JOC Article

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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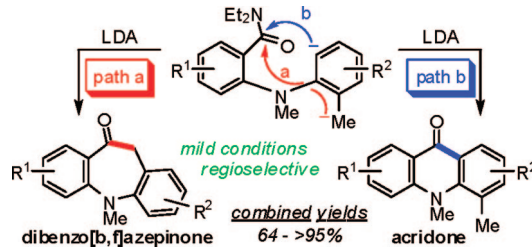

Carbanion-mediated general regioselective routes to acridones **4** (Table 2) and dibenzo[*b*,*f*]azepinones **20** (Table 4) are described. Buchwald−Hartwig C−N cross coupling of *o*-halo benzamides **1** with anilines **2** or **16**, followed by simple *N*-methylation, dependably provides *N*-methyl 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 (D*o*M)−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 previously[3] communicated the application of this methodology, showcasing Buchwald−Hartwig aryl amination[4]−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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† Albert I. Meyers, In Memoriam. See: Snieckus, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1−2.

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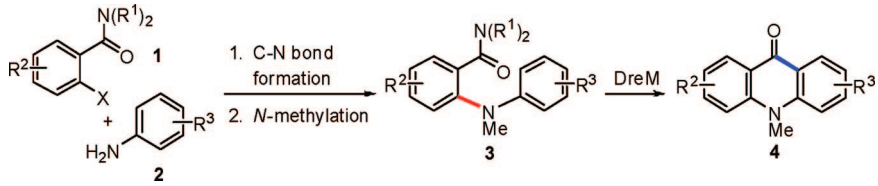
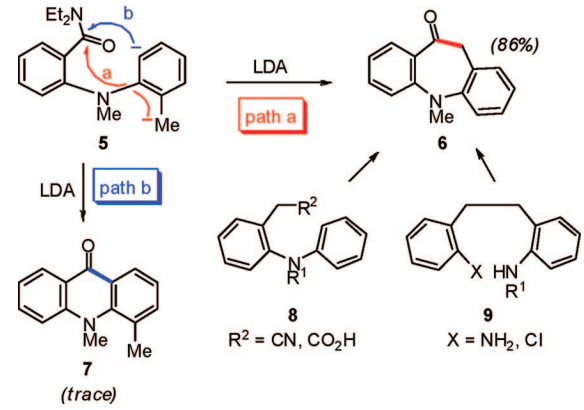
SCHEME 1



proach to these and other heterocyclic systems[3] 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 activity[12] 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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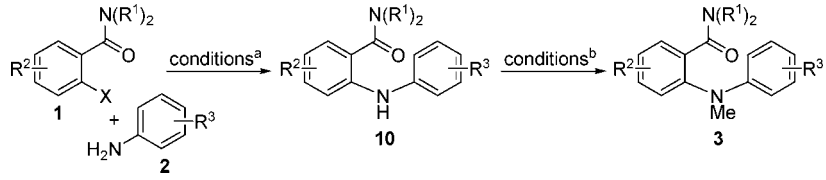
TABLE 1. Synthesis of *N*,*N*-Dialkyl-2-anilinobenzamides 10 and 3



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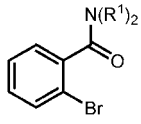
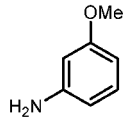
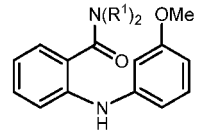
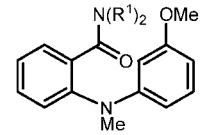
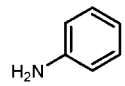
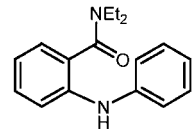
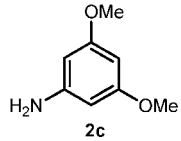
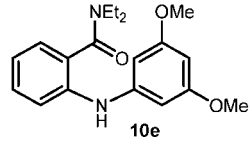
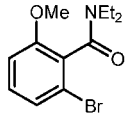
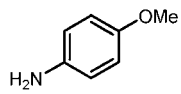
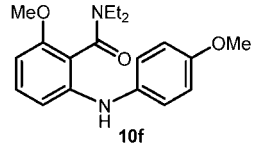
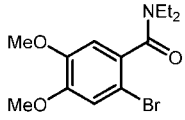
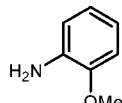
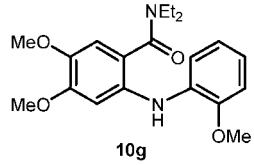
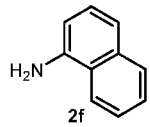
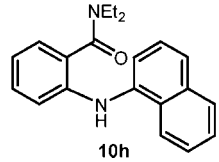
						
