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New synthesis of *cis*-3,4-diaryl-1-tosylpyrrolidines

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Abstract—Unsymmetrically substituted *cis*-3,4-diarylpyrrolidines are synthesized in nearly 25% overall yields starting from 4-aryl-1,2,5,6-tetrahydropyridines by iterative reactions using the combination of *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) followed by Grignard addition, elimination and hydrogenation sequence.

1. Introduction

Depending on the substitution pattern and functionalization, different substituted pyrrolidines have been shown to be effective antibacterials or fungicides agents and glycosidase inhibitors.[1] In addition, the chiral pyrrolidine system can be a synthetically useful ligand in the asymmetric reactions. Consequently, a significant effort has been directed toward the development of new methods for the synthesis of mono-, di-, and polysubstituted pyrrolidines.[2,3] While a great number of pyrrolidines and their derivatives with this specific substitution pattern are of particular interest,[4] new methods for their preparation are needed. Basically, the adopted synthetic strategies of 3,4-diarylpyrrolidines can be summarized in Figure 1.

The stereocontrolled functionalization of diarylpyrrolidines has been established as a reliable method. Difficulties are often encountered in this process due to lack of stereo- or regiochemistry, harshness of reaction conditions and availability of starting materials.[5] During the course of our investigation, it became apparent that many of unsymmetrically substituted *cis*-3,4-diarylpyrrolidines required by us could not be obtained in satisfactory yields following reported methods. Herein, we report an efficient method of synthesis of unsymmetrically substituted *cis*-3,4-diarylpyrrolidines starting from

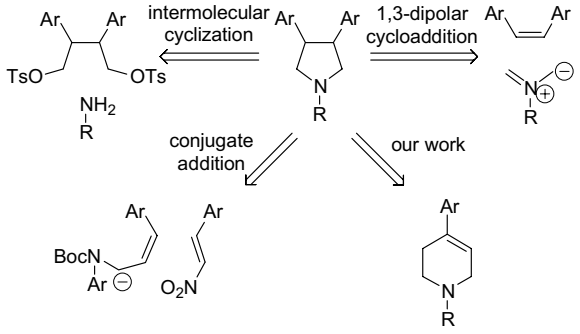

Figure 1.

4-aryl-1,2,5,6-tetrahydropyridines via an iterative reaction sequence using the combination of *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate ($BF_3{\cdot}OEt_2$).

2. Results and discussion

Two 4-aryl-1,2,5,6-tetrahydropyridines **1A** ($Ar_1 = C_6H_5$) and **1B** ($Ar_1 = 4\text{-}FC_6H_4$) were chosen as the starting materials in the synthesis of asymmetric *cis*-3,4-diarylpyrrolidines as shown in Scheme 1.[6] 3-Arylpyrrolidin-4-ones **4A** and **4B** were prepared by the treatment of olefins **1A** and **1B** with three repeated combinations of MCPBA and $BF_3{\cdot}OEt_2$.

The continuous transformation with the combination of MCPBA and $BF_3{\cdot}OEt_2$ was described as follows. Initially, aldehydes **2A** and **2B** were first provided by epoxidation of olefins **1A** and **1B** with MCPBA at rt

Keywords: 4-Aryl-1,2,5,6-tetrahydropyridines; 3-Arylpyrrolines; *cis*-3,4-Diarylpyrrolidines; Grignard addition; *m*-Chloroperoxybenzoic acid; Boron trifluoride etherate.
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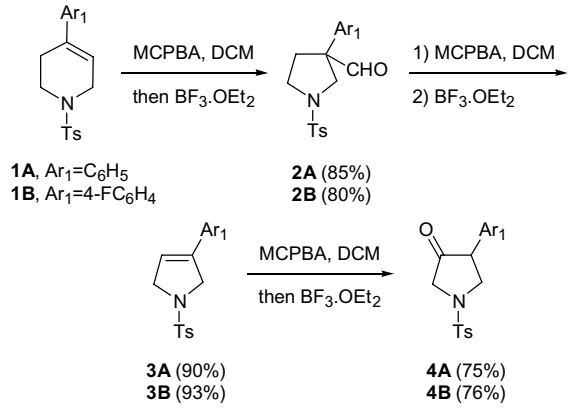
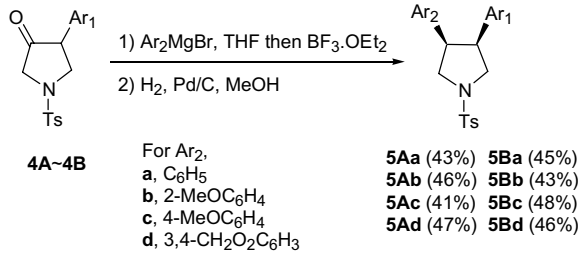


