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DIASTEREOSELECTIVE SYNTHESIS OF *trans*-*N*-BENZYL-2-(2-METHYLPHENYL)-6-PHENYL-4-PIPERIDONE

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Abstract - Diastereoselective synthesis of *trans*-*N*-benzyl-2-(2-methylphenyl)-6-phenyl-4-piperidone (**6a**) was performed by cycloaddition of the aldimine (**1c**) with 2-silyloxy-1,3-butadiene in the presence of trimethylsilyl triflate. The use of the *p*-trimethylsilyl substituent of the aromatic ring of the aldimine gave high diastereoselectivity of the product.

[4+2] Type cycloaddition of aldimines with dienes is a powerful method for the construction of piperidone or piperidine derivatives which are contained in numerous alkaloids.[1] Asymmetric cycloaddition of aldimines with dienes has received considerable attention,[2] however, many examples have been reported on the cycloaddition with Danishefsky's diene which created one new chiral carbon center piperidones.[3] The difficulty to construct two new chiral carbons on the piperidones might lie in the diastereocontrol of the product, and the substituent at α-position of aldimine was quite limited.[4] This paper reports the effective method for diastereoselective preparation of *trans*-2,6-diaryl-4-piperidones by [4+2] type cycloaddition of the aldimines having a trimethylsilyl substituent as a protecting group with 2-silyloxy-1,3-butadiene.

Recently, we have reported [4+2] type cycloaddition of the aldimines with 2-silyloxy-1,3-butadienes, and found that the 2,6-*trans* selectivity of the product increased by increasing the bulkiness of the substituent at α-position of aldimine.[4b] Next, we applied the reaction of benzaldiminetricarbonylchromium complexes derived from benzaldehyde, *o*- or *p*-anisaldehyde, or *p*-tolualdehyde with 2-silyloxy-1,3-butadiene, and the tricarbonylchromium moiety enhanced the diastereoselectivities of the products compared to that with benzaldimine derivatives. We also achieved the enantioselective reaction of the chromium complex.[5] However, the reaction of aldimine complex (**1a**) derived from the *o*-tolualdehyde gave only 56% de of the product (85% isolated yield) even though tricarbonylchromium moiety was attached to the aromatic ring of the aldimine (Scheme 1).[6] The cycloaddition of the aldimine (**1b**) with 2-silyloxy-1,3-butadiene also gave 54% de of the product in 95% isolated yield.[6] From the results, we were interested in investigating a method for increasing the diastereoselectivity of the product in the case of the *o*-tolualdimine. The reason of the low de was not clear,but we thought that the steric hindrance between the alkyl substituent (methyl group) and Lewis acid might resulted in instability of the structure (**A**) (Figure 1), and the reaction of the

aldimine (**1a** or **1b**) having structure (**B**) would lower the production of the *trans* isomer because there would be no steric hindrance between methyl group and the silyloxydiene, increasing the production of *cis* isomer. To circumvent the problem, we envisioned that a silyl bulky substituent at *para* position of the aromatic ring of the aldimine would give *trans* isomer selectively because there would be no steric hindrance between Lewis acid and the silyl group at *para* position, and the silyl group would increase the bulkiness of α-position of the aldimine. Actually, the reaction of aldimine derived from *p*-tolualdehyde gave >98% de of the product,[5] indicating that *para* substituent played an important role for diastereoselectivity. The bulkiness of *para* TMS group would significantly affect the diastereoselectivity rather than that of *ortho* methyl group.

