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Regioselective synthetic processes based on the aromatic directed metalation strategy

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Abstract: Three new methodologies based on the directed *ortho* metalation tactic are described: a) silylated benzamides as dual *ortho*- and α-carbanion synthons (**Schemes 2, 5**) for use in heteroannelation (**Schemes 2, 6, 7**), lateral functionalization (**Schemes 2, 4, 6**) alkaloid synthesis (**Schemes 3, 4**), and 1,3-dipolar cycloaddition (**Scheme 8**); b) cross coupling reactions of functionalized aryl boronic acids with aryl bromides (**Scheme 10**) leading to heteroaromatics (**Schemes 11, 12**) and alkaloids (**Scheme 14**); and c) original 1,5-radical switch reactions (**Scheme 16**) providing new routes for heteroannelation (**Schemes 18, 19, 21**) and α′-amide functionalization (**Scheme 22**).

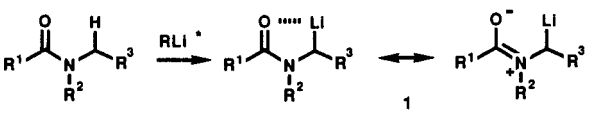
INTRODUCTION

Recent work in our laboratories has been concerned with expanding the synthetic utility of the directed *ortho* metalation strategy[1] by developing links to new C-C bond forming processes. Three selected areas of current work will be described: a) the development of silylated tertiary benzamides as dual *ortho*- and α′-carbanion synthons for heteroannelation and α′-amide functionalization; b) the use of the transition metal catalyzed cross coupling reaction of aryl boronic acids with aryl bromides for the preparation of heteroaromatics, heterocycles, and alkaloids; c) the discovery of a 1,5-radical switch reaction which leads to further new protocols for heteroannelation and α′-amide functionalization.

SILYLATED TERTIARY BENZAMIDES AS DUAL ORTHO- AND α′-CARBANION SYNTHONS[2]

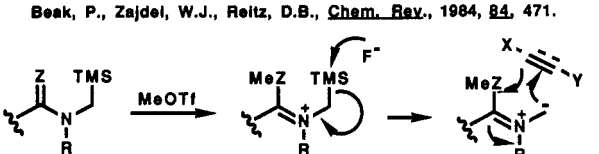
Dipole-stabilized carbanions are promising synthons for umpolung α-amine functionalization methodology. In context of α′-amide carbanions (**1, Scheme 1**), broad utility has been compromised by low kinetic acidity of the α-hydrogens, dimerization, and necessarily severe hydrolysis conditions to the derived amines. In another synthetic arena, α′-silylated amides and thioamides **2** have been generally used, as their corresponding imidate salts **3**, for 1,3-dipolar cycloaddition chemistry (**4**). Recently, Katritzky and Sengupta have achieved fluoride-mediated hydroxylalkylation and acylation of N-trimethylsilyl 2-pyridone.[3] These developments led to our investigation of α′-silylated and α′,α′-disilylated benzamides as potential *ortho* and lateral carbanion synthons.

Scheme 1 **α - AMIDE DIPOLE STABILIZED CARBANIONS**



R^1 = Ph_3C, Et_3C, i-Pr-(2,6-di-i-Pr-C$_6$H$_3$)

* Schlecker, R., Seebach, D., Lubosch, W., Helv. Chim. Acta, 1978, 61, 512
Beak, P., Zajdel, W.J., Reitz, D.B., Chem. Rev., 1984, 84, 471.



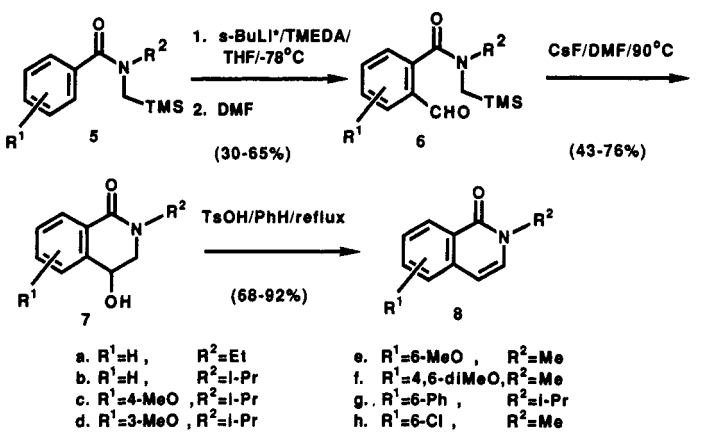
Vedejs, E., West, F.G., Chem. Rev., 1986, 86, 941
Padwa, A., Haffmanns, G., Tomas, M., J. Org. Chem., 1984, 49, 3314

