Direct Experimental Evidence for the Priority of Flexible Ligand Skeleton in Asymmetric Friedel-Crafts Alkylation of Indole with Nitroalkenes

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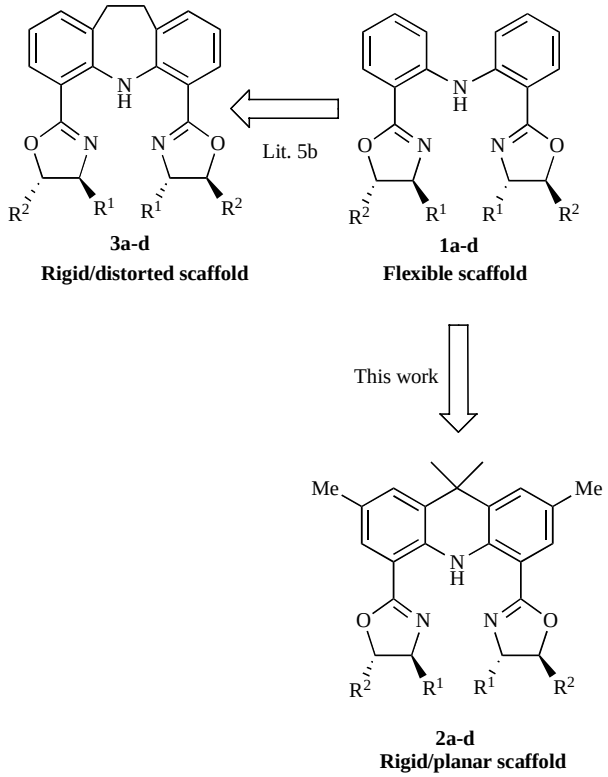
Abstract: Direct experimental evidence for the priority of flexible ligand skeleton in asymmetric Friedel-Crafts alkylation was obtained through XRD analysis of flexible ligand/$ZnCl_2$ complex, as well as synthesis of dihydroacridine-linked bis(oxazoline) ligands with planar rigid scaffold. A transition state model without NH$^{\cdots}\pi$ interaction was proposed for the rigid ligands to interpret the inversion of absolute configuration.

Keywords: Rigid scaffold, flexible scaffold, diphenylamine, dihydroacridine, bis(oxazoline), Friedel-Crafts alkylation.

INTRODUCTION

Since the pioneering reports on oxazolines [1], chiral bis(oxazoline) ligands have been extensively developed by chemists in the fields of coordination chemistry, synthetic chemistry, and catalysis [2]. Large number of ligands with diverse scaffolds have been synthesized from commercially available amino alcohols and carboxylic acids/aldehydes through facile procedures, which illustrates their great potency in application. Some ligand scaffolds stand out from vast reports and gain broad applications in different asymmetric transformations [3], while most ligand scaffolds give satisfying results only in specific cases. Such a situation makes the design of novel ligands for designated reactions a difficult and unprofitable work. In recent years, some groups dedicated to the research on the relationship of ligand structure and enantioselectivity, especially the tuning of electronic effect and rigidity of ligand scaffold. Compared with the encouraging results achieved in the former case [4], much less attention has been paid on the tuning of rigidity [5]. Herein, we would like to document our recent progress on this subject.

Diphenylamine-linked bis(oxazoline) ligands **1a-d** (Fig. **1**), which were developed by Guiry *et al.* [6] and us [7], have been successfully used in the asymmetric Henry reaction of α-ketoesters [7a, b], asymmetric Micheal addition of nitroalkanes to nitroalkenes [7c], asymmetric Nozaki-Hiyama-Kishi reaction of aldehydes [6b], asymmetric hydrosilylation of prochiral ketones [8], and asymmetric Friedel-Crafts alkylation of electron-rich aromatic systems with nitroalkenes [7d-f]. As a 'privileged' ligand scaffold, more attention should be paid on the origin of its priority in these asymmetric transformations, which may provide meaningful information for ligand design. Herein, we would like to document our recent results on the priority of flexible ligand scaffold in asymmetric Friedel-Crafts alkylation.



(**a** R^1 = Ph, R^2 = H**; b** R^1 = Bn, R^2 = H ; **c** R^1 = *i*-Pr, R^2 = H ; **d** R^1 = R^2 = Ph)

Fig. (1). Designed ligand for the tuning of ligand scaffold rigidity.

RESULT AND DISCUSSION

During our research on the asymmetric Friedel-Crafts alkylation of electron-rich aromatic systems, good reactivity and excellent enantioselectivity were obtained with diphenylamine-linked bis(oxazoline)-$Zn(OTf)_2$ complexes.

