CARBANIONIC ROUTES TO SUBSTITUTED TOLYL SULFONAMIDES, ACRIDONES, AND 5*H*-DIBENZO[b,f]AZEPIN-10-ONES

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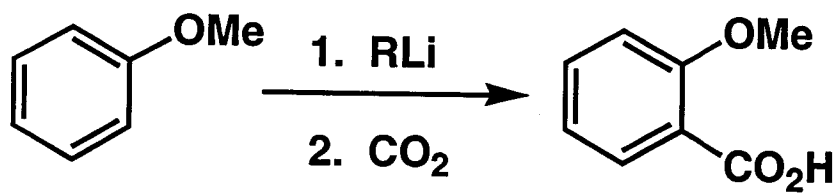
February 12, 2002

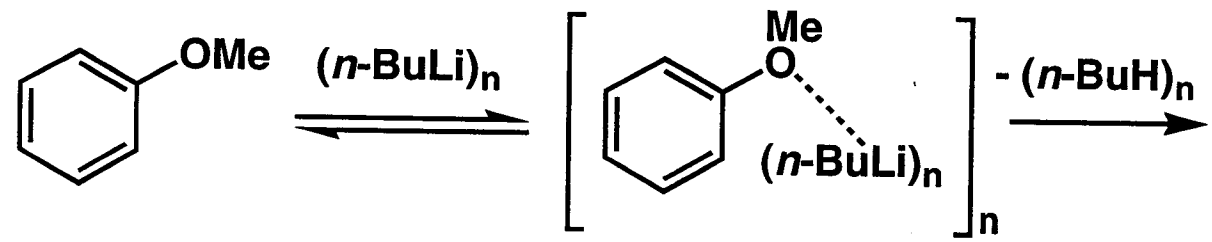
The Directed *ortho* Metalation (D*o*M) Reaction

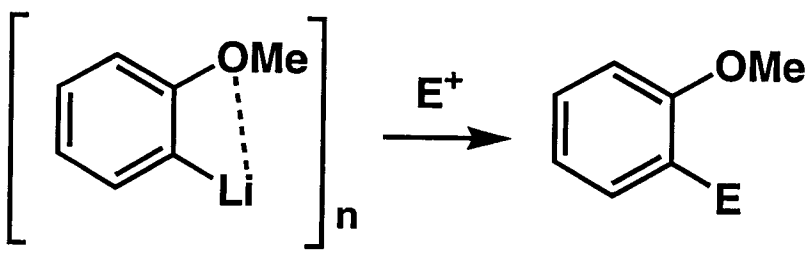
Discovery



Gilman, H.; Bebb, R.L. ~~J. Org. Chem.~~ JACS 1939, *61*, 109-112
Wittig, G.; Fuhrnam, G. *Chem. Ber.* 1940, *73*, 1197-1218

Early Mechanistic Rationale

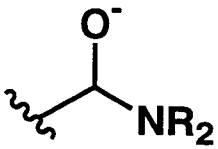
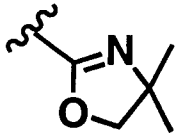
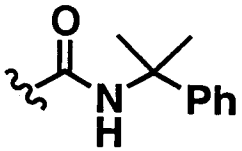




DMG = Directed Metalation Group

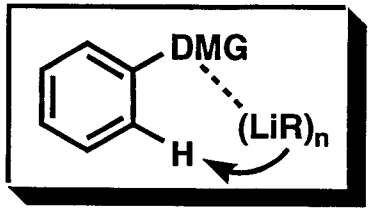
Roberts, J.D.; Curtin, D.Y. *J. Am. Chem. Soc.* 1946, *68*, 1658-1660

Development of DoM. Directed Metalation Groups

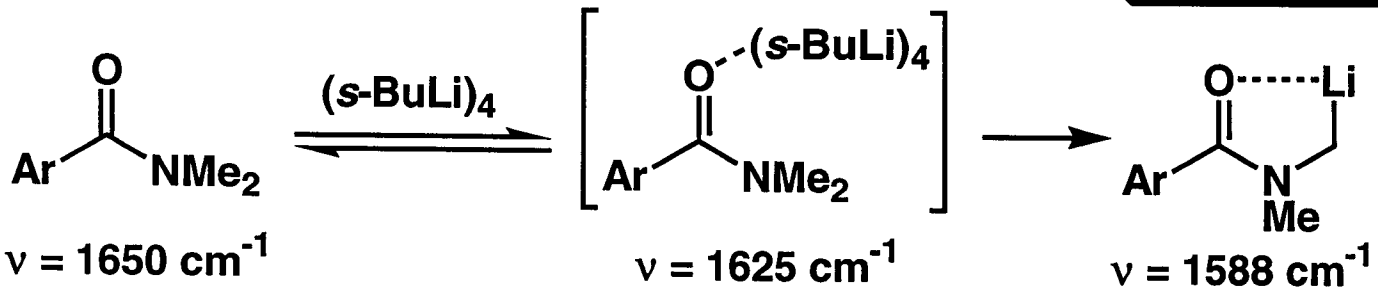
C-based DMG		Hetatom-based DMG	
$CON^{-}R$	Hauser, 1964	*N-t*-BOC	Gschwend, 1979
	Gronowitz, 1968 Gschwend, 1976 Comins, 1983	*N*-CO*t*-Bu	Muchowski, 1980
		OCH_2OMe	Christensen, 1975
		$OCONEt_2$	Snieckus, 1983
	Meyers, Gschwend, 1975	$OCON(Me)C(Me)_2Ph$	Snieckus, 1999
$CONEt_2$	Beak, 1977	$SO_2N^{-}R$ SO_2NR_2	Hauser, 1969
$CON(Me)CH(TMS)_2$	Snieckus 1989	$SO_2NHC(Me)_2Ph$	Snieckus, 1999
		$OCH_2OCH_2CH_2TMS$	Snieckus, 1991
	Snieckus, 1999	$P(O)(t\text{-}Bu)_2$	Snieckus, 1998

Gilman, H.; Morton, Jr., J.W. *Org. React.* (N.Y.) 1954, *8*, 258-304
Gschwend, H.W.; Rodriguez, H.R. *Org. React.* (N.Y.) 1979, *26*, 1-360
Snieckus, V. *Heterocycles* 1980, *14*, 1649-1676
Beak, P.; Snieckus, V. *Acc. Chem. Res.* 1982, *15*, 306-312
Beak, P.; Meyers, A.I. *Acc. Chem. Res.* 1986, *19*, 356-363
Snieckus, V. *Chem. Rev.* 1990, *90*, 879-933
Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* 1999, *71*, 1521-1529
Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* 1999, *36*, 1453-1468

Mechanism of Directed Metalation. The Complex-Induced Proximity Effect (CIPE)

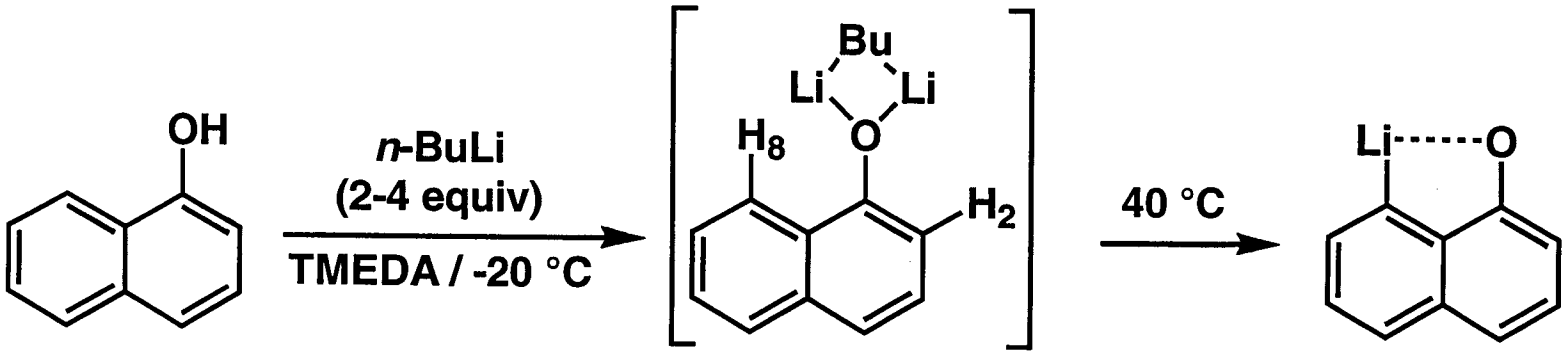


Evidence from Stopped-flow IR:



Beak 83 *JACS* 2080, 88 *JACS* 8145

Direct NMR Evidence:

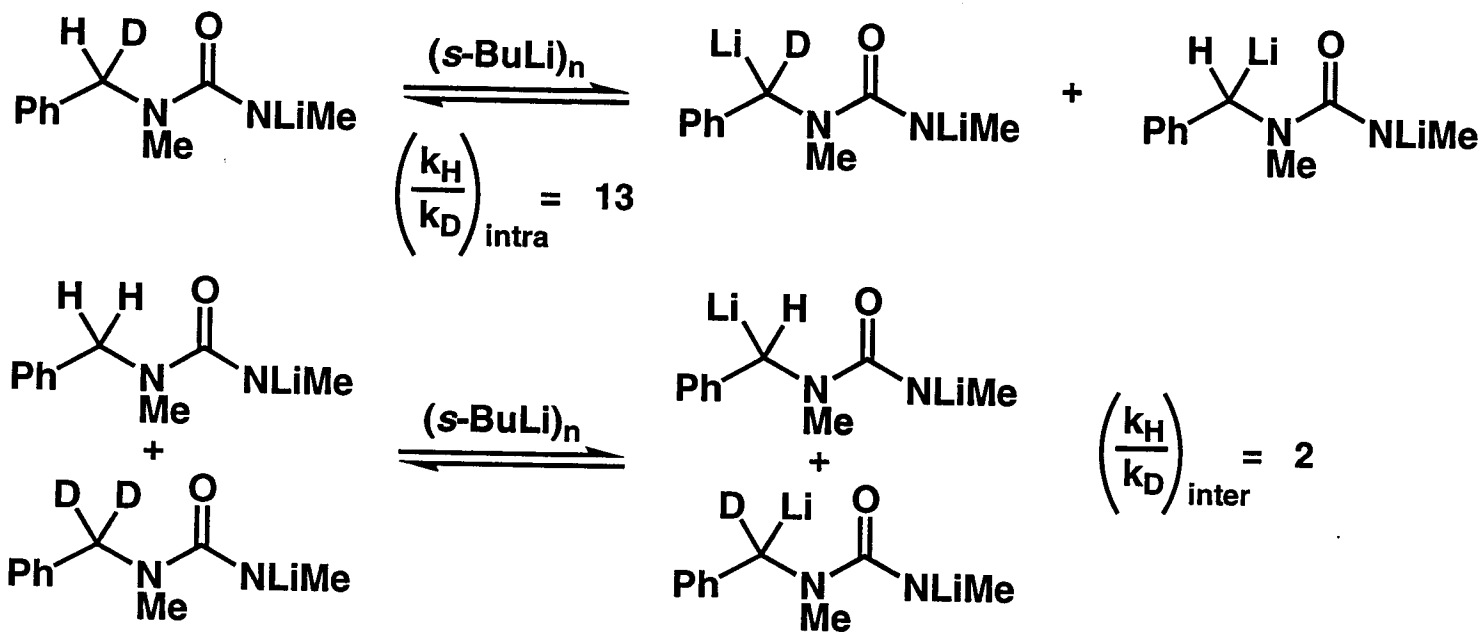


^{7}Li-^{1}H HOESY NMR - strong contacts with H_8

Saá 96 *JOC* 5194

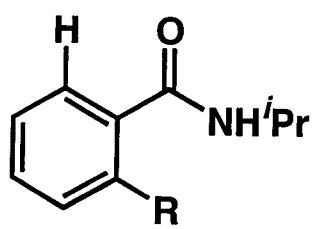
Mechanism of Directed Metalation. The Complex-Induced Proximity Effect (CIPE)

Support from Kinetic Isotope Effects:



Beak 94 *JACS* 405, 99 *JACS* 7553

Effect of Directing Group Orientation on Competitive Efficiencies (CE) of Metalation:

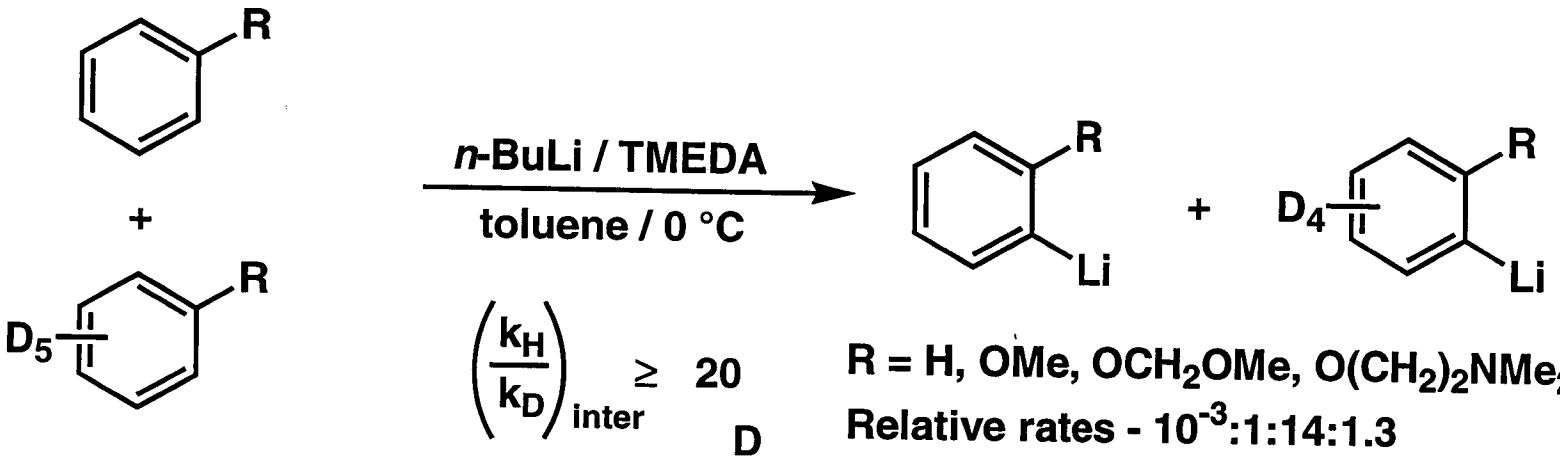


R	dihedral angle (deg)	CE
H	19	100
^{i}Pr	89	17
^{t}Bu	91	9
TMS	118	1

Beak 95 *JACS* 10628, 01 *JACS* 315

Mechanism of Directed Metalation. Inductive Effects

Support from KIEs, rate studies and *ab initio* calculations:



$\left(\frac{k_H}{k_D}\right)_{inter} \geq 20$

R = H, OMe, OCH_2OMe, $O(CH_2)_2NMe_2$

Relative rates - 10^{-3}:1:14:1.3

- substituent-dependent rates but substituent-independent mechanisms, i.e., all transition states have stoichiometry [(*n*-BuLi)$_2$(TMEDA)$_2$(Ar-H)] suggest relative insignificance of CIPE

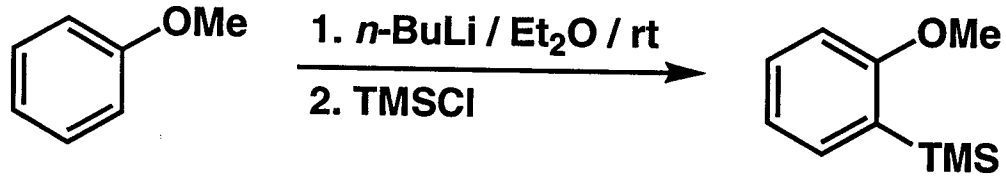
- supported by by *ab initio* calculations showing minor or non-existent Li-alkoxy interactions in rate-limiting transition structures

Collum 98 *JACS* 421, 00 *JACS* 8640

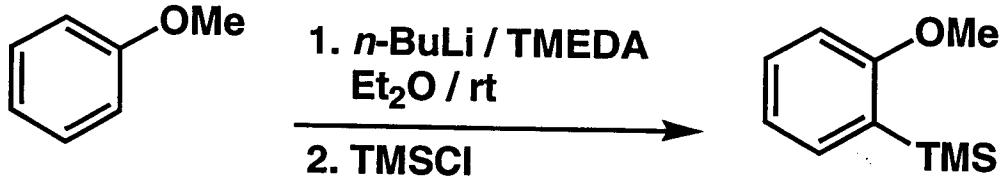
Mechanism of Directed Metalation. Inductive Effects

Effects of TMEDA:

Rate Acceleration:



~50% conversion in 24 h

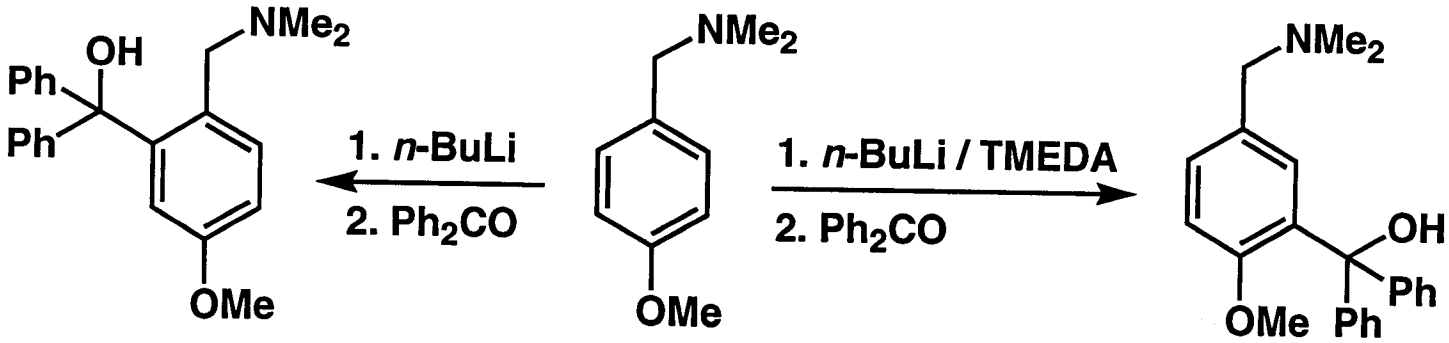


>95% conversion in 30 min

- coordination of methoxy group is slow as a result of ground state resonance; addition of TMEDA gives metalation without coordination

