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Synthesis of Acridines and Persubstituted Phenols from Cyclobutenones and Active Methylene Ketones

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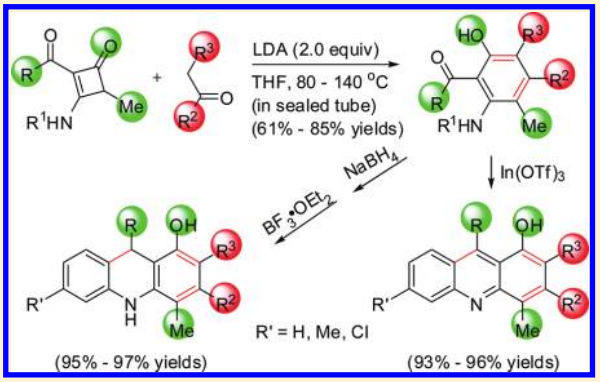
Supporting Information

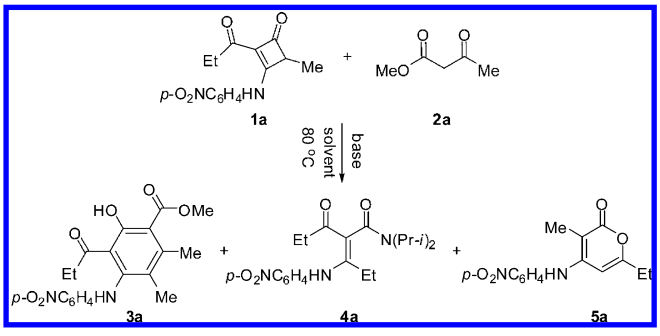
ABSTRACT: A new benzannulation strategy that proceeds via a regiospecific [4 + 2] cycloaddition of readily available cyclobutenones and active methylene ketones has been developed. On the basis of this strategy, persubstituted phenols/anilines with up to six different functional groups on the benzene ring were synthesized in a single step. In addition, a series of acridine derivatives were prepared in excellent yield from persubstituted phenols/anilines.



Substituted phenols are important structural motifs found in a variety of natural products, biologically active compounds, and agrochemicals.[1] In the past few decades, the efficient synthesis of substituted phenols from acyclic precursors with high atom and step economy has become a powerful tool in the arsenal of synthetic organic chemist.[2−4] In this context, the significance of cyclobutenones in the synthesis of six-membered carbocycles[5] and, in particular, substituted phenols via Moore rearrangement[6] or by reaction with alkynes has been described.[7] The predication of the regiochemistry is still a stimulating challenge, especially for highly functionalized benzene derivatives.[1−4,6,7,9,10] As a continuing interest in the development of new benzannulation[3] and heterocyclization[8] reactions, we report here a new strategy for the regiospecific synthesis of persubstituted phenols via a formal [4 + 2] cycloaddition between cyclobutenones (as 1,4-dipoles) and active methylene ketones (carbon−carbon dipolarophiles) in a single step. In addition, the efficient synthesis of acridine derivatives from persubstituted phenols is also described.

In the present work, the reaction of the readily available 3-aminocyclobutenone **1a**[11] with methyl acetoacetate **2a** was first examined under various conditions (Table 1). It was found that persubstituted phenol **3a** could be obtained in 85% yield under optimized reaction conditions, where **1a** (0.5 mmol) was treated with **2a** (0.6 mmol) in the presence of LDA (1.0 mmol, LDA = lithium diisopropylamide) in THF (2.0 mL) in a sealed tube at 80 °C for 8 h (Table 1, entry 1). In this case, enaminone **4a** was also obtained as the byproduct in 3% yield (entry 1). Decreasing the amount of LDA led to lower yields of **3a** (entries 2 and 3). Under otherwise identical conditions, however, highly substituted α-pyrone **5a** instead of **3a** was produced in excellent yields when NaOH, *t*-BuOK or LiOH was used as the base (entries 4−6). Among the solvents tested, THF was the best choice (entry 1). Other solvents, such as DMF and dioxane, gave lower yields of **3a** (entries 7 and 8). In comparison, no **3a** could be detected with DCE (1,2-dichloroethane) or toluene as the solvent (entries 9 and 10).

Table 1. Optimization of Reaction Conditions



entry	base (equiv)	solvent	time (h)	3a[a] (%)	4a[a] (%)	5a[a] (%)
1	**LDA (2.0)**	**THF**	**8**	**85**	3	0
2[b]	LDA (0.5)	THF	12	18	20	0
3[c]	LDA (1.5)	THF	8	60	10	0
4	NaOH (2.0)	THF	8	0	0	90
5	*t*-BuOK (2.0)	THF	8	0	0	91
6	LiOH (2.0)	THF	8	0	0	86
7	LDA	DMF	15	13	0	80
8	LDA	dioxane	15	23	0	71
9	LDA	toluene	15	0	0	88
10[d]	LDA	DCE	15	0	0	30

[a]Isolated yield. [b]**1a** was recovered in 50% yield. [c]**1a** was recovered in 14% yield. [d]**1a** was recovered in 61% yield.

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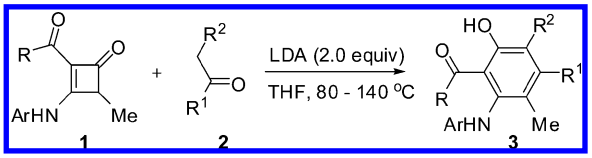
Table 2. Synthesis of Persubstituted Phenols 3[a]