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In order to interpret the better behaviour and inversed absolute configuration than the systems developed by Zhou *et al.* [9] and Singh *et al.* [10], a transition state model containing bent ligand scaffold and NH···π interaction was proposed, as illustrated in Fig. (**2**). Though the critical role of NH moiety for the reactivity and enantioselectivity was proved through comparison with diphenylether [7f] and diphenylmethane-linked [7d] bis(oxazoline) ligands, the XRD structure of the complex had not been obtained. Recently, a single crystal of complex containing ligand **2a** and $ZnCl_2$ was obtained from petroleum ether/CH_2Cl_2. As illustrated in Fig. (**3**), the diphenylamine shows nonplanar conformation, similar to our proposed model.

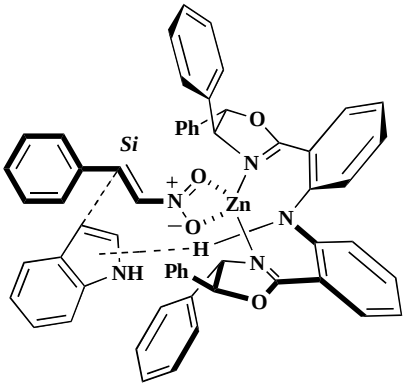


Fig. (2). Proposed transition state model.

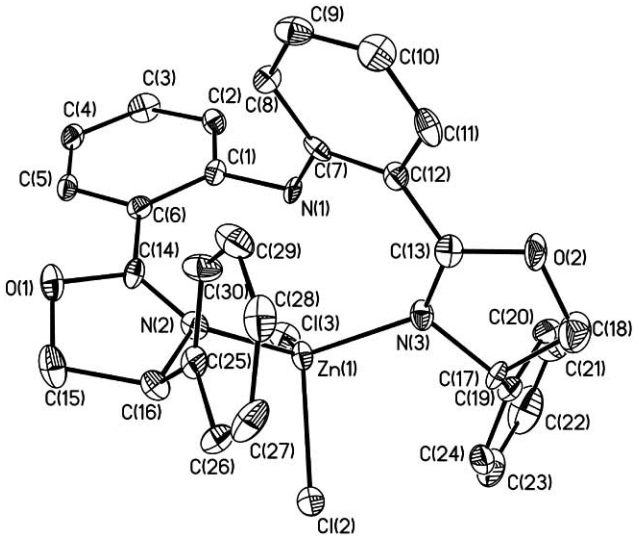


Fig. (3). XRD structure of complex **2a**-$ZnCl_2$.