Standard *s*-BuLi/TMEDA metalation of tertiary trimethylsilylmethyl benzamides **5** R = Et, i-Pr **(Scheme 2)** followed by DMF quench afforded *ortho*-formyl products **6** in good yields. Under these conditions, **5**, R^2 = Me led only to self-condensation presumably as a result of an insufficient steric effect. Treatment of **6** with CsF furnished the hydroxy dihydroquinolones **7** which were directly subjected to TsOH dehydration to give the isoquinolones **8**. To illustrate the potential of this intramolecular carbodesilylaton for alkaloid synthesis, compound **10 (Scheme 3)**, prepared from **9** by LiTMP/TMSCl treatment, was subjected to similar conditions to yield a mixture of **11** and **12** which represent the protoberberine alkaloid skeleton. To show utility of intermolecular carbodesilylation, the N-methyl amides **13 (Scheme 4)** were treated with aromatic aldehydes in the presence of CsF to afford the amide carbinols **14** which upon diborane reduction and acid-catalyzed cyclization furnished 4-aryl tetrahydroisoquinolines **15**, one of which is the dimethyl ether of the alkaloid cherylline.[4]

The serendipidous discovery that treatment of N,N-dimethylbenzamide **18 (Scheme 5)** under Martin's conditions (LiTMP/TMSCl)[5] leads to the α',α'-disilylated benzamide **16** in high yield allowed the development of a new dual *ortho*- and α'-carbanion synthon which has greater synthetic potential than the corresponding α'-monosilylated derivative **(Scheme 2)**. Metalation of **16** under *t*-BuLi- or *s*-BuLi-TMEDA conditions followed by quench with electrophiles, smoothly provided a variety of diversely *ortho*-functionalized products **17**. Inter- and intra-molecular modes of α'-amide functionalization (**19** → **20** Z:E = 2:3, **19** → **21** + **22**, **Scheme 6**) were also readily achieved in modest yields. Overall conversion into isoquinolones **21** was improved by acid-catalyzed dehydration of **22**. The o-stannylated benzamide **23 (Scheme 7)** was cross coupled with salicylaldehyde triflate using Stille's excellent regimen to give the biphenyl **24** which, upon CsF-induced amide Petersen olefination, furnished the dibenzazocinone **25**, R = R′ = H. On the basis of benzamide conformational studies and mechanistic hypothesis, the *syn* rotamer **16** is assigned to the product of the bisilylation reaction. This implies

Scheme 2

DIRECTED METALATION-CARBODESILYLATION ROUTE TO ISOQUINOLONES

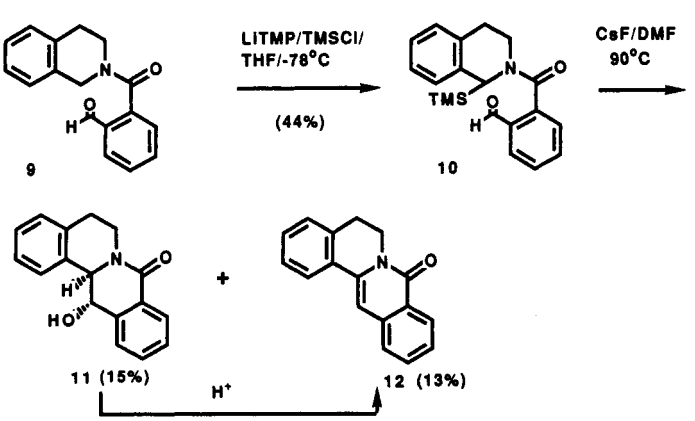


a. R^1=H, R^2=Et
b. R^1=H, R^2=i-Pr
c. R^1=4-MeO, R^2=i-Pr
d. R^1=3-MeO, R^2=i-Pr
e. R^1=6-MeO, R^2=Me
f. R^1=4,6-diMeO, R^2=Me
g. R^1=6-Ph, R^2=i-Pr
h. R^1=6-Cl, R^2=Me

