyl ketones **65** via oxygen to nitrogen carbamoyl migration **66**.

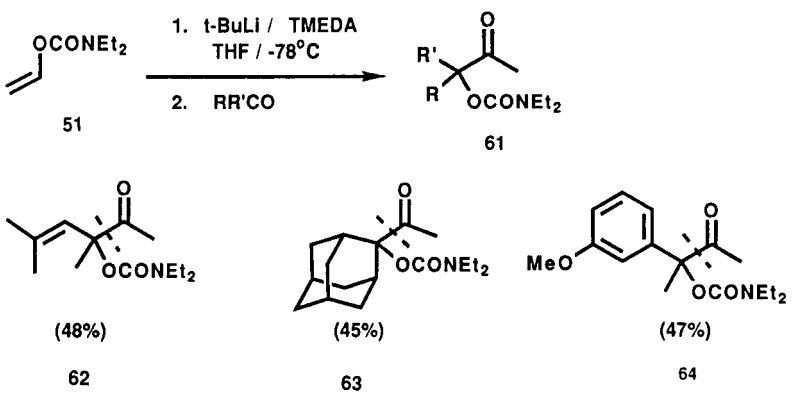
Scheme 18

Umpolung and Normal Reactivity of α-Metalated Enol Carbamates



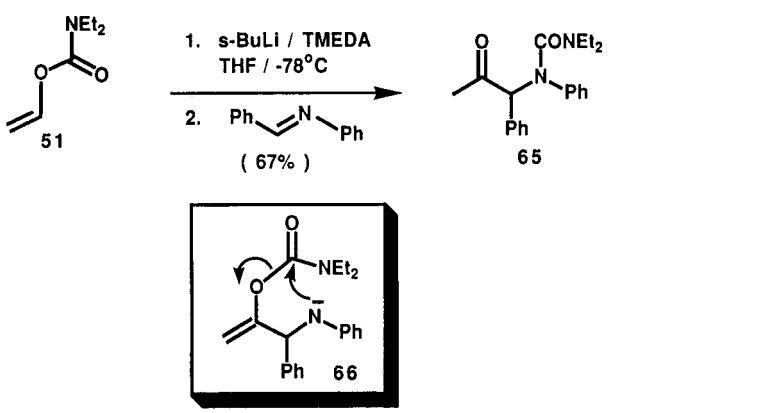
Scheme 19

Preparation of α-Carbamoyloxy Methyl Ketones



Scheme 20

α-Lithio Enol Carbamates: Reaction with Imines



SUMMARY

Work summarized above indicates the expanding horizons of Directed *ortho* Metalation (DoM) chemistry in three selected areas: a) the discovery of OSEM, a new oxygen-based directed metalation group, of value in substituted benzene, naphthalene (**Schemes 3, 4**) and pyridine (**Scheme 4**) synthesis; b) the development of a tandem one-pot DoM - metal halogen exchange route to anthraquinones (**Scheme 6, 7**) including the antitumor ellipticine alkaloids (**Scheme 8**); and c) the exploitation of the DoM - transition metal catalyzed cross coupling link in a new remote metalation of *m*-terphenyls and biaryls leading to condensed, aza (**Schemes 10, 11**), and simple (**Scheme 12**) fluorenones including a natural product (**Scheme 13**). The work on α-metalated enol carbamates, which conceptually arose from DoM work, is opening new territories in acyl anion equivalent chemistry (**Schemes 15-20**). In sum, these contributions further attest to the spring-board effect which aromatic and aliphatic carbanion chemistry has on the discovery of new synthetic methods.

Acknowledgements

P. Cox, J.-m. Fu, S. Sengupta, M.J. Sharp, W. Wang, X. Wang, and B. Zhao are thanked for their spirited and dedicated efforts. NSERC Canada, Merck Frosst, and MOE are gratefully acknowledged for support of our synthetic programs.

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