Scheme 1.

for 3 h and followed by ring contraction reaction of the resulting epoxides with $BF_3{\cdot}OEt_2$ at 0 °C for 15 min. Next, Baeyer–Villiger reaction of aldehydes **2A** and **2B** with MCPBA was further provided olefins **3A** and **3B** at rt for 3 h and followed by elimination reaction of the resulting formyl group with $BF_3{\cdot}OEt_2$ at 0 °C for 15 min.[7] Finally, ketones **4A** and **4B** were provided by epoxidation of olefins **3A** and **3B** with MCPBA at rt for 3 h and followed by isomerization of the resulting epoxides with $BF_3{\cdot}OEt_2$ at 0 °C for 15 min.[8,9]

The transformations from olefins **1** to aldehydes **2** and olefins **3** to ketones **4** are both the $BF_3{\cdot}OEt_2$-mediated selective rearrangement of trisubstituted epoxide, which is governed by the stability of intermediary tertiary carbocation, and alkyl migration in the former and hydride shift in the latter takes place, respectively. The total synthetic procedure can be monitored by TLC until the reaction was complete within a working day. As a whole, the overall synthetic procedure from 4-aryl-1,2,5,6-tetrahydropyridines **1A** and **1B** to 3-arylpyrrolidin-4-ones **4A** and **4B** exhibits three different reaction types via the useful combination of MCPBA and $BF_3{\cdot}OEt_2$.

With the above results and enough amounts of ketones **4A** and **4B**, the synthesis of *cis*-3,4-diarylpyrrolidines **5Aa**–**Ad** and **5Ba**–**Bd** takes place as shown in Scheme 2. Grignard addition of the ketones **4A** and **4B** with four different arylmagnesium bromide reagents (a, C_6H_5; b, 2-$MeOC_6H_4$; c, 4-$MeOC_6H_4$; d, 3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran at −78 °C for 2 h is followed by dehydration of the resulting tertiary alcohols with $BF_3{\cdot}OEt_2$ at 0 °C for 15 min. The olefins with fully four substituents were



Scheme 2.

provided as the major product accompanied with a trace amount of isomer with three substituents as judged by the ^1H NMR spectrum. Without further purification, the mixture of olefins was directly hydrogenated to the 3,4-diarylpyrrolidines **5Aa**–**Ad** and **5Ba**–**Bd** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon.[10]

The related ^1H and ^{13}C NMR spectral data of symmetrical *cis*-3,4-diphenylpyrrolidine **5Aa** were in accordance with the literature.[4a] According to Beak's reports, the assignment of two contiguous stereocenters on the framework of compound **5Aa** was made the cis configuration. With the result in hand, the other diaryl functional group on the pyrrolidine structure could also be arranged as the cis configuration.

3. Conclusion

In summary, we present an easy and straightforward synthesis of unsymmetrically substituted *cis*-3,4-diarylpyrrolidines by the treatment of 4-aryl-1,2,5,6-tetrahydropyridines by iterative synthetic operations using the combination of MCPBA and $BF_3{\cdot}OEt_2$, Grignard addition, elimination and hydrogenation. We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of *cis*-3,4,5-triarylpiperidines.

Acknowledgement

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Supplementary data

Photocopies of ^1H and ^{13}C NMR ($CDCl_3$) spectral data for **3A**–**B**, **4A**–**B**, **5Aa**–**Ad**, and **5Ba**–**Bd** were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.141.