* t-BuLi was used in cases a, e and f

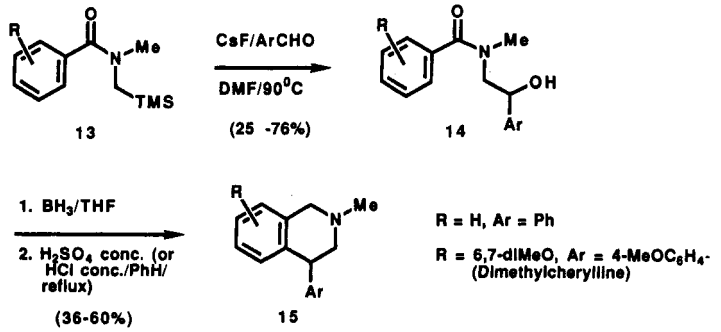
Scheme 3

SYNTHESIS OF PROTOBERBERINE ALKALOID SKELETON BY INTRAMOLECULAR CARBO-DESILYLATIVE CYCLIZATION



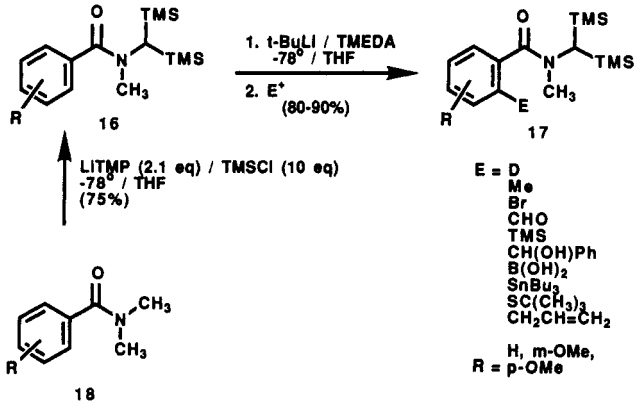
Scheme 4

AMIDE α-FUNCTIONALIZATION BY INTERMOLECULAR CARBODESILYLATION



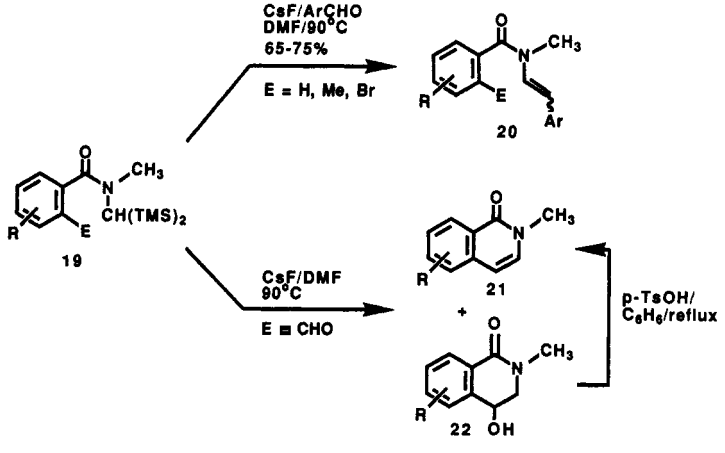
Scheme 5

The α,α-BisTMS Dimethyl Carboxamide DMG



Scheme 6

INTER- AND INTRA-MOLECULAR AMIDE α-FUNCTIONALIZATION BY PETERSON OLEFINATION

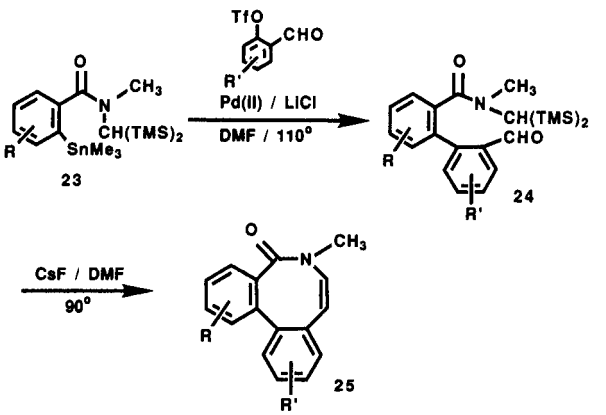


that, under the CsF/DMF conditions, amide *syn-anti* interconversion precedes cyclization to compounds **21**, **22** and **25**.

To determine potential of the α′,α′-disilylated benzamides and corresponding thiobenzamides in 1,3-dipolar cycloaddition reactions, compounds **26** was sequentially treated with methyl triflate, CsF/methyl acrylate and DDQ to give, via imidate intermediates **27**, mixtures of pyrroles **28** and **29** in unoptimized 40-48% yields. In another preliminary study of similar general significance, aliphatic N,N-dimethylamides **30** (**Scheme 9**) were subjected to the Martin conditions to give modest yields of α′,α′-disilylated derivatives **31** which, when subjected to the CsF-mediated condensation with benzaldehyde, gave N-acyl enamines **32**. On the basis of these results, the development of complementary methodology to the thoroughly investigated dipole-stabilized carbanion chemistry (**1**, **Schmem 1**) may be anticipated.

