Directed *ortho* and Remote Metalation - Cross Coupling Connections. Buchwald-Hartwig Synthesis of 2-Carbamoyl Diarylamines. Regioselective Anionic Routes to Acridones, Oxindoles, Dibenzo-[b,f]azepinones, and Anthranilate Esters

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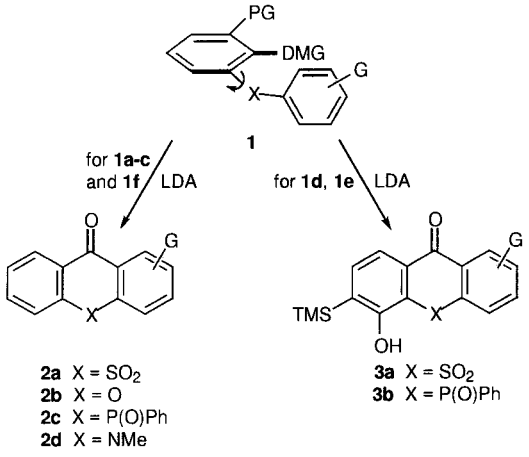
Abstract: 2-Carboxamido diarylamines **1f**, **7**, and **9**, efficiently available by Buchwald-Hartwig C-N cross coupling reactions, serve as starting materials for new anionic routes to acridones **2d,** oxindoles **10**, dibenzo[b, f]azepinones **11**, and anthranilate esters **8**.

Recent work in our laboratories has extended the Directed remote Metalation concept from its use for fluorenone[1] and highly substituted biaryl[2] construction to provision of general routes to a) thioxanthen-9-ones (**2a**),[3] xanthen-9-ones (**2b**),[4] and dibenzo[b,e]phosphorinones (**2c**)[5] from the 2-carbamoyl diarylsulfones (**1a**), diarylethers (**1b**) and triarylphosphane oxides, (**1c**) respectively and b) TMS hydroxy derivatives of two of these systems, **3a** and **3b** from the 2-carbamoyloxy derivatives **1d** and **1e** respectively (**Scheme 1**). Herein we delineate the diarylamine variant, **1f** → **2d** of this anionic Friedel-Crafts equivalent which provides a general regiospecific synthetic protocol for acridones. In addition, we report several other new anionic transformations of substituted 2-carbamoyl diarylamines, **7** → **8** and **9** → **10, 11** (**Scheme 3**), of potentially broad scope for synthetic heterocyclic and aromatic chemistry.

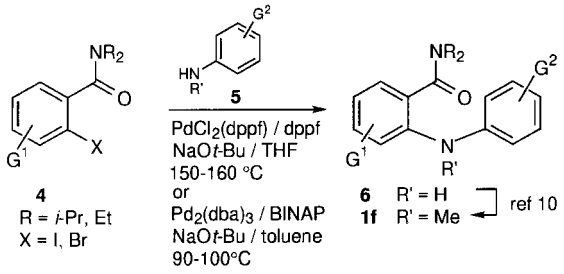


	DMG	X	PG	ref
1a	$CONEt_2$	SO_2	H	3
1b	$CONEt_2$	O	H	4
1c	$CONEt_2$	P(O)Ph	H	5
1d	$OCONEt_2$	SO_2	TMS	3
1e	$OCONEt_2$	P(O)Ph	TMS	5
1f	$CONEt_2$	NMe	H	this work

DMG = Directed Metalation Group

Scheme 1

The initially applied Ullmann[6] and Directed *ortho* Metalation (DoM)-cuprate[7] chemistry for the synthesis of the requisite diarylamines **1f**, although general, suffered from tedious work up and purification requirements. In contrast, adaptation of the recent notable C-N coupling methods of Buchwald[8] and Hartwig[9] led to the development of an excellent general route, **4** + **5** → **6** → **1f** (**Scheme 2**). Since coupling of **4** with *N*-methylanilines, **5**, R' = Me gave generally lower yields, reaction of **5**, R' = H followed by methylation[10] was the preferred route to compounds **1f** (**Table 1**). Although both methods were tested, the Buchwald procedure[8] on bromide **4**, X = Br rather than iodide **4**, X = I partners was generally employed.[11] Following the optimization of substrate and base parameters (entry 2), a number of diarylamines were converted into the corresponding acridones. Of particular note is the improvement in yields[12] (entry 1) and complementarity of the anionic route to the classical Friedel-Crafts reaction[13] dictated by DMG effects (entry 2), the facility of cyclization for a *m*-EDG system (entry 3) when compared to the severity of Friedel-Crafts conditions,[14] the preparation of an intermediate (entry 4) which constitutes a total synthesis of the acridone alkaloid, acronycine,[15] and an application to a naphthylphenylamine (entry 6).