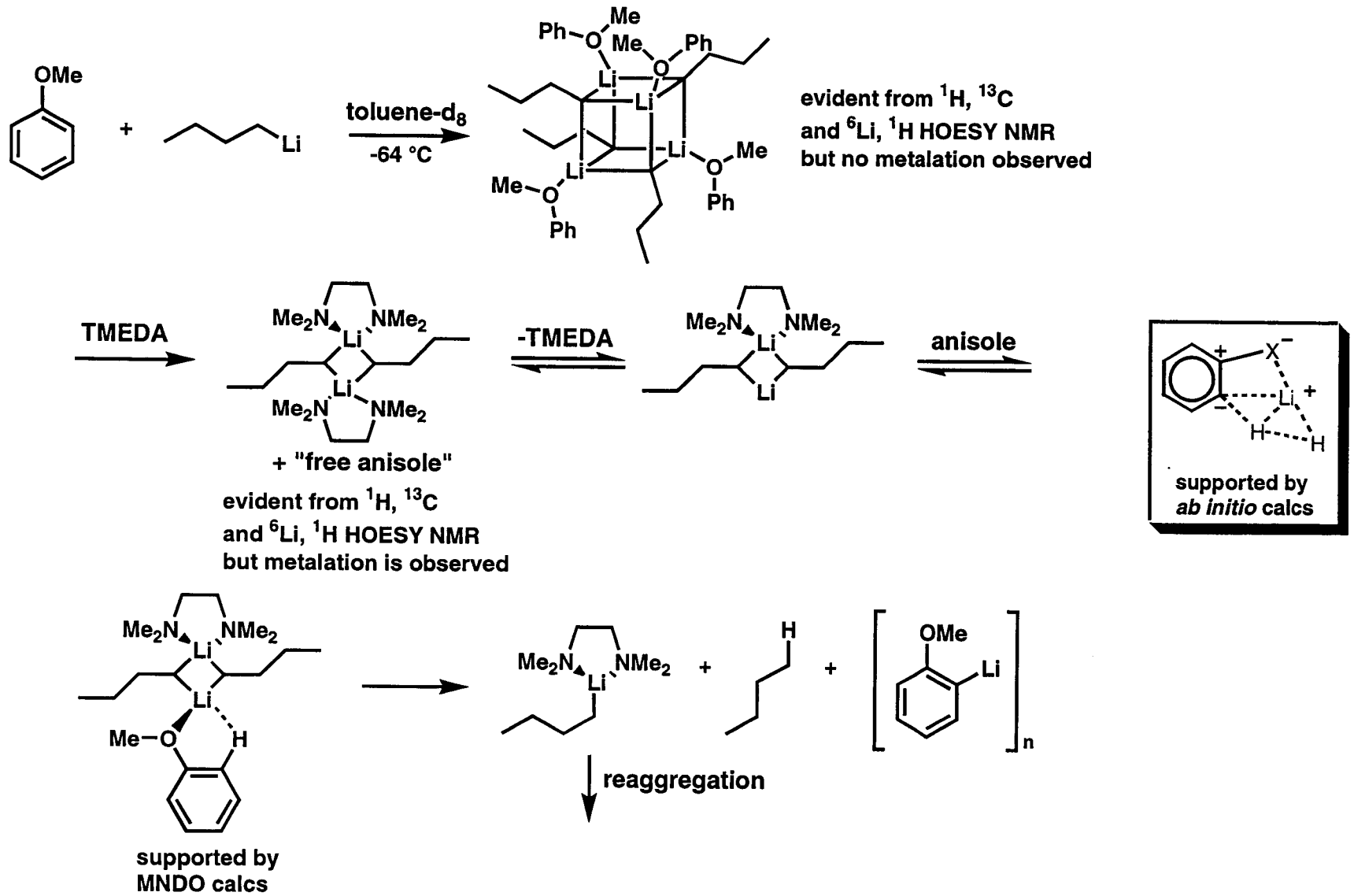
Slocum 94 *TL* 385

Regioselectivity of Metalation:



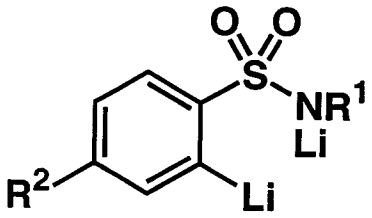
Slocum 70 *TL* 3443, 76 *JOC* 3653

Mechanism of Directed Metalation. Kinetically Enhanced Metalation



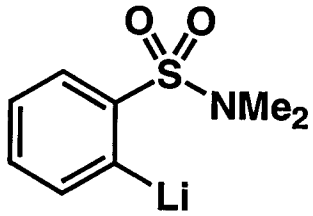
Schleyer 89 *JACS* 7191, 92 *AG(E)* 755, 94 *T* 5903, 96 *OM* 3345

Renaissance of Sulfonamide Metalation Chemistry

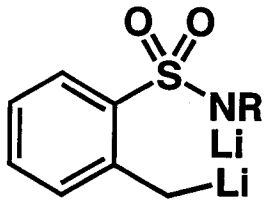


R^1 = Me, Ph; R^2 = H
R^1 = Ph; R^2 = Me

Hauser — DoM — 68 *JOC* 900

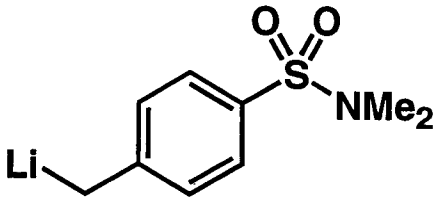


DoM — 69 *CJC* 1543

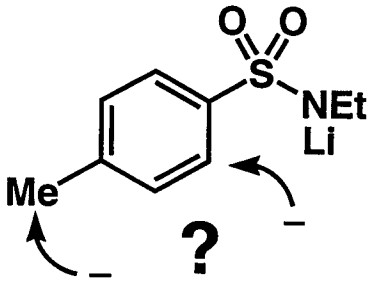


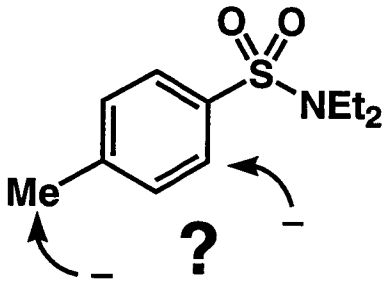
R = Me, Ph

LatMet — 68 *JOC* 4278

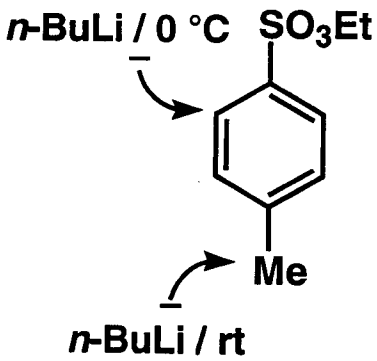


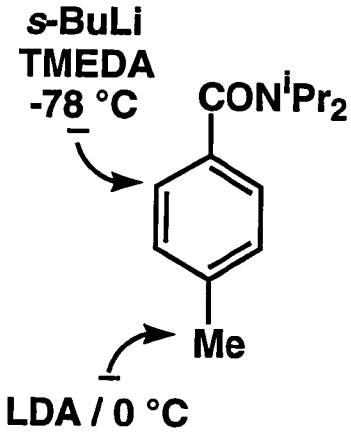
BenzMet — 67 *JOC* 3379





Queguiner
90 *JCS(P1)* ~~164~~
1611

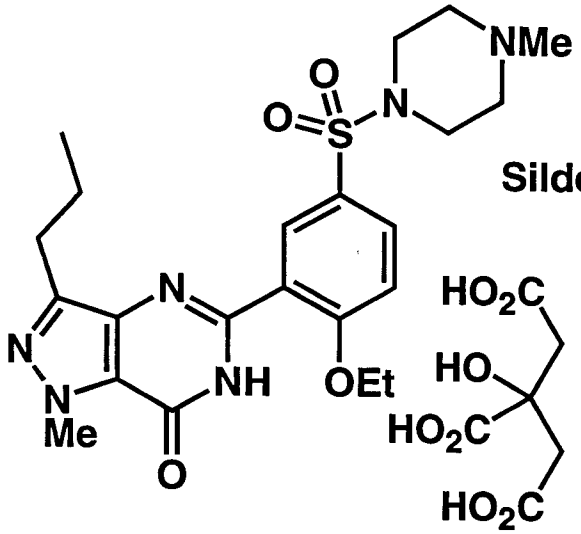




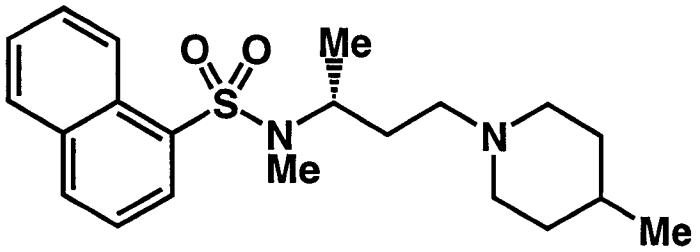
Beak
82 *JOC* 34

Snag 1c

Aromatic Sulfonamides as Drug Entities

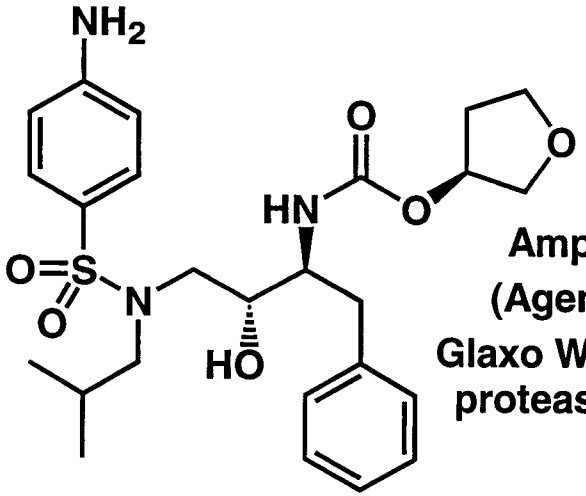


Sildenafil Citrate
(Viagra®)
Pfizer



SmithKline Beecham
antidepressant
(5-HT7 antagonist)

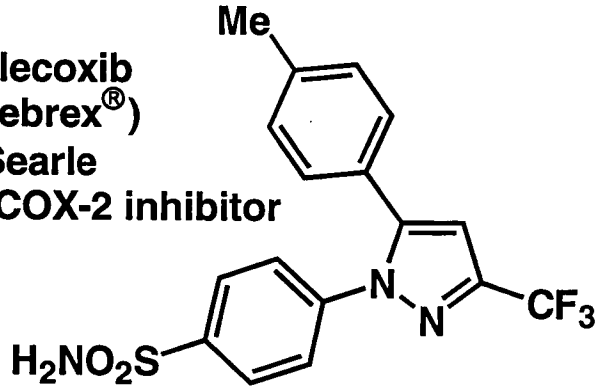
Ann. Rept. Med. Chem. 1999, *34*, p.7, 38, 46-47, 72, 74, 77-78, 84-85, 92-95, 114, 116, 133, 145, 185, 277-278, 318, 331



Amprenavir
(Agenerase®)
Glaxo Wellcome, UK
protease inhibitor

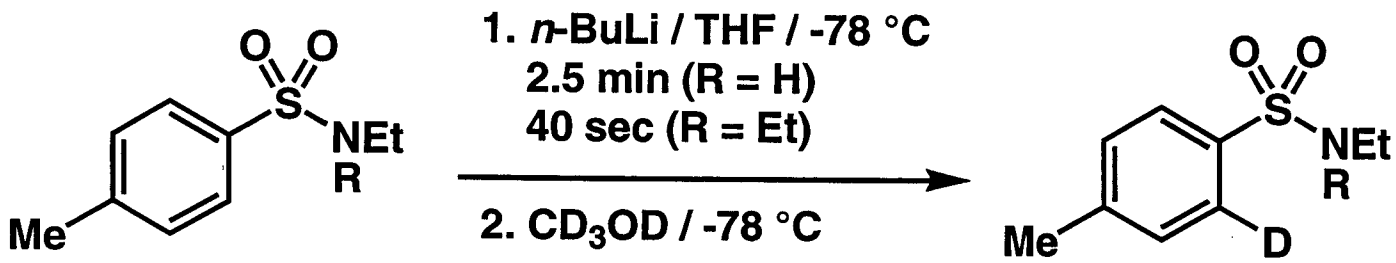
Exp. Opin. Invest. Drugs 2000, *9(2)*, 371

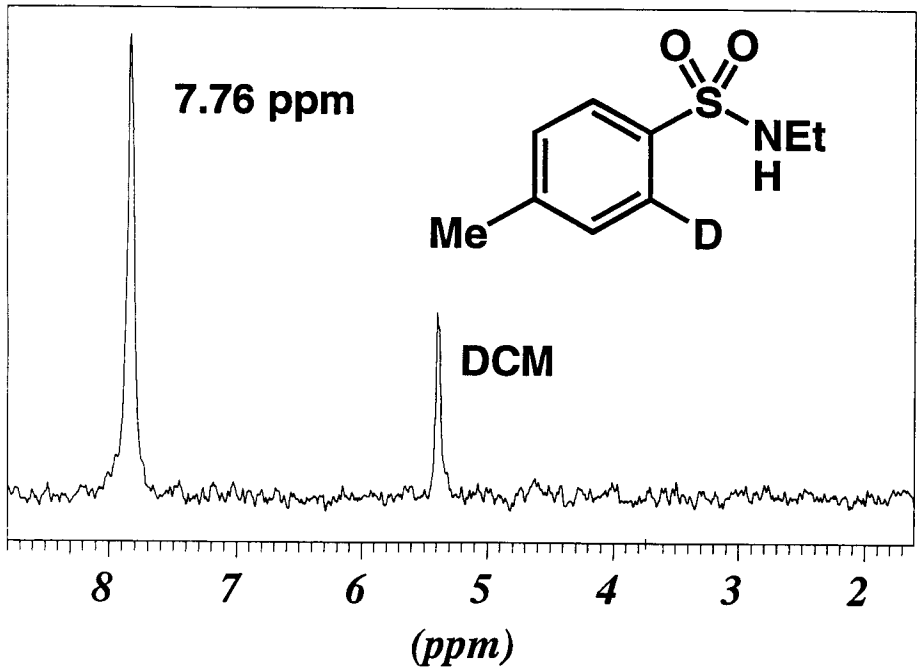
Celecoxib
(Celebrex®)
Searle
selective COX-2 inhibitor

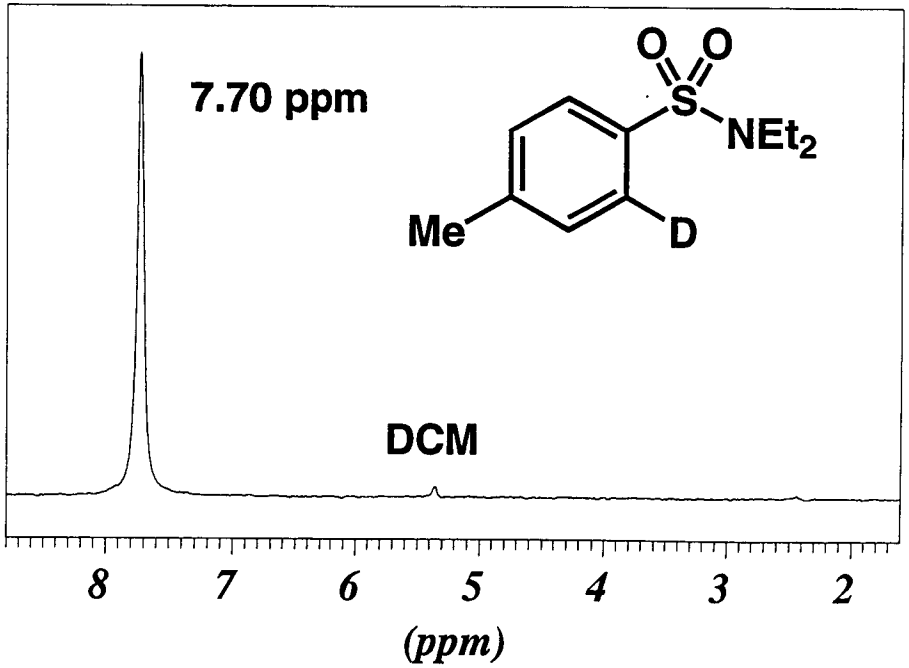


97 *JMC* 1347

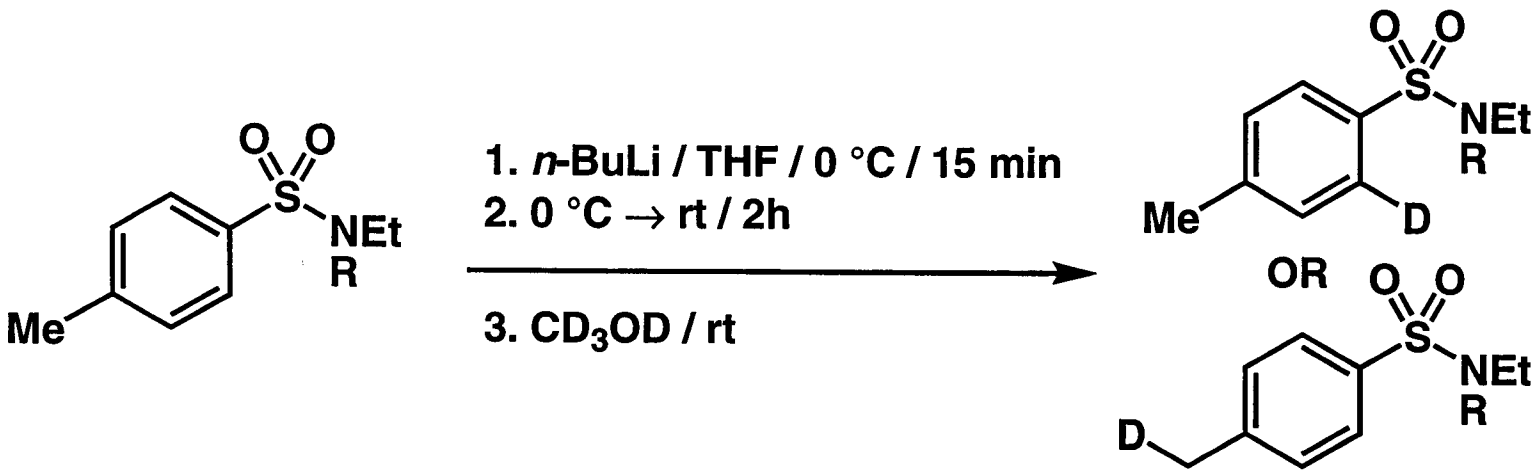
Deuterium Quench / ^{2}H NMR. Kinetic Conditions

