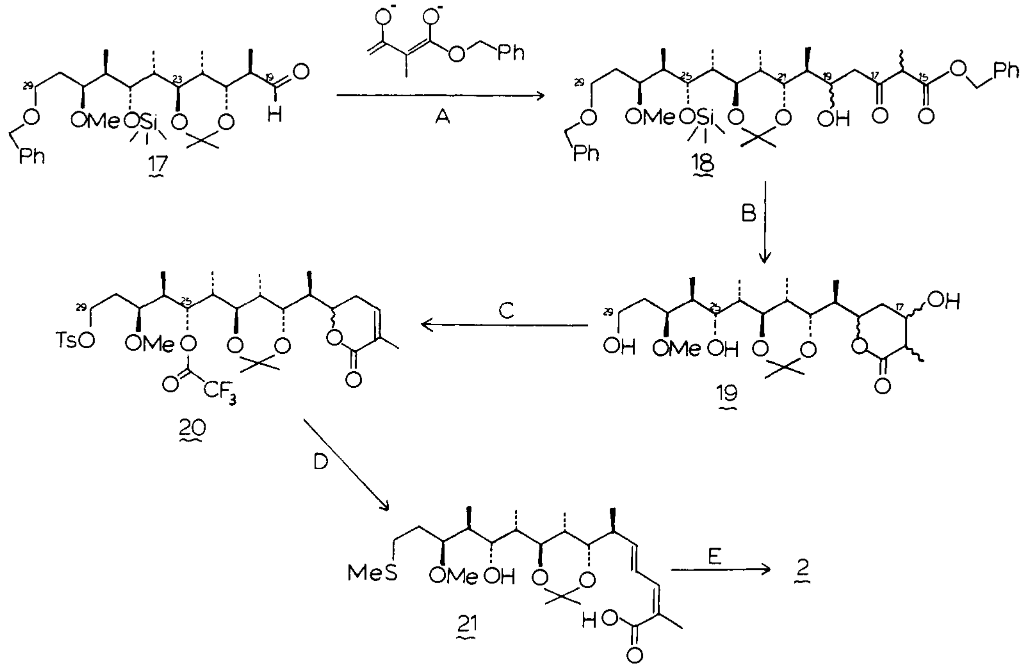
Scheme III[a]



[a] Key: (A) $(2\text{-}C_3H_7)_2NH$, n-BuLi (THF), −78 °C; (B) $NaBH_4$ (MeOH), −30 °C; 5% Pd–C, H_2(EtOH), 1.5 h, Δ, toluene; (C) $(CF_3CO)_2O$, Et_3N, (C_6H_6); TosCl, C_5H_5N, (CH_2Cl_2), 0 °C, 48 h; (D) MeSNa (excess), (DMF), room temperature, 10 min; (E) CH_2N_2 (Et_2O); Ac_2O, C_5H_5N, 70 °C, 36 h.

for a majority of the questions raised in our earlier review article.[25] Furthermore, the major problems associated with the more general subject of acyclic stereoselection,[26] which concern the diastereofacial selectivity of a chiral reagent or substrate or their interactions, are now clearly recognized.

Acknowledgment. We thank Drs. Sk. Asrof Ali and Tatsuo Toyoda of these laboratories for their important exploratory and degradative[10b] work in this project and Dr. Giancarlo Lancini, Gruppo Lepettit, Milano, for a generous gift of rifamycin S. We also thank the National Institutes of Health (CA 28337) and Hoffmann-La Roche for financial support. B.I. was a recipient of a Kennedy Memorial Trust Fellowship (September 1979–August 1981) and D.S.G. is a National Cancer Institute Trainee (NCI, 2-T32-CA 09112). High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resource Branch, Division of Research Resources.

