

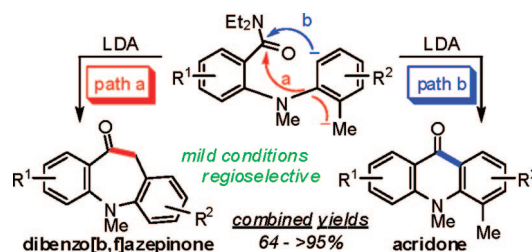
Carbanionic Friedel–Crafts Equivalents. Regioselective Directed *Ortho* and Remote Metalation–C–N Cross Coupling Routes to Acridones and Dibenzo[*b,f*]azepinones[†]

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Carbanion-mediated general regioselective routes to acridones **4** (Table 2) and dibenzo[*b,f*]azepinones **20** (Table 4) are described. Buchwald–Hartwig C–N cross coupling of *o*-halo benzamides **1** with anilines **2** or **16**, followed by simple *N*-methylation, dependably provides *N*-methyl diarylamines **3** (Table 1) and **18** (Table 3). Upon treatment with LDA, **3** and **18** are converted into acridones **4** and dibenzo[*b,f*]azepinones **20**, respectively, in good to excellent yields with regioselectivity which depends upon the presence or absence of directed metalation groups (DMGs). Brief investigations as follows are described: the synthesis of desmethyl acridone **15** (Scheme 4), an attempt to effect a double-directed remote metalation sequence which leads only to a monocyclization product **13** (Scheme 3), and an analogous but nonregioselective route to a xanthone **22** and dibenzo[*b,f*]oxepinone **24** (Scheme 5). DFT calculations reveal low energy conformations for compounds **18b** and **23** which account for product formation and indicate that the cyclization reactions are under kinetic control.

Introduction

The synthetic value of combined directed *ortho* metalation (DoM)–directed remote metalation (DreM)–transition-metal-mediated cross-coupling protocols for the synthesis of diversely functionalized condensed aromatic systems has been well demonstrated during the past decade.^{1,2} We previously³ communicated the application of this methodology, showcasing

Buchwald–Hartwig aryl amination⁴–DreM symbiosis, to efficient syntheses of acridones and acridone alkaloids (**4**) (Scheme 1). These compounds hold significant interest due to their diverse bioactivity,⁵ host–guest chemistry,⁶ applications in chemical, biochemical, and environmental analyses,⁷ and utility in synthetic method development.^{8,9} However, most synthetic approaches rely on classical Friedel–Crafts chemistry, are regioselectivity-compromised, and usually require harsh, acid-mediated conditions.^{5a,10,11} The recent evolution of the DreM strategy^{1a} provides an *anionic* Friedel–Crafts equivalent ap-

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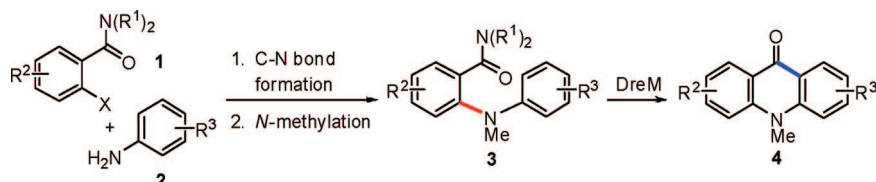
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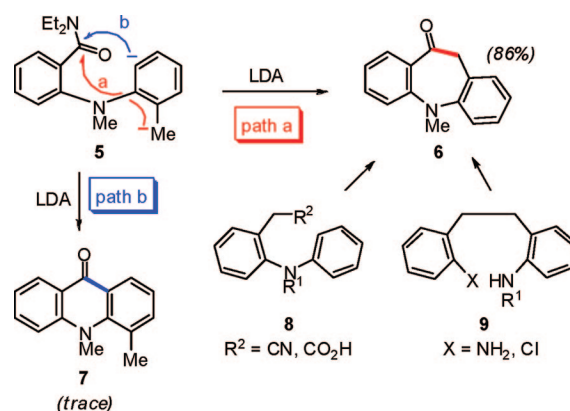
SCHEME 1



proach to these and other heterocyclic systems³ and offers, at the least, complementarity and, at best, significant advantages over the classical methodology.

During preliminary investigations, we were intrigued by the finding that the diarylamine **5** underwent regioselective ring closure to the dibenzo[*b,f*]azepinone **6** (Scheme 2, path a) in preference to the acridone **7** (path b) under mild LDA-mediated conditions. Since the dibenzo[*b,f*]azepinone skeleton **6** represents a class of compounds with significant biological activity¹² and the reaction, in prototype form, constitutes a considerable improvement over known synthetic methods (**8, 9** → **6**, Scheme 2),¹³ we pursued this observation and herein report the scope and

SCHEME 2



limitations of the DreM chemistry leading to both acridone and dibenzo[*b,f*]azepinone derivatives.³

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TABLE 1. Synthesis of *N,N*-Dialkyl-2-anilino benzamides **10** and **3**

