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Organocatalytic Asymmetric 1,4-Addition of Aldehydes to Acridiniums Catalyzed by a Diarylprolinol Silyl Ether

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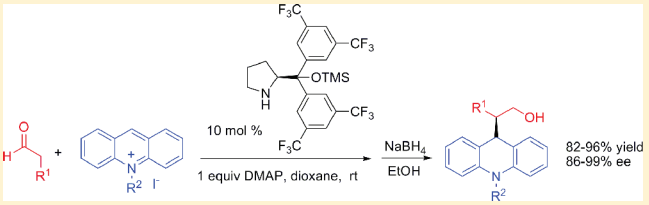
Supporting Information

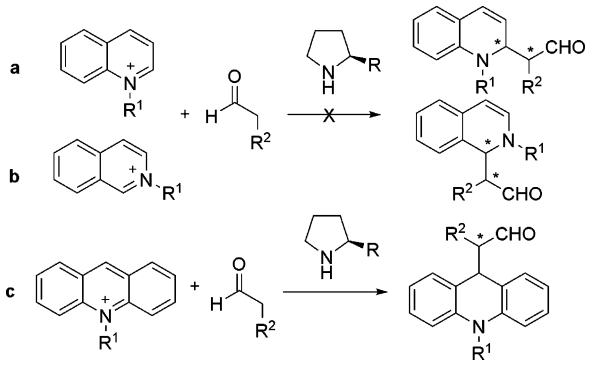
ABSTRACT: The organocatalytic enantioselective 1,4-addition of aldehydes to acridiniums catalyzed by diarylprolinol silyl ether was achieved to furnish chiral acridanes in both high yields (82−96%) and excellent enantioselectivities (up to 99% ee), which also provides the highly enantioselective intermolecular α-alkylation of aldehydes with acridiniums salt.



Azaaromatics are an important class of compounds in drug industry and in natural product synthesis.[1] Activation of nitrogen-containing aromatics toward nucleophilic addition by means of *N*-acylation, *N*-alkylation, and *N*-oxidation constitutes one of the most important and general strategies to construct new C−C bonds in heterocyclic chemistry.[2] Nevertheless, only limited asymmetric systems have been reported despite their significance in the synthesis of biologically active and enantioenriched azacycles.[3] Of all these 1,2-addition reactions of nucleophiles to nitrogen-containing heterocycles, the organocatalytic strategy is highly attractive owing to the thermal and moisture robustness and mild conditions.[4] As a well-known class of nucleophile in asymmetric catalysis, enamines[4a] can conceivably attack the covalently preactivated azaaromatics (such as quinoliniums and isoquinoliniums), producing optically active carbonyl-functionalized 1,2-dihydroquinolines and 1,2-dihydroisoquinolines, which can be further chemically manipulated. Despite the importance, this type of reaction is rather rare. Although Jørgensen reported the sole example of highly enantioselective organocatalytic intramolecular 1,2 addition of aldehydes to isoquinolinium ions in 2005,[5] the corresponding intermolecular version is unsuccessful (Scheme 1a,b). In contrast to the known 1,2 addition fashion, the intermolecular 1,4 addition of aldehydes to acridiniums was reported only recently.[6a] However, only low to moderate enantioselectivities were observed and no such highly enantioselective addition has been reported until now.[6] In our continuing efforts to develop new highly enantioselective organocatalytic reactions,[7] we herein report the highly enantioselective intermolecular 1,4-addition of aldehydes to acridiniums catalyzed by a chiral secondary amine (Scheme 1c).

It has been shown that diarylprolinol silyl ether (**I**) acts as a highly efficient catalyst for the asymmetric α-functionalization of aldehydes.[8] Therefore, we started to explore the reaction of aldehydes and *N*-methylquinolinium iodide in the presence of catalyst **I** (10 mol %) and 1 equiv of 2,6-lutidine. However, essentially no reaction occurred either at room temperature or