Registry No. 2, 76123-20-1; **4**, 77302-12-6; **5**, 82849-04-5; **6**, 82849-02-3; **7**, 82849-03-4; **8**, 82849-05-6; **9**, 82864-88-8; **10**, 82849-06-7; **11**, 82849-07-8; (20*R*)-**11**, 82890-02-6; **12**, 82849-08-9; **13**, 82849-09-0; **14**, 82849-10-3; **15**, 82849-11-4; **16**, 82849-12-5; **17**, 82849-13-6; **18**, 82849-15-8; **19**, 82849-16-9; **20**, 82849-17-0; **21**, 82849-18-1; iii, 68210-62-8; iv, 82849-24-9; 3-pentanone (ion 1−), lithium, 74016-27-6; benzyl 2-methylacetoacetate lithio dianion, 82849-14-7; methyl 2*S*-methyl-3-[(2-trimethylsilylethoxy)methoxy]propanoate, 82849-19-2; 2*S*-methyl-3-[(2-trimethylsilylethoxy)methoxy]propanol, 82849-20-5; 4*R*-[(2*R*,6-dihydroxy-1*S*,3*R*-dimethyl-4*S*-methoxy)hex-1-yl]-6*R*-[2-[2-(trimethylsilylethoxy)methoxy]-1*S*-methylethyl]-2,2,5*R*-trimethyl-1,3-dioxane, 82849-21-6; 4-[6-benzyloxy-1,3-dimethyl-4-methoxy-2-(trimethylsilyloxy)hex-1-yl]-6-[benzyl 3,5-dihydroxy-2,6-dimethylhexanoate-6-yl]-2,2,5-trimethyl-1,3-dioxane, 82864-89-9; 4*R*-[1*S*,3*R*-dimethyl-6-hydroxy-4*S*-methoxy-2*R*-(trifluoroacetate)hex-1-yl]-6*R*-[1-[3-methyl-5,6-dihydropyran-2-on-6-yl]ethyl]-2,2-5*R*-trimethyl-1,3-dioxane, 82849-22-7; 4*R*-[1*S*,3*R*-dimethyl-2*R*-hydroxy-4-methoxy-6-methylthio]-6*R*-[methyl 2-methylhept-2(*Z*),4(*E*)-dienoate-6*S*-yl]-2,2,5*R*-trimethyl-1,3-dioxane, 82849-23-8; rifamycin S, 13553-79-2.

Supplementary Material Available: Listing of spectral data and comments (6 pages). Ordering information is given on any current masthead page.

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(25) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

(26) For a recent review, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

Directed Metalation of Tertiary Benzamides. Ortho *N*-Aryl Amination and Synthesis of Acridones

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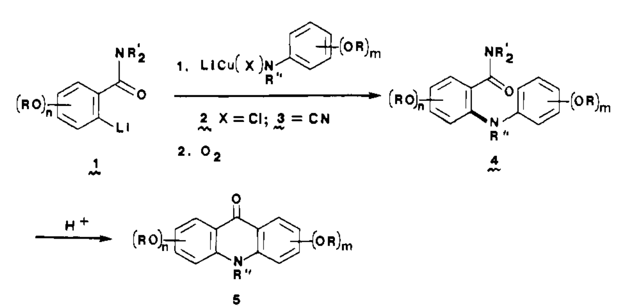
Received July 19, 1982

Umpolung methodology for direct formation of C–N bonds (i.e., $R\text{–}M + R^1R^2N^+ \rightarrow R\text{–}NR^1R^2$; M = metal)[1] is assuming significance as a result of the rapidly increasing accessibility of diverse organometallic reagents. Although numerous formally electrophilic nitrogen species have been investigated,[2] general and efficient utility of such reagents for the introduction of the $^+NH_2$ moiety has only recently surfaced, e.g., $PhSCH_2N_3$,[3] vinyl azides,[4] $H_2NOMe/MeLi$.[5] We report on the oxidative coupling reaction of ortho-lithiated benzamides (**1**) with anilido–chloro (**2**) or –cyano (**3**) cuprates to yield substituted *N*-arylanthranilamides (**4**, eq 1). We further delineate the direct conversion of this class of com-



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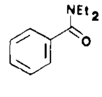
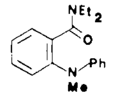
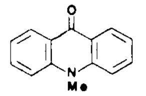
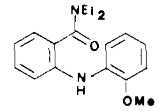
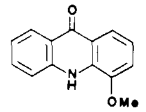
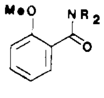
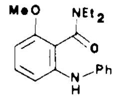
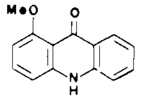
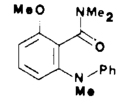
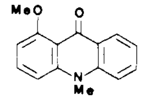
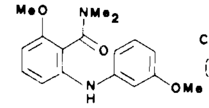
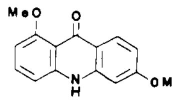
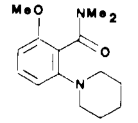
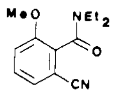
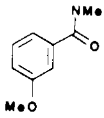
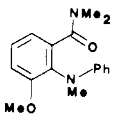
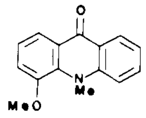
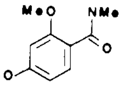
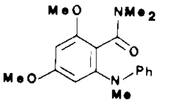
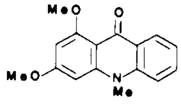
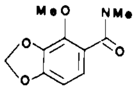
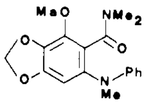
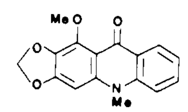
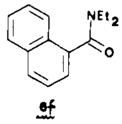
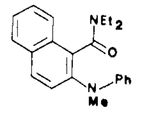
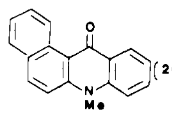
(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