entry	1	R	Ar	R^1	R^2	temp (°C)	time (h)	yield[b] (%)
1	**1a**	Et	4-$NO_2C_6H_4$	Me	CO_2Me (**2a**)	80	8	**3a** (85)
2	**1b**	Et	4-ClC_6H_4	Me	CO_2Me	80	8	**3b** (65)
3	**1c**	Et	C_6H_5	Me	CO_2Me	80	8	**3c** (85)
4	**1d**	Et	4-MeC_6H_4	Me	CO_2Me	80	8	**3d** (81)
5	**1e**	Et	2-MeC_6H_4	Me	CO_2Me	80	8	**3e** (80)
6	**1f**	Et	2,4-$Me_2C_6H_3$	Me	CO_2Me	80	10	**3f** (78)
7	**1g**	Et	4-$MeOC_6H_4$	Me	CO_2Me	80	8	**3g** (80)
8	**1h**	Et	1-naphthyl	Me	CO_2Me	80	8	**3h** (70)
9	**1i**	Me	4-MeC_6H_4	Me	CO_2Me	80	8	**3i** (80)
10	**1j**	MeO	4-MeC_6H_4	Me	CO_2Me	80	8	**3j** (78)
11	**1d**	Et	4-MeC_6H_4	Me	CO_2Et (**2b**)	80	9	**3k** (77)
12	**1d**	Et	4-MeC_6H_4	Et	CO_2Me (**2c**)	80	12	**3l** (68)
13	**1d**	Et	4-MeC_6H_4	Ph	CO_2Et (**2d**)	130	8	**3m** (76)
14	**1d**	Et	4-MeC_6H_4	Me	CONHPh (**2e**)	130	8	**3n** (71)
15	**1d**	Et	4-MeC_6H_4	Me	CONH(4-MeC_6H_4) (**2f**)	130	8	**3o** (75)
16	**1d**	Et	4-MeC_6H_4	Me	$CONH_2$ (**2g**)	130	8	**3p** (68)
17[c]	**1d**	Et	4-MeC_6H_4	Ph	COMe (**2h**)	140	12	**3q** (64)

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), LDA (1.0 mmol), THF (2.0 mL), 8−12 h. [b]Isolated yield. [c]8.0 equiv of **2h** was used.

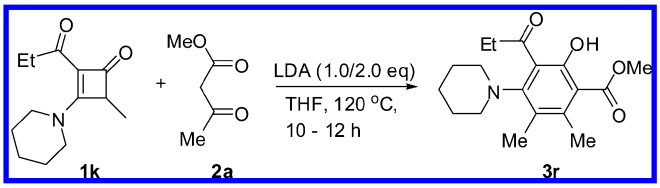
The above results indicate that the reaction of 3-aminocyclobutenone **1a** with methyl acetoacetate **2a** can afford persubstituted phenol **3a** successfully or 3-aminocyclobutenone **1a** itself is converted to highly substituted α-pyrone **5a**, depending on the reaction conditions. In the formation of **3a**, the methyl, *N*-aryl, and propionyl groups on the cyclobutenone ring of **1a** and the methoxycarbonyl group of **2a** remained intact, and no other benzannulation products were detected. To our knowledge, the successful synthesis of **3a** represents a new synthetic strategy for highly functionalized phenols from cyclobutenones[6,7] in a regiospecific manner.[3a] In this regiospecific benzannulation reaction, cyclobutenones act as four-carbon 1,4-dipoles,[3b] while a methylene ketone plays the role of carbon−carbon dipolarophiles. Thus, the formal [4 + 2] cycloaddition reaction (see Scheme 3) for the preparation of **3a** (also a persubstituted aniline) substantially expands the synthetic potential of cyclobutenones **1**.[7b,11,12] Prompted by this observation, the scope of the [4 + 2] cycloaddition reaction was investigated under the optimal conditions (Table 1, entry 1), and the results are summarized in Table 2.

On the basis of the experimental results, the [4 + 2] cycloaddition reaction shows broad tolerance for various *N*-aryl-substituted cyclobutenones **1**, including phenyl (Table 2, entry 3), electron-deficient (Table 2, entries 1 and 2), electron-rich (Table 2, entries 4−7) *N*-aryl groups and *N*-(1-naphthyl) (Table 2, entry 8). All of the reactions of **1a−h** with methyl acetoacetate **2a** gave the corresponding persubstituted phenols **3a−h** in good to high yields (Table 2, entries 1−8). Similarly, the desired phenols **3i** and **3j** were synthesized in 80% and 78% yields from reactions **1i** (R = Me) and **1j** (R = MeO) with **2a**, respectively (Table 2, entries 9 and 10).[13]

To extend the scope of the [4 + 2] cycloaddition reaction, the reactions of **1d** with active methylene ketones, including ethyl acetoacetate **2b** (Table 2, entry 11), methyl propionylacetate **2c** (Table 2, entry 12), ethyl benzoylacetate **2d** (Table 2, entry 13), 3-oxo-*N*-phenylbutanamide **2e** (Table 2, entry 14), 3-oxo-*N*-*p*-tolylbutanamide **2f** (Table 2, entry 15), 3-oxobutanamide **2g** (Table 2, entry 16), and benzoyl acetone **2h** (Table 2, entry 17) as carbon−carbon dipolarophiles were examined. As a result, the corresponding phenols **3l−q** were prepared in good to high yields (Table 2, entries 11−17).

To gain insight into the reaction mechanism, the reaction of methyl acetoacetate **2a** with cyclobutenone **1k** having a dialkylamino group (piperidin-1-yl) was performed under similar conditions as in Table 2. As a result, the desired persubstituted phenol **3r** was obtained in 60% and 61% yields under the conditions with 2.0 equiv of LDA at 120 °C for 10 h and with 1.0 equiv of LDA at 120 °C for 12 h, respectively (Scheme 1). The above results indicate that the [4 + 2] benzannulation reaction can tolerate various amino groups on the cyclobutenone ring (see also Table 2) and exhibit good flexibility.