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7. A representative procedure for olefins **3** is as follows: *m*-Chloroperoxybenzoic acid (255 mg, 75%, 1.1 mmol) was added to a solution of aldehydes **3** (0.5 mmol) and sodium carbonate (130 mg, 1.2 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Saturated sodium carbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, Boron trifluoride etherate (0.1 mL) was added to a stirring solution of the resulting crude product in dichloromethane (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 10:1) afforded olefins **3**. For **3A**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.5$ Hz, 2H), 7.33–7.27 (m, 7H), 6.01 (t, $J = 2.0$ Hz, 1H), 4.49 (td, $J = 2.0$, 4.0 Hz, 2H), 4.31 (td, $J = 2.0$, 4.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.56, 137.34, 134.08, 132.48, 129.83 (2×), 128.68 (2×), 128.43, 127.47 (2×), 125.38 (2×), 118.86, 55.66, 54.90, 21.50; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{18}NO_2S$ (M^++1) 300.1058, found 300.1058. For **3B**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.27–7.24 (m, 2H), 7.02 (t, $J = 8.5$ Hz, 2H), 5.94 (t, $J = 2.0$ Hz, 1H), 4.46–4.44 (m, 2H), 4.31–4.28 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.59, 161.62, 143.62, 136.28, 133.99, 129.85 (2×), 127.45 (2×), 127.13, 127.06, 118.64, 115.77, 115.59, 55.60, 54.92, 21.50; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}FNO_2S$ (M^++1) 318.0964, found 318.0963.
8. A representative procedure for ketones **4** with one-pot reaction is as follows: *m*-Chloroperoxybenzoic acid (255 mg, 75%, 1.1 mmol) was added to a solution of olefins **3** (0.8 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (0.1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude products under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 8:1–4:1) afforded ketones **4**. For **4A** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.33–7.28 (m, 3H), 7.15 (d, $J = 8.0$ Hz, 2H), 4.09 (dd, $J = 9.0$, 10.0 Hz, 1H), 3.83 (d, $J = 17.5$ Hz, 1H), 3.73 (t, $J = 8.5$ Hz, 1H), 3.54 (d, $J = 17.5$ Hz, 1H), 3.49 (dd, $J = 9.0$, 10.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.28, 144.62, 134.16, 131.47, 130.08 (2×), 128.99 (2×), 127.96 (3×), 127.88 (2×), 53.84, 53.57, 51.79, 21.59; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{18}NO_3S$ (M^++1) 316.1007, found 316.1009. For **4B** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.0$ Hz, 2H),

7.40 (d, $J = 8.0$ Hz, 2H), 7.14–7.12 (m, 2H), 7.02 (t, $J = 8.5$ Hz, 2H), 4.07 (dd, $J = 9.0$, 10.0 Hz, 1H), 3.82 (d, $J = 17.5$ Hz, 1H), 3.72 (t, $J = 8.5$ Hz, 1H), 3.53 (d, $J = 17.5$ Hz, 1H), 3.45 (dd, $J = 9.0$, 10.0 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.07, 163.34, 161.37, 144.72, 131.45, 130.12 (2×), 129.59, 129.52, 127.99 (2×), 116.08, 115.91, 53.75, 52.83, 51.74, 21.62; HRMS (ESI) m/z calcd for $C_{17}H_{17}FNO_3S$ (M^++1) 334.0913, found 334.0913.