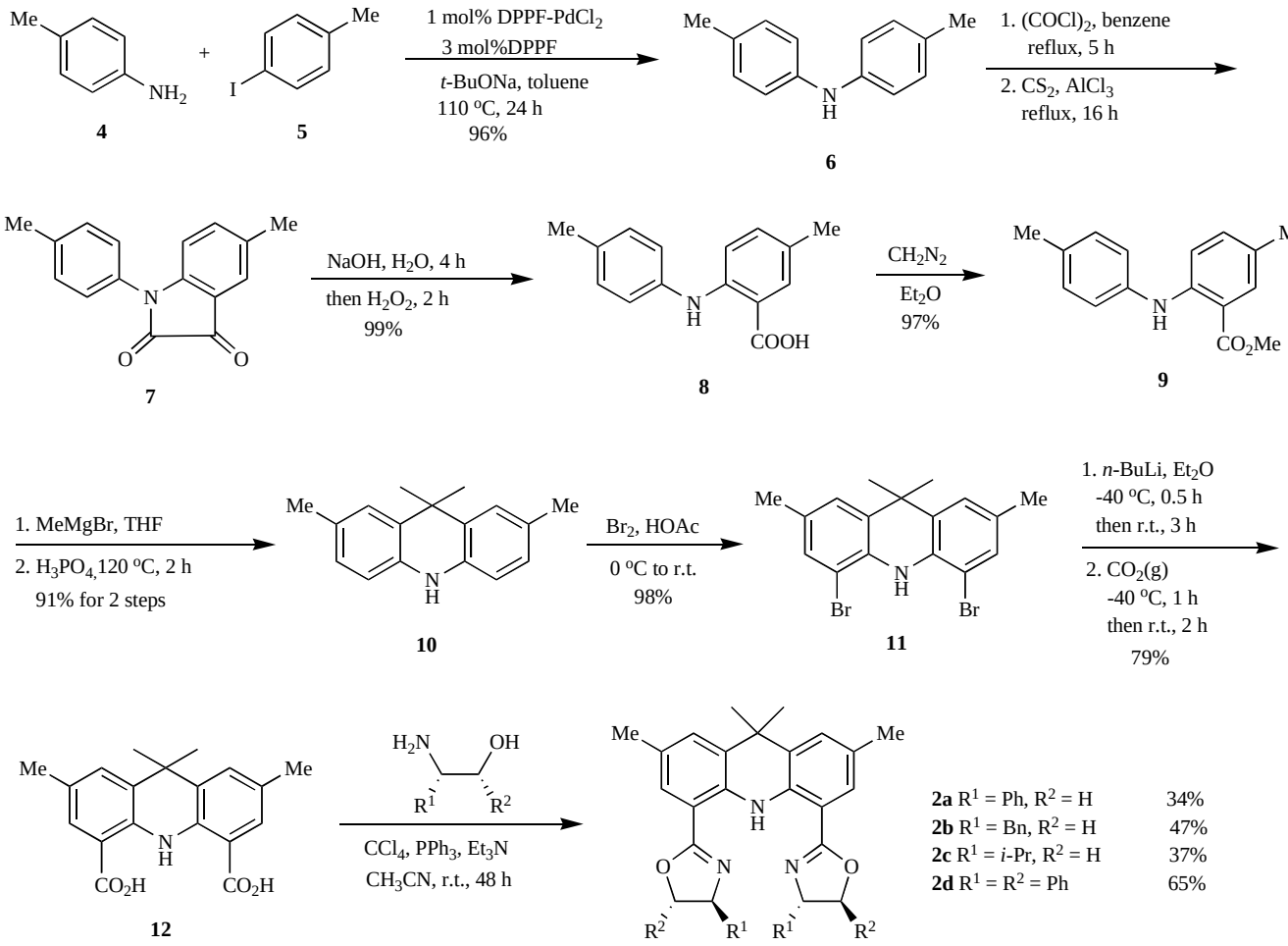
To get further information about the priority of the flexible ligand scaffold, we designed two kinds of bis(oxazoline) ligands containing NH moiety with different scaffolds. As shown in Fig. (**1**), the iminodibenzyl-linked ligands **3a-d** with rigid but distorted scaffold were investigated in our former work. These ligands gave much lower reactivity and nearly no enantioselectivity in the model Friedel-Crafts alkylation of indole with β-nitrostyrene. As a natural extension, we designed the dihydroacridine-linked ligands **2a-d** with rigid and planar scaffold.

Synthesis of the designed ligands **2a-d** was shown in Scheme **1**. The 4,4'-dimethyldiphenylamine **6** was prepared through Buchwald-Hartwig coupling of **4** and **5** using a modified procedure. Compared with literature condition using 5 mol% catalyst at 100 °C in THF [11], the catalyst loading was reduced to 1 mol% and the solvent was changed to toluene. Excellent yield can be achieved when the reaction time was prolonged to 24 h. The methyl groups are critical for the regioselective dibromination. A methoxycarbonyl group was introduced through isatin formation, oxidative cleavage, and esterification, similar to our former report [5b]. The dihydroacridine ring was formed *via* tertiary alcohol formation and acid mediated intramolecular Friedel-Crafts alkylation [12]. The preparation of the dicarboxylic acid **12** was facilitated through dibromination, lithium/bromine exchange, and CO_2 insertion. The product can be collected conveniently *via* filtration in pure form. Though one carboxyl group can be introduced *via* isatin formation and oxidative cleavage similar to the preparation of **8**, we failed in the introduction of the second carboxyl group in this way for the high strain of the ring system. The desired bis(oxazoline) ligands **2a-d** were obtained in one step from acid **12**.