Scheme 1. Reactions of Aldehydes and Azaaromatics



at 60 °C. Noting that acridine and acridane moieties are present in natural products and are widely used as biological dyes, fluorescent materials, and chiroptical molecular switches,[9] we turned our attention to the more reactive acridinium salts. The reaction of *N*-methylacridinium iodide **2a** and valeryl aldehyde **1c** was conducted as the model reaction using 2,6-lutidine as a base. To our delight, the desired product **3c** was obtained in 89% yield and 86% ee in CH_2Cl_2 (Table 1, entry 1). A base proved necessary to absorb the HI byproduct (Table 1, entry 2). Next, different bases were screened, and it was found that commonly used organic bases such as pyridine and Et_3N gave the desired product in good yields and moderate to good enantioselectivity (Table 1, entries 3−6). Gratifyingly, DMAP afford the best result with 91% yield and 96% ee (Table 1, entry 7).[10] In contrast, when inorganic bases were used, the product was obtained in low yield, albeit with high enantioselectivity (Table 1, entries 8 and 9). The low efficiency of these bases is probably due to their poor solubility and low reactivity in organic solvents. Screening of different solvents indicated that

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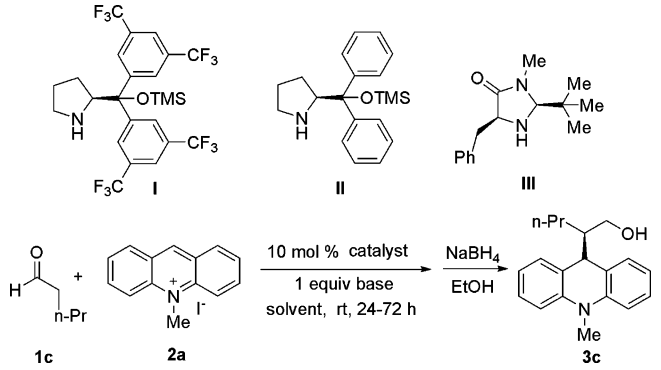
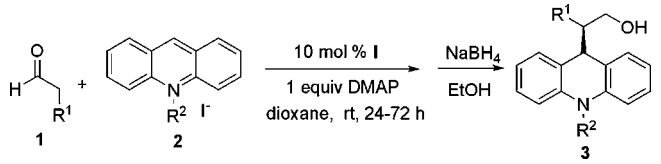
Table 1. Screening of the Catalyst and Base[a]



entry	base	catalyst	solvent	yield[b] (%)	ee[c] (%)
1	2,6-lutidine	**I**	CH_2Cl_2	89	86
2		**I**	CH_2Cl_2	<5	
3	pyridine	**I**	CH_2Cl_2	83	−61
4	imidazole	**I**	CH_2Cl_2	86	30
5	Et_3N	**I**	CH_2Cl_2	67	48
6	acridine	**I**	CH_2Cl_2	53	88
7	DMAP	**I**	CH_2Cl_2	91	96
8	$NaHCO_3$	**I**	CH_2Cl_2	32	94
9	Na_2CO_3	**I**	CH_2Cl_2	37	97
10	DMAP	**I**	$CHCl_3$	94	97
11	DMAP	**I**	DCE	92	96
12	DMAP	**I**	toluene	78	94
13	DMAP	**I**	THF	67	92
14	DMAP	**I**	dioxane	96	97
15	DMAP	**I**	MeOH	trace	
16	DMAP	**I**	DMF	trace	
17	DMAP	**I**	DMSO	trace	
18	DMAP	**I**	H_2O	trace	
19[d]	DMAP	**I**	dioxane	79	97
20[e]	DMAP	**I**	dioxane	35	95
21	DMAP	**II**	dioxane	73	76
22	DMAP	**III**	dioxane	35	−5

[a]Reactions were conducted with **1a** (0.4 mmol), **2a** (0.1 mmol), catalyst **I** (0.01 mmol), and base (0.1 mmol) in 1 mL of solvent at room temperature. [b]Isolated yield. [c]ee was determined by HPLC analysis on a chiral stationary phase. [d]5 mol % of **I** was used. [e]1 mol % of **I** was used.

Table 2. Substrate Scope[a]



entry	R^1	R^2	product	yield[b] (%)	ee[c] (%)
1	CH_3	Me	**3a**	90	94
2	C_2H_5	Me	**3b**	86	96
3	C_3H_7	Me	**3c**	96	98
4	C_4H_9	Me	**3d**	91	95
5	C_6H_{13}	Me	**3e**	93	97
6	C_7H_{15}	Me	**3f**	93	97
7	$PhCH_2$	Me	**3g**	92	90
8[d]	i-Pr	Me	**3h**	83	86
9	C_3H_7	Et	**3i**	82	89
10	C_3H_7	Pr	**3j**	84	95
11	C_3H_7	Bu	**3k**	85	99

[a]Reactions were conducted with aldehyde **1** (0.4 mmol), **2** (0.1 mmol), catalyst **I** (0.01 mmol), and DMAP (0.1 mmol) in 1 mL of dioxane at room temperature. [b]Isolated yield. [c]ee was determined by HPLC analysis on a chiral stationary phase. [d]Reaction time was 72 h.