1	**1a**: R^1 = Me	**2a**	**10a**: R^1 = Me	68	**3a**: R^1 = Me	84
2	**1b**: R^1 = Et		**10b**: R^1 = Et	60	**3b**: R^1 = Et	86
3	**1c**: R^1 = ^{i}Pr		**10c**: R^1 = ^{i}Pr	83	**3c**: R^1 = ^{i}Pr	>95
4	**1b**	 **2b**	 **10d**	81	**3d**	>95
5	**1b**	 **2c**	 **10e**	93	**3e**	>95
6	 **1d**	 **2d**	 **10f**	60	**3f**	>95
7	 **1e**	 **2e**	 **10g**	53	**3g**	>95
8	**1b**	 **2f**	 **10h**	81	**3h**	84

[a] Conditions: $Pd_2(dba)_3$ (0.22−0.48 mol %), (±)-BINAP (0.74−1.36 mol %), NaO^{t}Bu, 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 Buchwald[14] and Hartwig[15] as attractive alternatives to the harsh conditions and tedious workup and purification procedures typical of Ullmann chemistry.[16] Initial Pd-catalyzed conditions reported by Buchwald[14] 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 Buchwald[17] for electron-rich aryl bromides.

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

(14) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.

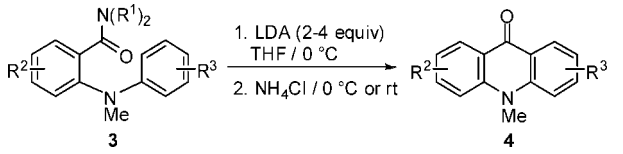
(15) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

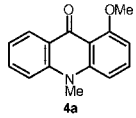
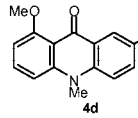
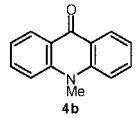
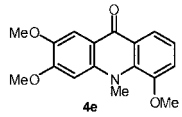
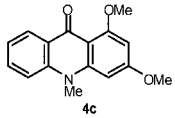
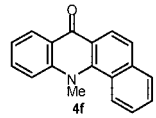
(16) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. (b) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496–1502.

(17) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.

(18) We thank Professors Steve Buchwald and John Hartwig and their students for generously providing experimental details.

TABLE 2. Synthesis of Acridones 4a−f



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

[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 procedure[19] 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 thioxanthen-9-one 10,10-dioxides,[20] dibenzo[*b*,*e*]phosphorinones,[21] and xanthen-9-ones[22] 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 methods[24] 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 5[28]) 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).

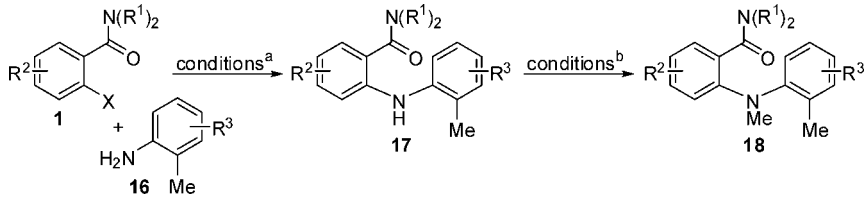
In order to extend the utility of the Buchwald−Hartwig amination−DreM protocol, the bis DreM cyclization of the *N*,*N*′-(bis)diaryl-1,4-diaminobenzene **12**, prepared in two steps (16−23% overall yield) from *N*,*N*-diethyl-2-bromobenzamide and 1,4-diaminobenzene, to bis-acridone, **11**,[30,31] was 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 systems[32] and may be rationalized, in part, by the potential hydride-transfer reduction of acridones by LDA[33] to acridinium salts followed by further decomposition. Based on these preliminary results, further exploration of the double-DreM methodology is warranted.