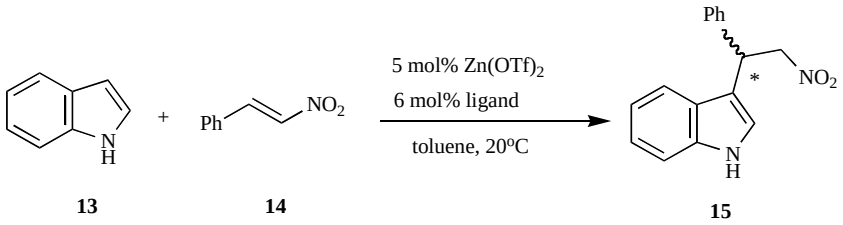
With the designed ligands in hand, their reactivity was tested in the model Friedel-Crafts alkylation (Scheme **2**). The results are summarized in Table **1**. Compared with diphenylamine-linked ligands **1a-d** (entries 1-4), the ligands **2a-d** with planar rigid scaffold gave much lower yields and enantioselectivities (entries 5-8). To our surprise, the absolute configuration of the products in the cases of catalyzed by ligands **2a-c** complex catalyst was inversed. The results indicate that two types of ligands catalyze the reaction through different transition state structure. On the basis of our knowledge obtained in former research of this system, a novel transition state was proposed, as illustrated in Fig. (**4**). The absence of NH···π interaction led to a relaxant transition state with weaker differentiation between *Re* and *Si* face attack. Without the direction of NH moiety, the indole comes close to the coordinated nitroalkene from the less hindered *Re* face and forms the *S* product, similar to the case of other bis(oxazoline) ligands without NH moiety [9]. The enough flexibility of diphenylamine scaffold is critical for the participation of NH···π interaction, while the highly rigid scaffold cannot accommodate a proper conformation for this interaction.

CONCLUSION

In conclusion, we have provided the direct evidence for the bent conformation of diphenylamine-linked bis(oxazoline) ligands in the transition state of Friedel-Crafts reaction through XRD analysis of the ligand/$ZnCl_2$ complex. The priority of the flexible ligand scaffold was confirmed by synthesis of dihydroacridine-linked bis(oxazoline) ligands with planar rigid scaffold and comparison of the catalytic reactivity/enantioselectivity. The information obtained in this research will be useful for the expansion of the application of diphenylamine-linked bis(oxazoline) ligands and novel ligand design.



Scheme 1. Synthesis of dihydroacridine-linked bis(oxazoline) ligands.



Scheme 2. Asymmetric Friedel-Crafts alkylation of indole with β-nitrostyrene.

Table 1. Comparison Between Diphenylamine and Dihydroacridine-Linked Bis(oxazoline) Ligands in Asymmetric Friedel-Crafts Alkylation[a]

Entry	Ligand	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**1a** (R^1 = Ph, R^2 = H)	99	83[e]	*R*
2	**1b** (R^1 = Bn, R^2 = H)	99	66[e]	*R*
3	**1c** (R^1 = *i*-Pr, R^2 = H)	94	30[e]	*R*
4	**1d** (R^1 = R^2 = Ph)	99	88[e]	*R*
5	**2a** (R^1 = Ph, R^2 = H)	40	7	*S*
6	**2b** (R^1 = Bn, R^2 = H)	68	22	*S*
7	**2c** (R^1 = *i*-Pr, R^2 = H)	26	53	*S*
8	**2d** (R^1 = R^2 = Ph)	36	12	*R*

[a]The reactions were conducted at 0.5 mmol scale under the catalysis of 5 mol% catalyst in 3 mL toluene at room temperature for 24 h. [b]Isolated yield. [c]Determined by HPLC on Daicel Chiracel OD-H column using *n*-hexane–isopropanol 70 : 30 *V/V* as eluent. [d]Determined by comparison of retension time with standard sample. [e]data from reference [7d].

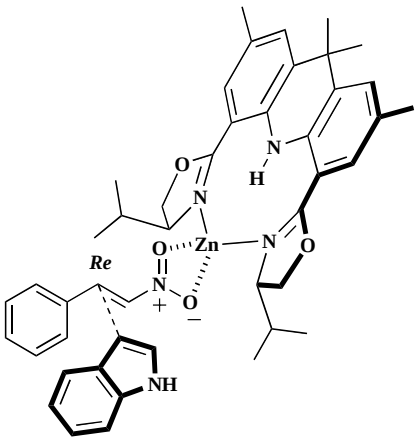


Fig. (4). Proposed transition state model for the dihydroacridine-linked bis(oxazoline) ligand.

EXPERIMENTAL

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200-300 mesh). Melting points were measured on a XT-4 melting point apparatus without correction. The ^{1}H NMR spectra were recorded on Mercury 300 MHz spectrometers, while ^{13}C NMR spectra were recorded at 75 MHz, respectively. Infrared spectra were obtained on a Nicolet AVATAR 330 FTIR spectrometer. The ESI-MS spectra were obtained on Thermo Firrnigan LCQ Deca XP Plus mass spectrometer. Optical rotations were measured on Perkin-Elmer 341 LC spectrometer. The enantiomeric excesses of the products were determined by chiral HPLC using Agilent 1200 LC instrument on Daicel Chiracel OD-H column.