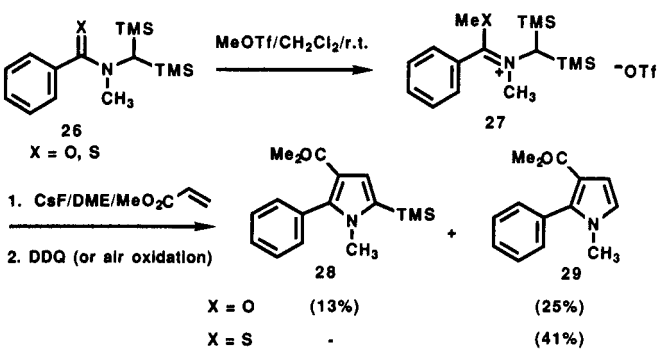
Scheme 7

α-Amido Intramolecular Peterson Olefination : Synthesis of Dibenzoazacinones



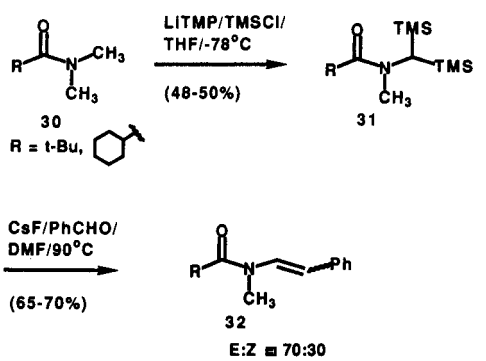
Scheme 8

αα-BIS-TMSBENZAMIDES FOR 1,3-DIPOLAR CYCLOADDITION



Scheme 9

ALIPHATIC α,α-BIS-TMSAMIDES BY METALATION. α-AMIDE CARBANION EQUIVALENTS



In addition to broadening the scope of the Directed *ortho* Metalation strategy, α′,α′-disilylated derivatives **16**, **17** constitute, by the expedient of fluoride desilylation, masked dimethylbenzamides. The ready manipulation of the latter to other functionality suggests that **16** may replace the hydrolytically recalcitrant diethylamide in *ortho* lithiation chemistry.[1]

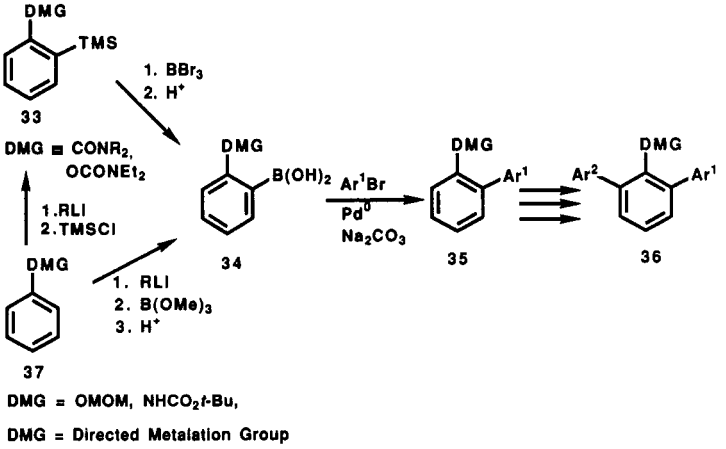
SEQUENTIAL DIRECTED ORTHO METALATION-CROSS COUPLING REACTIONS

The emergence of transition metal-catalyzed cross coupling reactions has provided new regimens and stimulated fresh strategies in organic synthesis. Following the seminal discovery of Suzuki that arylboronic acids undergo cross coupling with aryl bromides under Pd(0) catalysis,[6] we undertook to develop methodology for the preparation of unsymmetrical biaryls which would take advantage of the regioselective directed *ortho* metalation reaction. In the event, aryl boronic acids *ortho*-substituted with directed metalation groups (DMGs) **34** (**Scheme 10**) were readily obtained either by directed boronation of *ortho*-lithiated species **37** or by ipso borodesilylation of *ortho*-TMS derivatives **33**. The crude materials were subjected to the Suzuki cross coupling conditions, or modifications thereof,[7] to afford biaryls, **35**, and thence teraryls **36**, polyaryls, and certain heteroaryl analogues.[8] Furthermore, the utility of this protocol has been demonstrated in the development of new general methods for the construction of 9-phenanthrols,[9] phenanthridines, phenanthridones,[10] and benzo[b,d]pyran-6-ones.[11]

In recent work aimed at extension and generalization, the one-step syntheses of the isomeric benzophenanthridines **40**, **43**, **46** (**Scheme 11**) from the cross coupling reaction of *ortho*-N-t-BOC aryl boronic acids **38**, **41**, **44** with aromatic aldehydes **39**, **42**, **45** respectively, has been achieved.[12] Compound **40** represents the prototype of the significant benzophenanthridine class of alkaloids.[4] All aza aromatics **40**, **43**, and **46** have been previously prepared by tedious and inefficient classical methods.