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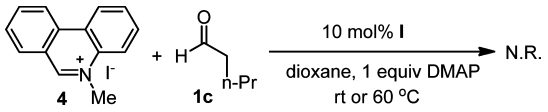
halogenated solvents such as $CHCl_3$ and $ClCH_2CH_2Cl$ consistently gave excellent yields and excellent enantioselectivities (Table 1, entries 10 and 11), while lower yields but high enantioselectivity were obtained in toluene or THF (Table 1, entries 12 and 13). Eventually, dioxane proved to be the optimal solvent, in which product **3c** was obtained in 96% isolated yield and 97% ee (Table 1, entry 14). In addition, only traces of products were detected when polar solvents such as MeOH, DMF, DMSO, and water were used (Table 1, entries 15−18). Under the optimal conditions, when the catalyst loading was decreased to 5 mol %, high yield and high enantioselectivity could still be obtainable (Table 1, entry 19). Using 1 mol % of catalyst loading resulted in lower chemical yield but still high enantioselectivity (Table 1, entry 20). In comparison, lower yield and lower enantioselectivity were obtained for catalyst **II** (Table 1, entry 21), highlighting the importance of substituted trifluoromethyl group for this reaction, which not only affects the enantioselectivity but also the reactivity. In contrast, the well-known MacMillan catalyst (**III**)[11] afforded the desired product **3c** only in 35% yield and 5% ee (Table 1, entry 22).

Various aldehydes were allowed to react with *N*-methylacridinium iodide to define the scope of aldehydes. Gratifyingly, in all cases, the desired products were obtained in high yields (83−96%) and excellent enantioselectivities (86−98% ee), making this methodology highly valuable. Not only linear aldehydes, but also branched aldehydes such as isovaleryl aldehyde, are applicable (Table 2, entries 1−8). Various alkylated salts could also be tolerated without loss of any efficiency or stereoselectivity (Table 2, entries 9−11).

Further expansion of the substrate scope by moving to *N*-methyl phenanthridinium iodide (**4**) failed even when the mixture was heated at 60 °C (Scheme 2). This indicates that 1,

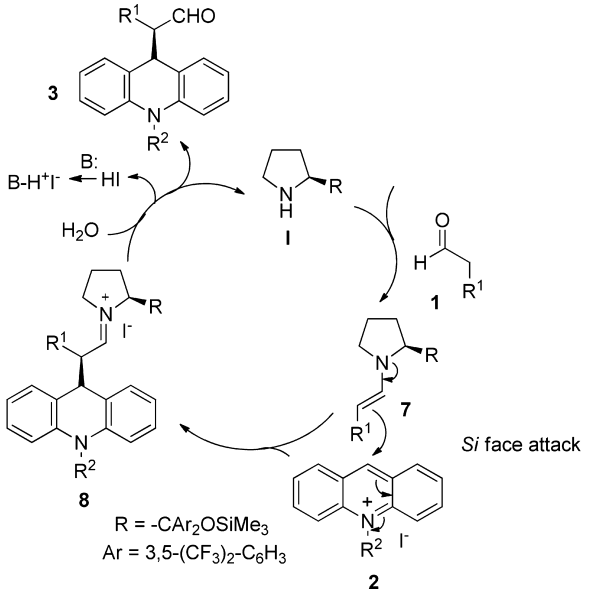
Scheme 2. Substrate Scope



2 addition failed to proceed in this system. However, when we extended the electrophile to the commercially available and air stable tropylium hexafluorophosphate **5**, successful reaction was achieved under the standard conditions to give the desired products **6a−e** in comparably high yields and excellent enantioselectivities (91−99% ee, Table 3).