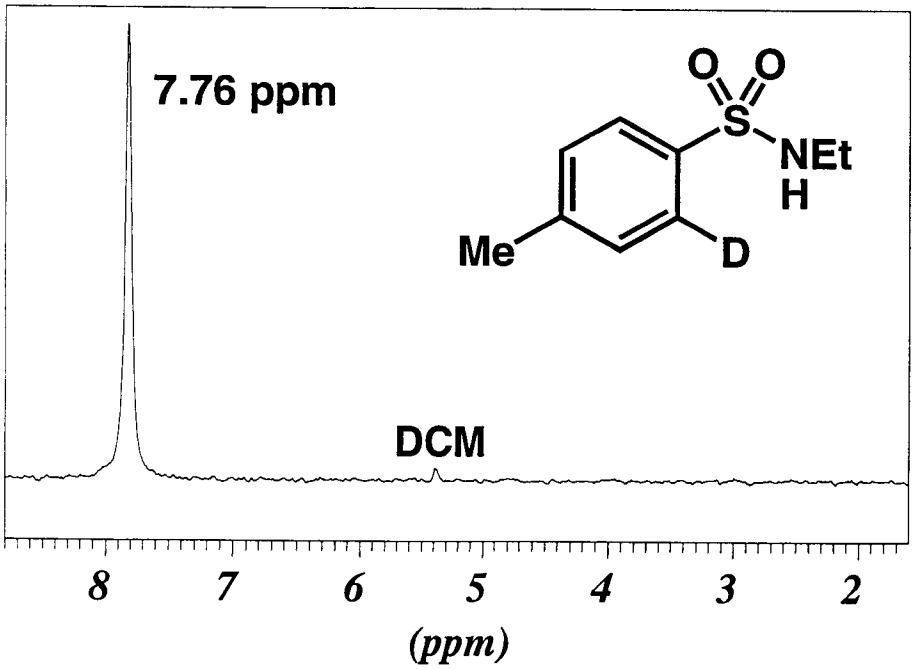


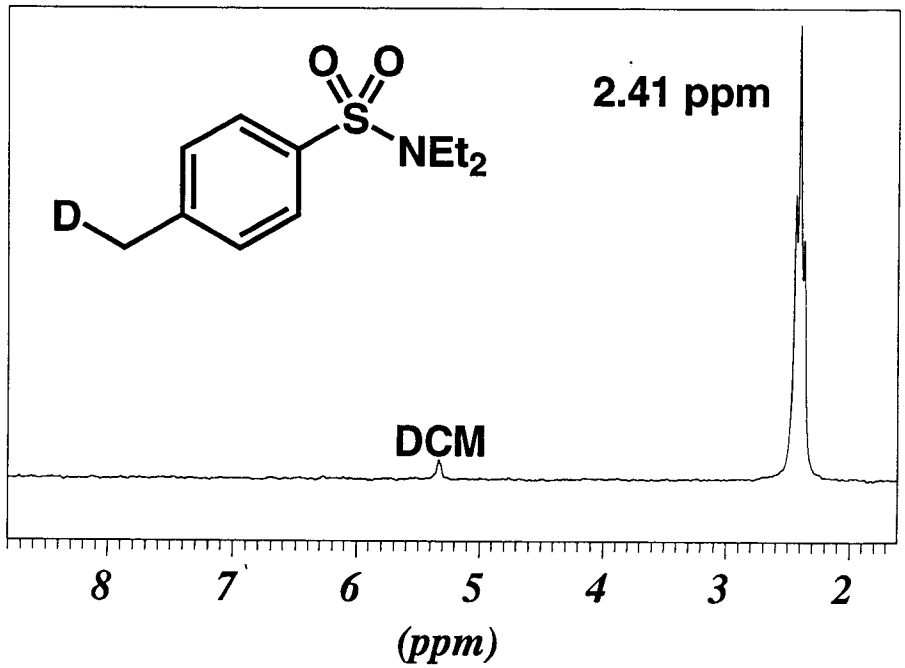




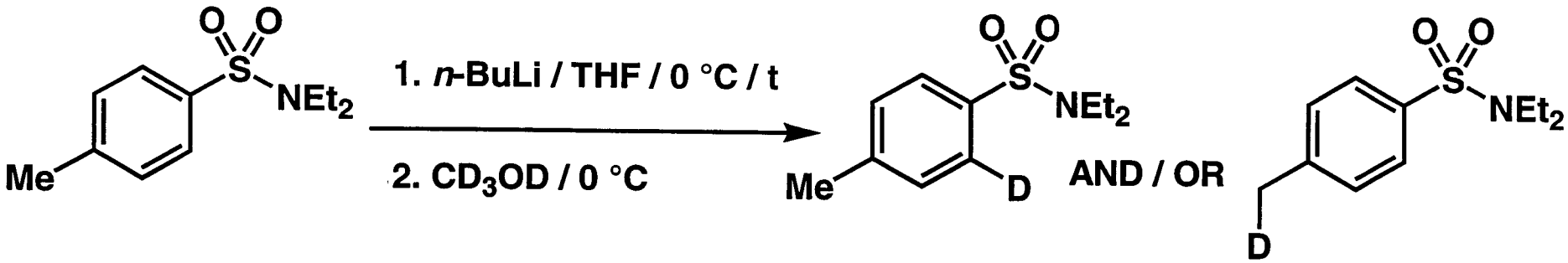
Deuterium Quench / ^{2}H NMR. Thermodynamic Conditions

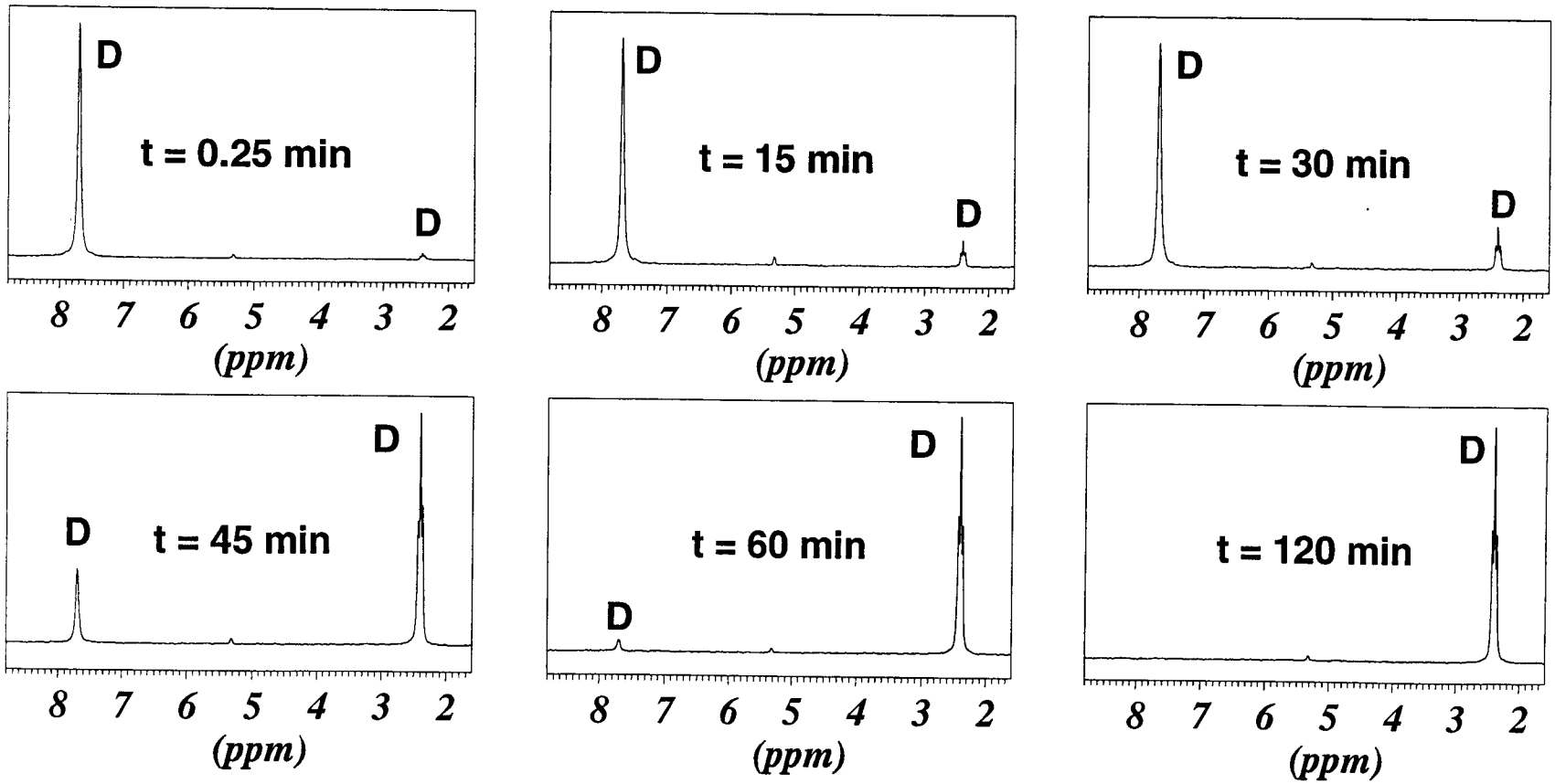




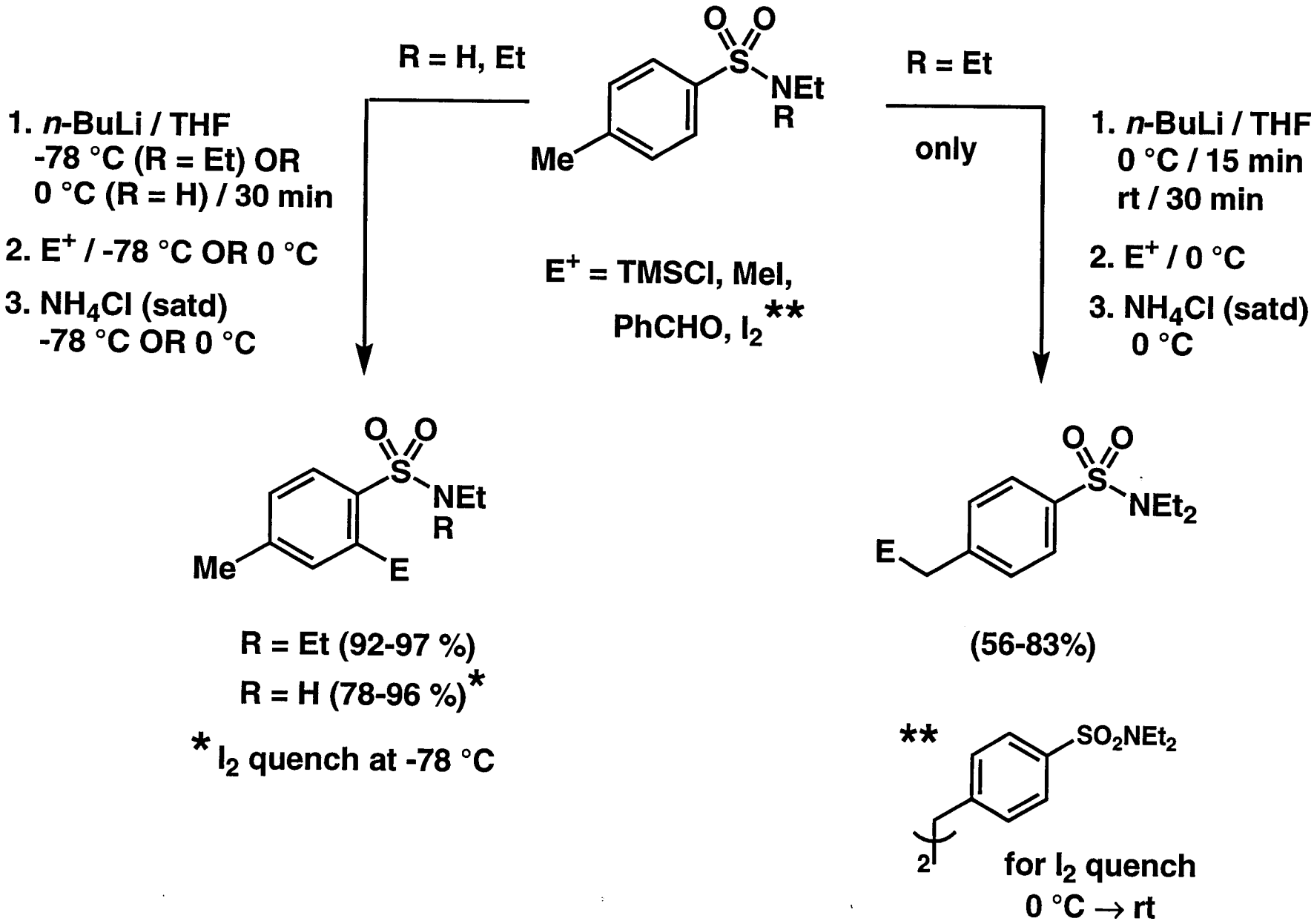


Deuterium Quench / ^{2}H NMR. Anion Equilibration in Tertiary *p*-Tolylsulfonamide

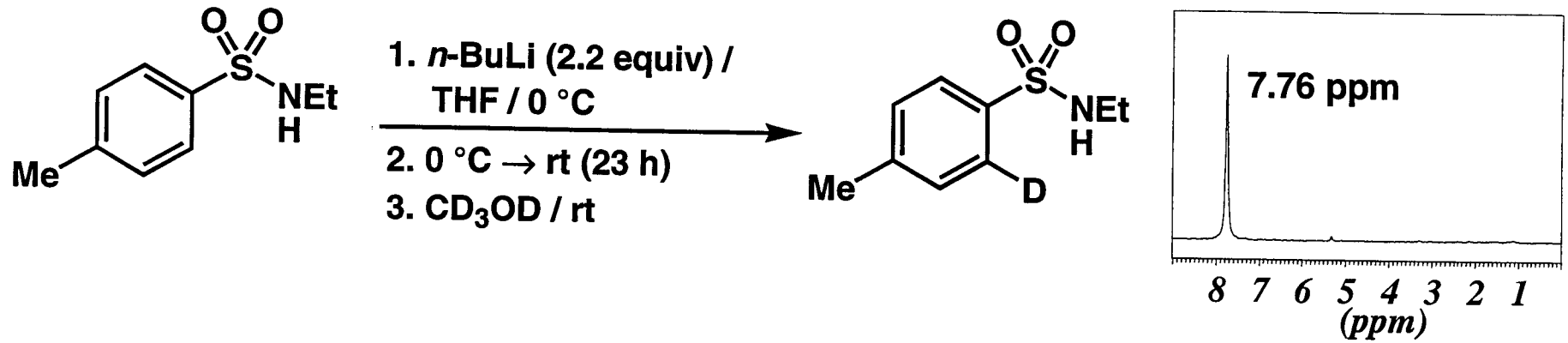


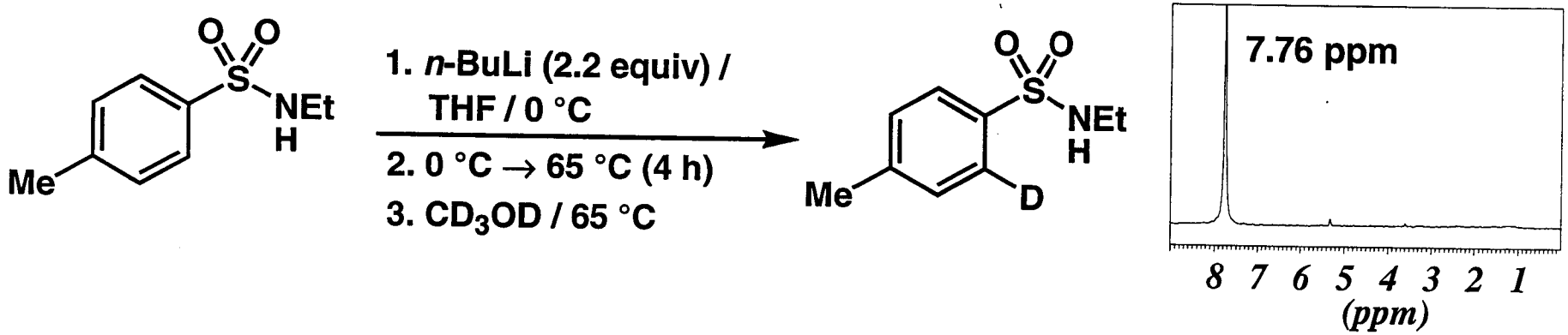


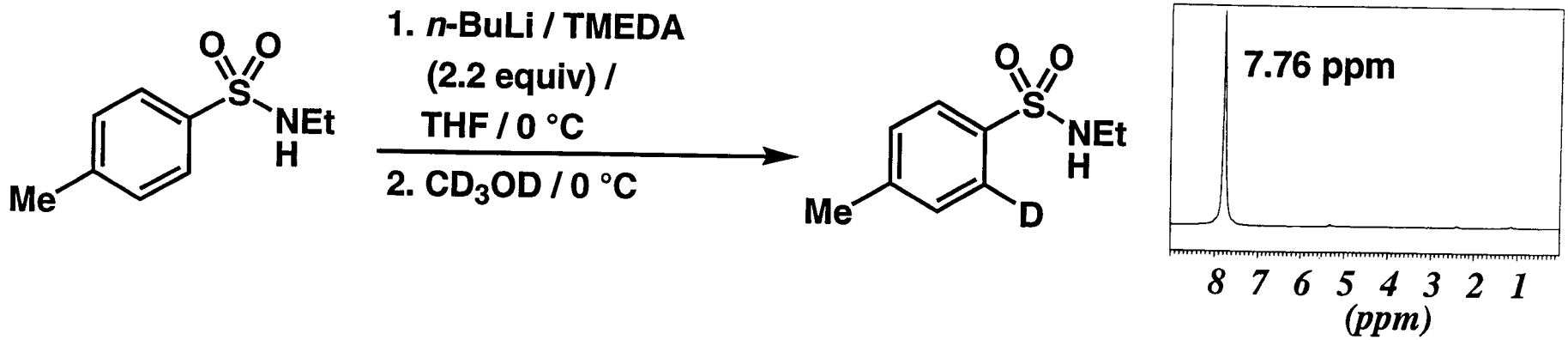
Selective *ortho vs* Benzylic Metalation. Synthetic Results



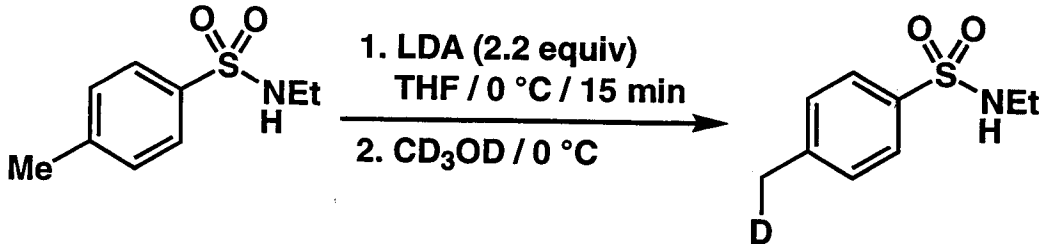
Attempted Benzylic Metalation of Secondary *p*-Tolylsulfonamide. Effect of Metalation Time, Temperature and TMEDA Additive