4,4'-Dimethyl-1,1'-diphenylamine (6)

To a Schlenk tube were added 4-methylaniline (2.14 g, 20 mmol), 4-iodotoluene (4.36 g, 20 mmol), DPPF-$PdCl_2$ (164 mg, 0.2 mmol), DPPF (332 mg, 0.6 mmol). The tube was filled with argon and anhydrous toluene (12 mL) was added, followed by *t*-BuONa (2.40 g, 25 mmol). The mixture turned red immediately after the addition of *t*-BuONa, and was stirred at 110 ^{o}C for 24 h. After being cooled to room temperature, the mixture was filtered through celite to remove the inorganic salts, and the crude product was purified by silica gel flash chromatography using petroleum ether-ethyl acetate 100: 1 *V*/*V* as eluent. The desired product was obtained as white solid (3.783 g, 96% yield). m.p. 78–80 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.4 Hz, 4H), 6.93 (d, *J* = 8.4 Hz, 4H), 5.47 (s, 1H), 2.28 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 130.1, 129.8, 117.9, 20.6.

1-(4-Methylphenyl)-5-methyloxindole (7)

A dried round-bottom flask containing 4,4'-dimethyl-1,1'-diphenylamine (7.312 g, 37.1 mmol) and anhydrous benzene (100 mL) was equipped with a dropping funnel containing a solution of $(COCl)_2$ (5.1 mL, 58 mmol) in benzene (40 mL). The flask was heated to reflux, and the solution of $(COCl)_2$ was added dropwise during 1 h. After the addition, the mixture was stirred under reflux for another 5 h. All the solvents and unreacted $(COCl)_2$ were removed under vacuum. The residue was dissolved in CS_2 (40 mL) and added to a dropping funnel. The mixture of $AlCl_3$ (8.6 g, 64 mmol) and CS_2 (120 mL) was heated to reflux, and the aforementioned solution was added dropwise during 1 h. The mixture was stirred under reflux for 16 h. After being cooled to 0 ^{o}C, the reaction mixture was quenched by concentrated HCl (aq) (50 mL) and water (100 mL). The mixture was extracted with $CHCl_3$ (3 × 200 mL), and the organic phase was dried with anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by recrystallization in toluene. The desired product was obtained as red solid (6.197 g, 66% yield). m.p.178–180 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.29–7.35 (m, 5H), 6.78 (d, *J* = 7.8 Hz, 1H), 2.42 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2, 157.5, 149.6, 138.7, 134.0, 130.4, 130.3, 125.7, 125.6, 117.4, 111.0, 21.2, 20.6. IR (neat): 3033, 1732, 1621, 1599, 1515, 1488, 1353, 1298, 1192, 1163, 828, 814 cm^{-1}. HR-ESIMS: m/z cacld for $C_{16}H_{14}NO_2$ (M+H): 252.10245. Found: 252.10173.

2-(*N*-(4-Methylphenyl)amino)-5-methylbenzoic acid (8)

To a round-bottom flask were added 1-(4-methylphenyl)-5-methyloxindole (6.197 g, 24.7 mmol), NaOH (7.0 g, 175 mmol), and water (900 mL). The mixtrue was stirred at room temperature for 4 h to generate a orange solution. A solution of 30% H_2O_2 (7.0 mL, 62 mmol) in water (50 mL) was added slowly to the mixture, and the color of the solution turned to light yellow. The mixture was stirred for another 2 h. After removing the insoluable residue through filtration, the mixture was acidified with concentrated HCl (aq), and the solid was collected through filtration and washed throughly with water. The desired product was obatined as yellow solid (5.806 g, 97% yield). m.p.180–183 ^{o}C. ^{1}H NMR (300 MHz, d^6-DMSO): δ = 12.96 (s, 1H), 9.38 (s, 1H), 7.69 (s, 1H), 7.06–7.20 (m, 6H), 2.27 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, d^6-DMSO): δ = 169.8, 145.2, 138.1, 134.9, 131.8, 131.5, 129.8, 125.5, 121.4, 113.7, 112.0, 20.3, 19.8.