Scheme 1. Synthesis of Persubstituted Phenol 3r



It was noted that in the absence of active methylene ketones an enaminone product, (*E*)-3-(4-chlorophenylamino)-*N*,*N*-diisopropyl-2-propionylpent-2-enamide **4b**, was obtained in 75% yield by treatment of cyclobutenone **1b** with LDA (2.0 equiv) in THF at 80 °C for 10 h (Scheme 2).[13] Similarly, under essentially identical conditions, highly substituted α-pyrone **5b** was produced in 90% yield when NaOH (2.0 equiv) or *t*-BuOK (2.0 equiv) was used as the base (Scheme 2; see also Table 1, entries 4 and 5). Furthermore, the reaction of **5b** with **2a** was attempted. As a result, **5b** was recovered in nearly quantitative yield after treatment of the mixture of **5b** (0.5 mmol) and **2a**

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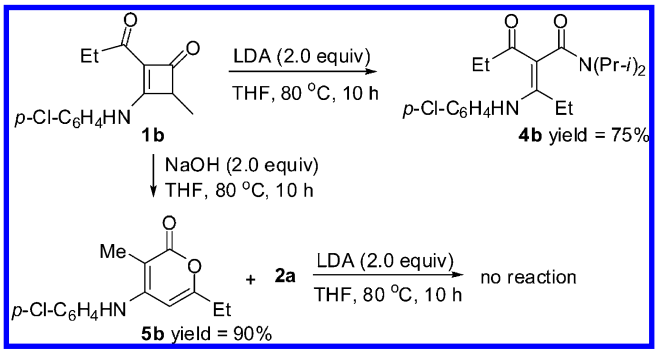
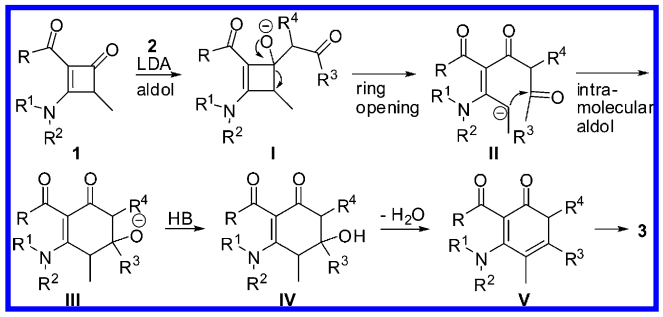
Scheme 2. Synthesis of Enaminone 4b and α-Pyrone 5b



(0.6 mmol) with LDA (1.0 mmol) in THF (2.0 mL) at 80 °C for 10 h (Scheme 2).

The α-pyrone ring system has been found in various important natural products and has found versatile applications in organic synthesis.[14,15] The transformation of cyclobutenone **1** to **5** (Table 1, entries 4−10, and Scheme 2) provides a convenient pathway for the synthesis of α-pyrones and deserves further research, whereas according to the experimental results (Scheme 2, reaction **5b** with **2a**), α-pyrone **5** would not be involved in the formation of persubstituted phenols **3**. Therefore, a mechanism for the [4 + 2] benzannulation between cyclobutenones **1** and methylene ketones **2** is proposed in Scheme 3. In the presence of

Scheme 3. Proposed Mechanism for Formation of Phenols 3

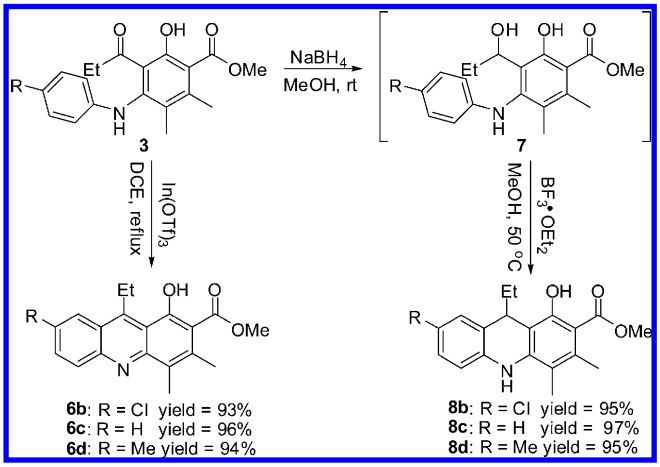


LDA, the reaction starts from the deprotonation of **2** and subsequent intermolecular aldol reaction with **1** to give cyclobutenolate intermediate **I**. Then a ring-opening process (**I**→**II**, see also the transformation of **1b**→**4b** in Scheme 2) followed by intramolecular aldol cyclization to afford six-membered intermediate **III**. Finally, the benzannulation product **3** is formed via a sequential protonation (**III**→**IV**), dehydration (**IV**→**V**), and aromatization (**V**→**3**) process.

Obviously, the above benzannulation reaction provides a simple and efficient procedure for the synthesis of persubstituted phenols **3** from easily available starting materials. In this cyclization reaction, the carbonyl oxygen on the cyclobutenone ring is converted into the hydroxyl group of phenols **3**. Other functional groups on the cyclobutenone ring and the R^3 and R^4 groups on the methylene ketones **2** are introduced onto the benzene ring in a regiospecific manner (Scheme 3). Next, to explore the synthetic potential of these highly functionalized phenols (anilines), the cyclization reaction of **3** was examined.

It was found that the highly substituted acridines **6b−d** could be easily obtained in excellent yield by treatment of selected **3b−d** (having a phenyl (**3c**), electron-deficient (**3b**), and electron-rich *N*-aryl groups (**3d**), respectively) in the presence of $In(OTf)_3$ (8.0 mol %) in 1,2-dichloroethane (DCE) at reflux temperature for 10−12 h (Scheme 4). Since acridine derivatives display a broad spectrum of biological activities,[16] the synthesis

Scheme 4. Synthesis of Acridine Derivatives 6 and 8



of substituted 9,10-dihydroacridins **8b−d** were further examined. To our delight, dihydroacridins **8b−d** could be prepared in excellent total yields by a one-pot procedure, including reduction of **3b−d** with $NaBH_4$ (1.0 equiv) in methanol at room temperature for 2 h followed by treatment of the reaction mixture with $BF_3{\cdot}OEt_2$ (1.0 equiv) at 50 °C for 15 min (Scheme 4). Thus, the above transformation provides an efficient approach for the synthesis of acridine derivatives with flexible substituents.[16,17]

In summary, a new benzannulation strategy has been developed. Using this strategy, persubstituted phenols (anilines) were prepared from the reaction of cyclobutenones (as four-carbon 1,4-dipoles) with active methylene ketones (as carbon−carbon dipolarophiles) via a formal [4 + 2] cycloaddition. This base-promoted benzannulation reaction is totally regiocontrolled with respect to the relative orientation of coupling partners and various functional groups are introduced into the benzene ring in a single step. In addition, highly substituted acridine derivatives were synthesized in excellent yields from the persubstituted benzenes. Further investigations are focused on expanding the scope of this benzannulation reaction with respect to the dipolarophiles, and will be reported in due course.