0002-7863/82/1504-5531$01.25/0

Table I. Synthesis of Anthranilamides and Acridones[a]

Entry	Benzamide	Anthranilamide	Copper Reagent (equiv)	Yield, % (mp °C)	Acridone[b]	Yield, % (mp °C)
1	 **6a**		CuCl (5)	46 (70-72)		32[c] (202-203)[d]
2	**6a**		CuCN (5)	50 (91-92)		58 (284-285)[e]
3	 **6b**, R = Et		CuCN (5)	63 (92)		80 (>320)[f]
4	**6b**, R = Et		CuCN (5)	54[g]		
5	**6b**, R = Me		CuCl (5)	33 (122-123)		95 (163-164)[h]
6	**6b**, R = Me		CuCN (5)	36 (121-122)		95 (279-260)[i]
7	**6b**, R = Me		CuCN (5)	33 (117-119)		
8	**6b**, R = Et		CuCN[j] (5)	16 (90-91)		
9	 **6c**		CuCN (5)	26 (97-98)		25 (90)[k]
10	 **6d**		CuCl (5)	43 (oil)		79[l] (161-162)[m]
11	 **6e**		CuCl (5)	48 (109-109.5)		61[n] (217-219)[o]
12	 **6f**		CuCN (5)	61 (oil)		85 (203.5-204)[a]

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[a] Analytical and spectral data (IR, NMR, MS) data are in accord with the structures of all new compounds. Yields refer to pure, crystallized products. [b] Acridones obtained in refluxing heptafluorobutyric acid (24-72 h) unless otherwise indicated. [c] Obtained by using $POCl_3$ (PhMe, reflux, 10 h). [d] Lit. mp 203-204 °C: Gilman, H.; Spatz, M. *J. Org. Chem.* **1952**, *17*, 860. [e] Lit. mp 295-296 °C: Ullmann, F. *Annalen* **1907**, *355*, 312. [f] Lit. mp 346-348 °C: Kliegl, A.; Fehrle, A. *Chem. Ber.* **1914**, *47*, 1629. [g] This result obtained by coupling with anilinotrimethylsilane (Moeller, T. *Inorg. Synth.* **1957**, *5*, 59). [h] Lit. mp 165 °C: Hughes, G. K.; Matheson, N. K.; Norman, A. T.; Ritchie, E. *Aust. J. Sci.* **1952**, *A5*, 206; *Chem. Abstr.* **1953**, *47*, 2176. [i] Lit. mp not given: Mester, I.; Bergenthal, D.; Rozsa, Zs.; Reisch, J. *Z Naturforsch. Sect. B* **1979**, *B34*, 516. [j] This result obtained by coupling with $LiCu(CN)N(SiMe_3)_2$ (5 equiv) prepared by treatment of $LiN(SiMe_3)_2$ with CuCN. In addition, 2,2'-(*N*,*N*-diethylcarbamoyl)-3,3'-dimethoxybiphenyl (17%) was isolated. [k] Lit. mp 91 °C: footnote h. [l] Obtained by using trifluoroacetic acid (reflux, 60 h). [m] Lit. mp 163-165 °C: Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1970**, *23*, 1881. [n] Obtained by using formic acid (reflux, 60 h). [o] Lit. mp 217-218 °C: see ref 23.

pounds, generally accessible only by the Ullmann reaction,[6,7] into acridones (**5**),[6] including acridone alkaloids.[6,8,9] This work provides first cases of ligand transfer other than carbon from heterocuprates[10] and constitutes a new general protocol for regiospecific ortho introduction of *N*-substituents into benzamides via directed metalation, a synthetic strategy of considerable scope and application.[11,12]