A plausible mechanism for the formation of **3** is given in Scheme 3. Reaction of aldehyde **1** with chiral secondary amine

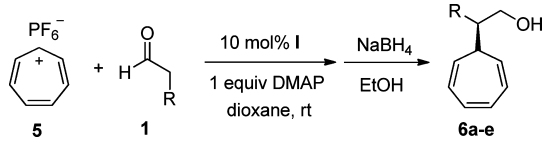
Scheme 3. Proposed Catalytic Cycle



catalyst **I** forms the (*E*)-enamine **7**, which attacks the acridinium salt **2** from the *Si* face to afford intermediate **8** since the *Re* face was efficiently shielded by the bulky silyl ether group. Hydrolysis of **8** afforded product **3** together with the regeneration of the catalyst **I**. The released HI was scavenged by DMAP. Screening experimentation indicated that DMAP is crucial in both reactivity and enantioselectivity. We believe that in addition to acting as an acid scavenger, DMAP helps to form a well-organized transition state during the attack of the enamine **7** to the acridinium salt **2**. In connection with the significant effect of trifluoromethyl group in catalyst **I**, it is possible that electrostatic interactions among the enamine, acridinium salt, DMAP, and trifluoromethyl-substituted aromatic ring were involved to stabilize the transition state.

In summary, we have developed an organocatalytic enantioselective intermolecular 1,4-addition of aldehydes to acridinium salts catalyzed by a chiral secondary amine. This methodology provides the general protocol toward the highly enantioenriched chiral acridane and tropylium derivatives, thus overcoming the lack of which in the past. The high yields and

Table 3. Substrate Scope[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1	CH_3	**6a**	85	95
2	C_2H_5	**6b**	83	91
3	C_3H_7	**6c**	80	99
4	C_4H_9	**6d**	81	97
5	$PhCH_2$	**6e**	71	97

[a]Reactions were conducted with aldehyde **1** (0.4 mmol), **2** (0.1 mmol), catalyst **I** (0.01 mmol), and DMAP (0.1 mmol) in 1 mL of dioxane at room temperature. [b]Isolated yield. [c]ee was determined by HPLC analysis on a chiral stationary phase.

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excellent enantioselectivities in this reaction make this methodology highly attractive in the synthesis of optically pure useful acridane derivatives. This open air, room temperature reaction without resort to any dry solvent or reagent is quite promising for future applications. Furthermore, the success of this reaction provides the rare highly enantioselective example for the asymmetric intermolecular α-alkylation of aldehydes.[12]

EXPERIMENTAL SECTION

General Methods. All reagents were purchased from commercial sources and were used as received, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$. ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.2600, singlet). ^{13}C NMR are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet). Enantioselectivities were determined by HPLC analysis employing a chiral column at 25 °C. Optical rotation was measured using a polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per deciliters (g/100 mL).

General Procedure for the Enantioselective 1,4-Addition of Aldehydes to Acridinium Salts. To a solution of acridinium salt **2** (0.1 mmol) and catalyst **I** (0.01 mmol) in dioxane (1 mL) was added propyl aldehyde (0.4 mmol). The resulting solution was stirred at room temperature for 24 h. Upon the completion of reaction as monitored by TLC, EtOH (1 mL) was added. $NaBH_4$ was then cautiously added to the solution, which was stirred at room temperature for 0.5 h. The reaction was subsequently quenched with saturated NH_4Cl solution. The aqueous solution was extracted with ethyl acetate (2 mL × 3). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the resulting yellow oil was purified by preparative chromatography or column chromatography (hexane/ethyl acetate = 10/1) to afford the desired product **3a** as a colorless oil (22.8 mg, 90% yield). The enantiomeric excess was determined by HPLC analysis using a chiral AD-H column. The absolute configuration was determined by comparison of optical rotations with those reported products in the literature (ref 6a).