EXPERIMENTAL SECTION

Commercially available reagents were used without further purification. All solvents were purified and dried according to standard methods prior to use. Chromatography was carried on flash silica gel (300−400 mesh). All reactions were monitored using TLC on silica gel plates. Unless noted, the ^1H NMR spectra were recorded at 500 or 600 MHz in $CDCl_3$ and the ^{13}C NMR spectra were recorded at 125 or 150 MHz in $CDCl_3$ with TMS as internal standard. All coupling constants (*J* values) are reported in hertz (Hz). High-resolution mass spectra (ESI/HRMS) were recorded on a mass spectrometer.

General Procedure for Synthesis of 3 (3a, for Example). An oven-dried Schlenck tube charged with 3-aminocyclobutenone **1a** (0.5 mmol, 137 mg) and a magnetic bar was evacuated and refilled with N_2 three times. Then methyl acetoacetate **2a** (0.6 mmol, 0.065 mL), LDA (1.0 mmol, 0.12 mL), and 2 mL of dried THF were injected under N_2 via syringe, and the reaction mixture was stirred at 80 °C for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography

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(petroleum ether/acetone = 6/1, v/v) to give **3a** (158 mg, 85%) as a yellow solid.

Methyl 2-hydroxy-5,6-dimethyl-4-(4-nitrophenylamino)-3-propionylbenzoate (3a): yellow solid (158 mg, 85%); mp 184−186 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (t, J = 7.5 Hz, 3H), 1.97 (s, 3H), 2.47 (s, 3H), 2.88 (q, J = 7.0 Hz, 2H), 4.00 (s, 3H), 6.56 (d, J = 9.0 Hz, 2H), 7.83 (s, 1H), 8.08 (d, J = 8.5 Hz, 2H), 11.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.7, 15.6, 19.6, 37.5, 52.8, 114.2 (3C), 120.8, 125.5, 126.1 (2C), 140.1, 140.3, 143.8, 150.3, 158.6, 171.2, 207.5; HRMS (ESI-TOF) calcd for $C_{19}H_{21}N_2O_6^+$ ([M + H]$^+$): 373.1394, found 373.1381.

Methyl 4-(4-chlorophenylamino)-2-hydroxy-5,6-dimethyl-3-propionylbenzoate (3b): yellow solid (117 mg, 65%); mp 210−212 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, J = 7.5 Hz, 3H), 1.92 (s, 3H), 2.45 (s, 3H), 2.94 (q, J = 7.0 Hz, 2H), 3.99 (s, 3H), 6.57 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 11.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 16.1, 19.7, 37.5, 52.4, 110.7, 118.2 (2C), 119.2, 123.4, 125.4, 129.1 (2C), 142.8, 143.8, 143.9, 159.7, 171.6, 207.8; HRMS (ESI-TOF) calcd for $C_{19}H_{21}ClNO_4^+$ ([M + H]$^+$) 362.1154, found 362.1153.

Methyl 2-hydroxy-5,6-dimethyl-4-(phenylamino)-3-propionylbenzoate (3c): yellow solid (139 mg, 85%); mp 166−168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, J = 7.5 Hz, 3H), 1.94 (s, 3H), 2.45 (s, 3H), 2.95 (q, J = 7.5 Hz, 2H), 3.99 (s, 3H), 6.67 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 7.85 (s, 1H), 11.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 16.1, 19.7, 37.4, 52.4, 110.7, 117.2 (2C), 119.0, 120.8, 123.4, 129.1 (2C), 143.6, 144.2 (2C), 159.6, 171.6, 208.0; HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO_4^+$ ([M + H]$^+$) 328.1543, found 328.1531.

Methyl 2-hydroxy-5,6-dimethyl-3-propionyl-4-(*p*-tolylamino)benzoate (3d): yellow solid (138 mg, 81%); mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, J = 7.5 Hz, 3H), 1.92 (s, 3H), 2.27 (s, 3H), 2.43 (s, 3H), 2.95 (q, J = 7.5 Hz, 2H), 3.98 (s, 3H), 6.58 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 11.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 16.2, 19.7, 20.6, 37.4, 52.3, 110.0, 117.6 (2C), 118.5, 122.8, 129.6 (2C), 130.4, 141.7, 143.6, 145.0, 159.8, 171.7, 207.9; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO_4^+$ ([M + H]$^+$) 342.1700, found 342.1687.

Methyl 2-hydroxy-5,6-dimethyl-3-propionyl-4-(*o*-tolylamino)benzoate (3e): yellow solid (136 mg, 80%); mp 146−148 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.05 (t, J = 7.2 Hz, 3H), 1.85 (s, 3H), 2.34 (s, 3H), 2.45 (s, 3H), 2.95 (q, J = 7.2 Hz, 2H), 3.98 (s, 3H), 6.38 (d, J = 6.6 Hz, 1H), 6.84 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 11.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.0, 16.2, 17.9, 19.7, 37.5, 52.3, 109.5, 116.5, 118.5, 121.1, 122.9, 126.4, 126.6, 130.5, 142.5, 143.6, 145.7, 160.2, 171.9, 207.7; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO_4^+$ ([M + H]$^+$) 342.1700, found 342.1702.

Methyl 4-(2,4-dimethylphenylamino)-2-hydroxy-5,6-dimethyl-3-propionylbenzoate (3f): yellow solid (139 mg, 78%); mp 179−181 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, J = 7.0 Hz, 3H), 1.82 (s, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.95 (q, J = 7.0 Hz, 2H), 3.98 (s, 3H), 6.30 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 11.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.0, 16.3, 18.0, 19.8, 20.6, 37.5, 52.2, 108.9, 117.2, 118.0, 122.4, 126.8, 127.1, 130.8, 131.3, 140.1, 143.6, 146.4, 160.4, 172.0, 207.7; HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_4^+$ ([M + H]$^+$) 356.1856, found 356.1866.