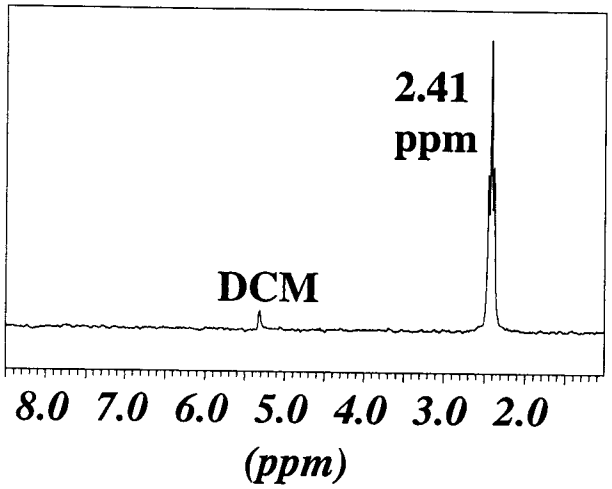


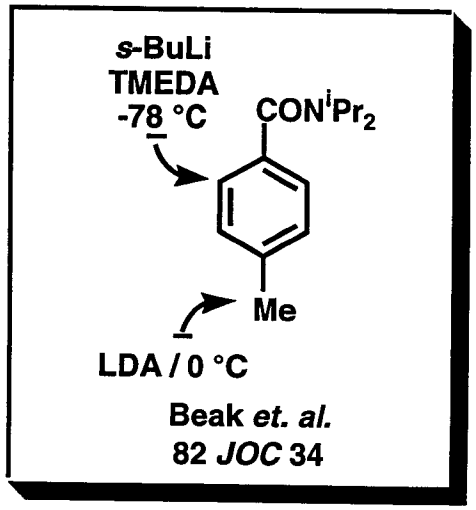


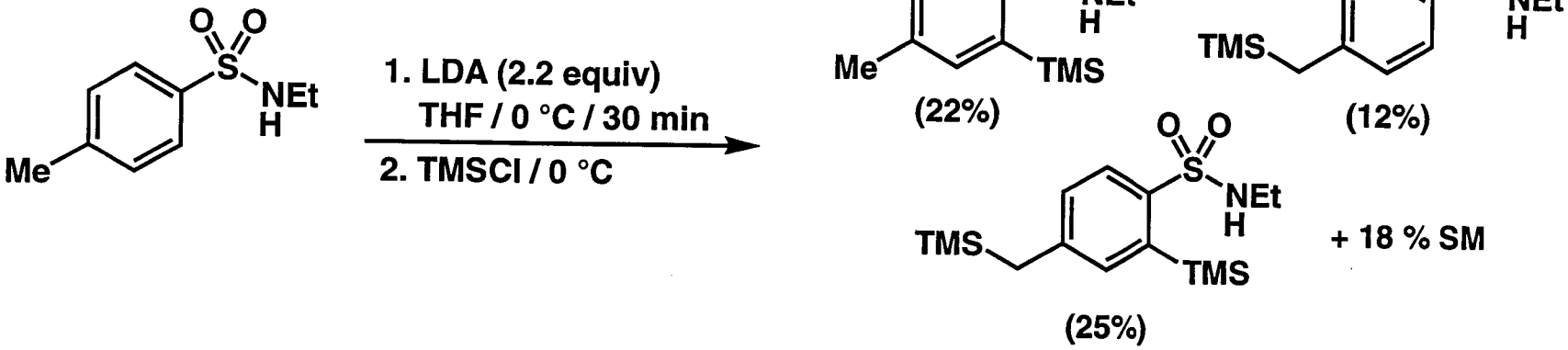


Benzylic Metalation of Secondary *p*-Tolylsulfonamide. Effect of Amide Base

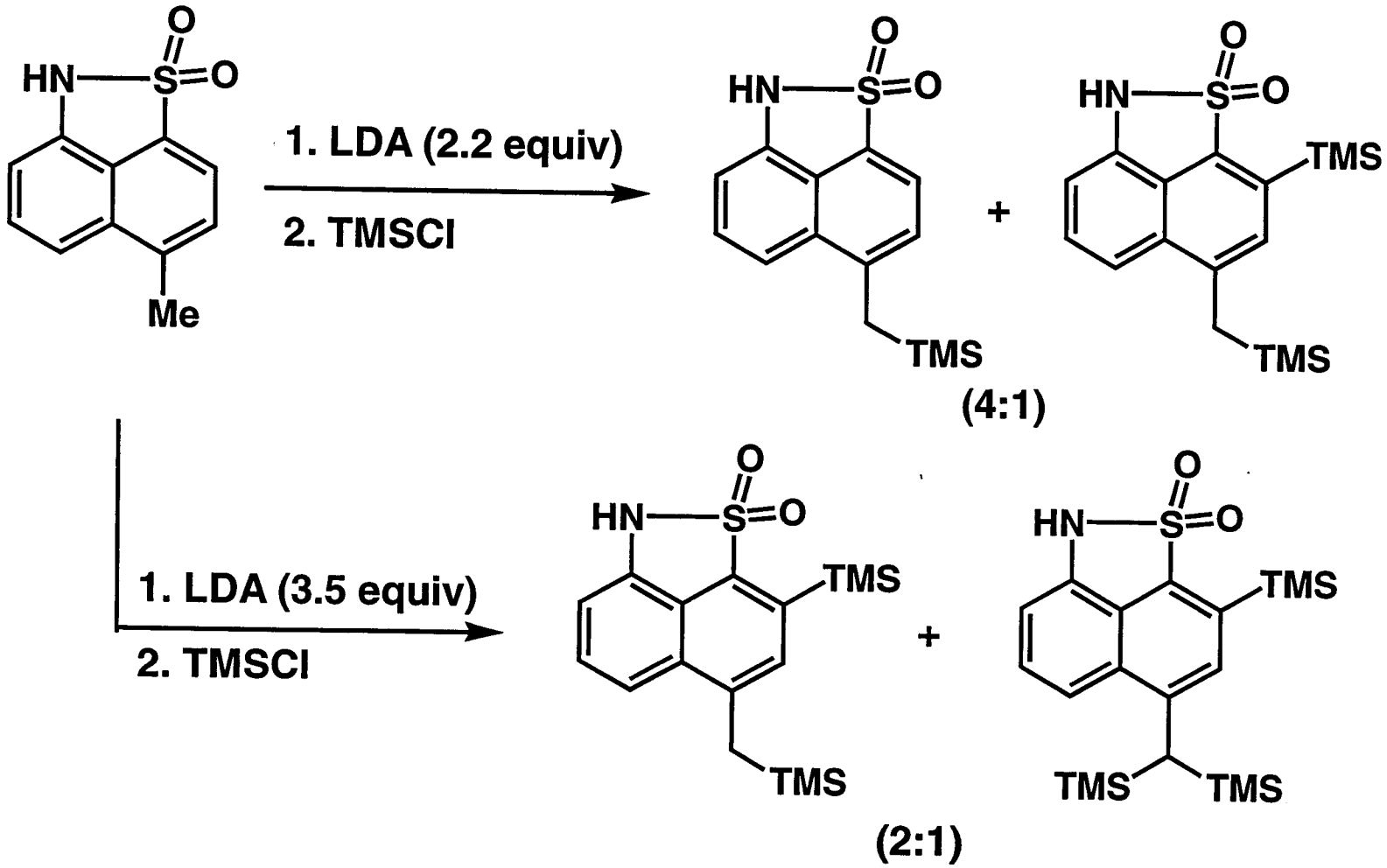






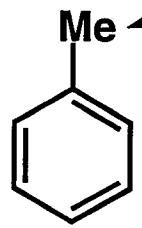


Benzylic Metalation of Secondary *p*-Tolylsulfonamide. Relevant Literature Precedent



Reider *et al* 00 *JOC* 1399

Benzylic Metalation of Secondary *p*-Tolylsulfonamide. Success using "Superbase"



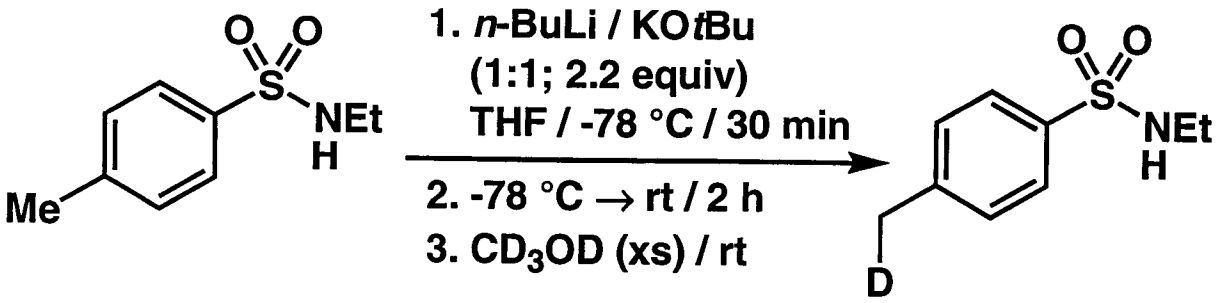
n-BuLi / KO*t*Bu /
-75 °C

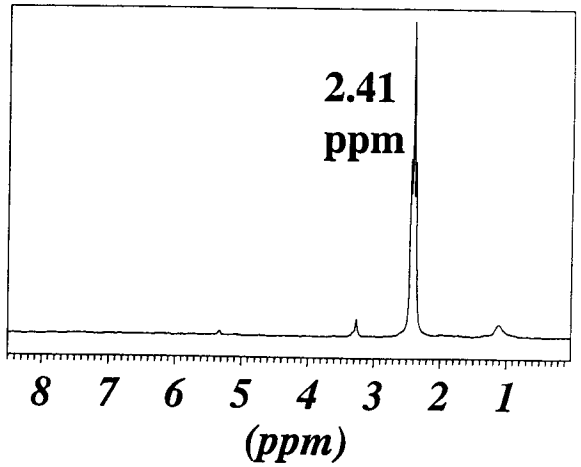
Lochmann 66 *TL* 257 Schlosser 67 *JOM* 9

Reviews: Mordini, A. *Advances in Carbanionic Chemistry*, Snieckus, V.(Ed.), Jai Press, Greenwich, CT, 1992, *Vol.1*, pp 1-44.

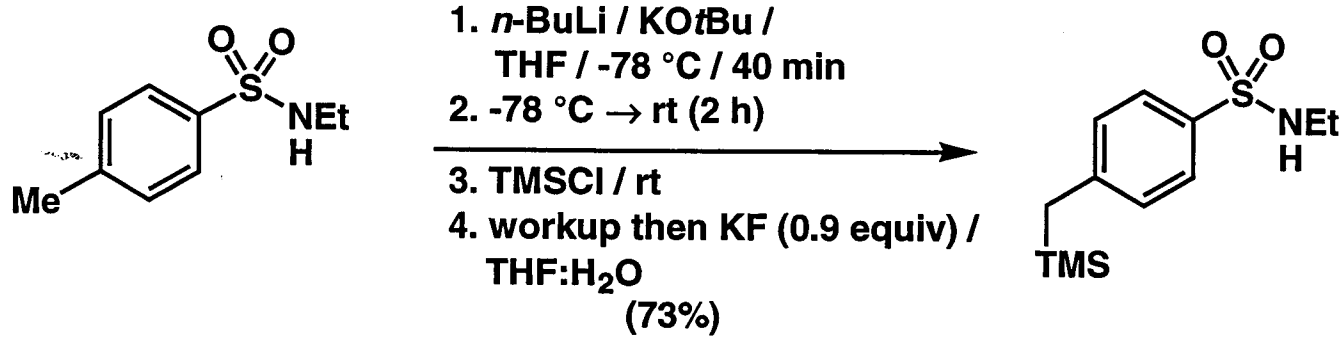
Schlosser *et al Chimia* 1996, 50, 650-652

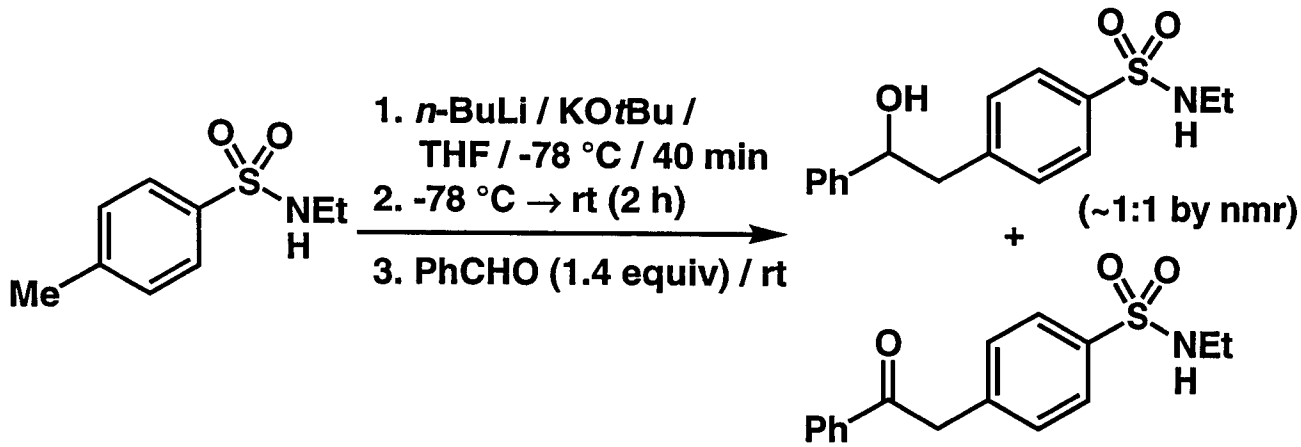
Lochmann *et al Eur. J. Inorg. Chem.* 2000, 1115-1126

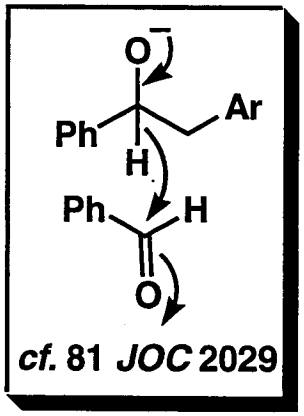


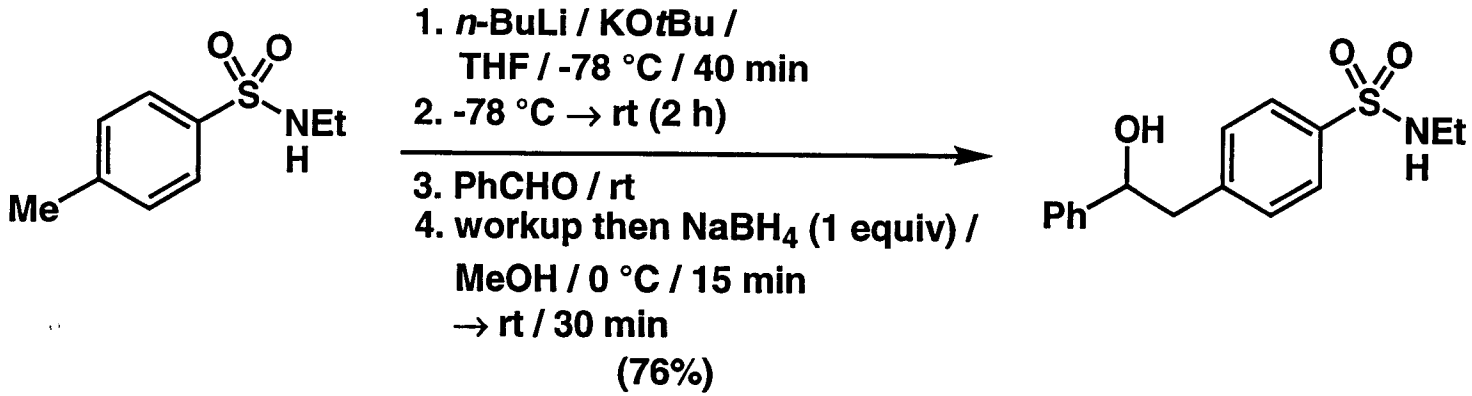


Benzylic Metalation of Secondary *p*-Tolylsulfonamide. Success Using "Superbase". TMSCl and PhCHO Quench



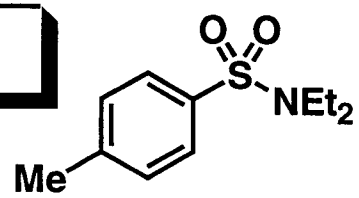




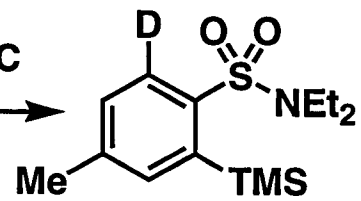


Further Chemistry of *p*-Tolylsulfonamides

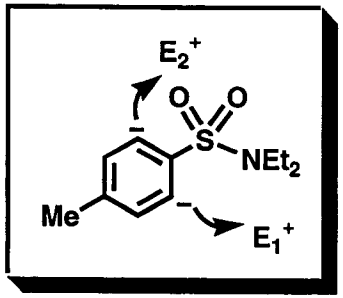
Sequential D*o*M

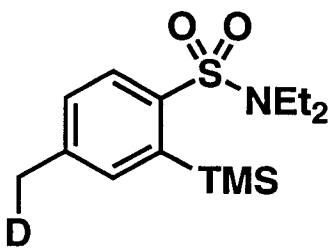


1. *n*-BuLi / THF -78°C / 1h
2. TMSCl / -78°C
3. *n*-BuLi / THF 0°C / 30 min
4. D_2O / 0°C



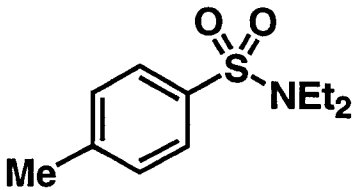
(90%)





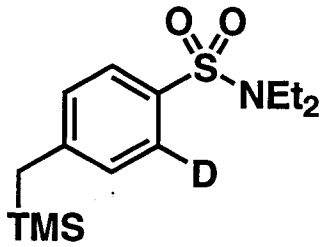
1. *n*-BuLi / THF -78 °C / 30 min
2. TMSCl / -78 °C
3. *n*-BuLi / THF 0 °C / 15 min then rt / 30 min
4. CD_3OD / 0 °C

(37%)

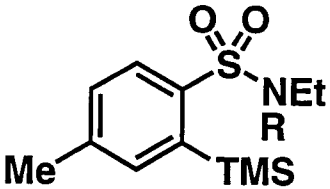


1. *n*-BuLi / THF 0 °C / 20 min then rt / 30 min
2. TMSCl / 0 °C
3. *n*-BuLi / THF -78 °C / 30 min
4. CD_3OD / -78 °C