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)propan-1-ol (3a): colorless oil; 22.8 mg, 0.090 mmol, yield 90%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26−7.12 (m, 4H), 6.98−6.88 (m, 4H), 3.91 (d, J = 7.1 Hz, 1H), 3.48 (dd, J = 10.8, 5.8 Hz, 1H), 3.36 (s, 3H), 3.34 (dd, J = 10.9, 5.7 Hz, 1H), 1.83 (m, 1H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 143.0, 129.2, 128.6, 127.0, 126.9, 126.4, 125.5, 120.5, 120.3, 112.1, 112.04, 65.3, 45.9, 41.6, 32.9, 14.0; HRMS (ESI) calcd for $C_{17}H_{20}NO$ 254.1545 [M + H]$^+$, found 254.1550 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)butan-1-ol (3b). colorless oil; 23.0 mg, 0.086 mmol, yield 86%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.13 (m, 4H), 6.99−6.88 (m, 4H), 4.01 (d, J = 7.4 Hz, 1H), 3.50 (dd, J = 11.1, 5.4 Hz, 1H), 3.42 (dd, J = 11.2, 4.1 Hz, 1H), 3.37 (s, 3H), 1.62−1.53 (m, 1H), 1.40−1.20 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 143.2, 129.1, 128.7, 127.0, 126.8, 126.3, 126.3, 120.5, 120.4, 112.1, 112.1, 61.7, 47.8, 44.7, 32.9, 20.4, 11.7; HRMS (ESI) calcd for $C_{18}H_{22}NO$ 268.1701 [M + H]$^+$, found 268.1702 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)pentan-1-ol (3c): colorless oil; 27.0 mg, 0.096 mmol, yield 96%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.10 (m, 4H), 7.04−6.84 (m, 4H), 4.00 (d, J = 7.2 Hz, 1H), 3.48 (dd, J = 11.2, 5.5 Hz, 1H), 3.42−3.37 (dd, J = 11.2, 4.2 Hz, 1H), 3.37 (s, 3H), 1.75−1.61 (m, 1H), 1.29−1.22 (m, 2H), 1.16−1.02 (m, 2H), 0.78 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 143.2, 129.1, 128.7, 127.0, 126.8, 126.4, 126.2, 120.6, 120.5, 112.1, 112.1, 62.3, 46.2, 44.9, 32.9, 30.0, 20.3, 14.3; HRMS (ESI) calcd for $C_{19}H_{24}NO$ 282.1858 [M + H]$^+$, found 282.1860 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)hexan-1-ol (3d): colorless oil; 26.9 mg, 0.091 mmol, yield 91%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (m, 4H), 6.99−6.88 (m, 4H), 4.00 (d, J = 7.2 Hz, 1H), 3.62 (s, 1H), 3.48 (dd, J = 11.1, 5.5 Hz, 1H), 3.41−3.37 (dd, J = 11.1, 4.2 Hz 1H), 3.36 (s, 3H), 1.77−1.54 (m, 2H), 1.54−0.88 (m, 6H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 143.1, 129.1, 128.7, 127.0, 126.8, 126.4, 126.2, 120.5, 120.4, 112.1, 112.0, 62.3, 46.4, 44.8, 32.9, 29.3, 27.4, 22.9, 13.9; HRMS (ESI) calcd for $C_{20}H_{26}NO$ 296.2014 [M + H]$^+$, found 296.2015 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)octan-1-ol (3e): colorless oil; 30 mg, 0.093 mmol, yield 93%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.20 (m, 4H), 7.08−6.96 (m, 4H), 4.08 (d, J = 7.2 Hz, 1H), 3.56 (dd, J = 11.2, 5.4 Hz, 1H), 3.47 (dd, J = 11.2, 4.2 Hz, 1H), 3.45 (s, 3H), 1.71 (m, 1H), 1.58−1.11 (m, 10H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.2, 143.2, 129.1, 128.7, 127.0, 126.9, 126.4, 126.3, 120.6, 120.5, 112.1, 112.1, 62.5, 46.5, 44.9, 32.9, 31.7, 29.5, 27.7, 27.1, 22.6, 14.0; HRMS (ESI) calcd for $C_{22}H_{30}NO$ 324.2327 [M + H]$^+$, found 324.2330 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)nonan-1-ol (3f): colorless oil; 31.4 mg, 0.093 mmol, yield 93%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.18 (m, 4H), 7.14−6.90 (m, 4H), 4.08 (d, J = 7.2 Hz, 1H), 3.56 (dd, J = 11.2, 5.5 Hz, 1H), 3.50−3.45 (dd, J = 11.2, 4.2 Hz, 1H), 3.45 (s, 3H), 1.72 (m, 1H), 1.45−1.12 (m, 12H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 143.1, 129.1, 128.7, 127.0, 126.8, 126.4, 126.2, 120.5, 120.4, 112.1, 112.0, 62.4, 46.4, 44.8, 32.9, 31.8, 29.5, 29.1, 27.6, 27.1, 22.6, 14.1; HRMS (ESI) calcd for $C_{23}H_{32}NO$ 338.2484 [M + H]$^+$, found 338.2484 [M + H]$^+$.