Methyl 2-hydroxy-4-(4-methoxyphenylamino)-5,6-dimethyl-3-propionylbenzoate (3g): yellow solid (143 mg, 80%); mp 200−202 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, J = 7.5 Hz, 3H), 1.88 (s, 3H), 2.43 (s, 3H), 2.97 (q, J = 7.5 Hz, 2H), 3.76 (s, 3H), 3.97 (s, 3H), 6.66 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 8.13 (s, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.0, 16.3, 19.7, 37.6, 52.2, 55.5, 109.0, 114.4 (2C), 117.7, 119.8 (2C), 122.0, 137.8, 143.8, 146.2, 154.6, 160.4, 171.9, 207.8; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO_5^+$ ([M + H]$^+$) 358.1649, found 358.1670.

Methyl 2-hydroxy-5,6-dimethyl-4-(naphthalen-1-ylamino)-3-propionylbenzoate (3h): yellow solid (132 mg, 70%); mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, J = 7.5 Hz, 3H), 1.85 (s, 3H), 2.46 (s, 3H), 2.97 (q, J = 7.0 Hz, 2H), 4.00 (s, 3H), 6.47 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.51−7.58 (m, 2H), 7.85 (t, J = 7.5 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.72 (s, 1H), 11.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.1, 16.2, 19.8, 37.6, 52.3, 109.4, 113.0, 118.5, 121.6, 121.8, 122.8, 125.7, 125.9, 126.2, 126.3, 128.4, 134.5, 139.9, 143.9, 146.3, 160.4, 172.0, 207.9; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4^+$ ([M + H]$^+$) 378.1700, found 378.1715.

Methyl 3-acetyl-2-hydroxy-5,6-dimethyl-4-(*p*-tolylamino)-benzoate (3i): yellow solid (131 mg, 80%); mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.93 (s, 3H), 2.28 (s, 3H), 2.43 (s, 3H), 2.60 (s, 3H), 3.99 (s, 3H), 6.62 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 8.34 (s, 1H), 12.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 19.7, 20.6, 32.7, 52.3, 110.4, 117.3, 117.8 (2C), 122.3, 129.7 (2C), 130.6, 141.7, 144.2, 145.7, 160.7, 171.5, 204.1; HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO_4^+$ ([M + H]$^+$) 328.1543, found 328.1541.

Dimethyl 2-hydroxy-4,5-dimethyl-6-(*p*-tolylamino)-isophthalate (3j): yellow solid (134 mg, 78%); mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 6.57 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.48 (s, 1H), 11.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 18.5, 20.6, 52.4, 52.9, 105.3, 117.3 (2C), 117.8, 122.9, 129.7 (2C), 130.3, 142.1, 142.8, 144.3, 157.6, 169.1, 170.0; HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO_5^+$ ([M + H]$^+$) 344.1492, found 344.1508.

Ethyl 2-hydroxy-5,6-dimethyl-3-propionyl-4-(*p*-tolylamino)-benzoate (3k): yellow solid (137 mg, 77%); mp 131−133 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.04 (t, J = 7.2 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.91 (s, 3H), 2.26 (s, 3H), 2.45 (s, 3H), 2.94 (q, J = 7.2 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 6.58 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 7.87 (s, 1H), 11.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 14.2, 16.2, 19.7, 20.6, 37.5, 61.7, 110.2, 117.6 (2C), 118.6, 122.9, 129.6 (2C), 130.3, 141.9, 143.5, 144.9, 159.8, 171.3, 207.9; HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_4^+$ ([M + H]$^+$) 356.1856, found 356.1850.

Methyl 2-ethyl-6-hydroxy-3-methyl-5-propionyl-4-(*p*-tolylamino)benzoate (3l): yellow solid (121 mg, 68%); mp 155−157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, J = 7.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), 1.98 (s, 3H), 2.26 (s, 3H), 2.86 (q, J = 7.5 Hz, 2H), 2.93 (q, J = 7.0 Hz, 2H), 3.98 (s, 3H), 6.57 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 11.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 14.1, 14.8, 20.6, 25.5, 37.2, 52.3, 110.7, 117.3 (2C), 118.7, 122.4, 129.8 (2C), 130.3, 141.9, 145.0, 148.9, 159.5, 171.3, 208.0; HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_4^+$ ([M + H]$^+$) 356.1856, found 356.1864.

Ethyl 3-hydroxy-6-methyl-4-propionyl-5-(*p*-tolylamino)-biphenyl-2-carboxylate (3m): yellow solid (159 mg, 76%); mp 118−120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.70 (t, J = 7.5 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H), 1.57 (s, 3H), 2.27 (s, 3H), 3.03 (q, J = 7.0 Hz, 2H), 3.90 (q, J = 7.0 Hz, 2H), 6.69 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.0 Hz, 3H), 8.34 (s, 1H), 12.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.8, 12.9, 17.7, 20.6, 37.7, 60.9, 107.7, 118.6 (2C), 122.1, 126.7, 127.8 (2C), 128.2 (2C), 128.5, 129.6 (2C), 131.0, 141.2, 141.9, 146.3, 147.5, 160.3, 171.1, 207.7; HRMS (ESI-TOF) calcd for $C_{26}H_{28}NO_4^+$ ([M + H]$^+$) 418.2013, found 418.2030.

2-Hydroxy-5,6-dimethyl-*N*-phenyl-3-propionyl-4-(*p*-tolylamino)benzamide (3n): yellow solid (143 mg, 71%); mp 193−195 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, J = 7.0 Hz, 3H), 2.04 (s, 3H), 2.26 (s, 3H), 2.41 (s, 3H), 2.93 (q, J = 7.0 Hz, 2H), 6.13 (s, 1H), 6.56 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 7.17(t, J = 7.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.66 (s, 1H), 11.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.0, 14.3, 18.6, 20.5, 36.1, 115.4 (2C), 117.2, 120.1 (2C), 121.6, 123.9, 124.7, 129.1 (2C), 129.7, 130.1 (2C), 137.7, 141.6, 142.6, 142.7, 156.4, 166.3, 208.7; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_3^+$ ([M + H]$^+$) 403.2016, found 403.2028.