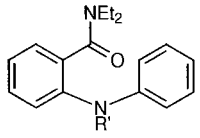
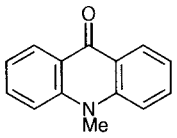
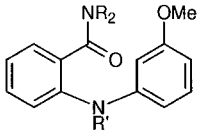
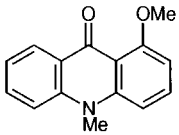
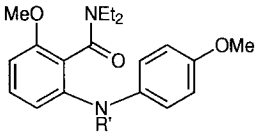
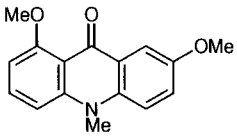
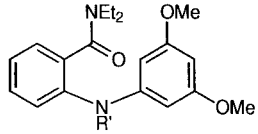
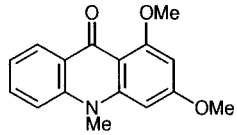
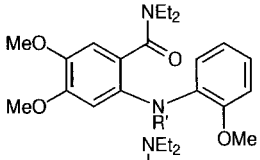
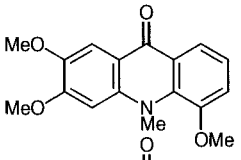
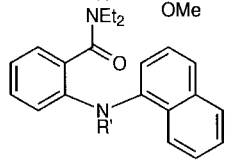
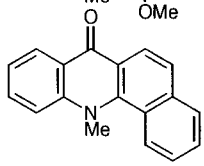


Scheme 2

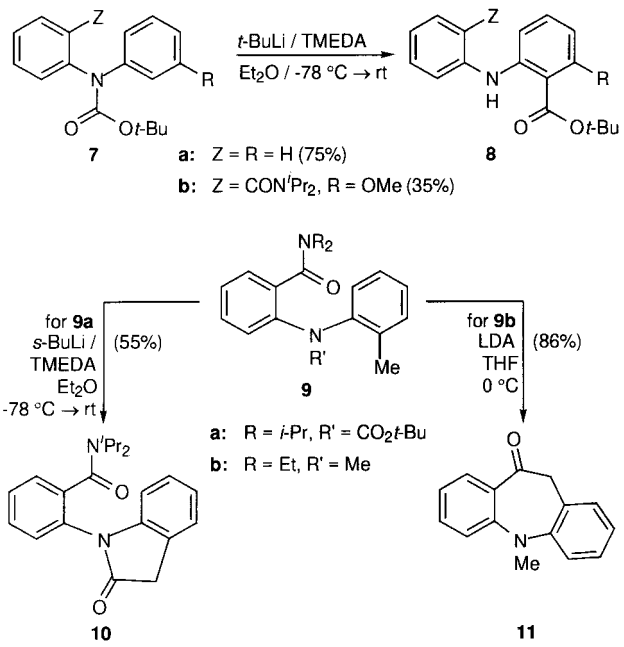
Additional synthetically useful anionic reactivity was observed for diarylamines **7a-b** and **9a-b** (**Scheme 3**). Thus subjecting **7a-b** to *t*-BuLi / TMEDA conditions led to N → C carbamoyl migration to give anthranilates **8a-b,** a reaction analogous to the anionic *ortho*-Fries rearrangement of aryl O-carbamates to salicylamides.[16-19] The corresponding *ortho*-tolyl derivative **9a**, on the other hand, upon treatment with *s*-BuLi/TMEDA[20] underwent lateral metalation and cyclization to give the oxindole **10**.[21] The simpler *N*-methyl system **9b**, upon treatment with LDA, followed an alternate cyclization mode subsequent to lateral metalation affording the dibenzo[b,f]azepinone **11** in excellent yield,[22] representative of the classical tricyclic antidepressant drugs.[23] Electronic, conformational, and, undoubtedly, Complex Induced Proximity Effect (CIPE)[24] factors play roles in the outcome of these diverse reactivities.