Entry	Benzamide	Aniline	<i>N</i> -Arylation Product	Yld, %	<i>N</i> -Methylation Product	Yld, %
1				68		84
2	1b : R ¹ = Et		10b : R ¹ = Et	60	3b : R ¹ = Et	86
3	1c : R ¹ = <i>i</i> Pr		10c : R ¹ = <i>i</i> Pr	83	3c : R ¹ = <i>i</i> Pr	>95
4	1b			81	3d	>95
5	1b			93	3e	>95
6				60	3f	>95
7				53	3g	>95
8	1b			81	3h	84

^a Conditions: Pd₂(dba)₃ (0.22–0.48 mol %), (±)-BINAP (0.74–1.36 mol %), NaO^tBu, toluene, 90–100 °C. ^b Conditions: (1) *n*-BuLi, THF, 0 °C; (2) MeI, dioxane, 0 °C.

Results and Discussion

To initiate the acridone synthesis (Scheme 1), we considered the preparation of the requisite diarylamines (**3**) according to the Pd-mediated C–N bond formation coupling methods established by Buchwald¹⁴ and Hartwig¹⁵ as attractive alternatives to the harsh conditions and tedious workup and purification procedures typical of Ullmann chemistry.¹⁶ Initial Pd-catalyzed conditions reported by Buchwald¹⁴ and Hartwig,¹⁵ utilizing P(*o*-tolyl)₃ as supporting ligand, proved to be unsatisfactory in our hands. However, application of subsequently reported conditions,^{17,18} employing (±)-BINAP as ligand for palladium, led to excellent results (Table 1). The diminished yields observed

for amination of methoxy-substituted benzamide substrates (Table 1, entries 6 and 7), relative to benzamide **1b**, are almost certainly a result of the increased electron density of these substrates which would decelerate the oxidative addition step to the Pd(0) catalyst. These yields of coupled products are, however, comparable to those reported by Buchwald¹⁷ for electron-rich aryl bromides.

In light of the inability to effect LDA-mediated cyclization of the diarylamines **10**, these derivatives were *N*-methylated

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TABLE 2. Synthesis of Acridones 4a–f

Entry	SM	Product	Yld, %	Entry	SM	Product	Yld, %
1	3a		88	6	3f		53
2	3b		91	7	3g		67
3	3c		55				
4	3d		79	8	3h		>95
5	3e		34 ^a				

^a 1-(Diethylamino)-3-methoxy-10-methylacridin-9(10*H*)-one was isolated as a byproduct in 33% yield (see the Supporting Information).

using a modification of a literature procedure¹⁹ to give the prerequisite *N*-methylated diarylamines (**3**) in excellent yields (Table 1). Although *N*-methylanilines may also be coupled under the conditions employed, yields tend to be lower presumably as a result of competing β -hydride elimination. Thus, a two-step sequence involving amination of primary anilines followed by facile *N*-methylation was employed.

With the required diarylamines in hand, LDA-mediated cyclization using conditions that had been optimized for anion-induced cyclization to analogous tricyclic compounds including thioxanthene-9-one, 10,10-dioxides,²⁰ dibenzo[*b,e*]phosphorinones,²¹ and xanthene-9-ones²² afforded the acridones **4** in moderate to excellent yields (Table 2).

The effectiveness and utility of this anion-mediated route to acridones is demonstrated by the following observations: yields are significantly improved relative to standard Friedel–Crafts protocols (entry 4);²³ regioisomers not readily accessible by Friedel–Crafts methods²⁴ are prepared in high yields (entries 1–3); substrates bearing *m*-electron-donating groups undergo cyclization (entry 5), in contrast to the difficult reaction under Friedel–Crafts conditions;²⁵ three of the examples (entries 1–3,²⁶ 4,²⁷ and 5²⁸) represent total syntheses of acridone alkaloids, entry 5 (compound **4c**) being a formal total synthesis

of acronycine,²⁹ a naturally occurring, broad-spectrum antitumor agent. Interestingly, the low isolated yield of **4c** is accounted for by the isolation, in 33% yield, of a byproduct tentatively assigned 1-diethylamino-3-methoxyacridone (see the Supporting Information).

In order to extend the utility of the Buchwald–Hartwig amination–DreM protocol, the bis DreM cyclization of the *N,N'*-(bis)diaryl-1,4-diaminobenzene **12**, prepared in two steps (16–23% overall yield) from *N,N*-diethyl-2-bromobenzamide and 1,4-diaminobenzene, to bis-acridone, **11**,^{30,31} was attempted (Scheme 3). Unfortunately, even forcing conditions (5–10 equiv of LDA) led only to the formation of **13** as the major product as well as significant decomposition. This observation is in accord with previous failed attempts to affect double DreM in aromatic systems³² and may be rationalized, in part, by the potential hydride-transfer reduction of acridones by LDA³³ to acridinium salts followed by further decomposition. Based on these preliminary results, further exploration of the double-DreM methodology is warranted.