Methyl 2-(*N*-(4-methylphenyl)amino)-5-methylbenzoate (9)

To a round-bottom flask was added 2-(*N*-(4-methylphenyl)amino)-5-methylbenzoic acid (4.40 g, 18.3 mmol) and Et_2O (300 mL). A solution of excess amount of CH_2N_2 (about 32 mmol) in Et_2O (150 mL) was added to a dropping funnel. The solution of CH_2N_2 was added to the solution of acid slowly at room temperature, and the mixture was stirred for another 1 h after the addition. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography using petroleum ether and petroleum ether-ethyl acetate 100 : 1 V/V as eluent. The desired product was obtained as yellow oil (4.302 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1H), 7.75 (s, 1H), 7.12 (br, 6H), 3.88 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 146.2, 138.4, 135.1, 132.9, 131.2, 129.8, 125.8, 122.6, 114.0, 111.4, 51.6, 20.8, 20.3. IR (neat): 3328, 2950, 1682, 1591, 1517, 1436, 1318, 1261, 1206, 1083, 805 cm^{-1}. HR-ESIMS: m/z cacld for

$C_{16}H_{18}NO_2$ (M+H): 256.13375. Found: 256.13304. A by product with higher retension on the column was obtained as yellow oil (365 mg, 7% yield), which was determined to be *O*,*N*-bismethylated product methyl 2-(*N*-methyl-*N*-(4-methylphenyl)amino)-5-methylbenzoate. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 2H), 6.42 (d, *J* = 7.2 Hz, 2H), 3.46 (s, 3H), 3.10 (s, 3H), 2.23 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 147.1, 145.7, 134.5, 133.7, 131.4, 129.2, 128.7, 128.5, 126.6, 114.0, 51.8, 40.2, 20.6, 20.2. IR (neat): 2948, 1730, 1617, 1573, 1516, 1498, 1435, 1345, 1297, 1243, 1205, 1090, 806 cm^{-1}. HR-ESIMS: m/z cacld for $C_{17}H_{20}NO_2$ (M+H): 270.14940. Found: 270.14868.

3,6,9,9-Tetramethyl-9,10-dihydroacridine (10)

A solution of methyl 2-(*N*-(4-methylphenyl)amino)-5-methylbenzoate (4.795 g, 18.8 mmol) in THF (60 mL) was adde to a dried flask under argon, which was equipped with a dropping funnel containing a solution of MeMgCl (75 mmol) in THF (40 mL). The mixture was cooled to 0 ^{o}C and the Grignard reagent was added slowly during 0.5 h, and the mixture was stirred for another 2 h at 0 ^{o}C. After being quenched by water, the mixture was extracted with Et_2O (3 × 100 mL), and the combined organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the desired product was directly used in the next step without further purification. To a round-bottom flask were added 85% H_3PO_4 (30 mL) and tertiary alcohol obtained in the former step. The mixture was stirred at 120 ^{o}C for 2 h and cooled to room temperature. After being diluted with water (200 mL), the mixture was basified with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by silica gel flash chromatography using petroleum ether–ethyl acetate 40 : 1 *V*/*V* as eluent. The desired product was obtained as colorless solid (4.069 g, 91% yield). m.p. 99–100 ^{o}C. ^{1}H NMR (300 MHz, d^6-DMSO): δ = 8.56 (s, 1H), 7.13 (s, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 6.67 (d, *J* = 7.8 Hz, 2H), 2.22 (s, 6H), 1.46 (s, 6H). ^{13}C NMR (75 MHz, d^6-DMSO): δ = 136.7, 127.8, 127.5, 127.0, 125.7, 113.1, 35.5, 31.0, 20.7.

1,8-Dibromo-3,6,9,9-tetramethyl-9,10-dihydroacridine (11)

To a solution of 3,6,9,9-tetramethyl-9,10-dihydroacridine (4.069 g, 17.2 mmol) in acetic acid (35 mL), was added Br_2 (5.60 g, 35 mmol) dropwise at 0 ^{o}C. After the additon, the mixture was stirred at 0 ^{o}C for 0.5 h, and then at room temperature for 2 h. The reaction was quenched with a solution $NaHSO_3$, and the desired product was obtained through filtration as light greenish solid (6.661 g, 98% yield). m.p.167–168 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 7.20 (s, 2H), 7.09 (s, 2H), 2.28 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.6, 130.9, 130.5, 130.3, 125.1, 108.9, 37.5, 30.3, 20.7. IR (neat): 3374, 2976, 2952, 1633, 1610, 1589, 1490, 1403, 1338, 1308, 1254, 1185, 1073, 1010, 967, 848, 812 cm^{-1}. Anal. cacld for $C_{17}H_{17}Br_2N$: C, 51.67; H, 4.34; N, 3.54. Found: C, 51.65; H, 4.39; N, 3.69.