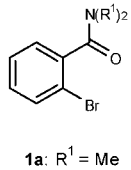
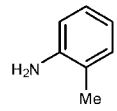
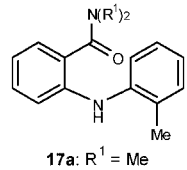
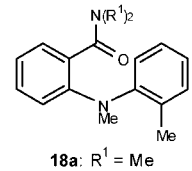
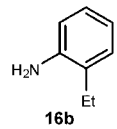
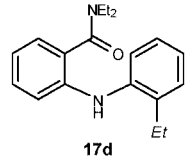
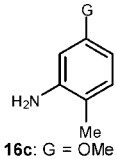
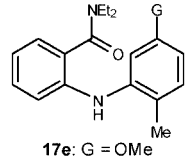
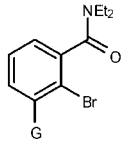
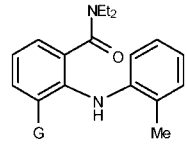
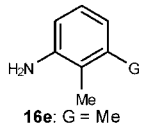
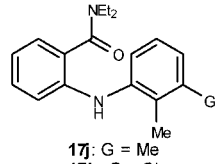
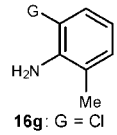
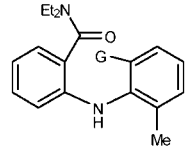
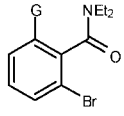
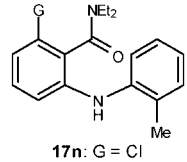
Although the described method represents a vast improvement over classical methods for acridone synthesis,[5a] an inherent limitation is the requirement for *N*-alkylation of substrates prior to LDA-mediated cyclization. Since heterotricyclic compounds of this type are usually inert to *N*-dealkylation 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** → **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%

(19) Vitale, A. A.; Chiocconi, A. A. *J. Chem. Res., Synop.* **1996**, 336–337.
(20) Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508–6509.
(21) Gray, M.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1558–1560.
(22) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081–1083.
(23) The use of acidic conditions provide this compound in only 32% isolated yield. See: Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531–5533.
(24) (a) Vieira, P. C.; Kubo, I.; Kujime, H.; Yamagiwa, Y.; Kamikawa, T. *J. Nat. Prod.* **1992**, *55*, 1112–1117. (b) Su, T.-L.; Dziewiszek, K.; Wu, T.-S. *Tetrahedron Lett.* **1991**, *32*, 1541–1544.
(25) (a) For general effects of *m*-EDGs on Friedel−Crafts chemistry, see: Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; p 236. (b) For examples, see: Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553–2563. (c) Sharp, M. J. M.Sc. Thesis, University of Waterloo, 1986.
(26) Gibbons, S.; Craven, L.; Dunlop, C.; Gray, A. I.; Hartley, T. G.; Waterman, P. G. *Phytochemistry* **1997**, *44*, 1109–1114.
(27) Dreyer, D. L. *Tetrahedron* **1966**, *22*, 2923–2927.
(28) Lamberton, J. A.; Price, J. R. *Aust. J. Chem.* **1953**, *6*, 66–77.
(29) (a) Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1046–1048. (b) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1970**, *23*, 1881–1881.
(30) This compound is available from Sigma-Aldrich (557587) but at a significant price (100 mg = $151.50; 500 mg = $536.00).
(31) Compounds of this type have potential applications as organic emitters in electroluminescent displays. See: Justel, T.; Nikol, H.; Ronda, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3084–3103.
(32) (a) Zhao, B.-p. Ph. D. Thesis, University of Waterloo, 1993. (b) Milburn, R. M.Sc. Thesis, University of Waterloo, 1999. (c) Field, J.; Snieckus, V. University of Waterloo, unpublished observations.
(33) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057–4060, and references cited therein.