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10. A representative procedure for *cis*-3,4-diarylpyrrolidines **5Aa**–**Ad** and **5Ba**–**Bd** is as follows: A solution of arylmagnesium bromide (0.5 M in tetrahydrofuran, 1 mL) was added to a stirred solution of ketones **4A** or **4B** (0.3 mmol) in tetrahydrofuran (5 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (0.1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (2 mL) and ethyl acetate (10 mL) were added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Without further purification, 10% palladium on activated carbon (10 mg) was added to a stirring solution of the resulting olefins in methanol (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir at rt for 10 h. The catalyst was filtered through a short plug of Celite and washing with methanol (2 × 10 mL). The combined organic layers were evaporated under reduced pressure to yield the crude compound. Purification on silica gel (hexane/ethyl acetate = 3:1) afforded *cis*-3,4-diarylpyrrolidines **5Aa**–**Ad** and **5Ba**–**Bd**. For **5Aa** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.10–7.02 (m, 6H), 6.64 (d, $J = 8.5$ Hz, 4H), 3.76 (dd, $J = 10.0$, 11.5 Hz, 4H), 3.50–3.46 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.62, 137.63 (2×), 134.31, 129.89 (2×), 128.13 (4×), 127.91 (4×), 127.51 (2×), 126.78 (2×), 51.74 (2×), 49.08 (2×), 21.58; HRMS (ESI) m/z calcd for $C_{23}H_{24}NO_2S$ (M^++1) 378.1528, found 378.1529. For **5Ab** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.04–6.95 (m, 4H), 6.65–6.60 (m, 5H), 3.93–3.61 (m, 6H), 3.49 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.89, 143.49, 138.57, 134.36, 129.84 (2×), 127.82 (2×), 127.78, 127.53 (2×), 127.51 (2×), 127.09, 126.42, 126.30, 120.10, 109.80, 54.86, 52.23, 50.69, 47.15, 41.79, 21.57; HRMS (ESI) m/z calcd for $C_{24}H_{26}NO_3S$ (M^++1) 408.1633, found 408.1636. For **5Ac** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.10–7.04 (m, 3H), 6.66 (d, $J = 8.5$ Hz, 2H), 6.59–6.55 (m, 4H), 3.77–3.68 (m, 4H), 3.71 (s, 3H), 3.44–3.42 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.28, 143.56, 137.79, 134.30, 129.86 (2×), 129.55, 129.12 (2×), 128.18 (2×), 127.92 (2×), 127.47 (2×), 126.71, 113.24 (2×), 55.08, 51.94, 51.74, 49.06, 48.35, 21.26; HRMS (ESI) m/z calcd for $C_{24}H_{26}NO_3S$ (M^++1) 408.1633, found 408.1634. For **5Ad** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.13–7.06 (m, 3H), 6.69 (d, $J = 8.5$ Hz, 2H), 6.48 (d, $J = 8.5$ Hz, 1H), 6.13 (dd, $J = 1.5$, 8.5 Hz, 1H), 6.10 (d, $J = 1.5$ Hz, 1H), 5.84 (s, 2H), 3.75–3.63 (m, 4H), 3.45–3.38 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.28, 146.20, 143.68, 137.65, 134.21, 131.44, 129.90 (2×), 128.13 (2×), 128.01 (2×), 127.48 (2×), 126.87, 121.37, 108.50, 107.68, 100.80, 52.01, 51.68, 49.07, 48.85, 21.59; HRMS (ESI) m/z calcd for $C_{24}H_{24}NO_4S$ (M^++1) 422.1426, found 422.1422. For **5Ba** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.12–7.04 (m, 3H), 6.74–6.71 (m, 2H), 6.65–6.59 (m, 4H), 3.76–3.69 (m, 4H), 3.49–3.43 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.61, 160.66, 143.69, 137.42, 134.24, 133.39, 133.36, 129.91 (2×), 129.63, 129.56, 128.09, 128.06, 127.51 (2×), 126.93, 114.86, 114.69, 51.94, 51.50, 49.02, 48.40, 21.59; HRMS (ESI) m/z calcd for $C_{23}H_{23}FNO_2S$ (M^++1) 396.1434, found 396.1435. For **5Bb** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.11–7.07 (m, 1H), 6.68–6.56 (m, 7H), 3.90–3.82 (m, 2H), 3.75–3.60 (m, 4H), 3.52 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.40, 160.65, 156.79, 143.57, 134.29, 129.86 (2×), 129.28, 129.21, 127.94, 127.53 (2×), 127.07, 126.06, 120.24, 114.38, 114.21, 109.82, 54.87, 52.32, 50.52, 46.41, 41.75, 21.58; HRMS (ESI) m/z calcd for $C_{24}H_{25}FNO_3S$ (M^++1) 426.1539, found 426.1540. For **5Bc** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 6.75 (t, $J = 8.5$ Hz, 2H),6.64–6.55 (m, 6H), 3.75–3.66 (m, 4H), 3.72 (s, 3H), 3.43–3.38 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.61, 160.66, 158.41, 143.66, 134.27, 133.54, 129.90 (2×), 129.69, 129.63, 129.12 (2×), 127.51 (2×), 114.88, 114.71, 113.39 (2×), 55.14, 51.95, 51.72, 48.42, 48.34, 21.60; HRMS (ESI) m/z calcd for $C_{24}H_{25}FNO_3S$ (M^++1) 426.1539, found 426.1542. For **5Bd** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, $J = 7.5$ Hz, 2H), 7.40 (d, $J = 7.5$ Hz, 2H), 6.77 (t, $J = 8.5$ Hz, 2H), 6.65 (dd, $J = 6.0$, 8.0 Hz, 2H), 6.50 (d, $J = 8.5$ Hz, 1H), 6.12–6.11 (m, 2H), 5.86 (s, 2H), 3.74–3.62 (m, 4H), 3.44–3.36 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.64, 160.69, 147.40, 146.30, 143.77, 134.12, 131.23, 129.93 (2×), 129.62, 129.56, 127.48 (2×), 121.32, 114.94, 114.78, 108.41, 107.79, 100.88, 51.86, 51.78, 48.77, 48.37, 21.59; HRMS (ESI) m/z calcd for $C_{24}H_{23}FNO_4S$ (M^++1) 440.1332, found 440.1334.