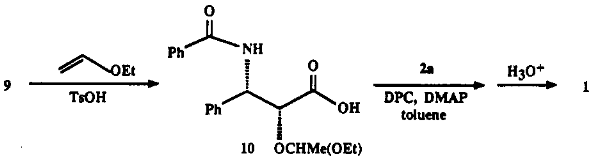
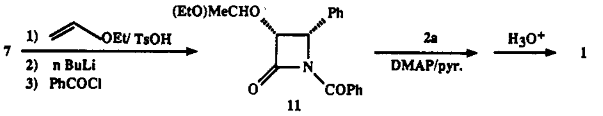
3-(silyloxy)-4-aryl-β-lactams, (+)-**6-C** and (+)-**6-D**, can be converted to the corresponding substituted *N*-benzoylphenylisoserines in the same manner.

N-Benzoylphenylisoserine (**9**) has already been coupled with 7-(trimethylsilyl)-**2** (**2a**) by Greene et al. (eq 2).[4] Quite recently, Holton et al. developed a more efficient coupling method, directly from **7** (eq 3).[20] Our method, described herein, provides the most efficient route to taxol (**1**) to date.



(2)



(3)

In summary, we have demonstrated that 3-hydroxy-4-aryl-β-lactams are efficient key intermediates for the asymmetric synthesis of the taxol C-13 side chain and its analogues, which are readily obtained via chiral ester enolate–imine cyclocondensations with extremely high enantiomeric purity. The most efficient and crucial chiral auxiliary, (−)-*trans*-2-phenylcyclohexanol, can be readily obtained in 100-g quantities using the lipase-catalyzed kinetic resolution of its racemic chloroacetate, as developed by Whitesell et al.,[11c] and is fully recyclable after the reaction. This synthetic method provides efficient and practical routes to a variety of modified taxol C-13 side chains, which are essential for the antitumor activity and the solubility of taxol (**1**).

Acknowledgment. This research was supported by grants from National Institute of Health (GM33665 and GM42798), the Center for Biotechnology, SUNY at Stony Brook, which is sponsored by the New York Science & Technology Foundation (for I.O., I.H., and M.Z.), American Cancer Society, and National Institute of Health (GM42260) and Biomedical Research Grant (RR 5606) (for G.I.G.). Generous support from Ajinomoto Co., Inc. (for I.O.) and Oread Laboratories, Inc. (for G.I.G. and L.R.J.) are also gratefully ackowledged. The authors are grateful to Dr. Alan Schwartz, Hoffmann-La Roche, Inc., for his generous gift of (−)-*trans*-2-phenyl-1-cyclohexanol and (+)-*trans*-2-phenyl-1-cyclohexyl chloroacetate at the beginning of this project.

Supplementary Material Available: Typical procedures and identification data for all new compounds (4 pages). Ordering information is given on any current masthead page.

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[20] Holton, R. A.; Liu, J. H.; Gentile, L. Submitted for publication. We thank Professor Holton for informing us of their results prior to publication.

Remote Aromatic Metalation. An Anionic Friedel–Crafts Equivalent for the Regioselective Synthesis of Condensed Fluorenones from Biaryl and *m*-Teraryl 2-Amides

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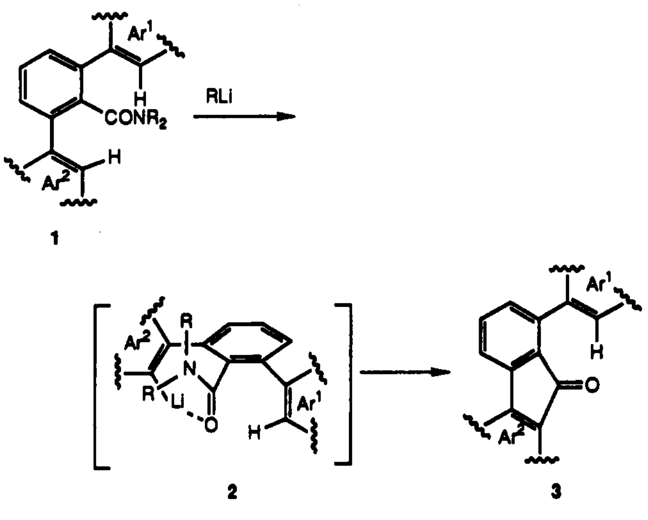
Received December 27, 1990