In summary, a new general synthesis of acridones has been established which constitutes a mild anionic Friedel-Crafts complement, overriding the characteristic electrophilic substituent effects normally observed in the latter reaction. Furthermore, using 2-carbamoyl diarylamines, readily available by Buchwald-Hartwig C-N catalytic coupling protocols, regioselective anionic routes to anthranilate esters, oxindoles, and dibenzazepinones (**12**, **13**) have been devised, thereby opening new doors in synthetic aromatic and heterocyclic chemistry.[25-28]

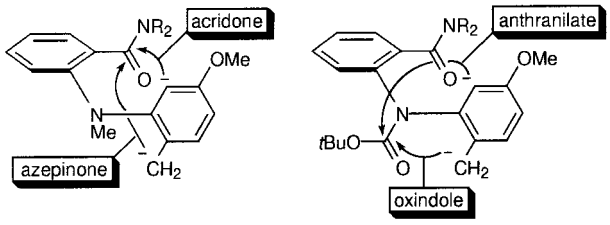
Table 1. Synthesis of 2-Carbamoyl Diaryl Amines (**1f**) and Acridones (**2d**)

Entry	Cross Coupling Product[a]	Cross Coupling yield **6**, % (R = H)	*N*-Methylation yield **1f**, % (R = Me)	LDA Cyclization Product[a]	LDA Cyclization yield **2d**, %
1		81	98		76
2		60 (R = Et) 84 (R = *i*-Pr)	86 (R = Et) 98 (R = *i*-Pr)		87 (R = Et) 55 (R = *i*-Pr) 22 (R = *i*-Pr)[b]
3		68	99		53
4		93	97		34
5		53	99		67
6		81	84		98

[a] Yields of isolated and purified (chromatographed, crystallized) materials. [b] Using LiTMP / THF / -15 °C → rt.



Scheme 3



References and Footnotes

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1. Fu, J.-m.; Zhao, B.-p.; Sharp, M.J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.
2. Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.
3. Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *56*, 6508.
4. Familoni, O.B.; Ionica, I.; Bower, J.F.; Snieckus, V. *Synlett* **1997**, 1081.
5. Gray, M.; Chapell, B.J.; Taylor, N.J.; Snieckus, V. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1558.
6. Lindley, J. *Tetrahedron* **1984**, *40*, 1433. See also citations in Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.
7. Iwao, M.; Reed, J.N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531.