Scheme 1

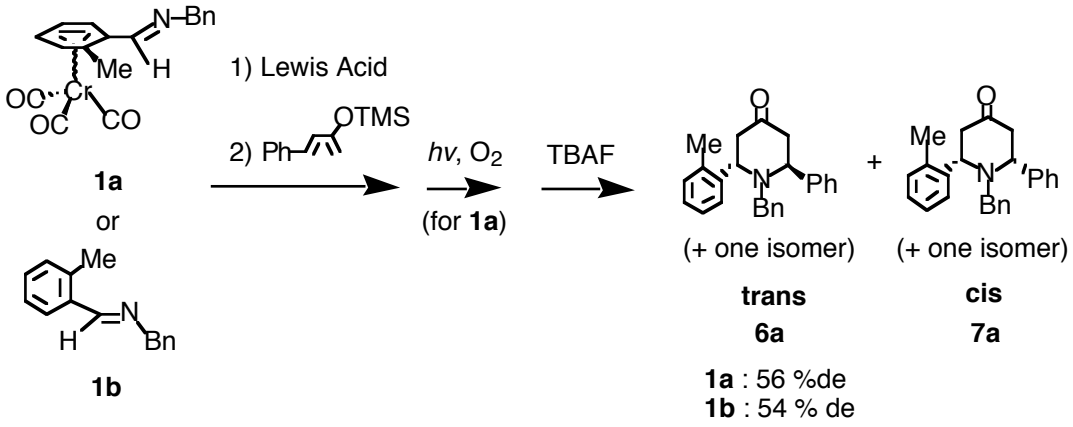
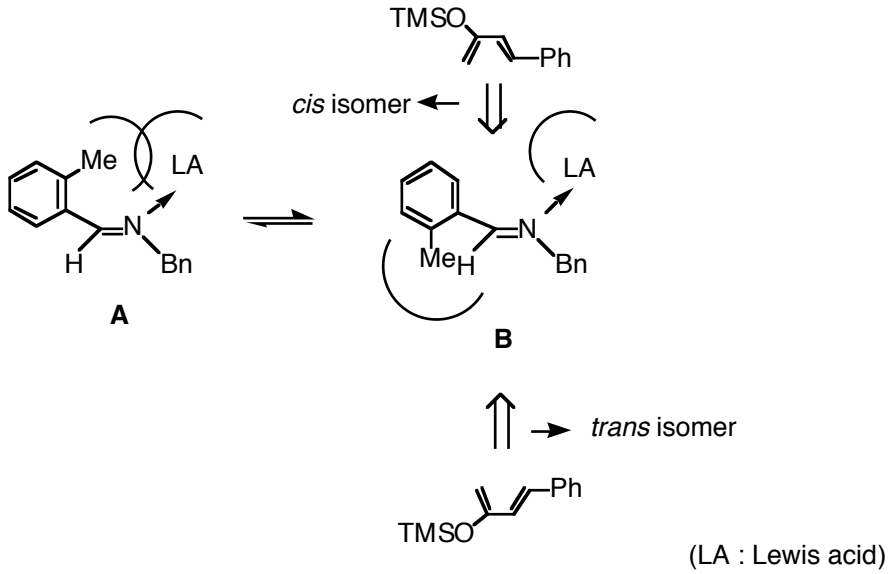