Summary: Remote metalation (*t*-BuLi, LDA) of *m*-teraryl and biaryl amides (Scheme I) constitutes a short and convenient route to a variety of substituted and condensed fluorenones, including aza analogues (Table I) and the natural product, dengibsinin (**6a**, Scheme II).

Scheme I



As part of expanding studies aimed to establish synthetic links between the directed ortho metalation strategy[1] and transition metal catalyzed cross coupling reactions,[2] we have developed a general route to functionalized biaryls, *m*-teraryls, and polyaryl systems.[3] Contemplation of X-ray crystal structure data of a *m*-teraryl[4] in context with the complex induced proximity effect (CIPE) concept,[5] suggested the prospect of remote metalation of teraryl amides[6] (Scheme I). Following initial amide–strong base coordination, **1** may be induced to undergo remote deprotonation as a function of Ar^1/Ar^2 hydrogen relative acidities to give species **2** that could cyclize to **3** in an intramolecular version of the classical amide–RLi condensation reaction. Herein we report the affirmation of this hypothesis on *m*-teraryls and biaryls and thereby provide a general, short, and regioselective new method for the construction of simple and condensed fluorenones and azafluorenones, including the Orchid natural product, dengibsinin (**6a**).[7,8] This anionic equivalent of the Frie-

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[1] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

[2] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665 and references cited therein.

[3] Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. Cheng, W.; Snieckus, V. *Ibid.* **1987**, *28*, 5097.

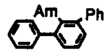
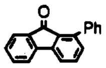
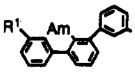
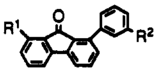
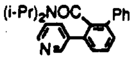
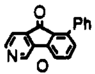
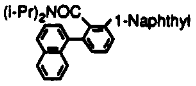
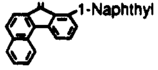
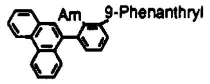
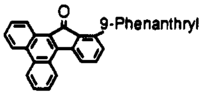
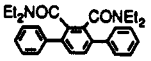
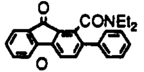
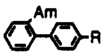
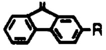
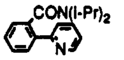
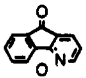
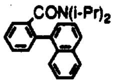
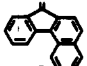
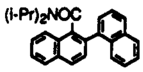
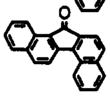
[4] N,N-Diisopropyl 2-phenyl-6-(1′-naphthyl)benzamide shows an approximately orthogonal amide carbonyl with respect to the central aromatic ring which is in close proximity to 2- and 6-aryl ortho hydrogens: Sharp, M. J.; Taylor, N.; Snieckus, V., unpublished results.

[5] Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

[6] For remote metalation of 2-aminobiphenyl, see: Narasimhan, N. S.; Alurhar, R. H. *Indian J. Chem.* **1969**, *7*, 1280. Narasimhan, N. S.; Chandrachood, P. S. *Synthesis* **1979**, 589. For an interesting intramolecular metalation–migration of *N,N*-dimethyltriphenylacetamide, see: Wykypiel, W.; Lohmann, J.-J.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1337.