2-Hydroxy-5,6-dimethyl-3-propionyl-*N*-p-tolyl-4-(*p*-tolylamino)benzamide (3o): yellow solid (156 mg, 75%); mp 190−192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, J = 7.0 Hz, 3H), 2.03 (s, 3H), 2.26 (s, 3H), 2.35 (s, 3H), 2.41 (s, 3H), 2.93 (q, J = 7.0 Hz,

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2H), 6.19 (s, 1H), 6.56 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.57 (s, 1H), 11.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 9.0, 14.4, 18.7, 20.5, 20.9, 36.2, 115.4 (2C), 117.4, 120.2 (2C), 121.5, 124.1, 129.6 (2C), 129.8, 130.1 (2C), 134.4, 135.2, 141.6, 142.4, 142.7, 156.4, 166.4, 208.7; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_3^+$ ([M + H]$^+$) 417.2173, found 417.2190.

2-Hydroxy-5,6-dimethyl-3-propionyl-4-(*p*-tolylamino)-benzamide (3p): yellow solid (111 mg, 68%); mp 131−133 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.84 (t, J = 7.25 Hz, 3H), 1.89 (s, 3H), 2.14 (s, 3H), 2.19 (s, 3H), 2.70 (q, J = 7.5 Hz, 2H), 6.38 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.55 (s, 2H), 7.71 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 8.4, 14.2, 17.7, 20.1, 36.0, 113.6 (2C), 122.1, 124.3, 125.1, 126.3, 129.6 (2C), 138.5, 138.7, 144.1, 152.0, 169.4, 207.0; HRMS (ESI-TOF) calcd for $C_{19}H_{23}N_2O_3^+$ ([M + H]$^+$) 327.1703, found 327.1709.

1-(3-Benzoyl-2-hydroxy-4,5-dimethyl-6-(*p*-tolylamino)-phenyl)propan-1-one (3q): yellow solid (124 mg, 64%); mp 135−137 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 1.57 (s, 3H), 1.69 (s, 3H), 2.29 (s, 3H), 3.06 (q, J = 7.5 Hz, 2H), 6.78 (d, J = 7.0 Hz, 2H), 7.06 (d, J = 7.5 Hz, 2H), 7.20 (d, J = 6.5 Hz, 2H), 7.42 (t, J = 7.0 Hz, 3H), 9.12 (s, 1H), 13.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 18.4, 20.7, 31.4, 37.9, 116.3, 117.2, 119.5 (2C), 120.5, 128.3 (2C), 128.7 (2C), 129.6, 129.7 (2C), 131.7, 140.7, 141.0, 147.8, 148.4, 162.5, 205.7, 207.6; HRMS (ESI-TOF) calcd for $C_{25}H_{26}NO_3^+$ ([M + H]$^+$) 388.1907, found 388.1914.

Methyl 2-hydroxy-5,6-dimethyl-4-(piperidin-1-yl)-3-propionylbenzoate (3r): yellow solid (96 mg, 60%); mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, J = 7.5 Hz, 3H), 1.59 (s, broad, 6H), 2.18 (s, 3H), 2.43 (s, 3H), 2.88 (q, J = 7.5 Hz, 2H), 2.93 (s, broad, 4H), 3.95 (s, 3H), 10.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.1, 15.2, 19.5, 24.2, 26.6 (2C), 38.2, 52.2 (3C), 109.9, 125.7, 126.8, 140.9, 153.6, 156.7, 171.7, 207.6; HRMS (ESI-TOF) calcd for $C_{18}H_{26}NO_4^+$ ([M + H]$^+$) 320.1856, found 320.1868.

Procedure for Preparation of 4 (4b, for Example). An oven-dried Schlenck tube charged with 3-aminocyclobutenone **1b** (0.5 mmol, 132 mg) and a magnetic bar was evacuated and refilled with N_2 three times. Then LDA (1.0 mmol, 0.12 mL) and 2 mL of dried THF were injected under N_2 via syringe, and the reaction mixture was stirred at 80 °C for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (petroleum ether/acetone = 8/1, v/v) to give **4b** (137 mg, 75%) as a white solid.

(*E*)-3-(4-Chlorophenylamino)-*N*,*N*-diisopropyl-2-propionylpent-2-enamide (4b): white solid (137 mg, 75%); mp 136−138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, J = 7.5 Hz, 3H), 1.11 (t, J = 7.5 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 6.5 Hz, 3H), 1.49 (d, J = 6.5 Hz, 3H), 1.52 (d, J = 6.5 Hz, 3H), 2.27−2.40 (m, 3H), 2.61 (q, J = 7.5 Hz, 1H), 3.47 (q, J = 7.0 Hz, 1H), 4.23 (q, J = 6.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 12.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.8, 12.3, 19.9, 20.2, 20.8, 21.0, 22.9, 32.3, 45.7, 51.0, 109.2, 126.8 (2C), 129.4 (2C), 131.7, 137.2, 162.7, 169.1, 197.8; HRMS (ESI-TOF) calcd for $C_{20}H_{30}ClN_2O_2^+$ ([M + H]$^+$) 365.1990, found 365.1996.

(E)-*N*,*N*-Diisopropyl-2-propionyl-3-(*p*-tolylamino)pent-2-enamide (4d): white solid (138 mg, 80%); mp 100−102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 6.5 Hz, 6H), 1.16 (d, J = 6.5 Hz, 3H), 1.48 (d, J = 6.5 Hz, 3H), 1.52 (d, J = 6.5 Hz, 3H), 2.21−2.32 (m, 2H), 2.34 (s, 3H), 2.35−2.42 (m, 1H), 2.60 (q, J = 7.0 Hz, 1H), 3.45 (q, J = 7.0 Hz, 1H), 4.26 (q, J = 6.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 12.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.9, 12.4, 19.9, 20.2, 20.9, 21.0 (2C), 23.0, 32.2, 45.6, 50.9, 108.3, 125.7 (2C), 129.8 (2C), 135.7, 136.1, 163.7, 169.5, 197.0; HRMS (ESI-TOF) calcd for $C_{21}H_{33}N_2O_2^+$ ([M + H]$^+$) 345.2537, found 345.2552.