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



Entry	Benzamide	*o*-Toluidine	*N*-Arylation Product	Yld, %	*N*-Methylation Product	Yld, %
						
1	**1a**: R^1 = Me	**16a**	**17a**: R^1 = Me	63	**18a**: R^1 = Me	81
2	**1b**: R^1 = Et		**17b**: R^1 = Et	85	**18b**: R^1 = Et	83
3	**1c**: R^1 = ^{i}Pr		**17c**: R^1 = ^{i}Pr	90	**18c**: R^1 = ^{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		**17h**: G = Me	87	**18h**	93[c]
9	**1h**: G = Cl		**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	**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		**17o**: G = OMe	40	**18o**	93
16	**1k**: G = Me		**17p**: G = Me	42	**18p**	86

[a] $Pd_2(dba)_3$ (0.23−0.87 mol %), (±)-BINAP (0.68−1.52 mol %), NaO^{t}Bu, 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]

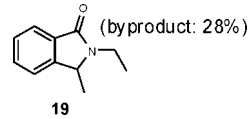


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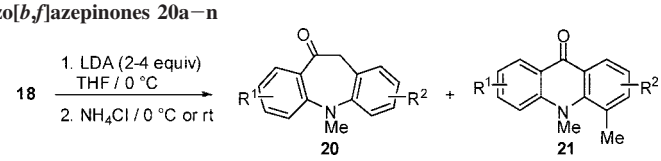
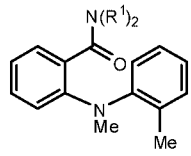
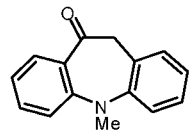
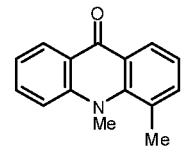
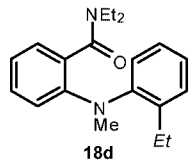
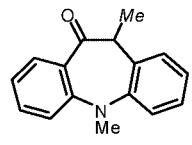
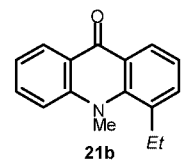
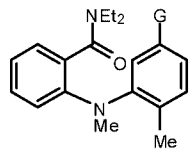
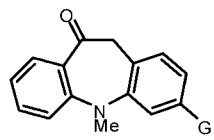
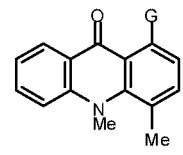
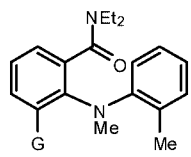
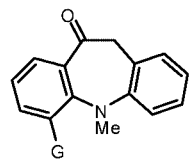
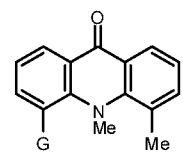
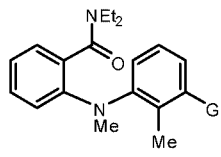
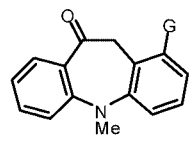
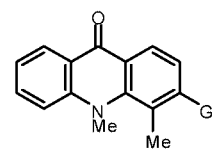
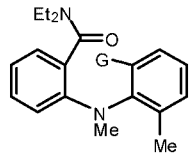
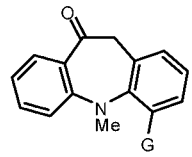
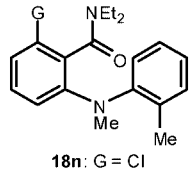
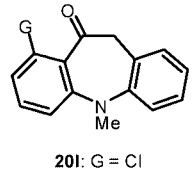
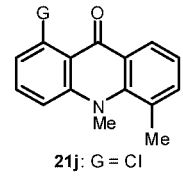
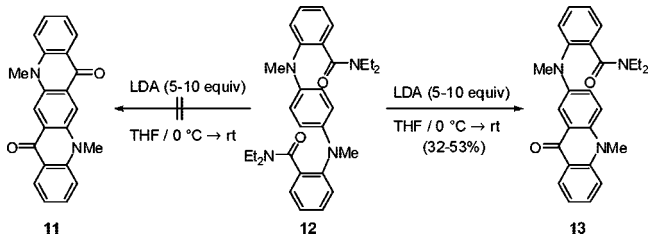
TABLE 4. Synthesis of 5*H*-Dibenzo[*b*,*f*]azepinones 20a–n



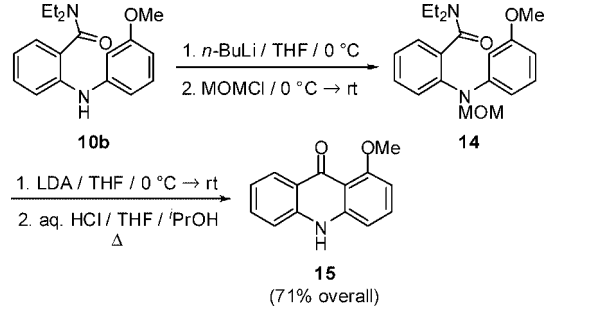
Entry	Diarylamine	5*H*-Dibenzo[b,f]azepinone	Yld, %	Acridone	Yld, %
					