0022-3263/91/1956-1683$02.50/0 © 1991 American Chemical Society

Table I. Synthesis of Fluorenones from Biaryl and *m*-Teraryl Amides

entry	amide	product	base	yield,[a] %	mp, °C
1			t-BuLi LDA t-BuLi	65[b] 66[b] 84[c]	119–121[d] (hexane)
2					
		R^1 = OMe, R^2 = H	t-BuLi	40[b]	103–105
		R^1 = H, R^2 = OMe		15	100–102 (hexane)
3			LDA	55	158–159 (hex-EtOAc)
4			t-BuLi	48	248–250 (hex-EtOAc)
5			t-BuLi	32[b]	252–254 (hex-EtOAc)
6			LDA	82	134–136 (hexane)
					
7		R = H	LDA	84[c]	83–85[e]
8		R = Me	LDA	52[b]	91–92[f] (hexane)
9			LDA	94	139–141[g] (EtOH)
10			LDA	58	158–160[h] (hexane)
11			LDA	51	165–166[i] (MeOH)

[a] Yields of chromatographed materials. [b] Am = CON(i-Pr)$_2$. [c] Am = CONEt$_2$. [d] Lit. mp 121–122 °C (Jones, D. H.; Wragg, W. R. *J. Chem. Soc. C* **1968**, 2154). [e] Lit. mp 83–85 °C (Aldrich Chem Co.). [f] Lit. mp 91 °C (Sellers, C. F.; Suschitzky, H. *J. Chem. Soc. C* **1969**, 2137). [g] Lit. mp 140–141 °C[7b] (Abramovitch, R. A.; Tertzakian, G. *Can. J. Chem.* **1965**, *43*, 940). [h] Lit. mp 157–158 °C (Ceustermans, R. A. E.; Martens, H. J.; Hoornaert, G. *J. Org. Chem.* **1979**, *44*, 1388). [i] Lit. mp 166–166.5 °C (Fuson, R. C.; Wassmundt, F. W. *J. Am. Chem. Soc.* **1965**, *78*, 5409).

del–Crafts process constitutes a mild and convenient alternative to more conventional methodology,[7b,9] whose scope is underscored by the ready availability of biaryls **1** using combined directed metalation–cross coupling tactics.[1]

Exposure of *N,N*-diethyl and *N,N*-diisopropyl 2,6-diphenylbenzamide[3] to 2 equiv of *t*-BuLi or LDA (0 °C → rt/12 h) afforded 1-phenylfluorenone in good yield (entry 1, Table I).[10] Similarly, a large number of fluorenones were obtained from readily available *m*-teraryls.[3,11] Selected examples indicate the scope of this reaction: methoxy substituents in unsymmetrical cases direct the regioselective cyclization (entry 2);[12] both *t*-BuLi and LDA are effective bases for the cyclization, but, as expected, formation of azafluorenones requires the use of nonnucleophilic base (LDA) and is dictated by pyridine ring hydrogen acidities (entry 3);[13] condensed fluorenones with aryl substitution are readily formed (entries 4 and 5); a *p*-terphenyl *o*-diamide provides a monocyclization result (4 equiv of LDA) (entry 6).

As previously established,[3] alkyllithium metalation of biaryl 2-amides leads to 3-lithio species; however, treatment with LDA (1 equiv) under the above conditions smoothly affords fluorenone in a thermodynamically controlled process (entry 7). Selected examples illustrate useful generality: methyl-substituted fluorenones are available (entry 8); biaryl amides with one available site for remote metalation furnish single condensed fluorenones (entries 10 and 11); unsubstituted azafluorenones are readily prepared (entry 9).

Dengibsinin and dengibsin, unique naturally occurring fluorenones isolated from *Dendrobium gibsonni* (Orchidaceae) and originally assigned[7a] structures **4a** and **4b**, respectively, provided a timely application for the remote metalation protocol. However, in the course of this study,

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[7] a) Talapatra, S. K.; Bose, S.; Mallik, A. K.; Talapatra, B. *Tetrahedron* **1985**, *41*, 2765. (b) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553. (c) Talapatra, S. K.; Chakraborty, S.; Talapatra, B. *Indian J. Chem.* **1988**, *27B*, 250.