3,6,9,9-Tetramethyl-9,10-dihydroacridine-1,8-dicarboxylic acid (12)

1,8-Dibromo-3,6,9,9-tetramethyl-9,10-dihydroacridine (790 mg, 2 mmol) and Et_2O (25 mL) were added to a flamed dried three necked flask equipped with a dropping funnel containing *n*-BuLi (8.8 mmoL). The mixture was cooled to –40 ^{o}C and the *n*-BuLi was added dropwise. The mixture became clear and turned yellow. After the additon, the mixture was stirred at room temperature for 3 h. Then the solution was cooled to –40 ^{o}C again and dry CO_2 was bulbed into the solution for 1 h. The mixtrue was treated with 2 N HCl (aq), and the solid was collected through filtration. After being washed with petroleum ether, the desired product was obtained as yellow solid (511 mg, 79% yield). m.p. > 250 ^{o}C. ^{1}H NMR (300 MHz, d^6-DMSO): δ = 12.93 (br, 2H), 12.13 (s, 1H), 7.60 (s, 2H), 7.46 (s, 2H), 2.27 (s, 6H), 1.50 (s, 6H). ^{13}C NMR (75 MHz, d^6-DMSO): δ = 168.6, 137.2, 131.0, 130.0, 129.4, 127.8, 112.0, 35.8, 31.0, 20.3. IR (neat): 3298, 2954, 2563, 1665, 1593, 1497, 1463, 1289, 1242, 956, 794, 720 cm^{-1}. Anal. cacld for $C_{19}H_{19}NO_4 \cdot 0.5H_2O$: C, 68.25; H, 6.03; N, 4.19. Found: C, 68.89; H, 6.01; N, 4.23.

1,8-Bis((4*S*)-4-phenyloxazolin-2-yl)-3,6,9,9-tetramethyl-9,10-dihydroacridine (2a)

To a round-bottom flask was added 3,6,9,9-tetramethyl-9,10-dihydroacridine-1,8-dicarboxylic acid (650 mg, 2 mmol), (*S*)-phenylglycinol (548 mg, 4 mmol), CCl_4 (6.7 mL, 154 mmol), Et_3N (5.0 mL, 35 mmol), triphenylphosphine (3.86 g, 14.7 mmol), and acetonitrile (40 mL). The mixture was stirred at room temperature for 48 h. The solvent was removed under vacuum, and the residue was treated with water and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was dired over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate 20 : 1 *V*/*V* as eluent. The desired product was obtained as yellow solid (364 mg, 34% yield). m.p. 85–87 ^{o}C. $[\alpha]_D^{20}$ = +477.3 (*c* 0.86 g/100 mL, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.30 (s, 1H), 7.55 (s, 2H), 7.24–7.32 (m, 8H), 7.14 (d, *J* = 7.2 Hz, 4H), 4.90 (t, *J* = 9.0 Hz, 2H), 4.39 (t, *J* = 9.1 Hz, 2H), 3.90 (t, *J* = 8.1 Hz, 2H), 2.33 (s, 6H), 1.58 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 143.0, 136.9, 130.1, 129.0, 128.5, 128.1, 128.0, 127.3, 126.7, 110.3, 73.5, 70.2, 36.4, 30.6, 20.8. IR (neat): 3062, 2971, 1649, 1593, 1492, 1454, 1427, 1358, 1263, 1193, 1094, 994, 757, 698 cm^{-1}. HR-ESIMS: m/z cacld for $C_{35}H_{34}N_3O_2$ (M+H): 528.26510. Found: 528.26362.

1,8-Bis((4*S*)-4-benzyloxazolin-2-yl)-3,6,9,9-tetramethyl-9,10-dihydroacridine (2b)

Prepared in similar procedure using 3,6,9,9-tetramethyl-9,10-dihydroacridine-1,8-dicarboxylic acid (650 mg, 2 mmol) and (*S*)-valinol (412 mg, 4 mmol). The desired product was obtained as yellow oil (338 mg, 37% yield). $[\alpha]_D^{20}$ = +266.4 (*c* 0.76 g/100 mL, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.01 (s, 1H), 7.52 (s, 2H), 7.20–7.29 (m, 12H), 4.54 (t, *J* = 5.9 Hz, 2H), 4.22 (t, *J* = 8.6 Hz, 2H), 4.05 (t, *J* = 7.5 Hz, 2H), 3.31 (dd, J_1 = 13.5 Hz, J_2 = 4.5 Hz,

2H), 2.74 (dd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, 2H), 2.31 (s, 6H), 1.58 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 138.1, 136.5, 129.9, 129.3, 129.1, 128.5, 128.1, 128.0, 126.5, 110.4, 70.5, 68.3, 42.2, 36.3, 31.2, 20.7. IR (neat): 3061, 3027, 2966, 2923, 1648, 1595, 1496, 1453, 1430, 1384, 1362, 1264, 1198, 1091, 991, 737, 702 cm^{-1}. HR-ESIMS: m/z cacld for $C_{37}H_{38}N_3O_2$ (M+H): 556.29640. Found: 556.29459.