(*R*)-2-(10-Methyl-9,10-dihydroacridin-9-yl)-3-phenylpropan-1-ol (3g): colorless oil; 30.3 mg, 0.092 mmol, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−6.82 (m, 13H), 4.16 (d, J = 6.9 Hz, 1H), 3.38 (s, 3H), 3.34 (dd, J = 6.7, 4.9 Hz, 2H), 2.66 (dd, J = 13.8, 4.7 Hz, 1H), 2.43 (dd, J = 13.8, 10.5 Hz, 1H), 2.01 (dd, J = 10.7, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 140.9, 129.3, 128.9, 128.7, 128.4, 128.3, 127.1, 127.1, 126.1, 125.7, 125.7, 120.7, 120.5, 112.2, 112.2, 61.2, 48.9, 44.4, 34.0, 33.0; HRMS (ESI) calcd for $C_{23}H_{24}NO$ 330.1858 [M + H]$^+$, found 330.1857 [M + H]$^+$.

(*R*)-3-Methyl-2-(10-methyl-9,10-dihydroacridin-9-yl)butan-1-ol (3h): yellow oil; 23.3 mg, 0.083 mmol, yield 83%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (m, 4H), 7.02−6.84 (m, 4H), 4.02 (d, J = 8.5 Hz, 1H), 3.68−3.44 (m, 2H), 3.37 (d, J = 5.3 Hz, 3H), 1.74 (m, 1H), 1.51 (m, 1H), 0.94−0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 143.0, 128.8, 128.0, 127.2, 127.0, 126.8, 126.3, 120.9, 120.5, 112.3, 112.1, 61.3, 51.0, 44.7, 32.9, 26.2, 22.3, 17.2; HRMS (ESI) calcd for $C_{19}H_{24}NO$ 282.1858 [M + H]$^+$, found 282.1858 [M + H]$^+$.

(*R*)-2-(10-Ethyl-9,10-dihydroacridin-9-yl)pentan-1-ol (3i): colorless oil; 24.2 mg, 0.082 mmol, yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 4H), 7.11−6.88 (m, 4H), 4.10 (d, J = 6.1 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 3.50 (dd, J = 11.1, 6.0 Hz, 1H), 3.42 (dd, J = 11.1, 4.4 Hz, 1H), 1.43 (t, J = 7.0 Hz, 3H), 1.24(m, 5H), 0.82 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5, 141.4, 129.4, 129.0, 126.9, 126.8, 125.5, 125.5, 120.2, 120.1, 112.2, 112.2, 62.3, 48.1, 43.9, 39.7, 29.6, 20.4, 14.2, 11.5; HRMS (ESI) calcd for $C_{20}H_{26}NO$ 296.2014 [M + H]$^+$, found 296.2017 [M + H]$^+$.

(*R*)-2-(10-Propyl-9,10-dihydroacridin-9-yl)pentan-1-ol (3j): colorless oil; 26.0 mg, 0.084 mmol, yield 84%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.08 (m, 4H), 6.92 (m, 4H), 4.02 (d, J = 6.5 Hz, 1H), 3.81 (dd, J = 9.1, 6.8 Hz, 2H), 3.46 (dd, J = 11.1, 5.9 Hz, 1H), 3.38 (dd, J = 11.2, 4.3 Hz, 1H), 2.02−1.74 (m, 2H), 1.35−1.07 (m, 5H), 1.04 (t, J = 7.4 Hz, 3H), 0.76 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.8, 141.8, 129.4, 129.0, 126.9, 126.8, 125.7, 125.6, 120.2, 120.1, 112.4, 112.4, 62.3, 47.8, 47.3, 44.2, 29.7, 20.4, 19.1, 14.2, 11.4; HRMS (ESI) calcd for $C_{21}H_{28}NO$ 310.2171 [M + H]$^+$, found 310.2174 [M + H]$^+$.

(*R*)-2-(10-Butyl-9,10-dihydroacridin-9-yl)pentan-1-ol (3k): colorless oil; 27.5 mg, yield 0.085 mmol, 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.07 (m, 4H), 6.92 (t, J = 9.2 Hz, 4H), 4.02 (d, J = 6.4 Hz, 1H), 3.95−3.77 (m, 2H), 3.45 (dd, J = 11.0, 5.9 Hz, 1H), 3.38 (dd, J = 11.1, 4.1 Hz, 1H), 1.97−1.71 (m, 2H), 1.54−1.38 (m, 2H), 1.35−1.05 (m, 5H), 1.01 (t, J = 7.3 Hz, 3H), 0.76 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.8, 141.8, 129.4, 129.0, 126.9, 126.8, 125.7, 125.6, 120.2, 120.1, 112.3, 112.3, 62.3, 47.8, 45.2, 44.2, 29.7, 27.8, 20.4, 20.4, 14.2, 13.8; HRMS (ESI) calcd for $C_{22}H_{30}NO$ 324.2327 [M + H]$^+$, found 324.2324 [M + H]$^+$.