Procedure for Preparation of 5b. An oven-dried Schlenck tube charged with 3-aminocyclobutenone **1b** (0.5 mmol, 132 mg), NaOH (1.0 mmol, 40 mg), and a magnetic bar was evacuated and refilled with N_2 three times. Then 2 mL of dried THF was injected under N_2 via syringe, and the reaction mixture was stirred at 80 °C for 10 h. After **1b** was consumed (monitored by TLC), the reaction mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (petroleum ether/acetone = 3/1, v/v) to give **5b** (118 mg, 90%) as a white solid.

4-(4-Chlorophenylamino)-6-ethyl-3-methyl-2*H*-pyran-2-one (5b): white solid (158 mg, 90%); mp 195−197 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (t, J = 7.5 Hz, 3H), 2.01 (s, 3H), 2.41 (q, J = 7.5 Hz, 2H), 5.85 (s, 1H), 6.18 (s, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.37 (t, J = 8.5 Hz, 2H),; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.3, 11.2, 27.1, 94.4, 94.6, 125.5 (2C), 129.7 (2C), 131.1, 137.0, 151.9, 164.5, 165.3; HRMS (ESI-TOF) calcd for $C_{14}H_{15}ClNO_2^+$ ([M + H]$^+$) 264.0786, found 264.0785.

General Procedure for the Preparation of 6 (6d as Example). To a solution of phenol **3d** (0.5 mmol, 171 mg) in 1,2-dichloroethane (3.0 mL) was added $In(OTf)_3$ (22.5 mg, 0.04 mmol) in one portion. Then the reaction mixture was heated at reflux for 10 h until compound **3d** was consumed (monitored by TLC). The reaction mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (petroleum ether/acetone = 30/1, v/v) to give **6d** (152 mg, 94%) as a yellow solid.

Methyl 7-chloro-9-ethyl-1-hydroxy-3,4-dimethylacridine-2-carboxylate (6b): yellow solid (160 mg, 93%); mp 168−170 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.50 (t, J = 7.0 Hz, 3H), 2.60 (s, 3H), 2.77 (s, 3H), 3.88 (q, J = 6.5 Hz, 2H), 4.03 (s, 3H), 7.66 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.26 (s, 1H), 13.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 16.0, 20.2, 24.1, 52.4, 106.8, 116.7, 123.2, 125.5, 126.5, 131.1, 131.5, 132.3, 134.5, 147.4, 150.2, 152.6, 162.8, 173.6; HRMS (ESI-TOF) calcd for $C_{19}H_{19}ClNO_3^+$ ([M + H]$^+$) 344.1048, found 344.1050.

Methyl 9-ethyl-1-hydroxy-3,4-dimethylacridine-2-carboxylate (6c): yellow solid (148 mg, 96%); mp 139−141 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52 (t, J = 7.5 Hz, 3H), 2.61 (s, 3H), 2.80 (s, 3H), 3.95 (q, J = 7.5 Hz, 2H), 4.02 (s, 3H), 7.52 (t, J = 7.0 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 13.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 16.1, 20.2, 24.1, 52.3, 106.2, 116.3, 124.5, 125.1, 125.3, 126.4, 130.5, 130.6, 134.0, 149.2, 150.2, 153.6, 163.2, 173.7; HRMS (ESI-TOF) calcd for $C_{19}H_{20}NO_3^+$ ([M + H]$^+$) 310.1438, found 310.1448.

Methyl 9-ethyl-1-hydroxy-3,4,7-trimethylacridine-2-carboxylate (6d): yellow solid (152 mg, 94%); mp 155−157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.51 (t, J = 7.0 Hz, 3H), 2.60 (s, 6H), 2.79 (s, 3H), 3.93 (q, J = 6.5 Hz, 2H), 4.02 (s, 3H), 7.59 (d, J = 9.0 Hz, 1H), 8.05 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 13.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 16.0, 20.1, 22.2, 23.9, 52.1, 106.3, 116.4, 122.8, 125.1, 126.5, 130.4, 133.1, 133.4, 134.9, 148.1, 149.8, 152.3, 163.1, 173.7; HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_3^+$ ([M + H]$^+$) 324.1594, found 324.1609.

General Procedure for Preparation of 8 (8d, for Example). To a solution of phenol **3d** (0.5 mmol, 171 mg) in CH_3OH (5.0 mL) was added $NaBH_4$ (0.5 mmol, 19 mg) in one portion. The reaction mixture was stirred for 2 h at room temperature until **3d** was consumed (monitored by TLC). Then $BF_3{\cdot}OEt_2$ (0.5 mmol, 0.062 mL) was added, and the mixture was stirred at 50 °C for 15 min. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (petroleum ether/acetone = 1/1, v/v) to give **8d** (154 mg, 95%) as a white solid.

Methyl 7-chloro-9-ethyl-1-hydroxy-3,4-dimethyl-9,10-dihydroacridine-2-carboxylate (8b): white solid (164 mg, 95%); mp 190−192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (t, J = 7.0 Hz, 3H), 1.60−1.74 (m, 2H), 2.16 (s, 3H), 2.48 (s, 3H), 3.94 (s, 3H), 4.34 (t, J = 6.0 Hz, 1H), 6.28 (s, 1H), 6.72 (d, J = 8.5 Hz, 1H), 7.08 (t, J = 8.5 Hz, 1H), 7.15 (s, 1H), 11.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.9, 12.4, 19.1, 30.5, 36.4, 51.7, 105.6, 107.5, 111.3, 115.1, 126.1, 126.3,

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126.6, 128.7, 137.1, 137.2, 142.6, 158.6, 172.6; HRMS (ESI-TOF) calcd for $C_{19}H_{21}ClNO_3^+$ ([M + H]$^+$) 346.1204, found 346.1219.