Although the described method represents a vast improvement over classical methods for acridone synthesis,^{5a} an inherent limitation is the requirement for *N*-alkylation of substrates prior to LDA-mediated cyclization. Since heterotricyclic compounds of this type are usually inert to *N*-dealkylation with conventional reagents,^{12d} *N*-functionalization post cyclization is not possible using the current protocol. To alleviate this problem, the MOM-protected **14** (Scheme 4), easily obtained from the diarylamine **10b**, was subjected, without purification, to the standard LDA conditions. A smooth cyclization ensued to give product which, upon mild acidic hydrolysis, afforded acridone (**15**) in 71% overall yield. Although this protocol was not generalized, its facile application to other diarylamine substrates may be envisioned, thus extending the DreM approach for the construction of *N*-unsubstituted acridones.

In order to evaluate the scope and limitations of the regioselective dibenzo[*b,f*]azepinone cyclization (**5** \rightarrow **6**, Scheme 2),³ a series of benzamides was subjected to coupling reactions with *o*-toluidines, under conditions similar to those employed for the preparation of acridone cyclization precursors (Table 1), to yield diarylamines **17** (Table 3) in good to excellent yields. The method was found to be quite general, accommodating substitution in both substrates. Not surprisingly, bromides coupled preferentially in the presence of chlorides (entries 9 and 14), which have been reported to be inert to the BINAP-ligated palladium system.¹⁷ In general, these couplings appear to be sensitive to steric effects, affording diminished yields of products using bulky substrates (entries 7–9, 12, and 13). In one case (entry 13), the isoindolinone **19** was isolated in 28%

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TABLE 3. Palladium-Catalyzed Synthesis of *N,N*-Dialkyl-2-(2-toluidino)benzamides **17** and **18**

Entry	Benzamide	<i>o</i> -Toluidine	<i>N</i> -Arylation Product	Yld, %	<i>N</i> -Methylation Product	Yld, %
1	 1a: R ¹ = Me	 16a	 17a: R ¹ = Me	63	 18a: R ¹ = Me	81
2	 1b: R ¹ = Et	 16a	 17b: R ¹ = Et	85	 18b: R ¹ = Et	83
3	 1c: R ¹ = <i>i</i> Pr	 16a	 17c: R ¹ = <i>i</i> Pr	90	 18c: R ¹ = <i>i</i> Pr	>95
4	 1b	 16b	 17d	45	 18d	93
5	 1b	 16c: G = OMe	 17e: G = OMe	90	 18e	92
6	 1b	 16d: G = Cl	 17f: G = Cl	93	 18f	>95
7	 1f: G = OMe	 16a	 17g: G = OMe	51	 18g	65
8	 1g: G = Me	 16a	 17h: G = Me	87	 18h	93 ^c
9	 1h: G = Cl	 16a	 17i: G = Cl	76	 18i	60 ^c
10	 1b	 16e: G = Me	 17j: G = Me	81	 18j	83
11	 1b	 16f: G = Cl	 17k: G = Cl	89	 18k	93
12	 1b	 16g: G = Cl	 17l: G = Cl	45 ^d	 18l	73
13	 1b	 16h: G = OMe	 17m: G = OMe	36 ^d	 18m	54
14	 1i: G = Cl	 16a	 17n: G = Cl	89	 18n	>95
15	 1j: G = OMe	 16a	 17o: G = OMe	40	 18o	93
16	 1k: G = Me	 16a	 17p: G = Me	42	 18p	86

^a Pd₂(dba)₃ (0.23–0.87 mol %), (±)-BINAP (0.68–1.52 mol %), NaO^tBu, toluene, 90–110 °C. ^b (1) *n*-BuLi, THF, 0 °C; (2) MeI, dioxane, 0 °C. ^c Conditions: (1) NaH, THF, rt; (2) MeI, rt. ^d

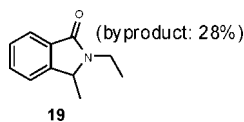


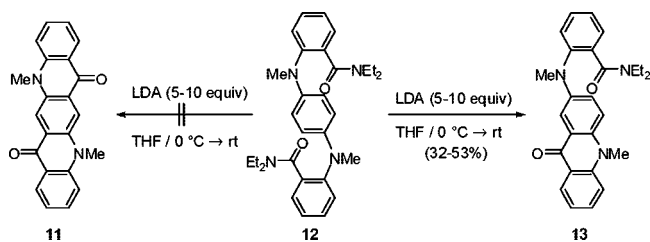
TABLE 4. Synthesis of 5*H*-Dibenzo[*b,f*]azepinones 20a–n