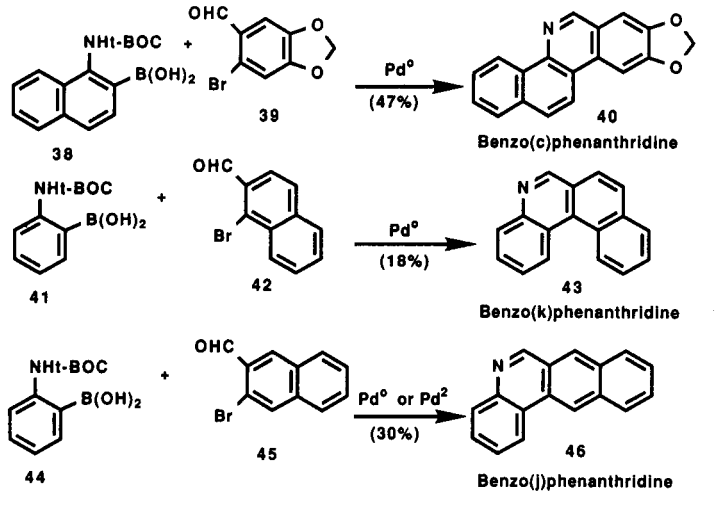
Scheme 10

General Directed Metalation-Cross Coupling Route to Unsymmetrical *m*-Terphenyls



Scheme 11

Synthesis of Diversely Fused Benzophenanthridines



To illustrate the utility of the metalation-cross coupling sequence for the preparation of more highly condensed systems, the pentacyclic dilactam **51** (**Scheme 12**) has been prepared.[12] Double ipso bromodesilylation of the phthalamide **48**, readily available from **47**,[13] followed by metal-halogen exchange and iodination furnished the diiodo derivative **49**. Coupling with an excess of the *ortho*-N-t-BOC phenyl boronic acid gave the terphenyl **50** which was subjected to prolonged treatment with heptafluorobutyric acid (HFBA) at reflux to give the highly insoluble phenanthrolin-dione **51**.

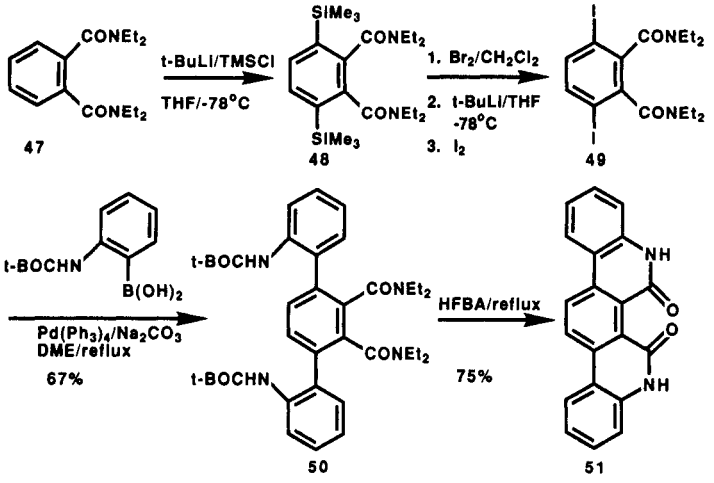
In order to further[10] enhance the methodology for alkaloid synthesis, the preparation of the *Ungernia minor* base ungerimine **52** (**Scheme 13**) according to indicated retrosynthetic analysis was undertaken. After the stops and starts expected in any synthetic endeavor, the first total synthesis of ungerimine has been achieved (**Scheme 14**).[12] The 7-bromoindoline **56** was prepared from commercial 5-hydroxyindole **53** via **54** and **55** according to standard procedures. Cross coupling of **56** with the *ortho*-formyl aryl boronic acid **57** afforded lactam **58**, a product resulting from the normal course of events (**Scheme 11**) which is followed by aerial oxidation of an intermediate carbinol amine. Redal reduction followed by careful processing afforded the zwitterionic alkaloid **52** in low yield. Optimization of this route is in progress.