(50%)

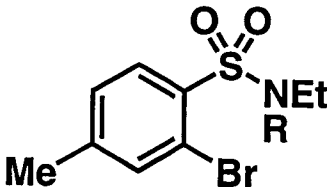


Br^+-induced *Ipso* deSi



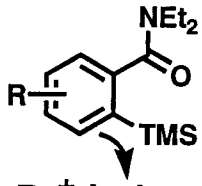
Br_2 / CH_2Cl_2

reflux



R = H (67%)

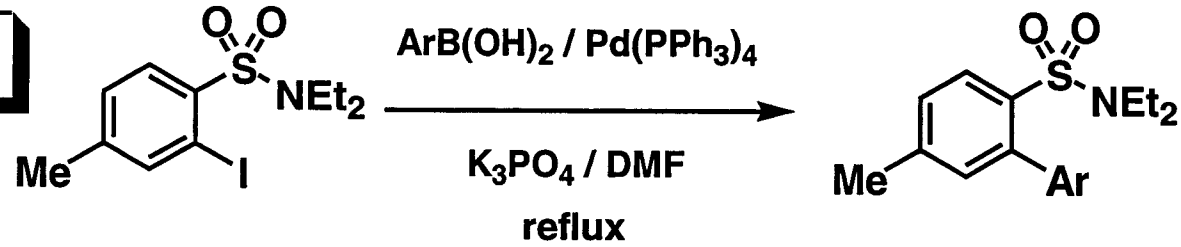
R = Et (79%)

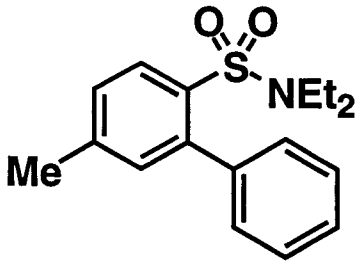


Br^+-induced *Ipso* deSi
84 *TL* 483

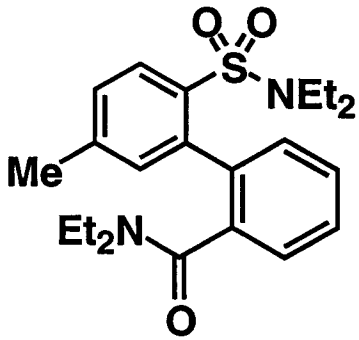
Further Chemistry of *p*-Tolylsulfonamides

Suzuki XCoupl

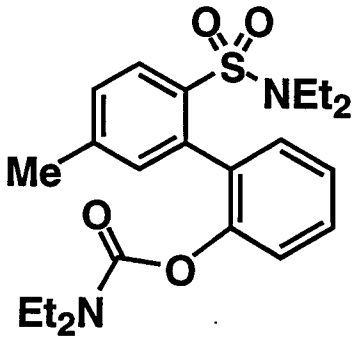




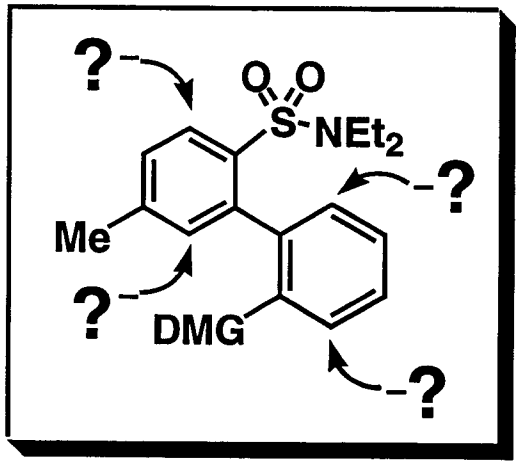
(95%)



(92%)



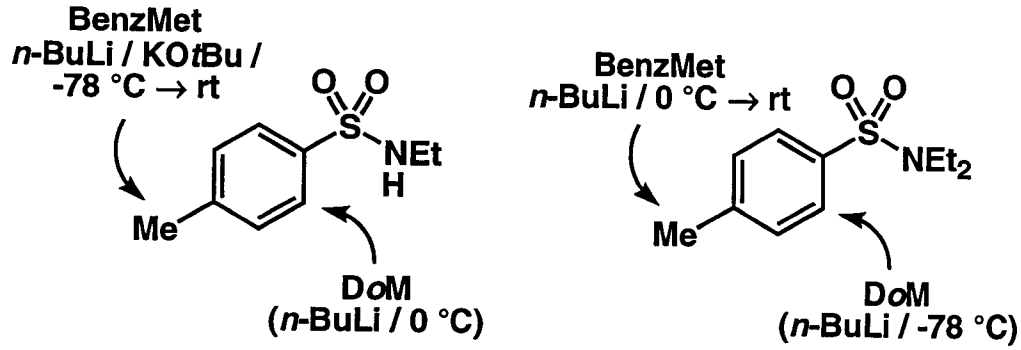
(87%)



MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* 2001, *66*, 3662

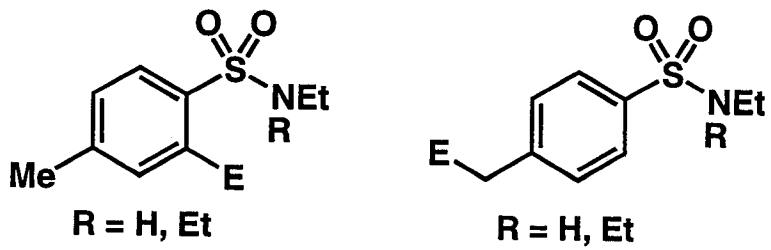
Summary

- Regioselective *ortho* and benzylic lithiation of *p*-tolyl-sulfonamides

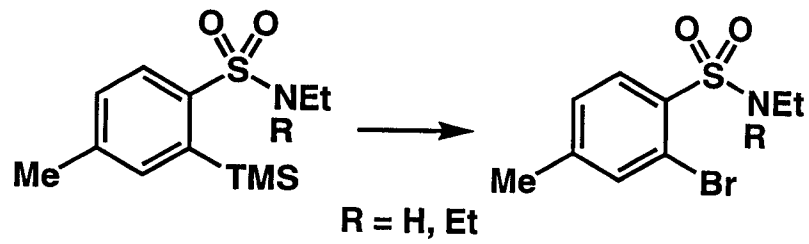


- Synthetic utility

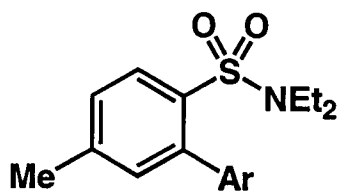
Electrophile incorporation



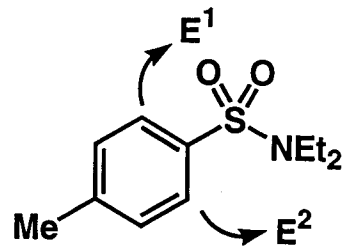
Br^+-induced *Ipso* desilylation



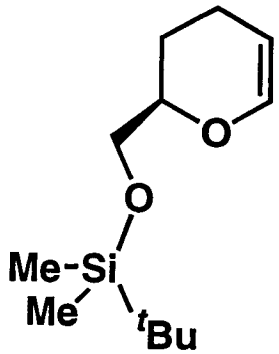
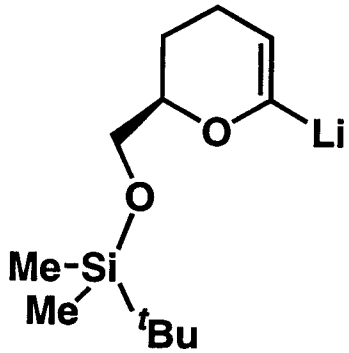
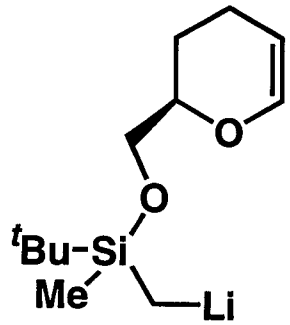
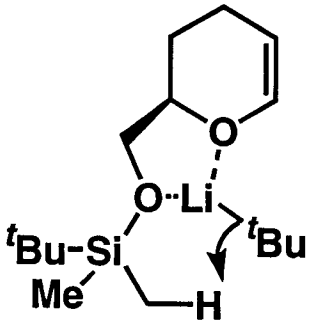
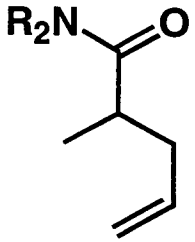
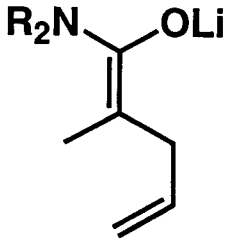
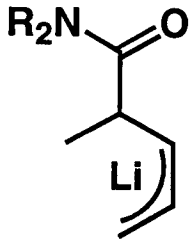
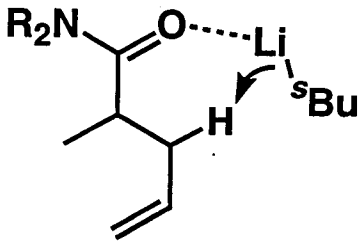
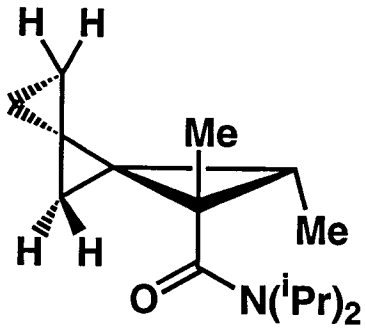
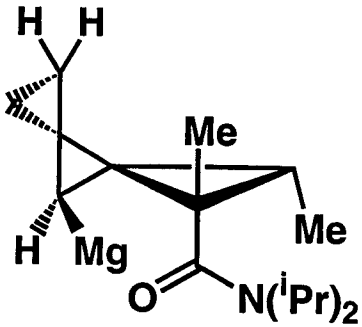
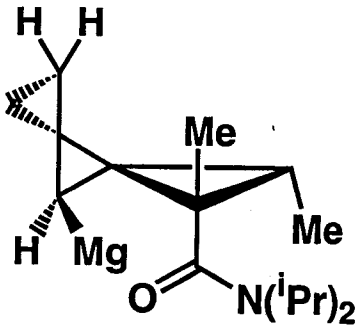
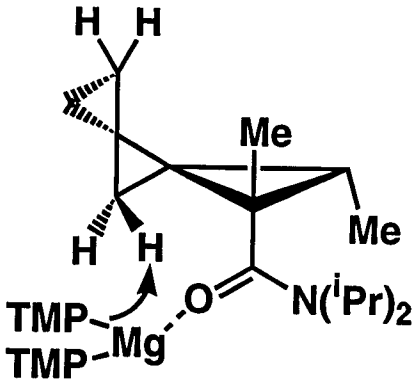
Suzuki Cross Coupling



Sequential DoM



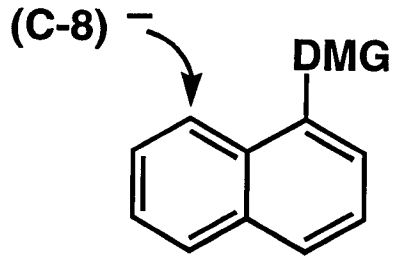
Directed Remote Metalation (DReM) in Aliphatic Systems

Substrate	Expected Anion	Anion Observed	CIPE Explanation
			
			
			

Quayle 92 *TL* 543 Beak 87 *JACS* 5403 Eaton 93 *JACS* 11370

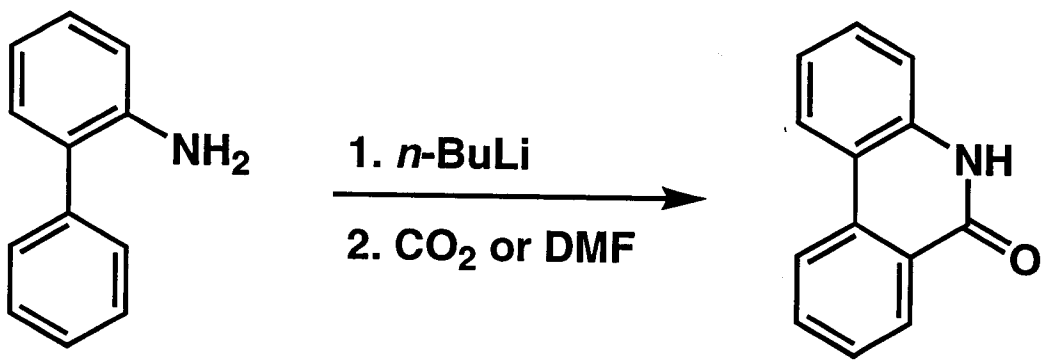
Review: Klumpp, G.W. *Recl. Trav. Chim. Pays-Bas* 1986, *105*, 1-21

DReM in Aromatic Systems. Early Examples



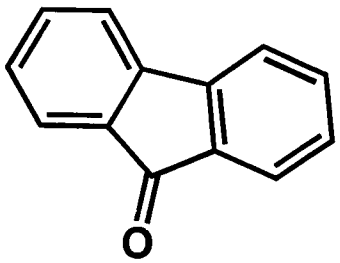
a: DMG = CH_2NMe_2
b: DMG = NHPh
c: DMG = NH_2
d: DMG = OMe

Hauser 67 *JACS* 2297; Narasimhan 69 *IJC* 538;
Eaborn 67 *JOM* 171; Shirley 69 *IJC* 251



Narasimhan 69 *IJC* 1280, 81 *T* 825

DReM in Aromatic Systems. Synthesis of Condensed Aromatics

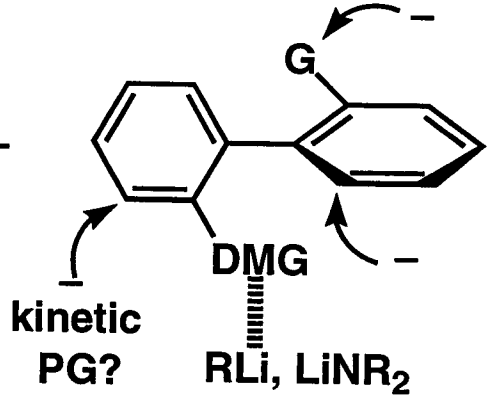


fluorenone

DMG = $CONR_2$

G = H

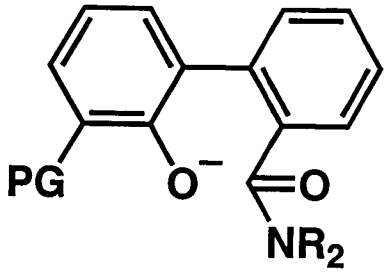
PG [X]



DMG = $OCONR_2$

G = H

PG [√]

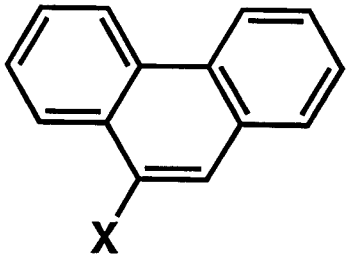


PG = OR, SiR_3

DMG = $CONR_2$, C≡N,

G = Me

PG [X]