[8] The fluorenone or azafluorenone skeleton is found in significant classes of alkaloids (Alves, T.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 2135 and references cited therein); physiologically active agents (Humber, L. G. *Prog. Med. Chem.* **1987**, *24*, 299. Kyba, E. P.; Liu, S.-T.; Chockalingam, K.; Reddy B. R. *J. Org. Chem.* **1988**, *53*, 3513 and references cited therein. Nicholas, A. W.; Wani, M. C.; Manikumara, G.; Wall, M. E.; Kohn, K. W.; Pommier, Y. *J. Med. Chem.* **1990**, *33*, 972); and environmental pollutants (Streitwieser, A., Jr.; Brown, S. M. *J. Org. Chem.* **1988**, *53*, 904 and references cited therein).

[9] Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley Interscience: New York, 1964; Vol. 3. See also: Leber, J. D.; Elliott, J. D. *Tetrahedron Lett.* **1989**, *30*, 6849.

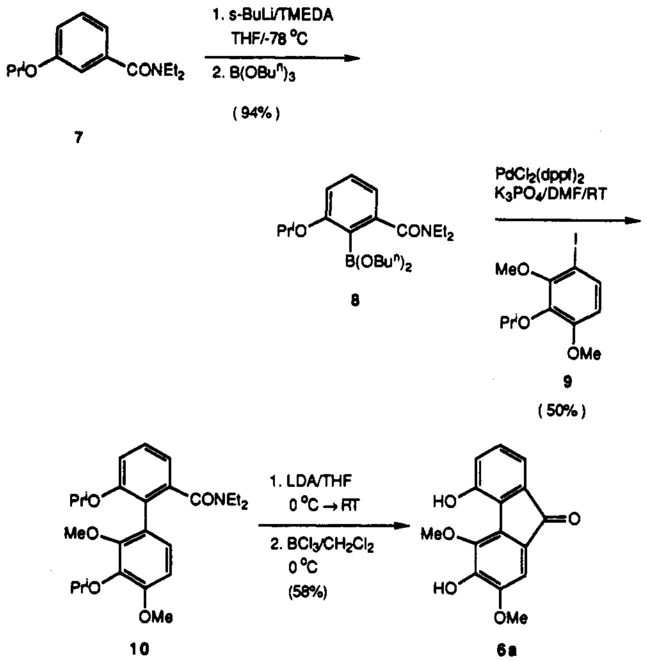
[10] Attempts to trap the intermediate metalated species at −78 °C with various electrophiles (MeI, TMSCl) have been unsuccessful.

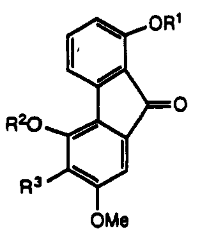
[11] In some cases (Table I, entries 10 and 11), LDA-induced reduction (Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057) produced mixtures of fluorenones and fluorenols. In this event, crude materials were directly oxidized (H$_2$CrO$_4$/THF/rt) to conveniently afford pure fluorenone products.

[12] Shirley, D. A.; Johnson, J. R.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209.

[13] Zoltewicz, J. A.; Grahe, G.; Smith, C. L. *J. Am. Chem. Soc.* **1969**, *91*, 5501. See also Verbeek, J.; George, A. V. E.; de Jong, R. L. P.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 257.

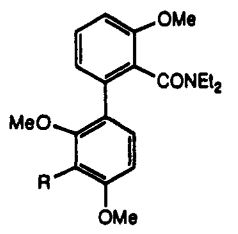
Scheme II





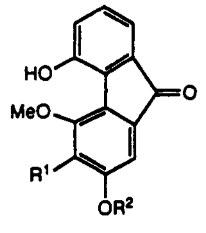
4

a: $R^1 = H$, $R^2 = Me$, $R^3 = OH$
b: $R^1 = R^2 = R^3 = H$
c: $R^1 = R^2 = Me$, $R^3 = OMe$
d: $R^1 = R^2 = Me$, $R^3 = H$