BENZAMIDE 1,5-ARYL TO α-AMIDYL RADICAL SWITCH REACTIONS

We have previously shown that the directed *ortho* metalation protocol serves as an advantageous link to tin hydride mediated radical-induced cyclizations which provide general routes to 4-oxygenated benzo dihydrofurans, **60a,b** → **61a,b** (**Scheme 15**)[14] including aflatoxin synthons.[15] However, the corresponding amide derivatives **60c** undergo exclusive 1,5-hydrogen atom switch reactions, **59** → **62**, as evidenced by formation of **63** under tin deuteride conditions.[16]

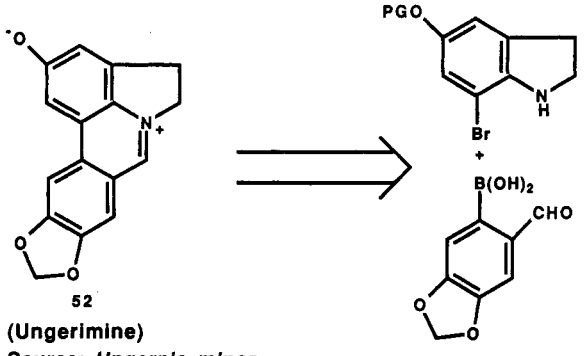
Scheme 12

Double Cross Coupling: Synthesis of 2,9-Dibenzo[*c,i*] phenanthrolin-1,10-dione



Scheme 13

Cross Coupling Strategy for Betaine Alkaloid Ungerimine



(Ungerimine)

Source: *Ungernia minor*

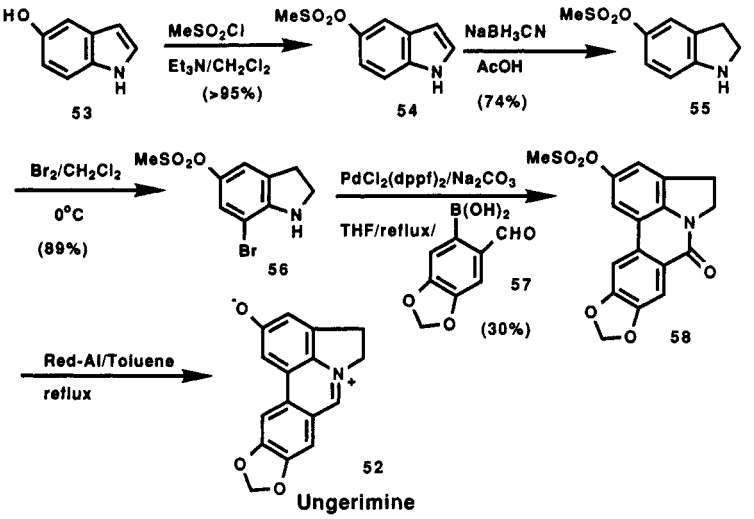
Biological Activity: Antileukemic (P388, mice)

Yunusov, S. *et al* Usbek. Khim. Zh. 1965, 77, 5885. CA 1965, 59, 6456a.
Ghosal, S. *et al* J. Chem. Res. (S), 1986, 112.
Steglich, W. *et al* Phytochemistry, 1986, 25, 2399.

This "failure" has been resurected in the discovery of a new heteroannelation leading to dihydroisoquinolones **68** (Scheme 16).[17] The initial C-X bond homolysis and 1,5-hydrogen atom switch, **64** → **65** may be envisaged to be followed by rapid C-CO bond rotation and 6-exo-trig cyclization, **66** → **67**, to lead, after bimolecular hydrogen transfer from tin hydride, to product **68**. In order to test this hypothesis, 2-halo-6-vinylbenzamides **72** (Scheme 17) were prepared. One-pot metalation-silylation-metalation-formylation on **69** gave **70** which, upon ipso halodesilylation furnished products **71**. Conventional Wittig chemistry led to the requisite derivatives