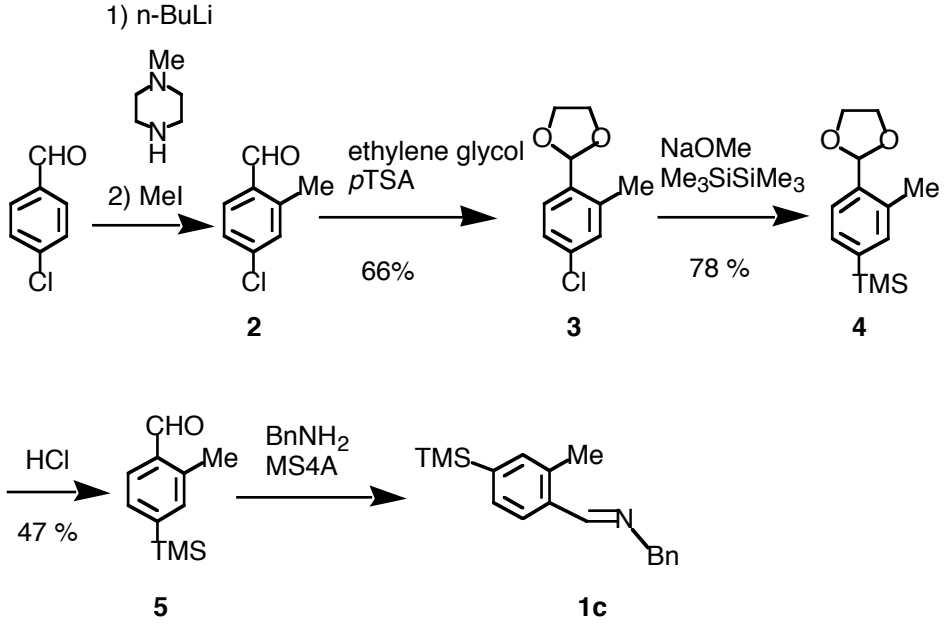
Figure 1



Based on the idea, we prepared the 2-methyl-4-trimethylsilylbenzylidene-*N*-benzylamine (**1c**) as shown in Scheme 2. 4-Chloro-2-methylbenzaldehyde (**2**) was prepared as described before,[7] and reaction of **2** with

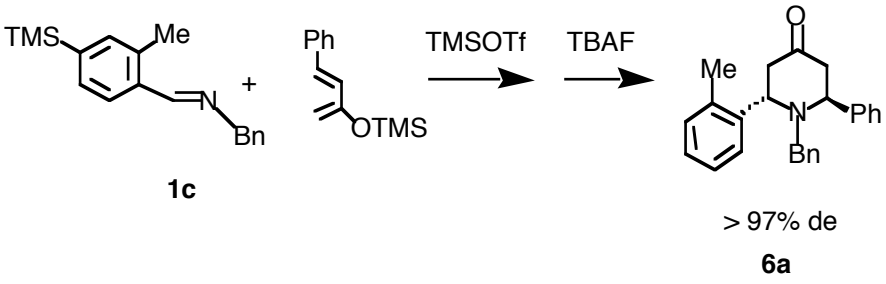
ethylene glycol in the presence of *p*TSA gave acetal (**3**) in 66% yield. Silylation at *para* position of the aromatic ring with disilane afforded 2-methyl-4-trimethylsilylbenzaldehyde ethylene acetal (**4**) in 78% yield.[8] Deprotection of the acetal moiety of **4** with concentrated HCl (47% yield) followed by condensation of the aldehyde (**5**) with benzylamine in the presence of MS 4A gave the corresponding aldimine (**1c**), which was used without purification.

Scheme 2



The cycloaddition of **1c** with 2-silyloxy-1,3-butadiene was carried out in the presence of TMSOTf in dichloromethane at room temperature for 12 h (Scheme 3). After work-up, removal of the TMS group with TBAF yielded the piperidone (**6a**) in 71% yield. The diastereomeric ratio (*trans*:*cis*) was determined by 500 MHz ^{1}H NMR spectrum of the crude products, and only one diastereomer (**6a**) was detected.

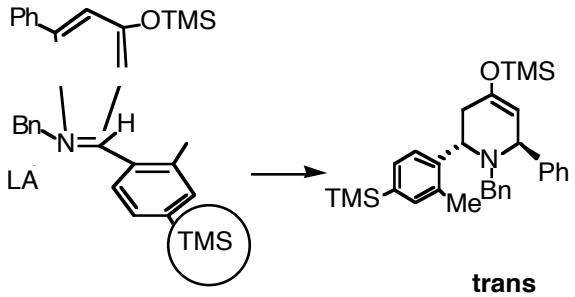
Scheme 3



The stepwise or concerted mechanism of the cycloaddition is a matter of debate,[2,3a] but the stereochemical course of the reaction can be explained by the assumed transition state in Figure 2, in which silyl enol ether moiety of the silyloxydiene might attack the aldimine (**1c**) closer than the another double bond of the silyloxydiene because the bulkiness of Lewis acids does not largely affect the diastereoselectivity.[9] The steric hindrance between the TMS group of the aldimine and the silyloxy group of the silyloxydiene would decrease the production of *cis* isomer.