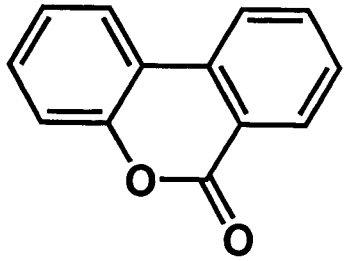


X = OH, NH_2

phenanthrol /

9-aminophenanthrene

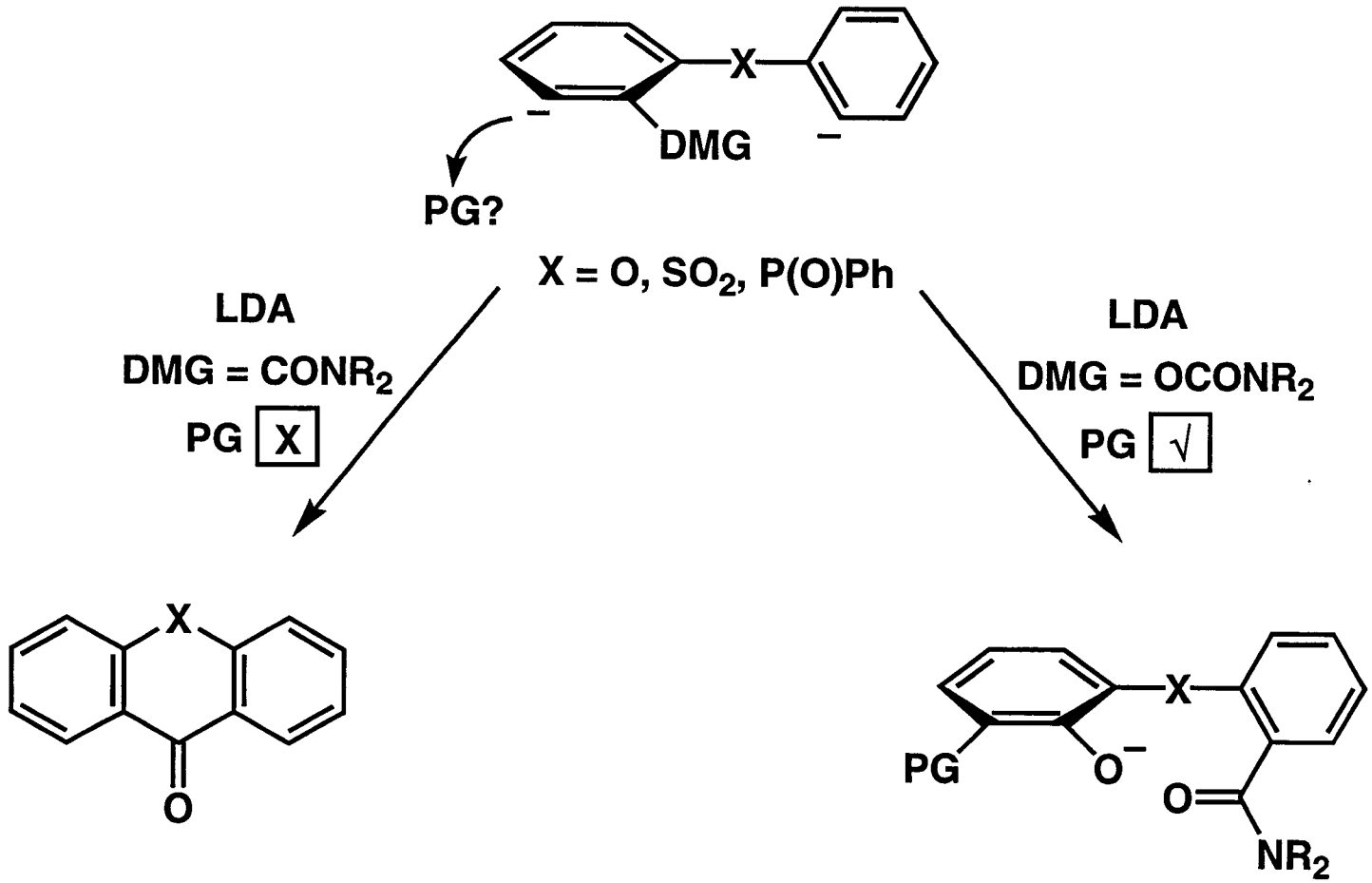
AcOH



dibenzopyranone

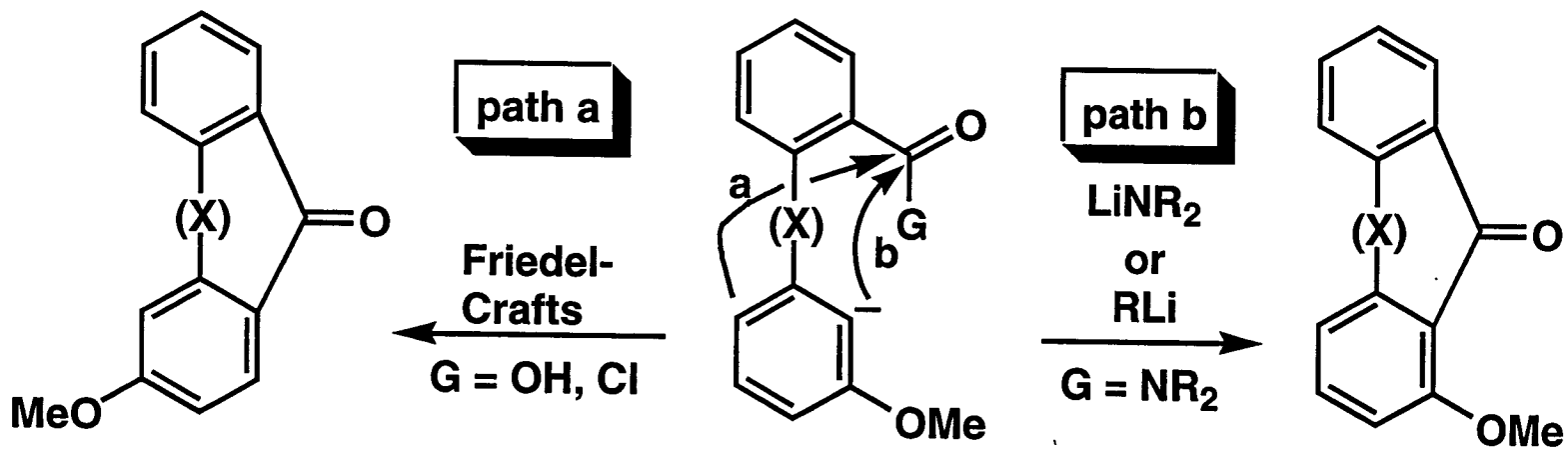
Snieckus: 91 *JOC* 1683
88 *TL* 5459
00 *CJC* 905
98 *TL* 961
83 *JOC* 1935
92 *JOC* 424

DReM in Aromatic Systems. Extension to Heteroatom-Linked Diaryls

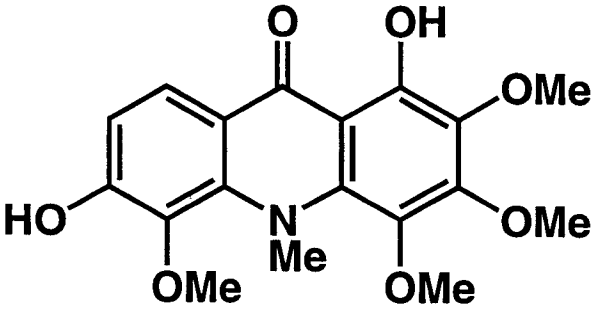


Snieckus 94 *JOC* 6508, 97 *Synlett* 1081, 96 *AG(E)* 1558

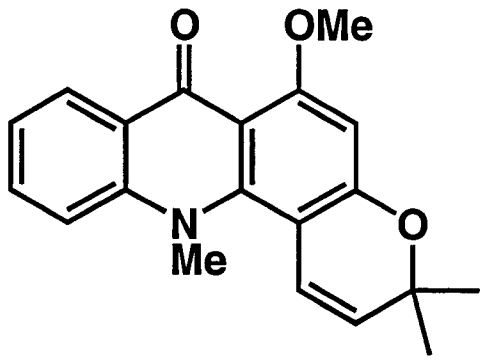
DReM in Heteroatom-Linked Diaryls. An Anionic Friedel-Crafts Equivalent. Regiochemical Complementarity



The Acridone Alkaloids. Attractive Targets for the DReM Protocol

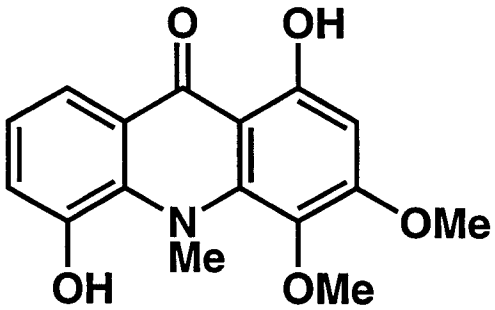


glyfoline

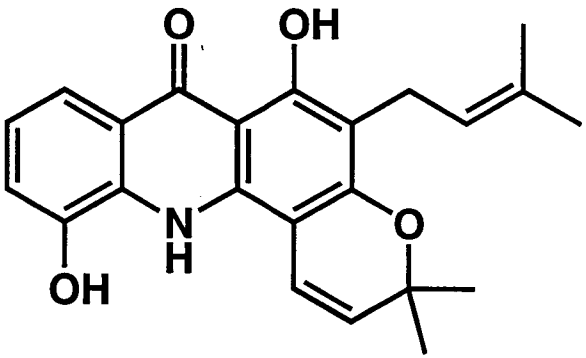


acronycine

broad spectrum antitumor activity



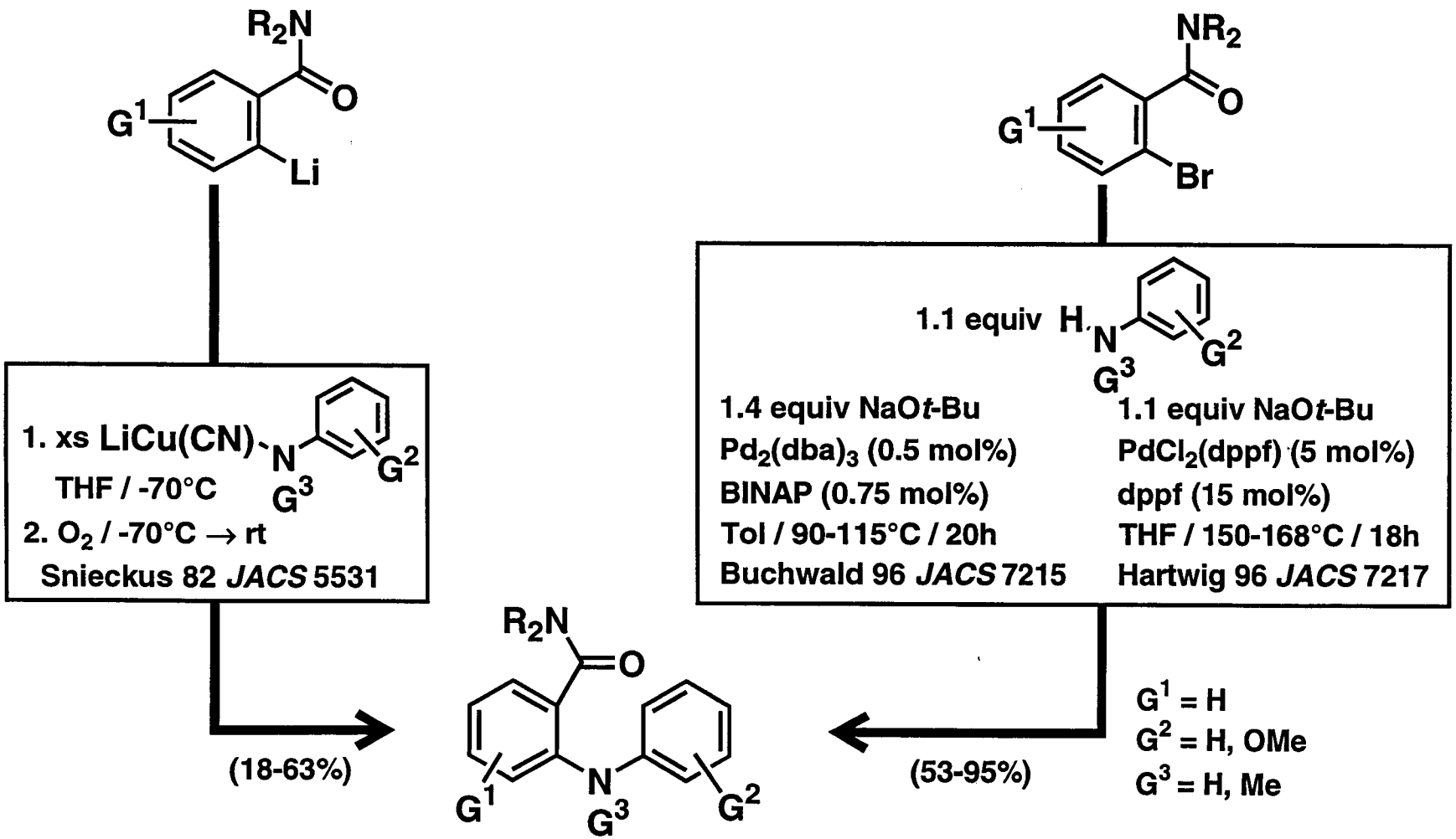
citrusinine-I
antiviral activity



atalaphillinine
antimalarial activity

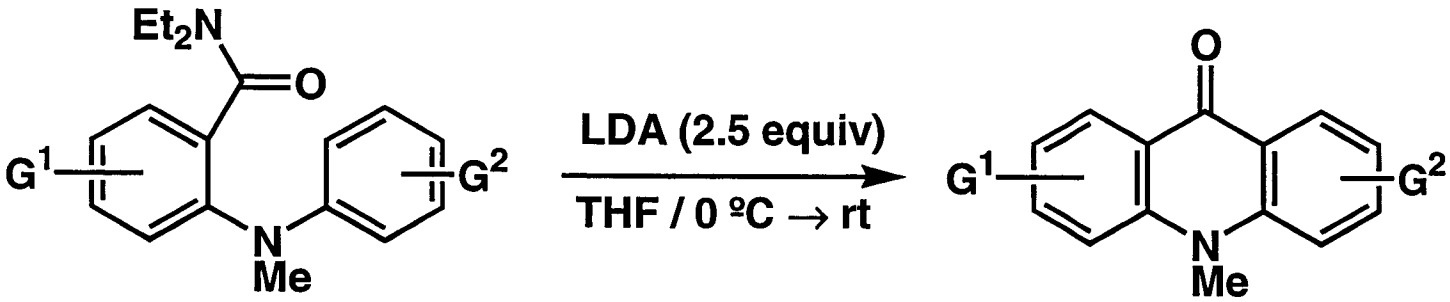
Skaltsounis *et al* in "The Alkaloids", Vol. 54, Academic Press, London, 2000, 259-377

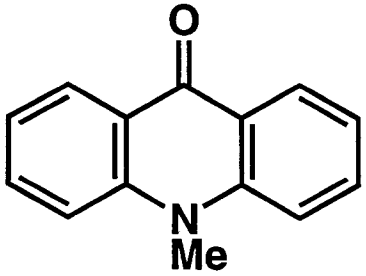
Synthesis of Substituted 2-CONR$_2$ Diarylamines. D*o*M-Mediated Coupling *vs* Pd-Catalyzed Cross Coupling



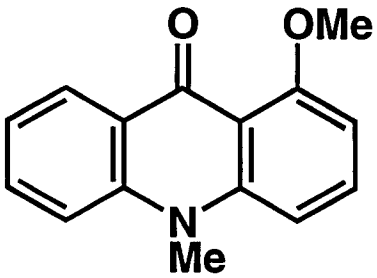
Aryl Amination Review: Hartwig, J.F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Toronto, 2000, pp 195-262

LDA-Mediated Cyclization to Acridones

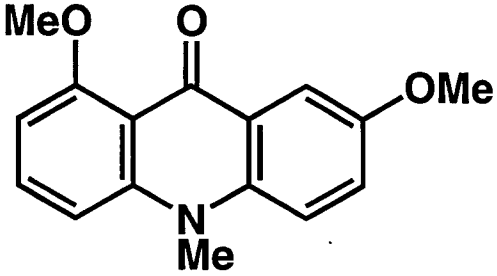




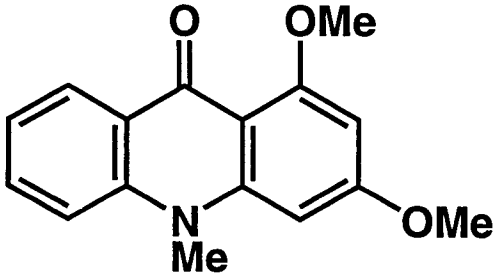
(76%)



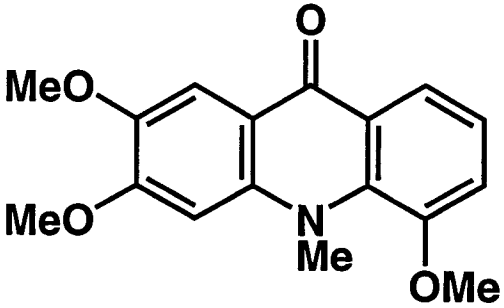
(89%)



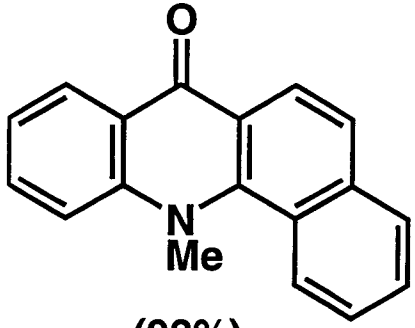
(53%)



(34%)



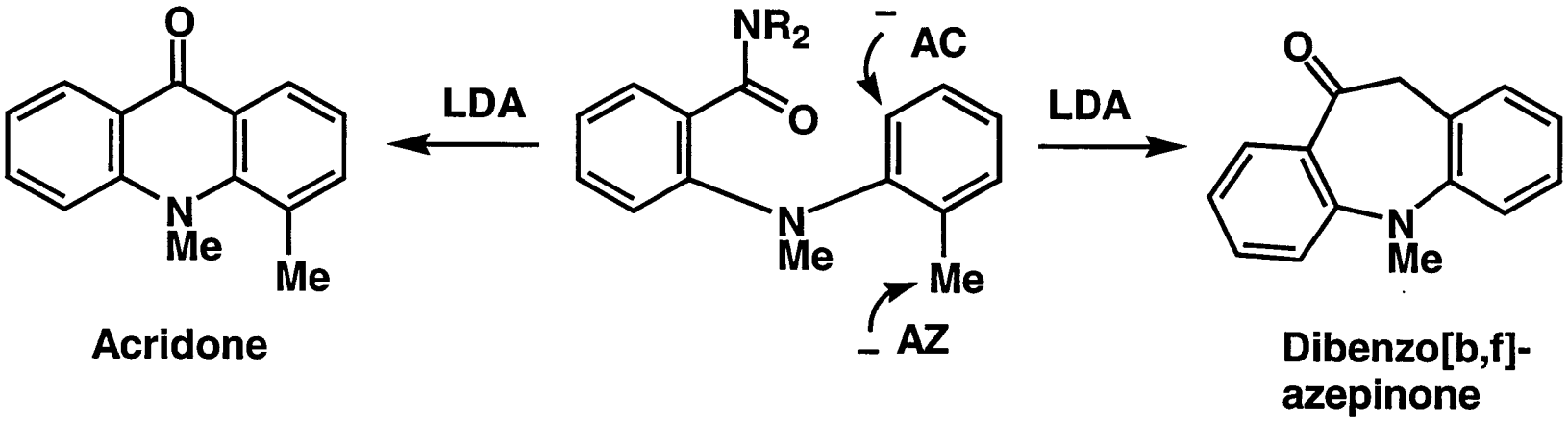
(67%)



(98%)

98 *Synlett* 419

Dibenzo[b,f]azepinones. Accessible by Directed Remote Benzylic Metalation?