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(*R*)-2-((2*Z*,4*Z*,6*Z*)-Cyclohepta-2,4,6-trienyl)propan-1-ol (6a): colorless oil; 12.8 mg, 0.085 mmol, yield 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72−6.61 (m, 2H), 6.38−6.14 (m, 2H), 5.30 (dd, J = 14.9, 8.4 Hz, 2H), 3.77 (dd, J = 10.8, 4.9 Hz, 1H), 3.60 (dd, J = 10.8, 6.5 Hz, 1H), 2.02 (m, 1H), 1.51 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.9, 130.8, 125.0, 124.9, 124.0, 123.12, 66.5, 41.4, 37.3, 14.5; HRMS (ESI) calcd for $C_{10}H_{15}O$ 151.1123 $[M + H]^+$, found 151.1120 $[M + H]^+$.

(*R*)-2-((2*Z*,4*Z*,6*Z*)-Cyclohepta-2,4,6-trienyl)butan-1-ol (6b): colorless oil; 13.6 mg, 0.083 mmol, yield 83%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72−6.62 (m, 2H), 6.22 (m, 2H), 5.38−5.25 (m, 2H), 3.88−3.72 (m, 2H), 1.87−1.71 (m, 1H), 1.67 (m, 1H), 1.50 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.9, 130.7, 125.0, 124.9, 123.8, 123.7, 63.1, 43.6, 40.2, 21.3, 11.4; HRMS (ESI) calcd for $C_{11}H_{17}O$ 165.1279 $[M + H]^+$, found 165.1280 $[M + H]^+$.

(*R*)-2-((2*Z*,4*Z*,6*Z*)-Cyclohepta-2,4,6-trienyl)pentan-1-ol (6c): yellow oil; 14.3 mg, 0.080 mmol, yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (m, 2H), 6.37−6.21 (m, 2H), 5.46−5.33 (m, 2H), 3.88−3.80 (m, 2H), 1.99−1.84 (m, 1H), 1.67−1.30 (m, 5H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.8, 130.7, 125.0, 124.9, 123.9, 123.8, 63.5, 41.9, 40.4, 31.0, 20.4, 14.4; HRMS (ESI) calcd for $C_{12}H_{19}O$ 179.1436 $[M + H]^+$, found 179.1440 $[M + H]^+$.

(*R*)-2-((2*Z*,4*Z*,6*Z*)-Cyclohepta-2,4,6-trienyl)hexan-1-ol (6d): colorless oil; 15.6 mg, 0.081 mmol, yield 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.71−6.61 (m, 2H), 6.22 (m, 2H), 5.38−5.25 (m, 2H), 3.78 (m, 2H), 1.82 (m, 1H), 1.71−1.21 (m, 7H), 0.91 (t, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.8, 130.7, 125.0, 125.0, 123.9, 123.8, 63.6, 42.1, 40.5, 29.5, 28.4, 23.1, 14.0; HRMS (ESI) calcd for $C_{13}H_{21}O$ 193.1592 $[M + H]^+$, found 193.1590 $[M + H]^+$.

(*R*)-2-((2*Z*,4*Z*,6*Z*)-Cyclohepta-2,4,6-trienyl)-3-phenylpropan-1-ol (6e): colorless oil; 16.1 mg, 0.071 mmol, yield 71%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (m, 5H), 6.67 (m, 2H), 6.33−6.13 (m, 2H), 5.39 (m, 2H), 3.79−3.60 (m, 2H), 2.96 (dd, J = 13.8, 4.5 Hz, 1H), 2.71 (dd, J = 13.8, 9.4 Hz, 1H), 2.18−2.04 (m, 1H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.5, 130.9, 130.8, 129.2, 128.4, 126.0, 125.2, 125.2, 123.7, 123.4, 62.5, 44.0, 40.2, 35.2; HRMS (ESI) calcd for $C_{16}H_{19}O$ 227.1436 $[M + H]^+$, found 227.1440 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C NMR, and HPLC spectra for all compounds. 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) Bentley, K. W.*The Isoquinoline Alkaloids*; CRC Press: Boca Raton, 1998; ISBN 905702229X, Vol. 1: Chemistry and Biochemistry of Organic Natural Products. (b) Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (c) β-Phenylethylamines and the Isoquinoline Alkaloids: Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (d) Quinoline, Quinazoline and Acridone Alkaloids: Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.