In conclusion, diastereoselective preparation of *trans*-2,6-diaryl-4-piperidone was achieved by [4+2] type cycloaddition of the aldimine having a TMS group at *para* position of aromatic ring with 2-silyloxy-1,3-butadiene. The TMS group played an important role for diastereocontrol of the product, and was easily deprotected.

Figure 2



EXPERIMENTAL

General

All reactions were performed with oven-dried glasswares under argon. Flash column chromatography was carried out by use of Merck silica gel 60 (0.063-0.200 mm) and silica gel 60N (for separation of diastereomers, spherical, neutral, Kanto Chemical Co.). IR spectra were measured using a JASCO FT IR-230 spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker 500 MHz instrument at room temperature using TMS as an internal standard. High-resolution MS spectra were measured with a JEOL SX-102A spectrometer at the Instrument Center for Chemical Analysis, Hiroshima University.

4-Chloro-2-methylbenzaldehyde ethylene acetal (3): To a stirred solution of the aldehyde (5.90 g, 38 mmol) and *p*TSA (84 mg) in benzene (120 mL) was added ethylene glycol (25.4 mL) at rt. The mixture was heated to 150°C using Dean-Stark apparatus for 12 h. The mixture was washed with water (50 mL x 3), the organic layers were dried over Na_2SO_4, and the solvent was evaporated. The crude mixture was purified by flash column chromatography on SiO_2 with ether-*n*-hexane (1/5) to give the 4-chloro-2-methylbenzaldehyde ethylene acetal as a colorless oil (4.96 g, 66%). IR (neat): 2958 cm^{-1}, 2887, 1601, 1485, 1227, 1076, 885, 810; ^{1}H NMR ($CDCl_3$): 2.39 (s, 3H), 4.04 (s, 2H), 4.13 (s, 2H), 5.91 (s, 1H), 7.05-7.47 (m, 3H); HRMS-FAB(M^+): Found m/z 198.0447. Calcd for $C_{10}H_{11}O_2Cl$: 198.0448; Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.36; H, 5.70.

2-Methyl-4-trimethylsilylbenzaldehyde ethylene acetal (4): To a stirred solution of NaOMe (0.17 g, 3.2 mmol) in HMPA (5 mL) were added the acetal (424 mg, 2.1 mmol) and hexamethyldisilane (0.7 mL, 3.4 mmol) at rt. The reaction mixture was stirred at rt for 6 h, quenched with aqueous 5% NH_4Cl, and the mixture was extracted with pentane. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. The crude products were purified by flash column chromatography on SiO_2 with dichloromethane-*n*-hexane (1/1) to give the 2-methyl-4-trimethylsilylbenzaldehyde ethylene acetal as a colorless oil (393 mg, 78%). IR (neat): 2954 cm^{-1}, 2887, 1603, 1454, 1377, 1248, 1074, 839; ^1H NMR ($CDCl_3$): 0.13 (s, 9H), 2.30 (s, 3H), 3.89-3.95 (m, 2H), 3.98-4.02 (m, 2H), 5.85 (s, 1H), 7.24-7.41 (m, 3H); HRMS-FAB(M^+): Found m/z 236.1223. Calcd for $C_{13}H_{20}O_2Si$: 236.1233; Anal. Calcd for $C_{13}H_{20}O_2Si$: C, 66.06; H, 8.53. Found: C, 66.31; H, 8.53.

2-Methyl-4-trimethylsilylbenzaldehyde (5): To a stirred solution of the acetal (393 mg, 1.66 mmol) in THF (5 mL) was added concentrated HCl (6 mL) at 0°C. The reaction mixture was stirred at 0°C for 3 min, and quenched with cold water. The mixture was extracted with ether (15 mL x 2), and the organic layers were washed with aqueous saturated $NaHCO_3$ (50 mL). After the organic layers were dried over Na_2SO_4, the solvent was evaporated and the crude aldehyde was purified by flash column chromatography on SiO_2 with *n*-hexane-dichloromethane (16/1~ 0/100) to give **5** as a colorless oil (0.149 g, 47 %). IR (neat): 2956 cm^{-1}, 2896, 1703, 1595, 1448, 1377, 1250, 899, 838; ^1H NMR ($CDCl_3$): 0.29 (s, 9H), 2.68 (s, 3H), 7.11-7.90 (m, 3H), 10.27 (s, 1H); HRMS-FAB(M^+): Found m/z 192.0978. Calcd for $C_{11}H_{16}OSi$: 192.0970; Anal. Calcd for $C_{11}H_{16}OSi$: C, 68.69; H, 8.39. Found: C, 68.73; H, 8.50.