The ortho-lithiated tertiary benzamide **1** was treated with the anilido cuprates **2** or **3**, generated from the lithioanilide and CuCl or CuCN, respectively.[13] Oxygenation (molecular O_2) gave the anthranilamide **4**.[14] The results of coupling reactions are summarized in Table I. The following selected experimental observations are pertinent: (a) 5 equiv of chlorocuprate **2**, prepared from CuCl and the aniline (1:1) gave poor (entry 5) to good (entries 10, 11) yields of products **4**; (b) in general, 1 equiv of cyanocuprate **3** failed to markedly improve the yields of products obtained under conditions a; (c) the use of 5 equiv of **3** constitutes the best conditions investigated to date—significantly cleaner, more easily manipulated, and higher yield reactions were observed vis-â-vis those using CuCl.[15]

A variety of alkoxy-substituted tertiary benzamides undergo the coupling reaction with aniline derivatives. A potential steric effect may be responsible for the low yields of product derived from a *m*-anisamide (entry 9). In comparison of aniline and *N*-methylaniline, no deleterious trend in yield due to the presence of acidic hydrogen in the presumed copper reagents **2** and **3**, $R'' = H$, derived from aniline was evident. Reaction with the cyanocuprate **3**, $R'' = SiMe_3$, gave a somewhat lower yield (compare entries 3 and 4) possibly due to the $d\pi$–$p\pi$ N–Si interaction, which disfavors the oxidative coupling process. In support of this contention, coupling of **6b**, R = Et, with the cuprate $LiCu(CN)N(SiMe_3)_2$ led to cyano ligand transfer (entry 8) in addition to 2,2′-(*N*,*N*-diethylcarbamoyl)-3,3′-dimethoxybiphenyl, a result characteristic of air oxidation of R_2CuLi systems.[16,17] The production of an *o*-piperidinobenzamide (entry 7) points toward the use of other secondary aliphatic amides. The successful coupling of an ortho-lithiated 1-naphthamide (entry 12)[18] suggests application of this reaction to more highly condensed aromatic amides.[19]

The direct cyclization of the *N*-arylanthranilamides **4** into the acridones **5**[20] was generally effected by using refluxing heptafluorobutyric acid.[21] Although long reflux times are required, the yields are good, and no qualitative difference in rate of cyclization of diethyl- and dimethylamides was observed. Several of the acridones obtained are natural products (entries 1,10, 11) among which evoxanthine (entry 11), prepared in four step and 13% overall yield from 3,4-methylenedioxy-*N*,*N*-dimethylbenzamide,[22] serves as a good example to compare with previous less efficient and lengthier approaches to this class of alkaloids.[23]

Notwithstanding the questions it raises concerning the nature of the intermediate(s) and overall mechanism,[10] the oxidative coupling methodology delineated here is an advantageous synthetic alternative to the classical Ullmann reaction[6] in that (a) it is effected under mild conditions (Ullmann process requires >150 °C) and (b) it circumvents the need for *o*-halobenzoic acids.

In view of the increasing number of groups that promote aromatic directed metalation,[11] the results reported herein may have broader synthetic implications for polysubstituted aromatic and heteroatom ring annelation methodologies.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Ontario Ministry of the Environment (Air Resources Branch) for financial support. J.N.R. thanks NSERC for the award of a postgraduate scholarship. Preprints of papers provided by Professor B. H. Lipshutz and Dr. R. K. Rajdan and correspondence with Dr. S. H. Bertz are gratefully acknowledged. We thank the referees for several helpful comments.

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(3) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483.

(4) Hassner, A.; Munger, P.; Belinka, B. A., Jr. *Tetrahedron Lett.* **1982**, 699.

(5) Beak, P.; Kokko, B. J. *J. Org. Chem.* **1982**, *47*, 2822.

(6) Acheson, R. M., Ed. "Acridones", 2nd ed.; Wiley: New York, 1973.

(7) For an approach via diphenyliodonium-2-carboxylate, see: Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1980**, *45*, 2127.

(8) Review of synthetic work: Johne, S.; Groger, J. *Pharmazie* **1972**, *27*, 195.

(9) For a different approach to acridones by reaction of *o*-(methoxyphenyl)oxazolines with lithioamides, see: Meyers, A. I.; Gable, R. *J. Org. Chem.* **1977**, *42*, 2654.

(10) Heterocuprates are synthetic intermediates of evolving utility. (a) Johnson, C. R.; Dhanoa, D. S. *J. Chem. Soc. Chem., Commun.* **1982**, *358*. (b) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. (c) Marino, J. P.; Jaen, J. C. *Ibid.* **1982**, *104*, 3165.