1	**18a**: R^1 = Me	**20a**	95	**21a**	<5
2	**18b**: R^1 = Et		89		<5
3	**18c**: R^1 = ^{i}Pr		72		14
4	 **18d**	 **20b**	65	 **21b**	34
					
5	**18e**: G = OMe	**20c**: G = OMe	20	**21c**: G = OMe	79
6	**18f**: G = Cl	**20d**: 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.

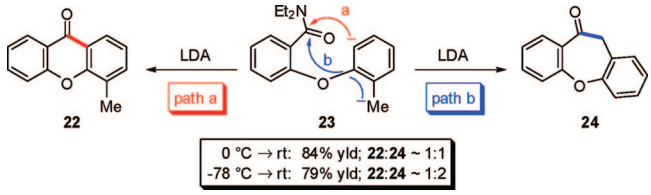
SCHEME 3



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 D*o*M 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 formation[35] owing to higher C−H acidities in the halobenzamide ring. Attempts to alleviate this problem by quenching the reaction mixture at −78 °C were unsuccessful, and further optimization studies were not pursued.

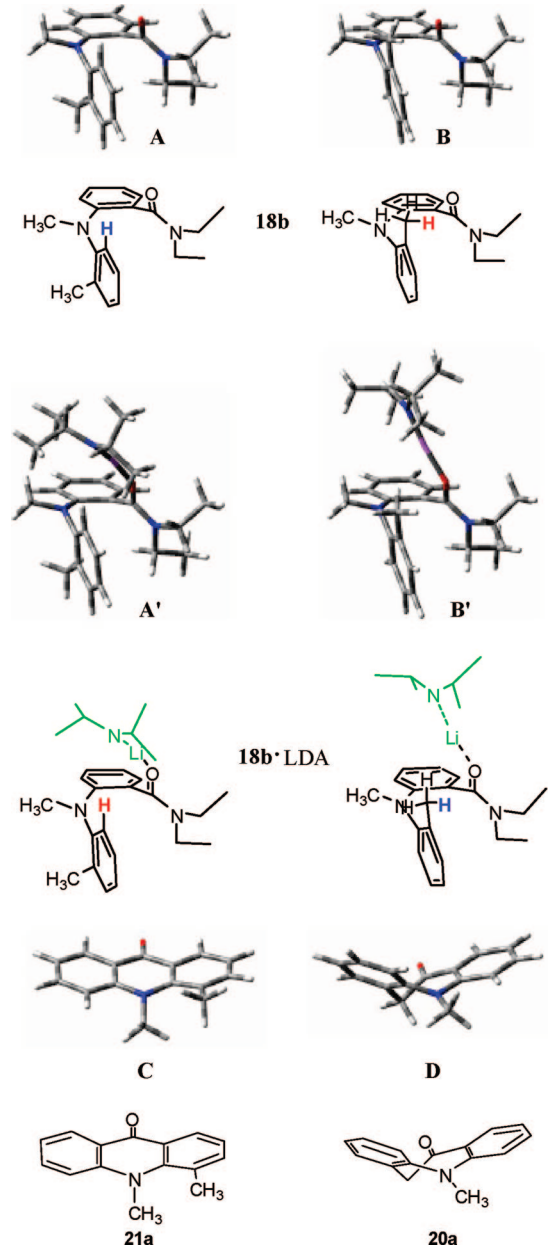


FIGURE 1. Low energy conformations of **18b**, **18b**·LDA, **20a**, and **21a**.

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

(34) Kessar, S. V. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.3.