5

a: R = OMe
b: R = H



6

a: $R^1 = OH$, $R^2 = Me$ (dengibsinin)
b: $R^1 = R^2 = H$ (dengibsin)

the structures were revised to **6a** and **6b**, respectively, on the basis of additional spectroscopic data[7c] and the synthesis of the misassigned **4a**, **4b**, their respectively dimethyl ethers **4c** and **4d**, and the natural products **6a** and **6b**.[7b] Concurrently, we applied our remote metalation process (2.5 equiv of LDA) on the readily accessible amides **5a** and **5b** to give **4c** (82%) and **4d** (72%), respectively, whose physical and spectra data were in agreement with those of the synthetic materials **4c** and **4d**[7b] but not with those of dengibsinin dimethyl ether and dengibsin dimethyl ether.[7a,14] The synthesis of dengibsinin **6a** (Scheme II) begins by standard metalation/B(OBu^n)$_3$ quench of the *m*-isopropoxybenzamide **7** to give the stable borate **8** in high yield. After considerable experimentation, the cross coupling of **8** with the alkoxylated iodobenzene **9**, constituting a case of high steric hindrance and propensity for protodeboronation, was achieved under anhydrous Suzuki conditions[15] to give **10**. Sequential LDA-induced cyclization and selective deisopropylation[16] furnished dengibsinin (**6a**, 24% overall yield) whose physical and spectral properties were identical with those reported for the natural product.[7a,b]

In summary, a new and general anionic equivalent of the Friedel–Crafts reaction for the construction of substituted and condensed fluorenones, including aza analogues and the natural product dengibsinin (**6a**), from readily available biaryls and *m*-teraryls has been developed. The established connection of this method to the evolving directed ortho metalation[1] and aryl boronic acid cross coupling[2] strategies as well as the potential[17] of fluorenones in Haller–Bauer,[18] Beckmann,[19] and Baeyer–Villiger[20] reactions augur well for its synthetic utility in aromatic and heteroaromatic chemistry.[21,22]

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[14] Compound **4d** was also prepared by a route which begins by cross-coupling chemistry and ends similarly to that executed by Sargent.[7b] See: Sharp, M. J. M.Sc. Thesis, University of Waterloo, 1986.

[15] Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.

[16] Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1979**, 2593.

[17] Zhao, B.-p.; Snieckus, V., work in progress.

[18] Gilday, J. P.; Paquette, L. A. *Org. Prep. Proc. Int.* **1990**, *22*, 167.

[19] Esteban, S.; Marinas, J. M. *An. Quim.* **1978**, *74*, 1413; *Chem. Abstr.* **1979**, *91*, 19537f.

[20] Andrievskii, A. M.; Poplavskii, A. N.; Dyumaev, K. M. *Khim. Geterotsikl. Soedin.* **1982**, 703; *Chem. Abstr.* **1982**, *97*, 92088p.

[21] All new compounds show analytical and spectral (IR, ^{1}H and ^{13}C NMR, MS) data consistent with the assigned structures.

[22] We are grateful to NSERC Canada and Merck Frosst for financial support of our synthetic programs.

A Novel Synthesis of Furans by Base-Catalyzed Isomerization of Alkynyloxiranes

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Department of Chemistry, The University of South Carolina, Columbia, South Carolina 29208

Received December 3, 1990

Summary: Treatment of alkynyloxiranes **3** with KO-*t*-Bu in *t*-BuOH causes isomerization to the furans **4**. A pathway involving a cumulene alkoxide is proposed.

Persuant to studies on the synthesis of hydrofuran and hydropyran natural products we were interested in examining intramolecular S$_N$2′ additions to alkynyloxiranes as exemplified in eqs 1 and 2. To determine the feasibility of these transformations, epoxy alcohols **3a** and **3b** were prepared as model systems (eq 3).[1] With the aim of ef-

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[1] The coupling method of Sonogashiro et al. was employed. Sonogashiro, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Vinyl iodide **2** was prepared from 2-butyn-1-ol by treatment with Red-Al (Aldrich) followed by I$_2$ in THF. Cf: Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863.

0022-3263/91/1956-1685$02.50/0