8. Wolfe, J.P.; Wagaw, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
9. Driver, M.S.; Hartwig, J.F. *J. Am. Chem. Soc.* **1996**, *118*, 217. Review: Hartwig, J.F. *Synlett* **1997**, 329.
10. Vitale, A.A.; Chiocconi, A.A. *J. Chem. Res. (S)*, **1996**, 336.
11. *Typical Coupling Procedure*: A thick-walled screw cap glass tube was charged with a mixture of *N*,*N*-diethyl 2-bromobenzamide (505 mg, 1.97 mmol), aniline (0.21 mL, 2.30 mmol), NaO*t*-Bu (266 mg, 2.77 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol), BINAP (11 mg, 0.017 mmol) and toluene (5 mL) under N_2 atmosphere. The tube was sealed and heated (90-100°C) with stirring for 21 h, and cooled to rt. Addition of aq NH_4Cl and standard workup, followed by flash column chromatography (10% EtOAc/hexane) afforded *N*, *N*-diethyl *N*-phenylanthranilamide (426 mg, 81%), mp 74-76°C (hexane); IR (neat) 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40 (d, 1H, J = 0.8 Hz), 7.37-7.16 (m, 4H), 7.10-7.05 (m, 2H), 6.96-6.84 (m, 3H), 3.45 (bs, 4H), 1.17 (bs, 6H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.1, 142.1, 141.1, 129.5, 128.9, 126.9, 125.0, 120.9, 119.4, 118.2, 116.8, 29.3, 13.3; m/z (EI) 268 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.08; H, 7.43; N, 10.70.
12. Compare with the corresponding Friedel-Crafts method (32% yield, see ref 7).
13. See, *inter alia*, Vieira, P.C.; Kubo, I. *J. Nat. Prod.* **1992**, *55*, 1112; Su, T.-l.; Dziewiszek, K.; Wu, T.-s. *Tetrahedron Lett.* **1991**, *32*, 1541.
14. For general effects of m-EDG on Friedel-Crafts chemistry, see Taylor, R. In *Electrophilic Aromatic Substitution* Wiley, New York, **1990**, p236. For examples, see Sargent, M.V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553; Sharp, M.J. MSc. Thesis, University of Waterloo, **1986**.
15. Svoboda, G.H. *Lloydia* **1966**, *29*, 206; Svoboda, G.H.; Poore, G.A.; Simpson, P.J.; Boder, G.B. *J. Pharm. Sci.* **1966**, *55*, 758. Review on acridone alkaloids: Su, T.-l. and Watanabe, K.A. In *Studies in Natural Product Chemistry*, Atta-ur-Rahman, Ed., Elsevier, Amsterdam, **1993**, *13*, 347.
16. Sibi, M.P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. For a recent list of citations, see James, C.A.; Snieckus, V. *Tetrahedron Lett*. **1997**, 38, 8149.
17. For similar reactions, see Hellwinkel, D.; Lammerzahl, F.; Hofmann, G. *Chem. Ber.* **1983**, *116*, 3375; Hallberg, A.; Svensson, A.; Martin, A.R. *Tetrahedron Lett.* **1986**, *27*, 1959; Billedeau, R. M.Sc. Thesis, University of Waterloo, **1983**.
18. Metalation of **7a** under these conditions for 60 min followed by electrophile quench afforded 2-TMS (58-77%), 2-Me (59%), and 2-PhCH(OH) (48%) *N*-*t*-Boc diphenylamines.
19. **8b** may be a useful intermediate for acridones related to Glaxo France pharmaceutical GF120918. See Dodic, N.; Dumaitre, B.; Daugan, A.; Pianetti, P. *J. Med. Chem.* **1995**, *38*, 2418.
20. Clark, R.D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.
21. This constitutes a variant of a Madelung result in which the carbonyl carbon originates from external CO_2, see Clark, R.D.; Muchowski, J.M.; Fisher, L.E.; Flippin, L.A.; Repke, D.B.; Souchet, M. *Synthesis*, **1991**, 871.
22. For analogous formation of dibenzooxepinone, dibenzophosphorinone, and dibenzothiepinone systems, see refs. 4 and 5, and footnote 11 in ref. 4, respectively.
23. Richelson, E. In *Antidepressants: Neurochemical, Behavioral, and Clinical Perspectives* Enna, S. J.; Malick, J. B.; Richelson, E. (Eds.), Raven Press, New York, **1981**, p53; Sulser, F. In *Antidepressants: Thirty Years On* Leonard, B. and Spencer, P. (Eds.), CNS Publishers, London, **1990**, p23.
24. Beak, P.; Meyers, A.I. *Acc. Chem. Res.* **1986**, *19*, 356.
25. All new compounds show analytical and spectral (IR, NMR, MS) data in full agreement with the depicted structures.
26. *Typical Cyclization Procedure*: A solution of *N*,*N*-diethyl *N*-methyl-*N*-phenylanthranilamide (0.1145 g, 0.41 mmol) in THF (3 mL) was cooled to 0 °C under argon atmosphere and treated with a solution of LDA (1.42 mmol) [*n*-BuLi, 0.85 mL, 1.67 M, 1.42 mmol; HN^iPr_2, 0.19 mL, 1.42 mmol], in THF (2 mL) precooled to 0 °C. The reaction mixture was maintained at 0 °C for 1.5 h and warmed to rt. Addition of aq NH_4Cl and standard workup, followed by silica gel flash column chromatography (30% EtOAc/ hexane eluent) afforded *N*-methylacridone (0.0680 g, 79% yield), mp 221.5-222°C ($MeOH/H_2O$), lit[27] mp 210-211°C (abs EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 8.51 (dd, J = 8.0, 1.5 Hz, 1H), 7.70-7.63 (m, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.27 - 7.21 (m, 1H), 3.81 (s, 3H).
27. Maskiewicz, R.; Sogah, D.; Bruice, T.C. *J. Am. Chem. Soc.* **1979**, *101*, 5355.

28. We are grateful to NSERC Canada and Monsanto/Searle for support of our synthetic programs under the Industrial Research Chair award. S. MacNeil is an NSERC Postgraduate Scholar. Professors Steve Buchwald and John Hartwig and their students graciously provided experimental details of their diarylamine synthesis and valuable advice. VS thanks the Dipartimento di Chimica, University of Pisa and Professors P. Salvadori and D. Pino for a Visiting Professorship and cultural hospitality during the preparation of this paper.