1. LDA (2-4 equiv)
THF / 0 °C
2. NH₄Cl / 0 °C or rt

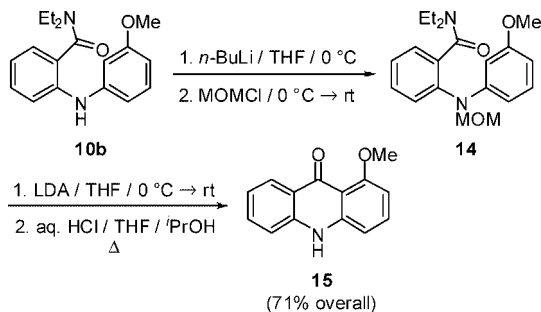
Entry	Diarylamine	5 <i>H</i> -Dibenzo[<i>b,f</i>]azepinone	Yld, %	Acridone	Yld, %
1	 18a: R ¹ = Me	 20a	95	 21a	<5
2	18b: R ¹ = Et		89		<5
3	18c: R ¹ = <i>i</i> Pr		72		14
4	 18d	 20b	65	 21b	34
5	 18e: G = OMe	 20c: G = OMe	20	 21c: G = OMe	79
6	18f: G = Cl	20d: G = Cl	8	21d: G = Cl	83
7	 18g: G = OMe	 20e: G = OMe	85	 21e: G = OMe	<5
8	18h: G = Me	20f: G = Me	70	21f: G = Me	<5
9	18i: G = Cl	20g: G = Cl	--	21g: G = Cl	--
10	 18j: G = Me	 20h: G = Me	89	 21h: G = Me	<5
11	18k: G = Cl	20i: G = Cl	87	21i: G = Cl	<5
12	 18l: G = Cl	 20j: G = Cl	65	N / A^a	--
13	18m: G = OMe	20k: G = OMe	95	N / A^a	--
14	 18n: G = Cl	 20l: G = Cl	--	 21j: G = Cl	--
15	18o: G = OMe	20m: G = OMe	--	21k: G = OMe	--
16	18p: G = Me	20n: G = Me	64	21l: G = Me	<5

^a “N/A” indicates substrate for which acridone formation is not possible.

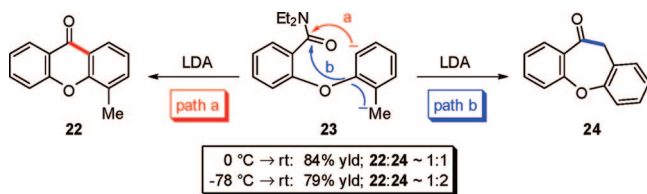
SCHEME 3



SCHEME 4



SCHEME 5



yield. Precedent exists for this type of base-mediated reaction,³⁴ and a control experiment in the absence of *o*-toluidine **16h** and catalyst system yielded **19** in an improved 51% yield. Using the conditions employed previously (Table 1), diarylamines **17** were converted into the corresponding *N*-methyl derivatives **18** (Table 3). Sterically encumbered substrates (entries 8 and 9) underwent methylation sluggishly under these conditions, providing incomplete reactions. However, the use of NaH in THF at room temperature facilitated *N*-methylation, providing the desired products in good to excellent yield.

Gratifyingly, treatment of the diarylamines (**18**) under the standard LDA conditions afforded dibenzo[*b,f*]azepinones in excellent yields with only minor formation of the corresponding acridones in most cases (Table 4). A trend in yield and regioselectivity was observed as a function of the steric requirement of the amide (entries 1–3). Despite the greater yield obtained with the dimethylamide, the diethylamide was adopted for generalization due to its widely proven robustness in *DoM* chemistry.¹ Generality of the method was demonstrated by the synthesis of alkyl (entries 4, 8, 10, and 16), alkoxy (entries 7 and 13), and halo (entries 11 and 12) dibenzo[*b,f*]azepinones. However, for substrates with halo substituents in the amide-bearing ring (entries 9 and 14), neither acridone nor dibenzo[*b,f*]azepinone product was isolated, and intractable mixtures resulted. A potential explanation for these results, especially when compared to the clean and high-yielding cyclizations observed for **18f** and **18k** (entries 6 and 11), is the increased likelihood of benzyne formation³⁵ owing to higher C–H acidities in the halobenzamide ring. Attempts to alleviate this