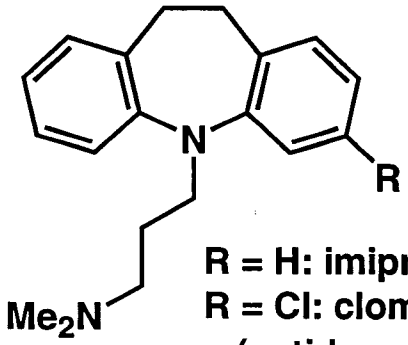
Acridone

(AC)

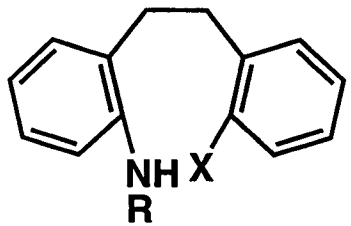
Dibenzo[b,f]-azepinone

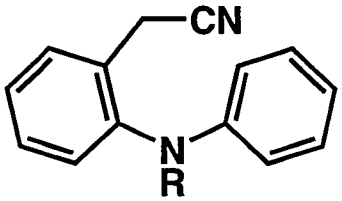
(AZ)

Dibenzo[b,f]azepines. Bioactivity and Synthesis



R = H: imipramine
R = Cl: clomipramine
(antidepressants)

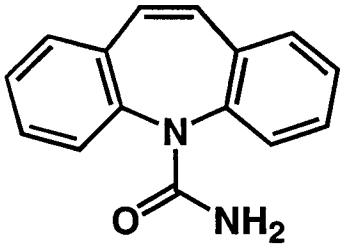




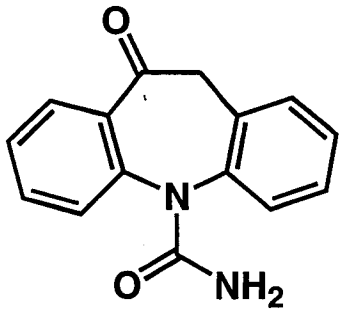
X = NH_2, Cl

Classical Cyclization Precursors

74 *CRV* 101, 78 *CPB* 3058



Carbamazepine
(Tegretol®)



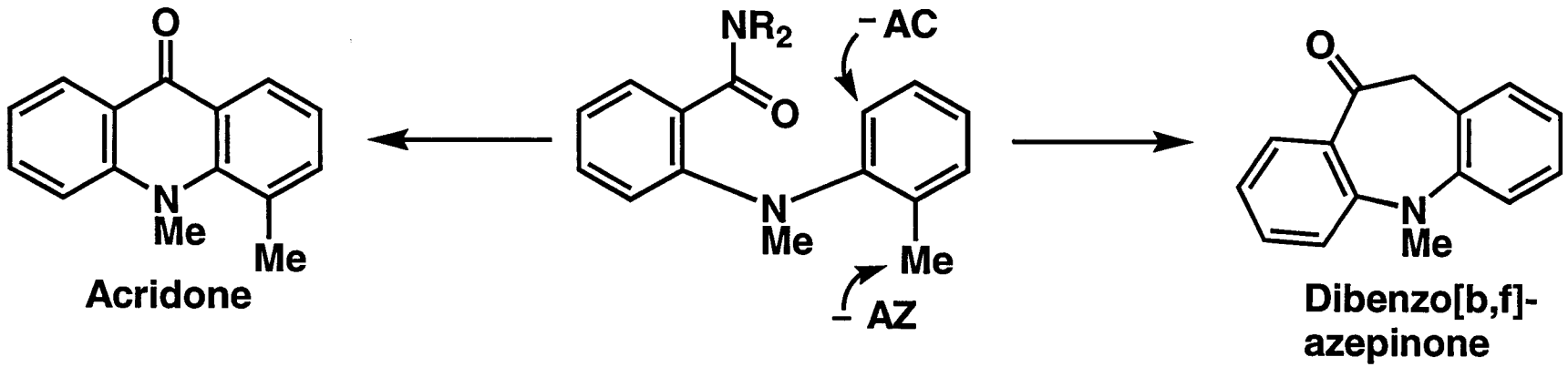
Oxcarbazepine
(Trileptal®)

anti-epilepsy drugs

Epilepsy, A Comprehensive Textbook, Volume II; Engel, Jr., J.; Pedley, T.A., Ed.; Lippincot-Ravens Publishers: Philadelphia, 1998

Beydoun, A. *Pharmacotherapy*, 2000, *20*, 152S-158S

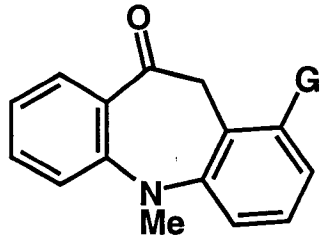
Regioselective Dibenzo[b,f]azepinone Formation by Directed Remote Benzylic Metalation



Conditions: LDA (2.5 equiv)
THF / 0 °C → rt

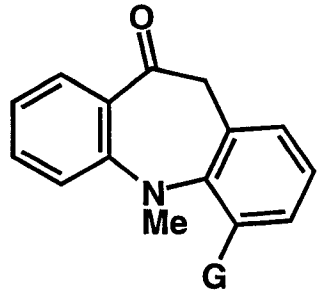
Yld, %	R	Yld, %
11	*i*Pr	78
<5	Et	86
<5	Me	94

Regioselective Dibenzo[b,f]azepinone Formation by Directed Remote Benzylic Metalation. Generalization*



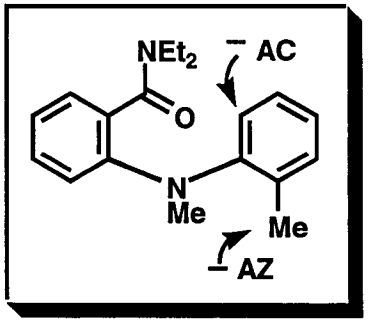
G = Cl: yld AZ, 87%
yld AC, <5%

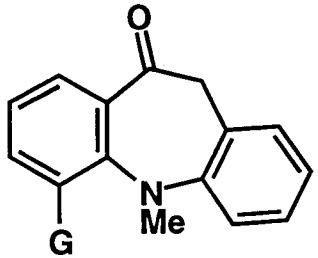
G = Me: yld AZ, 89%
yld AC, <5%



G = Cl: yld AZ, 65%
yld AC, --

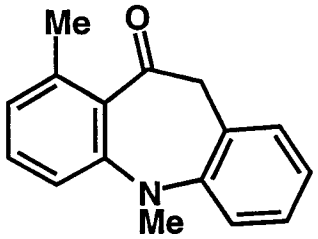
G = OMe: yld AZ, 95%
yld AC, --



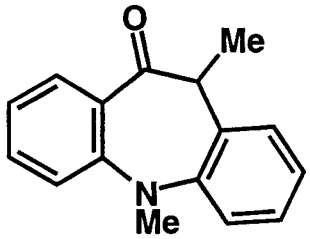


G = OMe: yld AZ, 85%
yld AC, <5%

G = Me: yld AZ, 70%
yld AC, <5%



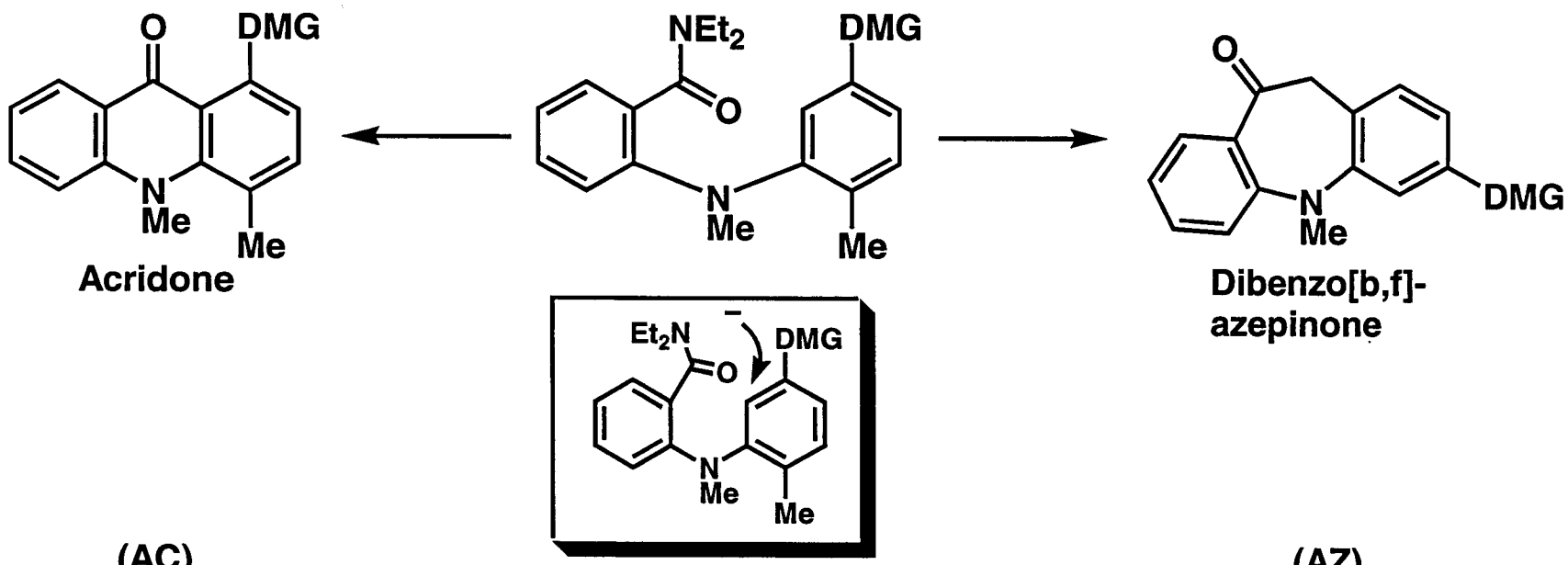
yld AZ, 65%
yld AC, 17%



yld AZ, 61%
yld AC, 31%

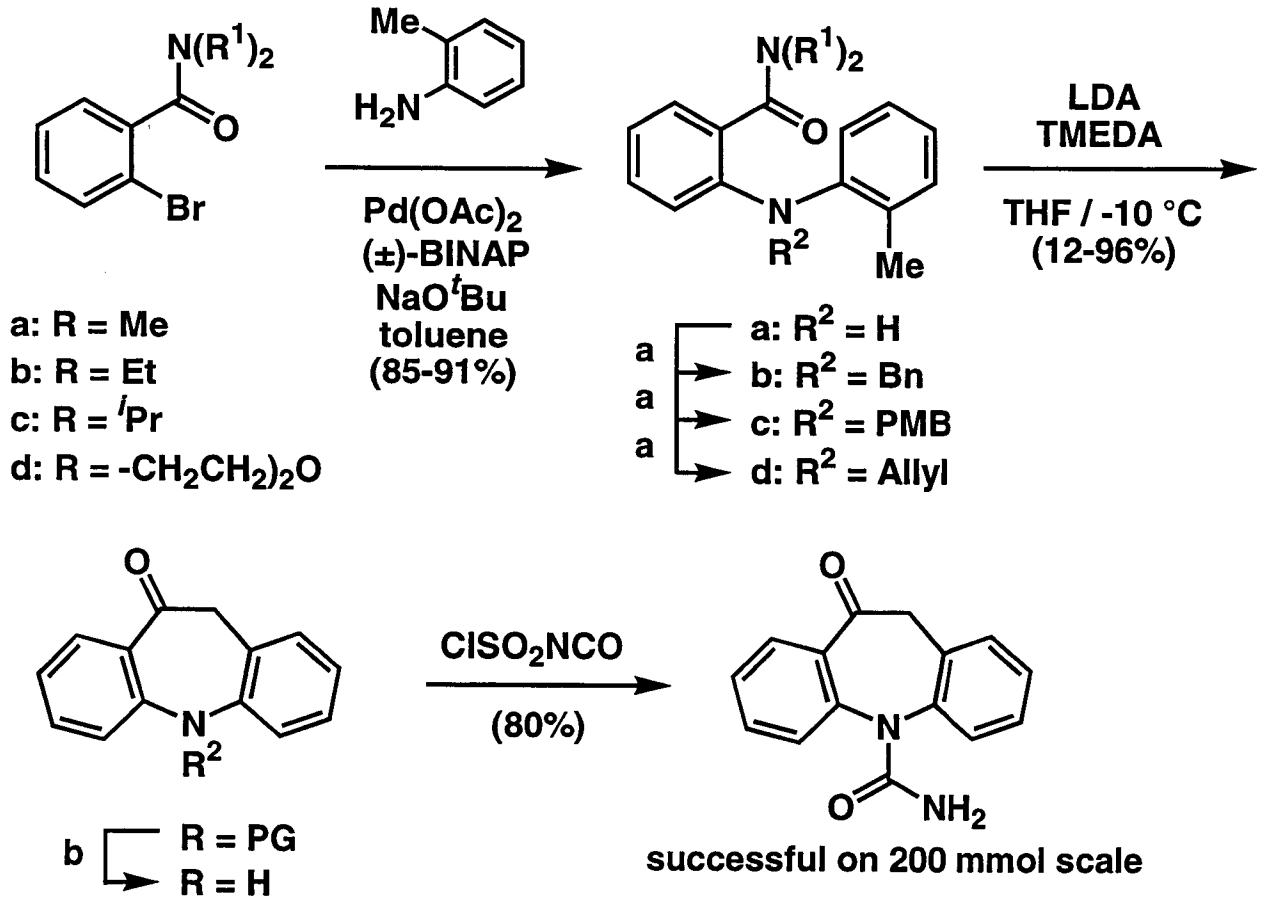
* Cyclization precursors prepared by Buchwald amination (24-93%) followed by *N*-methylation (54-97%)

Regioselective Dibenzo[b,f]azepinone Formation by Directed Remote Benzylic Metalation. Regioreversal by a Cooperative DMG Effect



(AC)		(AZ)
Yld, %	DMG	Yld, %
79	OMe	21
83	Cl	8

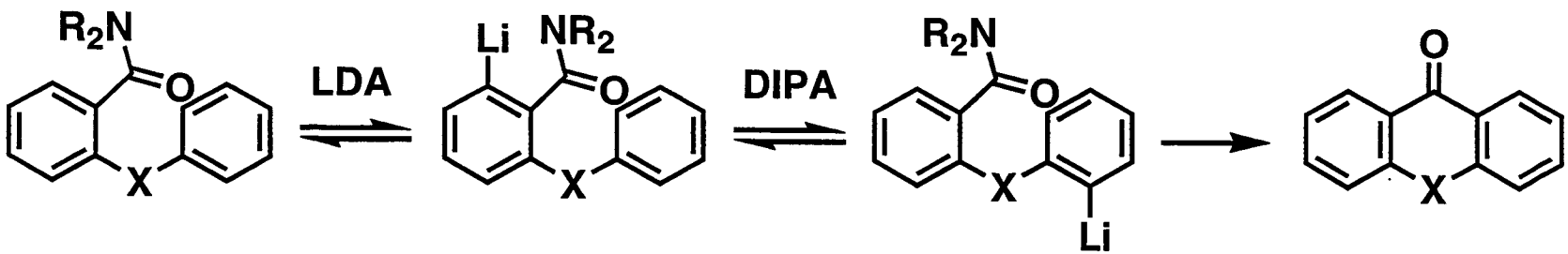
Regioselective Dibenzo[b,f]azepinone Formation by Directed Remote Benzylic Metalation. Industrial Application



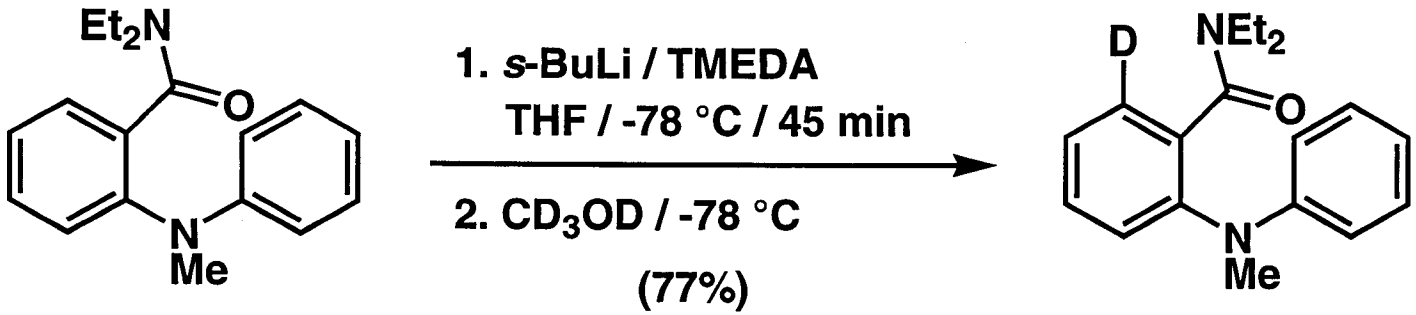
Conditions: (a) 1. NaH / DMF; 2. R^2Cl (70-99%); (b) For PG = Bn: TMSCl / NaI / acetonitrile (75%); For PG = PMB: $TiCl_4$ (95%); For PG = Allyl: $Rh(PPh_3)_3Cl$ (70%)

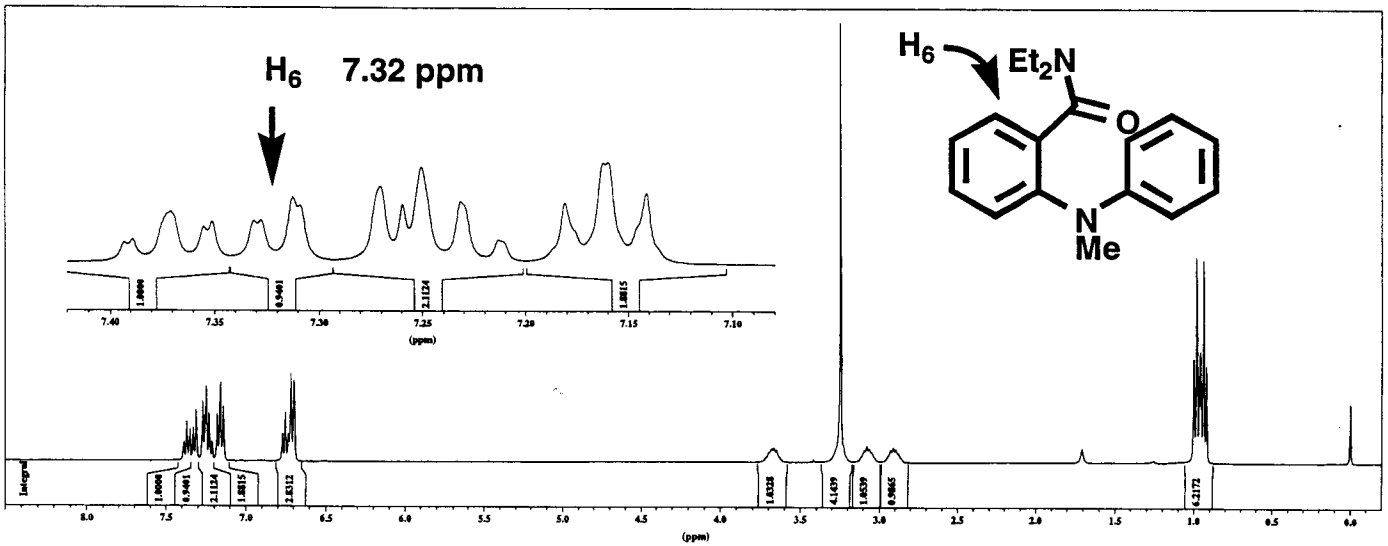
Lohse *et al* (Novartis Pharma AG) 01 *TL* 385