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 (2.75Å) 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 = 2.86Å; B′: Bn−H···N$^-$ distance = 3.65Å), 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

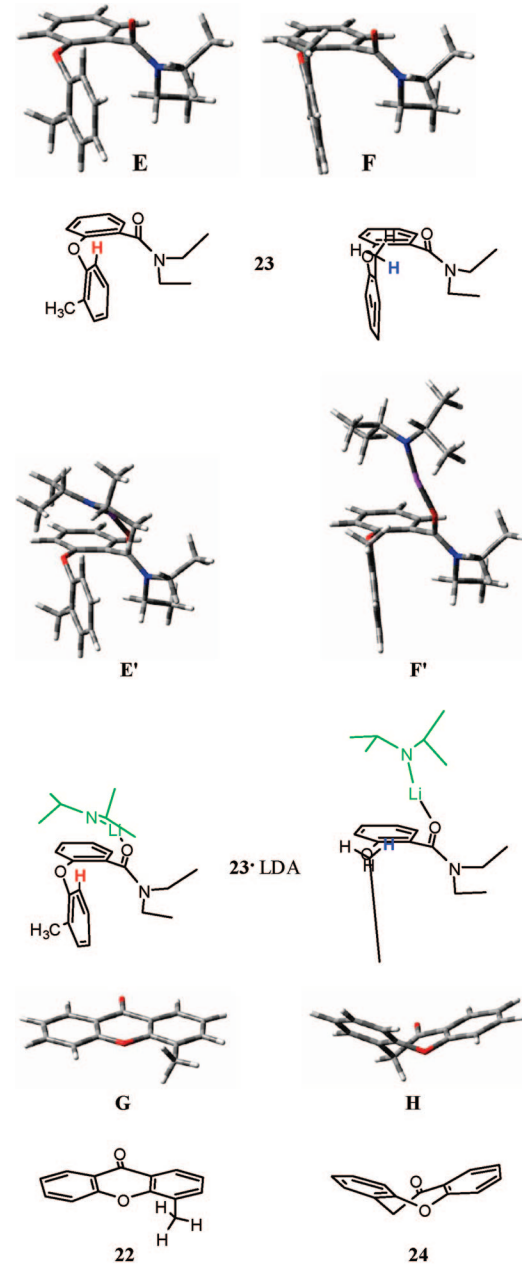


FIGURE 2. Low energy conformations of **23**, **23**·LDA, **22**, and **24**.

4a under anionic conditions, whereas formation of the corresponding 4-methoxyacridone occurs under Lewis acid catalysis[37]). 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-containing[22] heterotricyclics and, in view of their substantial history,[12] may find utility for abbreviated synthesis of molecules of pharmaceutical[38] and materials[39] interest.

(35) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974, pp 172−181.

(36) Attempts to improve the original regioselectivity (see ref 22) were unsuccessful: MacNeil, S. L.; Snieckus, V. Unpublished results.

(37) (a) Vieira, P. C.; Kubo, I. *J. Nat. Prod.* **1992**, *55*, 1112–1117. (b) Su, T.-l.; Dziewiszek, K.; Wu, T.-s. *Tetrahedron Lett.* **1991**, *32*, 1541–1544.

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^{t}Bu (1.4 equiv), $Pd_2(dba)_3$ (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^{t}Bu (1.0874 g, 11.31 mmol), $Pd_2(dba)_3$ (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}; ^{1}H (250 MHz, $CDCl_3$) 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); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1691. Anal. Calcd for $C_{18}H_{22}N_2O_2$ (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^{t}Bu (0.7946 g, 8.27 mmol), $Pd_2(dba)_3$ (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}; ^{1}H (250 MHz, $CDCl_3$) 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); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 $C_{18}H_{22}N_2O$ 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 NH_4Cl 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}; ^{1}H (250 MHz, $CDCl_3$) 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); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 $C_{19}H_{24}N_2O_2$ 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}; ^{1}H (250 MHz, $CDCl_3$) 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); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 $C_{19}H_{24}N_2O$ 296.1889, found 296.1894.

General Procedure C. LDA-Mediated Cyclization to 10*H*-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^{i}Pr$_2$ 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 NH_4Cl 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^{i}Pr$_2$ (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]; ^{1}H (200 MHz, $CDCl_3$) 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-5*H*-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^{i}Pr$_2$ (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)]; ^{1}H (200 MHz, $CDCl_3$) 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)]; ^{1}H (200 MHz, $CDCl_3$) 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.

(39) For potential applications in light-emitting diodes, see: Chen, Y.; Sheu, R.-B.; Wu, T.-Y. *J. Polym. Sci Part A: Polym. Chem.* **2003**, *41*, 725–731.

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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, ^{13}C 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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