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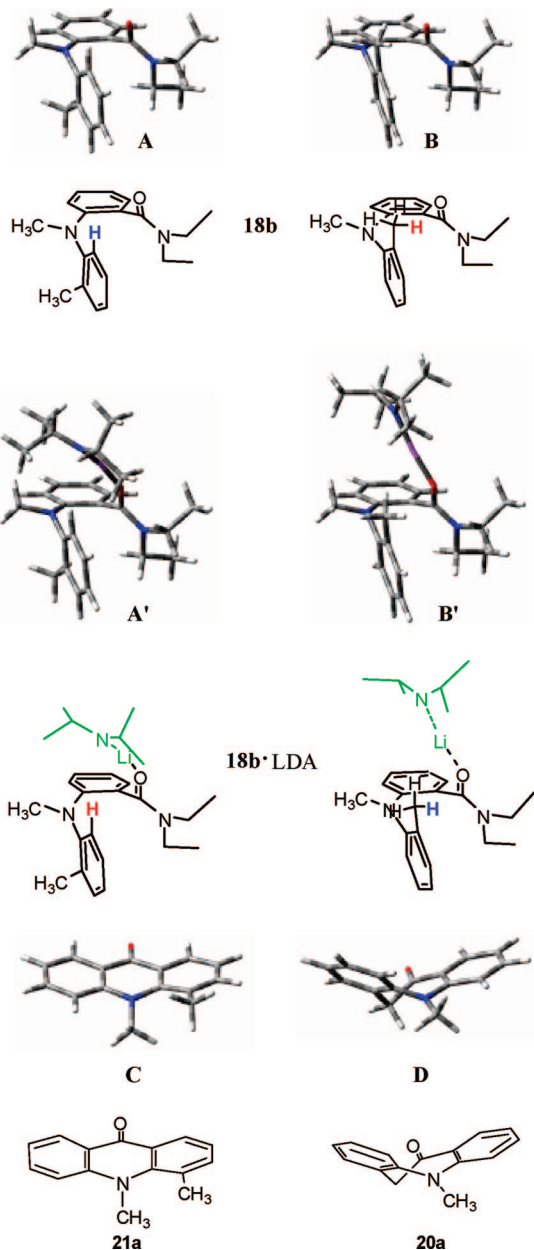


FIGURE 1. Low energy conformations of **18b**, **18b**·LDA, **20a**, and **21a**.

problem by quenching the reaction mixture at -78 °C were unsuccessful, and further optimization studies were not pursued.

The regioselectivity for dibenzo[*b,f*]azepinone over acridone formation is quite remarkable. Even for the case of an ethyl-substituted substrate (Table 4, entry 4), regioselectivity is only marginally compromised (2:1), and although not systematically explored, the tip toward acridone regioselectivity occurs only in the presence of an additional DMG (entries 5 and 6) which, in spite of a weak effect, may act by cooperating by CIPE^{1a} with the powerful amide DMG. To gain insight into the regioselectivity for dibenzo[*b,f*]azepinone formation, analyses of the parent compound **18b**, its 1:1 complex with LDA, and the products of its cyclization, **20a** and **21a**, were performed using DFT calculations.

The optimized geometries of **20a** and **21a** are shown in Figure 1 (structures D and C, respectively), and the calculations established that the acridone product **21a** should be more stable than the

dibenzo[*b,f*]azepinone product **20a** by 12.1 kcal/mol. Therefore, the major product **20a** is, in fact, thermodynamically unfavorable, and the observed regioselectivity of the cyclization process (**20a/21a** > **18**) must be due to kinetic control. The calculated low energy conformations of **18b** that assist to rationalize product formation are shown in Figure 1 (structures A and B). Conformation A, which should lead to acridone formation, shows close proximity (2.75 Å) between the aromatic hydrogen and the carbonyl oxygen of the amide DMG. Conformation B, which should lead to dibenzo[*b,f*]azepinone formation, shows close proximity (2.41 Å) between a benzylic hydrogen and the carbonyl oxygen of the DMG. Conformation B, leading to the observed major product **20a**, is more stable than conformation A by 2.0 kcal/mol. Given this enthalpy difference, a solution of **18b** is expected to have the conformer ratio B/A > 30 below 20 °C, therefore favoring cyclization of B compared to the ring closure of A in agreement with the observed formation of the thermodynamically unfavorable product, **20b**. To assess the effects of LDA complexation, DFT calculations were performed for 1:1 complexes of A and B with LDA. The corresponding structures A' and B' account for the formation of **21a** and **20a**, respectively (A': Ar–H...N⁻ distance = 2.86 Å; B': Bn–H...N⁻ distance = 3.65 Å), and the relative energies are in a qualitative agreement with the observed regioselectivity: B' is more stable than A' by 0.5 kcal/mol.

In contrast to the good to excellent regioselectivity observed for the product formation in the dibenzo[*b,f*]azepinone series (Table 4), the LDA-mediated cyclization of diphenyl ether **23** led reproducibly to an approximately equimolar mixture of xanthone **22** and dibenzo[*b,f*]oxepinone **24** under the same reaction conditions (0 °C → rt) (Scheme 5).³⁶ Treatment of **23** with LDA at –78 °C followed by warming to rt showed some selectivity for formation of dibenzo[*b,f*]oxepinones, **24/22** ≈ 2.

DFT calculations for products **22** and **24** (structures G and H in Figure 2) again established a significant thermodynamic preference for 6-membered ring formation (**22** more stable than **24** by 18.1 kcal/mol) and suggested that the reaction was under kinetic control. DFT calculations for **23** and its 1:1 complex with LDA found low energy conformations (E,F and E',F') shown in Figure 2 that account for formation of **22** and **24**, respectively. Similar to the differences found for **18b** (Figure 1), conformation F is more stable than E by 2.8 kcal/mol and the LDA complex F' is more stable than E' by 1.4 kcal/mol. These results qualitatively explain why the thermodynamically unfavorable product **24** is produced along with **22** in the cyclization reaction. However, the calculated energies suggest that a higher selectivity for **24** vs **22** may have been expected than that for the formation of **21a** vs **20a**, which is not the case. Obviously the rate constant of cyclization of E through E' must be greater than that of the cyclization reaction of F through F' to offset the effect of the higher populations of complexes F and F' in the reaction system.