***N*-(2-Methyl-4-trimethylsilylbenzylidene)benzylamine (1c):** To a stirred mixture of molecular sieves 4A (2 g) in ether (5 mL) were added benzylamine (0.084 mL, 0.77 mmol) and the aldehyde (0.77 mmol) in ether (3 mL). The reaction mixture was stirred at rt for 12 h, the molecular sieves were filtered off, and the solvent was evaporated to give the aldimine which was used without purification. IR (neat): 3028 cm^{-1}, 2954, 1714, 1603, 1495, 1454, 1373, 1248, 839; ^1H NMR ($CDCl_3$): 0.27 (s, 9H), 2.54 (s, 3H), 4.85 (s, 2H), 7.18-7.94 (m, 8H), 8.70 (s, 1H); Anal. Calcd for $C_{18}H_{23}NSi$: C, 76.81; N, 4.98; H, 8.24. Found: C, 77.09; N, 5.04; H, 8.50.

[4+2] Type cycloaddition

To a stirred solution of the crude aldimine (**1c**) (189 mg, 0.73 mmol) in dry dichloromethane (3 mL) was added 0.16 mL (0.73 mmol) of trimethylsilyl triflate and 0.31 mL (1.46 mmol) of 2-silyloxy-1,3-butadiene at rt. The reaction mixture was stirred at rt for 12 h, quenched with saturated aqueous $NaHCO_3$ (30 mL), and the mixture was extracted with dichloromethane (20 mL x 3). After the collected organic layers were dried over $MgSO_4$, the solvent was evaporated to give crude cycloadduct.

The mixture of the cycloadduct was dissolved in THF (2 mL), and TBAF in THF (1.46 mL, 1.0 M solution) was added to the mixture at rt. The reaction mixture was stirred at rt for 1 h, quenched with H_2O (50 mL), and the mixture was extracted with dichloromethane (20 mL x 3). The combined organic phases were collected and dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by

flash column chromatography on SiO_2 with CH_3COOEt-*n*-hexane (1/3) to give *trans*-2,6-diaryl-4-piperidone (**6a**) as a colorless oil (183 mg, 71%).

***trans*-2-(2-Methylphenyl)-6-phenyl-4-piperidone (6a):** IR (neat): 3062 cm^{-1}, 3028, 2962, 1714, 1495, 1454, 1259, 1101, 1024, 754; ^1H NMR (500 MHz, $CDCl_3$): δ 1.92 (3H, s), 2.65 (1H, d, *J* = 15.0 Hz), 2.71 (1H, d, *J* = 15.0 Hz), 2.96-2.98 (2H, m), 3.39 (1H, d, *J* = 13.7 Hz), 3.56 (1H, d, *J* = 13.7 Hz), 4.34-4.35 (2H, m), 7.01-7.45 (14H, m); HRMS-FAB(M^+): Found m/z 355.1940. Calcd for $C_{25}H_{25}NO$: 355.1936; Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; N, 3.94; H, 7.09. Found: C, 84.36; N, 4.04; H, 7.01.