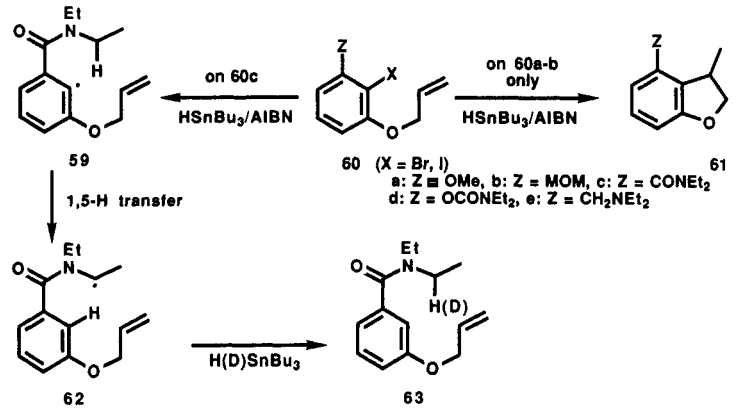
Scheme 14

First Total Synthesis of Ungerimine by Cross Coupling



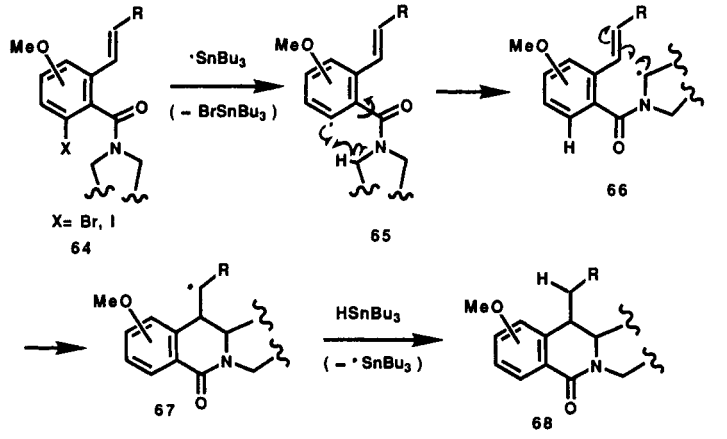
Scheme 15

ARYL TO α -AMIDYL RADICAL SWITCH



Scheme 16

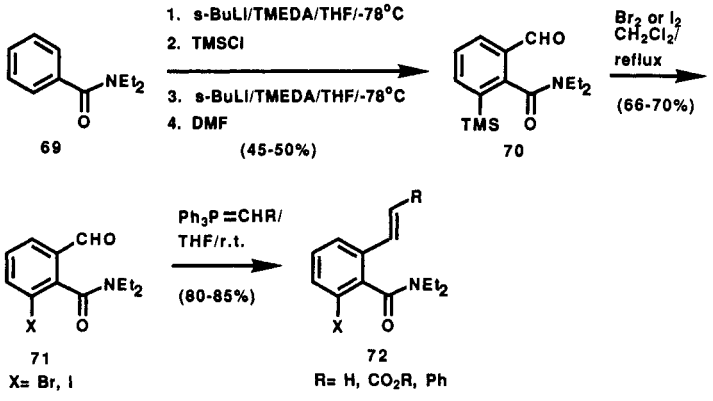
ARYL TO α -AMIDYL RADICAL SWITCH



72 in high yields. Application of standard tin hydride/AIBN conditions on **73** (**Scheme 18**) smoothly led to the dihydroisoquinolones **74** in good yields and inconsequential stereoselectivity. Similarly, the 1,5-radical switch cum cyclization sequence was demonstrated for the pyrrolidyl and piperidyl amides **75** (**Scheme 19**) to give 1:1 diastereomeric mixtures of benzo-indolizidine and -quinolizidine derivatives **76** in comparable yields.

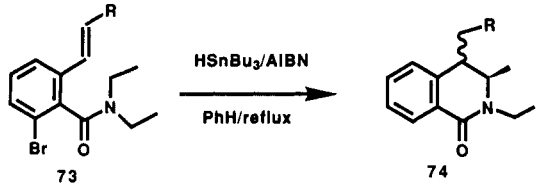
Scheme 17

PREPARATION OF 2-HALO-6-VINYLBENZAMIDES



Scheme 18

ATOM TRANSFER-INDUCED HETEROANNELATION



R	yield, %	diastereomeric ratio
H	67%	1:1
CO_2Et	61%	1:1
Ph	61%	1:1

Scheme 19

ATOM TRANSFER-INDUCED HETEROANNELATION

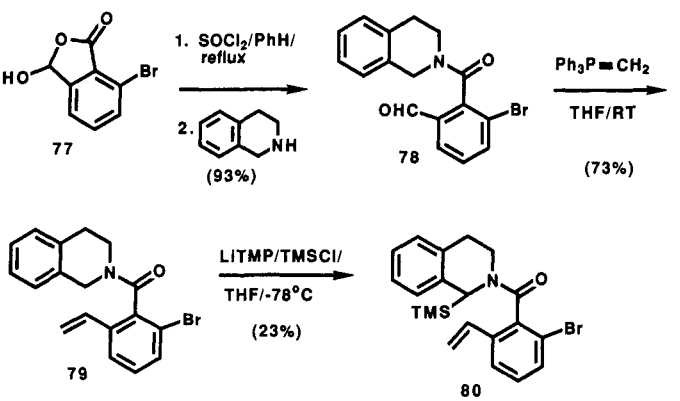
n	Yield, %	Diastereomeric ratio
0	45 %	3 : 1
1	60 %	4 : 1

As a test of the method for 13-methylprotoberberine alkaloid synthesis, the preparation of the model precursors **79** and **80** (**Scheme 20**) was undertaken. The hydroxyphthalide **77** was efficiently converted into the aldehyde amide **78** which, upon Wittig reaction gave the styrene **79**. Treatment of **79** under Martin's conditions (*vide supra*) afforded a low yield of the silylated derivative **80**. The results of preliminary experiments on **81**, Y = H, TMS (**Scheme 21**) indicate that conformational factors play a significant role in cyclization regiochemistry. Thus **81**, Y = H, R = H and OMe afforded mixtures of angular **82** and linear **83** products while the corresponding silylated substrate **81**, Y = TMS gave the linear heterocyle **83** exclusively. The amino ester **81**, R = Y = H, Z = CO_2Me provided equal amounts of **82** and **83** in high combined yield.