(2) For selected reviews, see: (a) Sliwa, W. *Heterocycles* **1986**, *24*, 181. (b) McEwen, W. E.; Cobb, R. L. *Chem. Rev.* **1955**, *55*, 511. (c) Popp, F. D. *Heterocycles* **1973**, *1*, 165.

(3) Ahamed, M.; Todd, M. H. *Eur. J. Org. Chem.* **2010**, 5935.

(4) For selected recent reviews for organocatalysis, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) Westermann, B.; Ayaz, M.; Berkel, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. (e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (f) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, 632.

(5) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058.

(6) For a similar reaction with poor to modest ee, see: (a) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem. Asian J.* **2010**, *5*, 2047. For selected examples of organocatalytic Michael additions, see: (b) Betancort, J. M.; Barbas, C. F. III *Org. Lett.* **2001**, *3*, 3737. (c) Ramachary, D. B.; Prasad, M. S.; Madhavachary, R. *Org. Biomol. Chem.* **2011**, *9*, 2715. (d) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656. (e) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (f) Uehara, H.; Barbas, C. F. III *Angew. Chem., Int. Ed.* **2009**, *48*, 9848.

(7) (a) Xiao, J. *Org. Lett.* **2012**, DOI: 10.1021/ol3002859. (b) Xiao, J.; Zhao, K.; Loh, T. P. *Chem. Commun.* **2012**, *48*, 3548. (c) Xiao, J.; Zhao, K.; Loh, T. P. *Chem. Asian J.* **2011**, *6*, 2890. (d) Xiao, J.; Lu, Y. P.; Liu, Y. L.; Wong, P. S.; Loh, T. P. *Org. Lett.* **2011**, *13*, 876. (e) Xiao, J.; Xu, F. X.; Lu, Y. P.; Liu, Y. L.; Loh, T. P. *Synthesis* **2011**, 1292. (f) Xiao, J.; Xu, F. X.; Lu, Y. P.; Loh, T. P. *Org. Lett.* **2010**, *12*, 1220.

(8) For reviews, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. For the pioneering work, see: (d) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (e) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (f) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (g) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(9) For representative examples, see: (a) Gonalves, M. S. T. *Chem. Rev.* **2009**, *109*, 190. (b) Troxler, T.; Hurth, K.; Mattes, H.; Prashad, M.; Schoeffter, P.; Langenegger, D.; Enz, A.; Hoyer, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1305. (c) Biwersi, J.; Tulk, B.; Verkman, A. S. *Anal. Biochem.* **1994**, *219*, 139. (d) Mccapra, F. In *The Chemistry of Heterocyclic Compounds: Acridines*; Acheson, R. M., Ed.; John Wiley & Sons: New York, 1973; Vol. *9*, p 615. (e) Guetzoyan, L.; Ramiandrasoa, F.; Dorizon, H.; Desprez, C.; Bridoux, A.; Rogier, C.; Pradines, B.; Perree-Fauvet, M. *Bioorg. Med. Chem.* **2007**, *15*, 3278. (f) Denny, W. *Curr. Med. Chem.* **2002**, *9*, 1655.

(10) For addition of DMAP to improve the efficiency, see: (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (b) Gu, L.; Zhao, G. *Adv. Synth. Catal.* **2007**, *349*, 1629. (c) Zhang, X. J.; Liu, S. P.; Li, X. M.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833. Also see ref 7e and 7f.

(11) (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.

(12) For reviews on asymmetric intermolecular α-alkylation of aldehydes, see: (a) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360. (b) Alba, A.-N.; Viciano, M.; Rios, R. *ChemCatChem* **2009**, *1*, 437. (c) Tak-Tak, L.; Dhimane, H.; Dalko, P. I. *Angew. Chem., Int. Ed.* **2011**, *50*, 12146. For a review on asymmetric β-functionalization of aldehydes, see: (d) Xiao, J. *ChemCatChem* **2012**, DOI: 10.1002/cctc.201100488.

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The toc/abstract graphic, Scheme 1, Table 1, and Table 2 contained errors in the version published ASAP March 5, 2012. The correct version reposted March 23, 2012.

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