(11) Excellent review: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *29*, 1. Reviews highlighting the use of tertiary benzamides: (b) Snieckus, V. *Heterocycles* **1981**, *14*, 1649. Beak, P.; Snieckus, V. *Acc. Chem. Res.*, in press.

(12) The isolated observation that reaction of 2,6-diethoxyphenyllithium with copper piperidide (from lithium piperidide + CuI) yields *N*-(2,6-diethoxyphenyl)piperidine was significant in initiating our studies. See: Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.

(13) CuCl was purified according to Keller and Wycoff (Keller, R. N.; Wycoff, H. D. *Inorg. Syn.* **1946**, *2*, 1). CuCN (Baker Chemical Co.) was dried under high vacuum at 100 °C and used directly.

(14) In a typical experiment, *sec*-BuLi (2.5 mL, 2.8 mmol, 1.3 M solution in cyclohexane) was injected by syringe into a stirred solution of TMEDA (0.5 mL, 3.0 mmol) in anhydrous THF (150 mL) maintained at −78 °C under nitrogen. A solution of **6b**, R = Et, (532 mg, 2.55 mmol) in THF (20 mL) under nitrogen was added, and the resulting yellow solution of the lithiated benzamide was stirred at −78 °C for 50 min. In a separate reaction vessel, a solution of lithioanilide, prepared from aniline (1.4 g, 15 mmol, freshly distilled from Zn powder) and *n*-BuLi (11.7 mL, 17 mmol, 1.45 M solution in hexane) in THF (50 mL) at − 10 °C under nitrogen, was treated with dry CuCN (1.34 g, 15 mmol). The resulting dark brown *solution* of the cuprate was stirred for 15 min at −10 °C and then slowly injected into the solution of the lithiated benzamide. After 2 h, oxygen gas was passed through the solution for 30 min at −78 °C, the cooling bath was removed, and the mixture was treated with concentrated NH_4OH. The resulting precipitate was collected by filtration and was washed with CH_2Cl_2. The filtrate was concentrated, and the residue was dissolved in CH_2Cl_2. After being washed with a mixture of concentrated NH_4OH and saturated NaCl solution (1:1), the organic layer was evaporated to dryness, and the crude material was chromatographed (silica gel, $CHCl_3:Me_2CO$ eluent, 20:1) to give the product (470 mg, 63%).

(15) This comparison is representative of a number of parallel reactions carried out by using CuCl and CuCN and various benzamides **1**. Details will be reported in the full paper.

(16) Whitesides, G. M.; San Fillippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. See, however: Lambert, G. J.; Duffley, R. P.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1982**, *47*, 3350.

(17) In an attempt to introduce an *o*-amino unit, **6b** (1 equiv), R = Et, was treated with a THF solution of $LiNH_2$ (5 equiv), CuCN (5 equiv), and TMEDA (1 equiv). However, 2,2′-(*N*,*N*-diethylcarbamoyl)-3,3′-dimethoxybiphenyl was the only isolable product (17%) from this reaction. Studies to find other synthetic equivalents of $^+NH_2$ and to exploit biphenyl synthesis via directed metalation are in progress.

(18) The inverse coupling reaction between the cyanocuprate derived from 1-naphthylamine with **1** was, perhaps fortunately, unsuccessful.

(19) For ortho metalated naphthamides, see: Harvey, R. A.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.* **1982**, *47*, 2120. Meyers, A. I.; Avila, W. B. *Ibid.* **1981**, *46*, 3881. For an ortho metalated phenanthrene amide, see: Iwao, M.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron Lett.* **1981**, 2349.

(20) Cyclizations of primary and secondary amides yielding 9-aminoacridines are well documented (ref 6, p 118).

(21) Commercially available from Aldrich Chemical Co.

(22) This compound was converted into **6e** by the useful procedure for ortho hydroxylation of ortho-lithiated *N*,*N*-diethylbenzamides described by Beak and Brown (Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34) followed by standard methylation. Metalation of *N*,*N*-dimethylbenzamides, heretofore considered impossible due to nucleophilic attack by *sec*-BuLi, thus appears feasible in alkoxy-substituted cases (see Table I and Watanabe et al. (Watanabe, M.; Sahara, M.; Furukawa, S.; Billedeau, R.; Snieckus, V. *Tetrahedron Lett.* **1982**, 1647).

(23) Govindachari, T. R.; Pai, B. R.; Subramaniam, P. S.; Subramanyan, V. *Tetrahedron* **1967**, *23*, 1827.