The 1,5-hydrogen atom switch process can also lead to synthetically useful intramolecular α'-amide functionalizations (**Scheme 22**). Thus treatment of *ortho*-bromo benzamides **84** and **86**, classically derived from the commercial o-bromobenzoic acid, with excess methyl acrylate under the tin hydride/AIBN conditions affords branched amides **85** and **87** respectively in modest to good yields. This process constitutes a new radical-based method of α'-amine functionalization initiated by a 1,5-hydrogen atom translocation from a disposable, "protecting" benzoyl group.

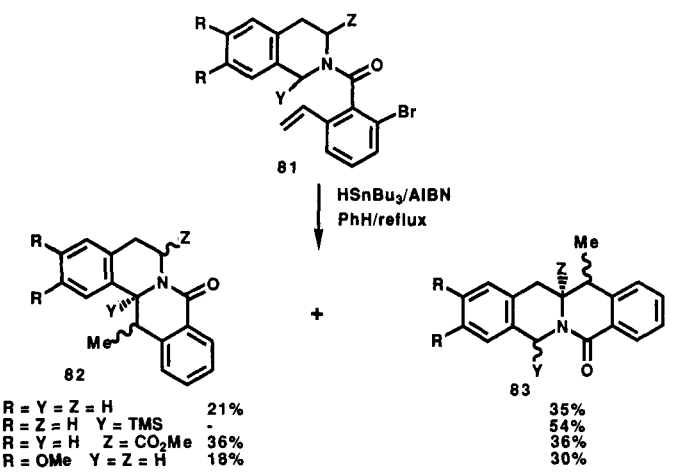
Scheme 20

AROMATIC TO α -AMIDYL 1,5-RADICAL SWITCH REACTION. PREPARATION OF 13-METHYL-PROTOBERBERINE ALKALOID MODEL



Scheme 21

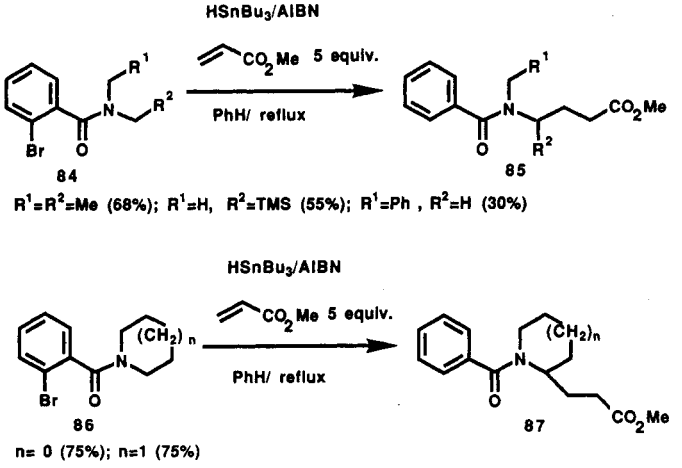
1,5-AROMATIC TO α -AMIDYL RADICAL SWITCH REACTION. PREPARATION OF 13-METHYL-PROTOBERBERINE ALKALOID MODEL



R = Y = Z = H	21%	35%
R = Z = H Y = TMS	-	54%
R = Y = H Z = CO_2Me	36%	36%
R = OMe Y = Z = H	18%	30%

Scheme 22

ATOM TRANSFER-INDUCED α -AMIDYL FUNCTIONALIZATION



SUMMARY

The utility of silylated benzamides as dual *ortho*- and α'-carbanion synthons of value for lateral functionalization and heteroannelation processes has been demonstrated **(Schemes 2-4, 6, 7)**. Initial results on establishing connections between the directed *ortho* metalation reaction and a) transition metal catalyzed cross coupling **(Scheme 11, 12, 14)** and b) 1,5-radical transfer-mediated cyclization **(Schemes 18, 19, 21, 22)** has been outlined. The former link provides new methodology for aryl-aryl C-C bond formation and construction of condensed aromatics and heteroaromatics, including alkaloids; the latter offers original methods of heteroannelation and α'-amine functionalization. The sum of these contributions suggests that further evolution of synthetic strategies based on directed *ortho* metalation may be anticipated.

Acknowledgements

Dedication, enthusiasm, and good humor are key word descriptors for the students, named in the references, who have executed the work described in this article. The support of our research programs by NSERC Canada, Merck Frosst Canada, and NATO (J.-C.C.) is gratefully acknowledged.

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