In summary, efficient and regioselective routes to acridones and dibenzo[*b,f*]azepinones have been realized through application of a combined Buchwald–Hartwig aryl amination–DreM protocol. The protocol for acridones (Tables 1 and 2) offers significant advantages over the classical Friedel–Crafts technology in the milder conditions for cyclization, usually higher yields, and complementary regiochemistry (e.g., formation of

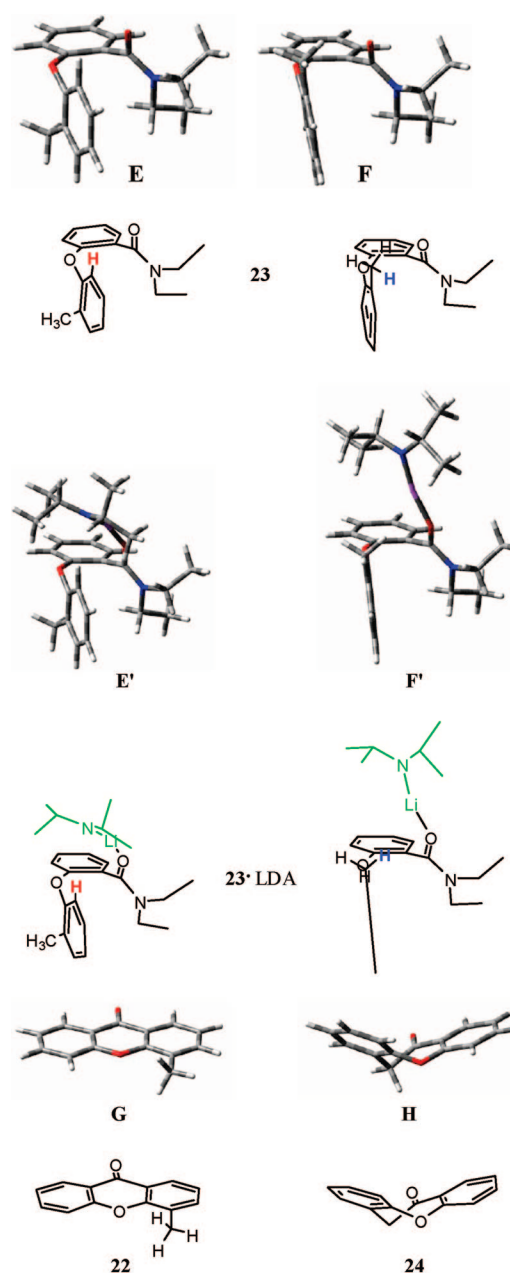


FIGURE 2. Low energy conformations of **23**, **23·LDA**, **22**, and **24**.

4a under anionic conditions, whereas formation of the corresponding 4-methoxyacridone occurs under Lewis acid catalysis³⁷). The operation of a DMG effect (Table 2, entries 1–3 and Scheme 4), although only peripherally studied, indicates potential for establishment of a general and complementary anionic Friedel–Crafts equivalent protocol allowing access of single isomers of not readily attainable substituted acridones. The methodology established for the regioselective synthesis of dibenzo[*b,f*]azepinones (Scheme 2, Table 4) may find generality for the construction of analogous sulfur-,²⁰ phosphorus-,²¹ and oxygen-containing²² heterotricyclics and, in view of their substantial history,¹² may find utility for abbreviated synthesis of molecules of pharmaceutical³⁸ and materials³⁹ interest.

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Experimental Section

General Procedure A. Palladium-Mediated Aryl Aminations. A thick-walled, screw-capped glass tube was charged with a mixture of the aryl bromide, substituted aniline (1.2 equiv), NaO^tBu (1.4 equiv), Pd₂(dba)₃ (0.22–0.87 mol %), BINAP (0.68–1.52 mol %), and toluene (0.25–0.5 M) and purged with argon. The tube was sealed, and the contents were heated with stirring for the time indicated. After cooling to rt, standard workup followed by flash column chromatography (EtOAc/hexanes) afforded the product.