1,8-Bis((4*S*)-4-isopropyloxazolin-2-yl)-3,6,9,9-tetramethyl-9,10-dihydroacridine (2c)

Prepared in similar procedure using 3,6,9,9-tetramethyl-9,10-dihydroacridine-1,8-dicarboxylic acid (487 mg, 1.5 mmol) and (*S*)-phenylalaninol (453 mg, 3 mmol). The desired product was obtained as yellow solid (394 mg, 47% yield). m.p. 105–107 °C. $[\alpha]_D^{20}$ = +335.2 (*c* 0.71 g/100 mL, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ =11.62 (s, 1H), 7.45 (s, 2H), 7.20 (s, 2H), 4.19–4.23 (m, 4H), 4.07–4.16 (m, 2H), 2.25 (s, 6H), 1.90–1.96 (m, 2H), 1.50 (s, 6H), 0.98 (d, *J* = 6.9 Hz, 6H), 0.85 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 136.4, 129.9, 128.8, 128.1, 128.0, 110.7, 72.5, 68.1, 36.3, 32.4, 30.9, 20.7, 19.3, 17.2. IR (neat): 2957, 1648, 1597, 1483, 1461, 1431, 1384, 1358, 1263, 1197, 1091, 992, 768, 739 cm^{-1}. HR-ESIMS: m/z cacld for $C_{29}H_{38}N_3O_2$ (M+H): 460.29640. Found: 460.29510.

1,8-Bis((4*S*,5*S*)-4,5-diphenyloxazolin-2-yl)-3,6,9,9-tetramethyl-9,10-dihydroacridine (2d)

Prepared in similar procedure using 3,6,9,9-tetramethyl-9,10-dihydroacridine-1,8-dicarboxylic acid (650 mg, 2 mmol) and (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol (852 mg, 4 mmol). The desired product was obtained as colorless solid (889 mg, 65% yield). m.p. 143–145 °C. $[\alpha]_D^{20}$ = +159.2 (*c* 0.96 g/100 mL, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.56 (s, 1H), 7.69 (s, 2H), 7.29–7.37 (m, 8H), 7.06–7.16 (m, 10H), 6.98–7.04 (m, 4H), 5.01 (d, *J* = 7.5 Hz, 2H), 4.55 (d, *J* = 7.8 Hz, 2H), 2.33 (s, 6H), 1.63 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 142.4, 140.4, 137.0, 130.2, 129.3, 128.6, 128.41, 128.36, 128.2, 128.0, 127.3, 126.5, 125.8, 110.1, 87.2, 78.8, 36.4, 31.1, 20.8. IR (neat): 3061, 3028, 2921, 1651, 1591, 1493, 1454, 1427, 1347, 1294, 1254, 1190, 1158, 1091, 983, 762, 696 cm^{-1}. HR-ESIMS: m/z cacld for $C_{47}H_{42}N_3O_2$ (M+H): 680.32770. Found: 680.32533.

General Procedure for Asymmetric Friedel-Crafts Reaction

To a flame dried Schlenk tube were added $Zn(OTf)_2$ (9 mg, 0.025 mmol) and ligand **1a-d** or **2a-d** (0.05 mmol) under argon, followed by addition of toluene (3 mL). The mixture was stirred at room temperature for 2 h and β-nitrostyrene **14** (74.5 mg, 0.5 mmol) was added. Then the mixture was stirred for another 10 min, and indole **13** (58.5 mg, 0.5 mmol) was added. The mixture was stirred at this temperature for 24 h. The mixture was separated directly by silica gel column chromatography using petroleum ether-EtOAc 10 : 1 to 5 : 1 *V*/*V* as eluent, and the product was obtained in pure form. The enantiomeric excess was determined by chiral HPLC on Daicel Chiracel OD-H column using *n*-hexane-isopropanol 70 : 30 *V*/*V* as eluent.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's Web site along with the published article.

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