Mechanism of DReM in Heteroatom-Linked Diaryls. Dogma Within the Snieckus Group

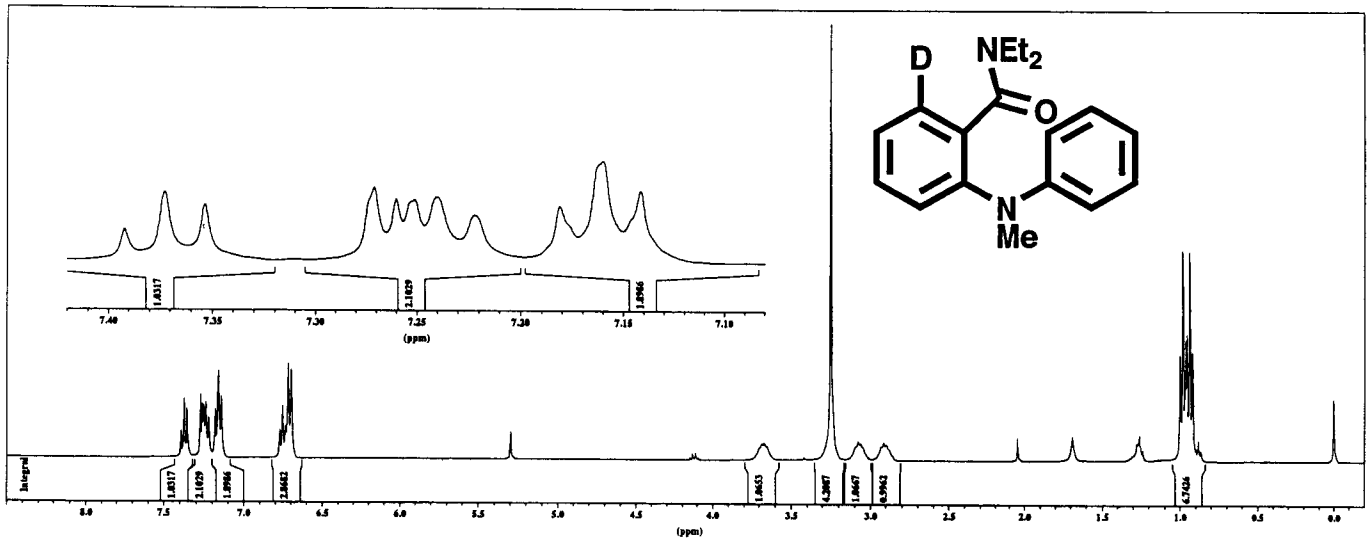


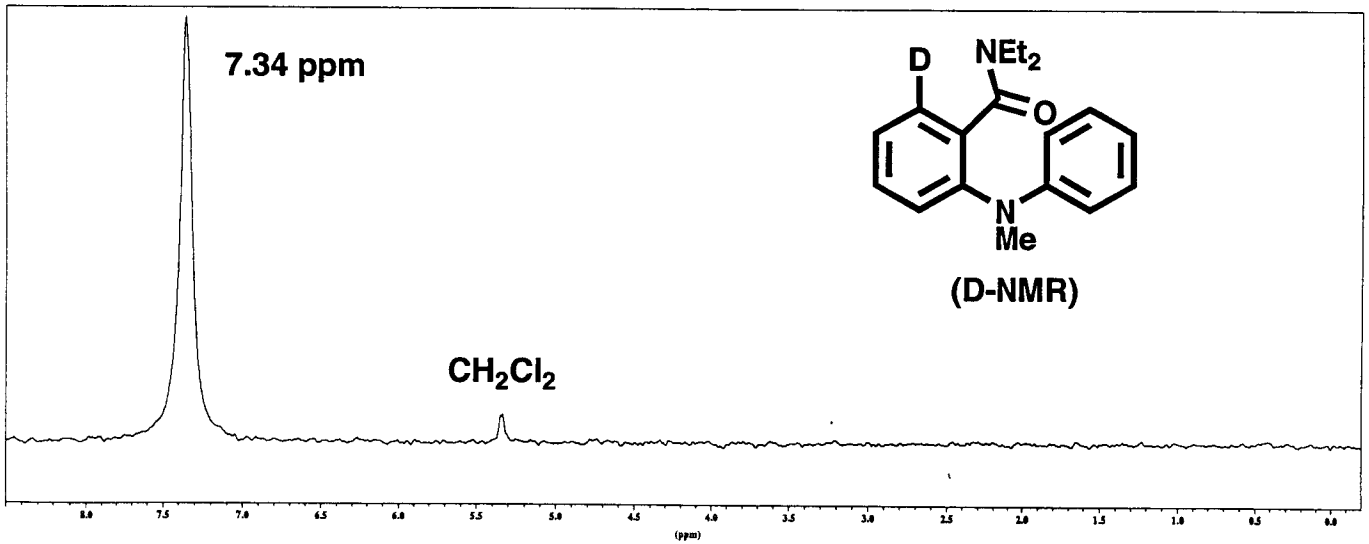
DReM in Heteroatom-Linked Diaryls. Mechanistic Studies



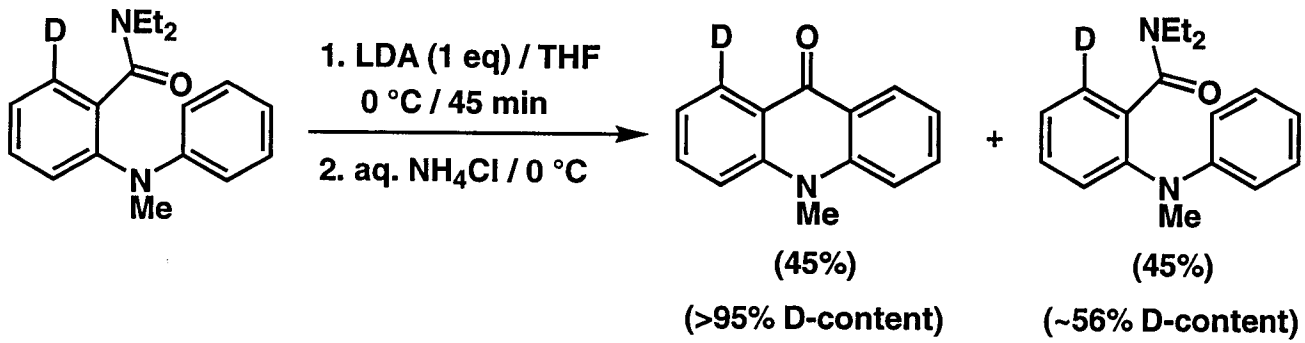


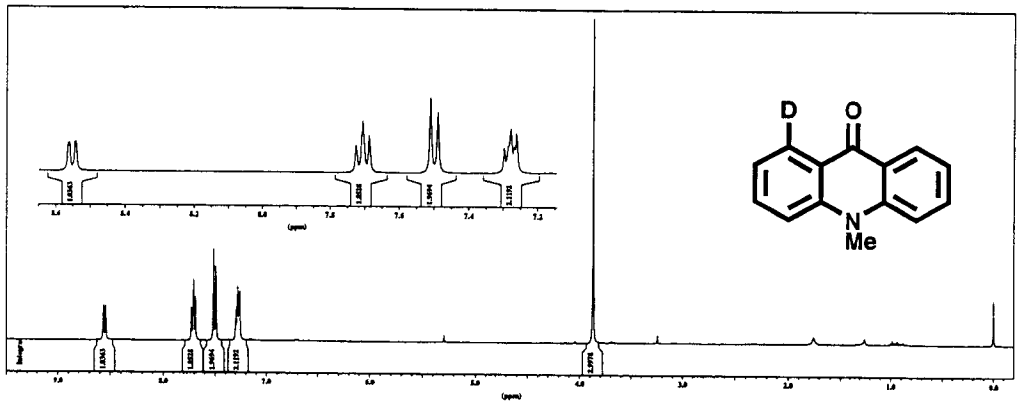
DReM in Heteroatom-Linked Diaryls. Mechanistic Studies

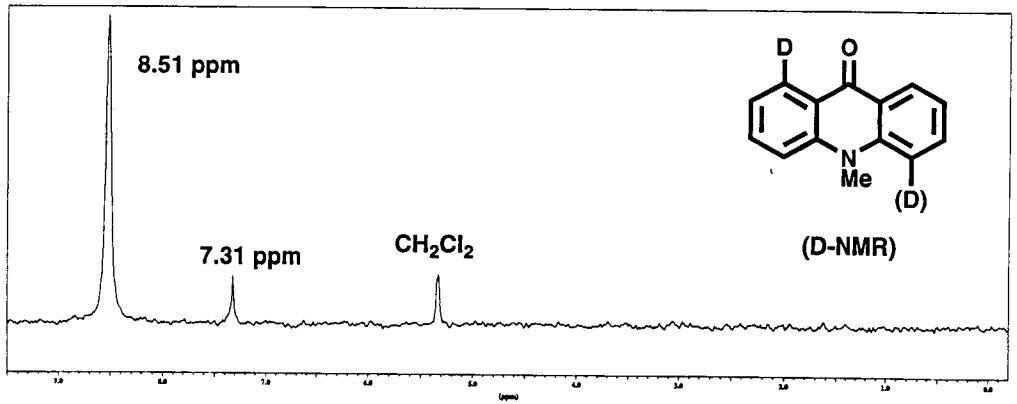




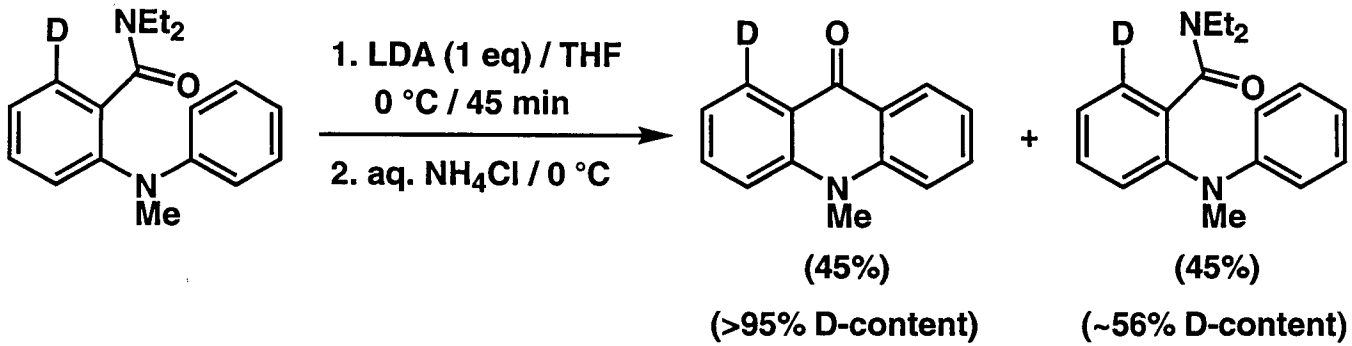
DReM in Heteroatom-Linked Diaryls. Mechanistic Studies

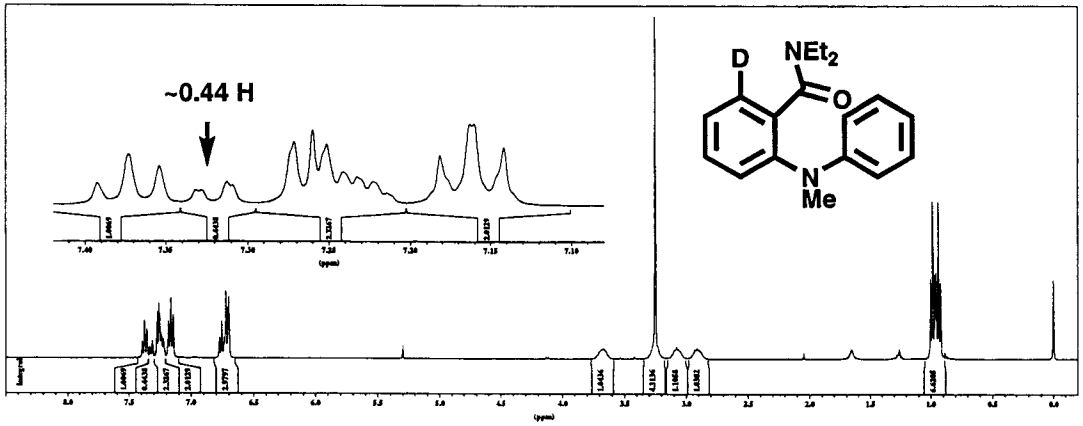


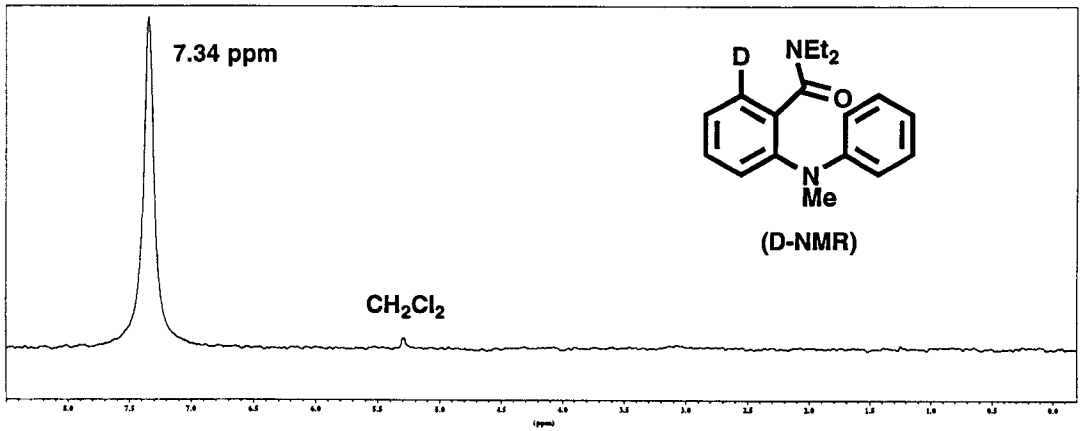




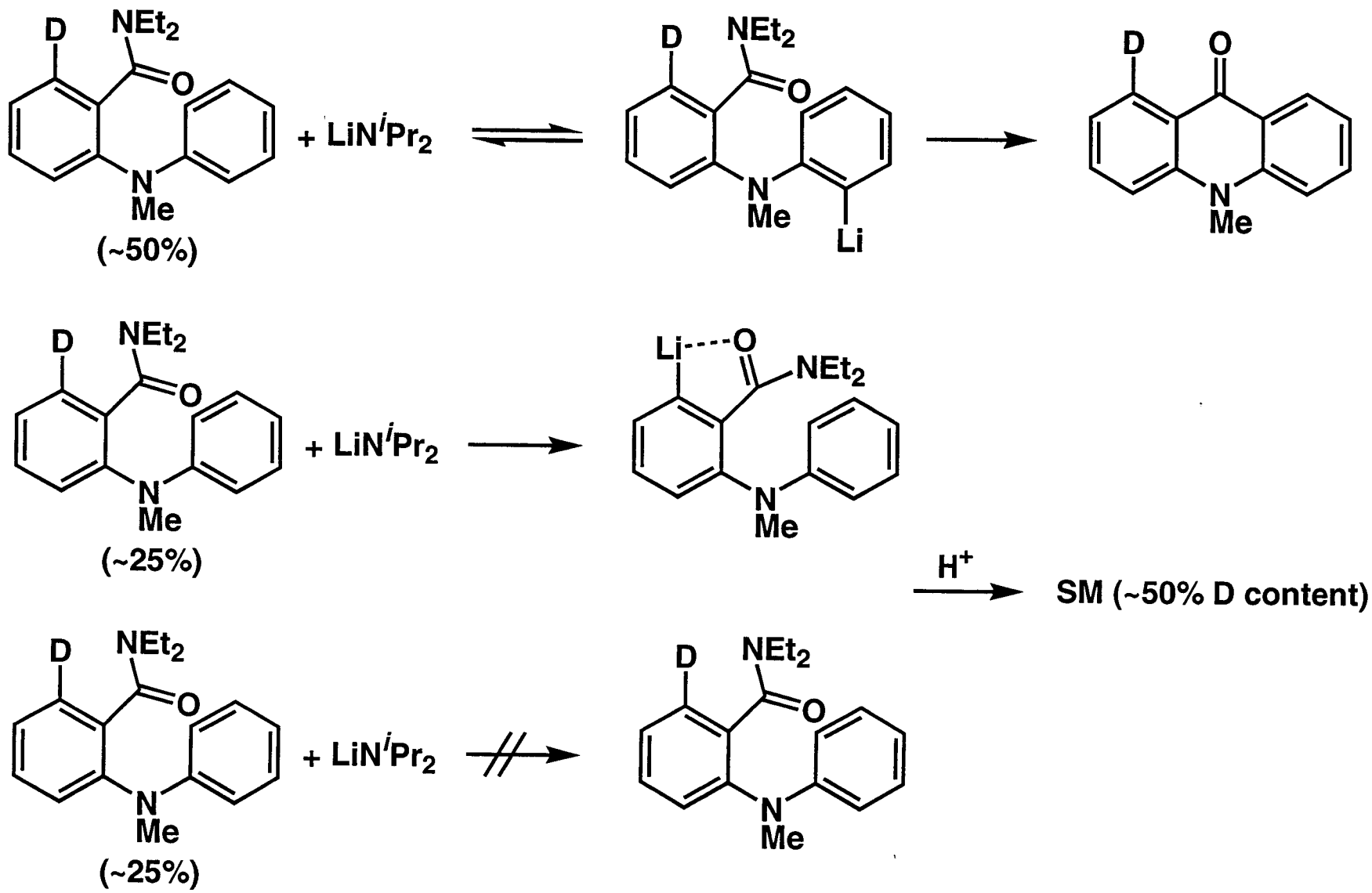
DReM in Heteroatom-Linked Diaryls. Mechanistic Studies





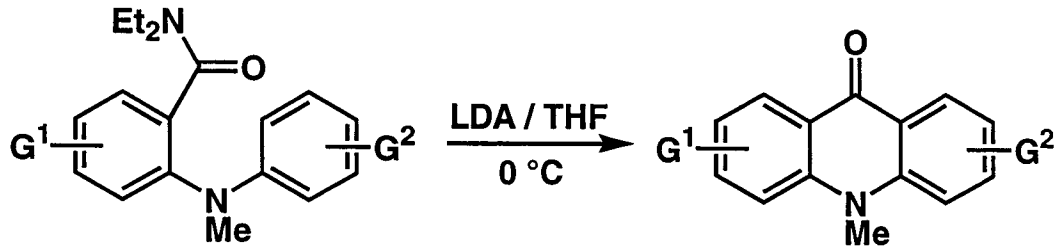


DReM in Heteroatom-Linked Diaryls. Mechanistic Studies

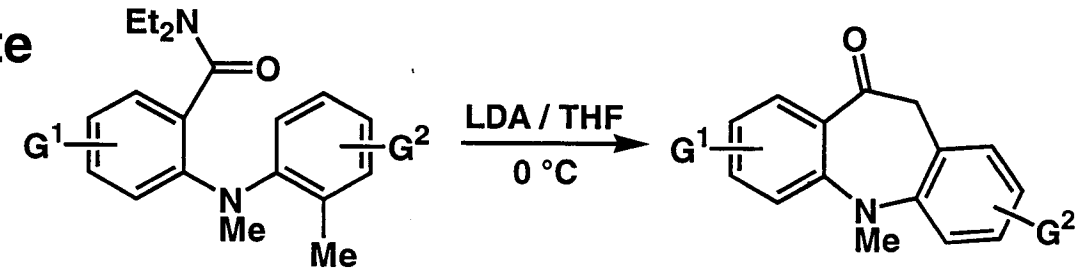


Summary

- **New Synthesis of Acridones by an Anionic Friedel-Crafts Equivalent**



- **Regioselective Anionic Route to Dibenzo[b,f]azepinones**



- **Preliminary Mechanistic Studies**