Representative Example: *N,N*-Diethyl-2-(3-methoxyanilino)benzamide (10b). Following general procedure A using the following materials [**1b** (2.0700 g, 8.08 mmol), **2a** (1.09 mL, 9.70 mmol), NaO^tBu (1.0874 g, 11.31 mmol), Pd₂(dba)₃ (0.0199 g, 0.020 mmol), BINAP (0.0393 g, 0.060 mmol), toluene (20 mL) at 100–110 °C for 20 h], standard workup followed by acid/base wash and flash column chromatography (10% EtOAc/hexane) afforded **10b** (1.4550 g, 60%) as colorless crystals: mp 58–60 °C (hexanes); IR (thin film) ν_{\max} 747, 1288, 1476, 1603, 3344 cm⁻¹; ¹H (250 MHz, CDCl₃) δ 7.43 (d, *J* = 8.2 Hz, 1H), 7.26–7.13 (m, 2H), 6.92–6.86 (m, 2H), 6.69–6.63 (m, 2H), 6.49 (dd, *J* = 1.7, 8.2 Hz, 1H), 3.77 (s, 3H), 3.44 (bs, 4H), 1.17 (bs, 6H); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.5, 160.6, 143.7, 141.1, 130.0, 129.8, 127.1, 125.5, 119.9, 117.7, 110.8, 106.6, 104.0, 55.2, 13.5; MS (FAB) *m/z* (rel intensity) 298 (M⁺, 100), 225 (90); HRMS calcd for C₁₈H₂₂N₂O₂ 298.1681, found 298.1691. Anal. Calcd for C₁₈H₂₂N₂O₂ (M⁺): C, 72.43; H, 7.43; N, 9.42. Found: C, 72.67; H, 7.32; N, 9.37.

***N,N*-Diethyl-2-(2-toluidino)benzamide (17b).** Following general procedure A using the following materials [**1b** (1.5144 g, 5.91 mmol), **16a** (0.76 mL, 7.09 mmol), NaO^tBu (0.7946 g, 8.27 mmol), Pd₂(dba)₃ (0.0180 g, 0.020 mmol), BINAP (0.0306 g, 0.049 mmol), toluene (15 mL) at 90–100 °C for 24 h], standard workup, and acid/base wash followed by flash column chromatography (10% EtOAc/hexane) afforded **17b** (1.4200 g, 85%) as a brown oil: IR (neat) ν_{\max} 3355, 1625 cm⁻¹; ¹H (250 MHz, CDCl₃) δ 7.27–7.11 (m, 6H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.83 (dt, *J* = 1.2, 7.3 Hz, 1H), 3.46 (bs, 4H), 2.24 (s, 3H), 1.19 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.5, 142.2, 140.3, 130.8, 129.7, 128.8, 127.0, 126.4, 124.0, 122.0, 119.1, 118.8, 116.3, 17.7, 13.5; MS (EI) *m/z* (rel intensity) 282 (M⁺, 50), 209 (100), 180 (22); HRMS calcd for C₁₈H₂₂N₂O 282.1732, found 282.1731.

General Procedure B. N-Methylation. A solution of the *N*-arylanthranilamide in THF (0.1–0.3 M) was cooled to 0 °C under an argon atmosphere and treated with a solution of *n*-BuLi in hexanes (1.0–1.1 equiv). The reaction mixture was stirred for 15 min and treated sequentially with MeI (5 equiv) and 1,4-dioxane (3.5 equiv). Following additional stirring (as indicated), the reaction mixture was either quenched with satd aq NH₄Cl at 0 °C or warmed to rt before quenching. Standard workup followed by flash column chromatography afforded the desired product.

***N,N*-Diethyl-2-[3-methoxy(methyl)anilino]benzamide (3b).** Following general procedure B using the following materials [**10b** (0.6605 g, 2.21 mmol), *n*-BuLi (1.33 mL, 1.67 M, 2.21 mmol), MeI (0.69 mL, 11.06 mmol), 1,4-dioxane (0.72 mL, 8.41 mmol), THF (10 mL)], standard workup followed by flash column chromatography (10% EtOAc/hexane) afforded **3b** (0.6150 g, 89%) as a yellow oil: IR (neat) ν_{\max} 1609 cm⁻¹; ¹H (250 MHz, CDCl₃) δ 7.41–7.20 (m, 4H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.34–6.25 (m, 3H), 3.74 (s, 3H), 3.23 (s, 3H), 3.13–3.07 (m, 2H), 2.96–2.91 (m, 2H), 0.99–0.94 (m, 6H); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.8, 160.0, 150.0, 145.0, 135.8, 129.7, 129.0, 128.2, 127.6, 125.4, 107.4, 102.5, 100.8, 54.7, 42.5, 40.3, 38.0, 13.5, 11.9; MS (EI) *m/z* (rel intensity) 312 (M⁺, 28), 240 (30), 169 (100); HRMS calcd for C₁₉H₂₄N₂O₂ 312.1838, found 312.1830.

***N,N*-Diethyl-2-(2-dimethylanilino)benzamide (18b).** Following general procedure B using the following materials [**17b** (1.3595 g, 4.81 mmol), *n*-BuLi (2.97 mL, 1.70 M, 5.06 mmol), MeI (1.50

mL, 24.07 mmol), 1,4-dioxane (1.56 mL, 18.29 mmol), THF (20 mL)], standard workup followed by flash column chromatography (20% EtOAc/hexane) afforded **18b** (1.1872 g, 83%) as an orange oil: IR (neat) ν_{\max} 1632 cm⁻¹; ¹H (250 MHz, CDCl₃) δ 7.26 (t, *J* = 7.5 Hz, 1H), 7.17–6.84 (m, 7H), 3.27–3.01 (m, 3H), 3.16 (s, 3H), 2.68–2.24 (m, 1H), 2.24 (s, 3H), 1.0 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.1, 147.8, 146.5, 134.3, 130.6, 128.7, 127.4, 127.2, 125.9, 125.3, 124.2, 118.8, 118.0, 42.3, 40.6, 38.0, 17.6, 13.0, 12.0; MS (EI) *m/z* (rel intensity) 296 (M⁺, 66), 224 (100), 209 (27); HRMS calcd for C₁₉H₂₄N₂O 296.1889, found 296.1894.