***cis*-2-(2-Methylphenyl)-6-phenyl-4-piperidone (7a):** IR (neat): 3028 cm^{-1}, 2964, 1716, 1493, 1456, 1259, 1074, 1018, 798, 758; ^1H NMR (500 MHz, $CDCl_3$): δ 2.33 (3H, s), 2.54 (1H, d, *J* = 13.5 Hz), 2.63 (1H, d, *J* = 13.6 Hz), 2.80 (1H, dd, *J* = 13.5, 12.0 Hz), 2.92 (1H, dd, *J* = 13.6, 11.9 Hz), 3.81 (1H, d, *J* = 14.8 Hz), 3.86 (1H, d, *J* = 14.8 Hz), 4.11 (1H, dd, *J* = 12.0, 2.9 Hz), 4.19 (1H, dd, *J* = 11.9, 2.7 Hz), 6.83-7.77 (14H, m); HRMS-FAB(M^+): Found m/z 355.1939. Calcd for $C_{25}H_{25}NO$: 355.1936; Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; N, 3.94; H, 7.09. Found: C, 84.58; N, 4.13; H, 6.88.

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REFERENCES AND NOTES

1. (a) H. Waldmann, *Gazz. Chim. Ital.*, 1991, **121**, 277. (b) H. Waldmann, *Nachr. Chem. Tech. Lab.*, 1992, **40**, 1377. (c) H. Waldmann, *Synthesis*, 1994, 535. (d) H. Kunz, B. Müller, W. Pfrengle, K. Rück, and W. Stähle, *ACS Symp. Ser.*, 1992, **494**, 131. (e) M. W. Edwards, H. M. Garraffo, and J. W. Daly, *Synthesis*, 1994, 1167 and references cited therein. (f) L. C. Dias, *J. Braz. Chem. Soc.*, 1997, **8**, 289.
2. K. A. Jørgensen, *Angew. Chem., Int. Ed.,* 2000, **39**, 3559.
3. (a) H. Waldmann and M. Brawn, *J. Org. Chem.*, 1992, **57**, 4444. (b) K. Hattori and H. Yamamoto, *J. Org. Chem.*, 1992, **57**, 3264. (c) K. Hattori and H. Yamamoto, *Synlett*, 1993, 129. (d) C. Baldoli, P. D. Buttero, M. D. Ciolo, S. Maiorana, and A. Papagni, *Synlett*, 1996, 258. (e) E. P. Kündig, L. F. Xu, P. Romanens, and G. Bernardinelli, *Synlett*, 1996, 270. (f) S. Bromidge, P. C. Wilson, and A. Whiting, *Tetrahedron Lett.,* 1998, **39**, 8905. (g) S. Kobayashi, S. Komiyama, and H. Ishitami, *Angew. Chem., Int. Ed.* 1998, **37**, 979. (h) S. Yao, M. Johnannsen, R. G. Hazell, and K. A. Jørgensen, *Angew. Chem., Int. Ed.,* 1998, **37**, 3121. (i) H. Ratni, B. Crousse, and E. P. Kündig, *Synlett*, 1999, 626. (j) R. Badorrey, C. Cativiela, M. D. Díaz-de-Villegas, and J. A. Gálvez, *Tetrahedron*, 1999, **55**, 7601 and references cited therein.

4. (a) J. Barluenga, F. Aznar, C. Valdés, and M. -P. Cabal, *J. Org. Chem.,* 1993, **58**, 3391. (b) K.-y. Akiba, T. Motoshima, K. Ishimaru, K. Yabuta, H. Hirota, and Y. Yamamoto, *Synlett*, 1993, 657. (c) K. Ishimaru, K. Watanabe, Y. Yamamoto, and K.-y. Akiba, *Synlett*, 1994, 495.
5. K. Ishimaru and T. Kojima, *J. Chem. Soc., Perkin Trans. 1,* 2000, 2105.
6. unpublished data
7. D. L. Commins, J. D. Brown, and N. B. Mantlo, *Tetrahedron Lett.,* 1982, **23**, 3979.
8. M. A. Shippey and P. B. Dervan, *J. Org. Chem.,* 1977, **42**, 2654.
9. When the reaction of the aldimine derived from *n*-butanal with the 2-silyloxy-1,3-diene in the presence of silyl triflate was carried out at room temperature for 1 day, the use of TMSOTf, TBDMSOTf, or TIPSOTf gave 74% de (52% yield), 76% de (58% yield), or 80% de (75% yield), respectively.