Methyl 9-ethyl-1-hydroxy-3,4-dimethyl-9,10-dihydroacridine-2-carboxylate (8c): white solid (151 mg, 97%); mp 201−203 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (t, J = 7.5 Hz, 3H), 1.63−1.72 (m, 2H), 2.17 (s, 3H), 2.48 (s, 3H), 3.94 (s, 3H), 4.36 (t, J = 6.5 Hz, 1H), 6.30 (s, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 7.15 (d, J = 6.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 11.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.2, 12.5, 19.2, 30.6, 36.5, 51.7, 105.4, 108.2, 111.3, 114.0, 121.6, 124.6, 126.7, 129.1, 136.9, 138.5, 143.1, 158.7, 172.7; HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO_3^+$ ([M + H]$^+$) 312.1594, found 312.1590.

Methyl 9-ethyl-1-hydroxy-3,4,7-trimethyl-9,10-dihydroacridine-2-carboxylate (8d): white solid (154 mg, 95%); mp 195−197 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.75 (t, J = 7.5 Hz, 3H), 1.59−1.73 (m, 2H), 2.16 (s, 3H), 2.31 (s, 3H), 2.47 (s, 3H), 3.93 (s, 3H), 4.33 (t, J = 6.5 Hz, 1H), 6.23 (s, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 11.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.1, 12.5, 19.2, 20.8, 30.7, 36.4, 51.7, 105.1, 108.0, 111.2, 113.9, 124.6, 127.2, 129.5, 130.9, 136.2, 136.8, 143.4, 158.8, 172.7; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO_3^+$ ([M + H]$^+$) 326.1751, found 326.1750.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **3**−**6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Synthetic and Natural Phenols*; Tyman, J. H. P., Ed.; Elsevier: New York, 1996. (b) Roche, S. P.; Porco, J. A., Jr *Angew. Chem., Int. Ed.* **2011**, *50*, 4068−4093.

(2) For recent reviews see: (a) Dötz, K. H.; Wenzel, B.; Jahr, H. C. *Top. Curr. Chem.* **2004**, *248*, 63−103. (b) Dötz, K. H.; Stendel, J., Jr. *Chem. Rev.* **2009**, *109*, 3227−3274. (c) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892−1918.

(3) (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578−4579. (b) Wang, M.; Fu, Z.; Feng, H.; Dong, Y.; Liu, J.; Liu, Q. *Chem. Commun.* **2010**, *46*, 9061−9063 and references therein.

(4) For selected recent reports, see: (a) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; Ramirez, M. A.; García-Tellado, F. *Chem.—Eur. J.* **2011**, *17*, 3318−3321. (b) Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6413−6417.

(5) (a) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 11004−11005. (b) Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 425−428. (c) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624−1625. (d) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369−5372.

(6) (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392−3393. (b) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem., Int. Ed.* **2005**, *44*, 1221−1222.

(7) (a) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771−2772. (b) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852−1873. (c) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407−3410. (d) Auvinet, A.-L.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2769−2772. (e) Kondo, T.; Niimi, M.; Nomura, M.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2007**, *48*, 2837−2839.

(8) For selected recent reports, see: (a) Li, Y.; Xu, X.; Tan, J.; Xia, C.; Zhang, D.; Liu, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1775−1777. (b) Tan, J.; Xu, X.; Zhang, L.; Li, Y.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868−2872. (c) Wang, H.; Zhao, Y.-L.; Ren, C.-Q.; Diallo, A.; Liu, Q. *Chem. Commun.* **2011**, *47*, 12316−12308.

(9) For recent reviews on benzannulation reactions, see: (a) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830−2834. (b) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430−3444 ([2 + 2 + 2] cycloadditions). (c) Feist, H.; Langer, P. *Synthesis* **2007**, 327−347 ([3 + 3] cyclizations). (d) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743−3782 (metathesis). (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. (f) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775−10790.

(10) For selected reports on [4 + 2] benzannulation reactions, see: (a) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970−3971. (b) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818−5827. (c) Kraus, G. A.; Riley, S.; Cordes, T. *Green Chem.* **2011**, *13*, 2734−2736. (d) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313−11314. (e) Danheiser, R. L.; Gould, A. E.; de la Pradilla, R. F.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514−5515.

(11) For preparation of 3-aminocyclobutenones, see: Zhao, Y.-L.; Yang, S.-C.; Di, C.-H.; Han, X.-D.; Liu, Q. *Chem. Commun.* **2010**, *46*, 7614−7616.

(12) For selected recent reports on the synthesis of substituted anilines, see: (a) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586−4587. (b) Zhang, K.; Louie, J. *J. Org. Chem.* **2011**, *76*, 4686−4691. (c) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776−5777. (d) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113−116 (fully substituted anilines).

(13) CCDC 849109 (**3d**) and CCDC 849110 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

(14) For a recent review, see: Goel, A.; Ram, V. J. *Tetrahedron* **2009**, *65*, 7865−7913.

(15) For selected reports, see: (a) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250−8253. (b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422−2423. (c) Li, L.; Chase, C. E.; West, F. G. *Chem. Commun.* **2008**, 4025−4027.

(16) For selected recent reports, see: (a) Lee, Y.; Hyun, S.; Kim, H. J.; Yu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 134−137 (picomolar affinity toward HIV-1 RRE and TAR). (b) Sparapani, S.; Haider, S. M.; Doria, F.; Gunaratnam, M.; Neidle, S. *J. Am. Chem. Soc.* **2010**, *132*, 12263−12272 (selectivity for human telomeric quadruplexes). (c) Campbell, N. H.; Parkinson, G. N.; Reszka, A. P.; Neidle, S. *J. Am. Chem. Soc.* **2008**, *130*, 6722−6724 (DNA quadruplex recognition).

(17) For a recent review, see: (a) Chiron, J.; Galy, J.-P. *Synthesis* **2004**, 313−325. For recent reports, see: (b) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 2289−2295. (c) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1580−1583.