General Procedure C. LDA-Mediated Cyclization to 10H-acridin-9-ones (4) and 5-Methyl-5,11-dihydro-dibenzo[*b,f*]azepin-10-ones (20). LDA (2.5–3.5 equiv) was prepared using a solution of *n*-BuLi in hexanes and HN^{Pr}Pr₂ in THF (~0.5 M) at 0 °C (ice/salt bath) and was added dropwise via cannula to a solution of the amide in THF (~0.5 M) precooled to 0 °C. The resulting solution was stirred for the time indicated and quenched, either at 0 °C or rt, with a satd aq NH₄Cl solution. Standard workup followed by flash column chromatography (EtOAc/hexanes) afforded the product.

1-Methoxy-10-methyl-9,10-dihydro-9-acridinone (4a). Following general procedure C using the following materials [**3b** (0.2755 g, 0.88 mmol), *n*-BuLi (1.32 mL, 1.67 M, 2.20 mmol), HN^{Pr}Pr₂ (0.29 mL, 2.20 mmol), THF (10 mL) (15 min at 0 °C)], standard workup followed by flash column chromatography (60% EtOAc/hexane) afforded **4a** (0.1920 g, 91%); yellow crystals, mp 164–166 °C (aq EtOH) [lit.⁴⁰ mp 162–164 °C]; ¹H (200 MHz, CDCl₃) δ 8.49 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.66–7.57 (m, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.27–7.18 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.01 (s, 3H), 3.78 (s, 3H).

5-Methyl-10,11-dihydro-5H-dibenzo[*b,f*]azepin-10-one (20a) and 4,10-Dimethyl-9,10-dihydro-9-acridinone (21a). Following general procedure C using the following materials [**18b** (0.1485 g, 0.50 mmol), *n*-BuLi (0.75 mL, 1.67 M, 1.25 mmol), HN^{Pr}Pr₂ (0.17 mL, 1.25 mmol), THF (5 mL) (1 h at 0 °C)], standard workup followed by flash column chromatography (5 → 20% EtOAc/hexanes) afforded **20a** (0.1004 g, 89%) and **21a** (0.0030 g, <5%).

20a: light yellow crystals; mp 102–104 °C (hexanes) [lit.⁴¹ mp 102–103 °C (aq EtOH)]; ¹H (200 MHz, CDCl₃) δ 8.14 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.49 (ddd, *J* = 1.8, 6.9, 8.7 Hz, 1H), 7.30–7.08 (m, 5H), 6.95 (dt, *J* = 0.9, 7.5 Hz, 1H), 3.88 (s, 2H), 3.55 (s, 3H).

21a: light yellow crystals; mp 89–91 °C (aq EtOH) [lit.⁴² mp 92 °C (EtOH)]; ¹H (200 MHz, CDCl₃) δ 8.43 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.36 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.72 (ddd, *J* = 8.6, 7.0, 1.8

(38) See ref 12d for application of the method to an industrial-scale synthesis of oxcarbezepine, an important dibenzo[*b,f*]azepinone widely prescribed for the treatment of epilepsy.

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Hz, 1H), 7.55–7.46 (m, 2H), 7.31–7.19 (m, 2H), 3.91 (s, 3H), 2.69 (m, 3H).

Computational Details. The DFT calculations were carried out using Gaussian 03.⁴³ All geometries were fully optimized without symmetry or internal coordinate constraints using the MPW1PW91 functional which included modified Perdew–Wang exchange and Perdew–Wang 91 correlation.⁴⁴ The 6-31g(d) basis set was employed in this work for all atoms.⁴⁵ The nature of all stationary points was verified by frequency calculations, and all reported enthalpies are at 293 K.

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Supporting Information Available: Specific experimental procedures, characterization data for all compounds, ¹³C NMR spectra for all new compounds, and computational data for **18b**, **18b**·LDA, **20a**, **21a**, **22**, **23**, **23**·LDA, and **24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(45) For more information about basis sets implemented in Gaussian 03 and references, see: Frish, A.; Frish, M. J.; Trucks, G. W. *Gaussian 03 User's Reference*; Gaussian, Inc.: Pittsburgh, PA, 2003. The basis sets are also available from the Extensible Computational Chemistry Environment Basis Set Database, which is developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory, which is part of the Pacific Northwest Laboratory, P.O. Box 999, Richland, WA 99352 (www.emsl.pnl.gov/forms/basisform.html).