Mechanistic Studies on the Catalytic Asymmetric Mannich-type Reaction with Dihydroisoquinolines and Development of Oxidative Mannich-type Reaction Starting from Tetrahydroisoquinolines

Christian Dubs,[1] Yoshitaka Hamashima,[1] Naoki Sasamoto,[1] Thomas M. Seidel,[1] Shoko Suzuki,[1] Daisuke Hashizume,[2] and Mikiko Sodeoka*,[1]

[1]Synthetic Organic Chemistry Laboratory, RIKEN, Hirosawa, Wako 351-0198, Japan, and

[2]Molecular Characterization Team, RIKEN, Hirosawa, Wako 351-0198, Japan.

sodeoka@riken.jp

Supporting Information

(A) General

General: NMR spectra were recorded at 400 MHz for ^{1}H NMR and 100.4 MHz for ^{13}C NMR, or at 300 MHz for ^{1}H-NMR and 75.0 MHz for ^{13}C NMR. Chemical shifts are reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported using the solvent signal as an internal reference. ^{19}F NMR was measured at 376 MHz, and CF_3COOH (TFA) was used as an external standard. ^{31}P NMR was measured at 100 MHz, and 85% H_3PO_4 was used as an external standard. FAB-LRMS was taken using *m*-nitrobenzyl alcohol (*m*NBA) or glycinol (Gly) as the matrix. FAB-HRMS was taken using *m*NBA/PEG300 as the matrix. Flash column chromatography was performed with silica gel 60 (40-100 μm). The enantiomeric excesses (ees) were determined by chiral HPLC analysis. Solvents used in this paper were purchased and used as supplied. Other reagents were purified by usual methods. All DHIQs were prepared by oxidation of the corresponding secondary amines or using the classical Bischler-Napieralski reaction according to the reported procedure (See reference 18 in the main text). The obtained imines were stored in a refrigerator and passed through neutral alumina (eluent: hexane/ethyl acetate = 1/1) before use. The NMR data of DHIQs were reported in the Supporting Information of reference 16.

(B) X-Ray Crystal Structure Analysis of 2a:

X-Ray Crystal Structure Analysis of 2a · 3CDCl₃

Crystal data: $C_{48}H_{44}F_6O_{10}P_2PdS_2$ · 3CDCl₃, *FW* = 1488.44, orthorhombic $P2_12_12_1$, a = 12.0672(14), b = 15.2049(18), c = 33.606(4) Å, V = 6166.0(13) Å^3; D_X = 1.603 Mg m^{-3}; Z = 4; μ(Mo Kα) = 0.882 mm^{-1}, T = 90 K. Needle shaped yellow crystals were grown from a CDCl₃ solution of **2a**. A single crystal with the dimensions of 0.57 x 0.08 x 0.05 mm was mounted on a MicroMount™ (MiTeGen, LLC) and set on a Rigaku AFC-8 diffractomter with a Saturn70 CCD detector. The diffraction data were collected using MoKα radiation, which was monochromated by a multi-layered confocal mirror. The unit cell dimensions were determined using 18889 reflections with $3.59 \leq 2\theta \leq 62.84°$. The diffraction data of 116652 within $3.58 \leq 2\theta \leq 60.08°$ were collected and merged to give 18030 unique reflections with the R_{int} of 0.0394. The structure was solved by a direct method and refined on F^2 by a least-squares method by the programs SIR92[1] and SHELXL97,[2] respectively. The final R values against 17529 unique reflections ($2\theta_{max}$ = 60.08°) with $I > 2\sigma(I)$ are 0.0344 and 0.0757 for the $R(F)$ and the $wR(F^2)$, respectively. The absolute structure of the crystal was determined by

anomalous dispersion effects (χ = -0.020(13)); the obtained configuration of the **2a** agrees with an R-configuration of the dm-segphos ligand.
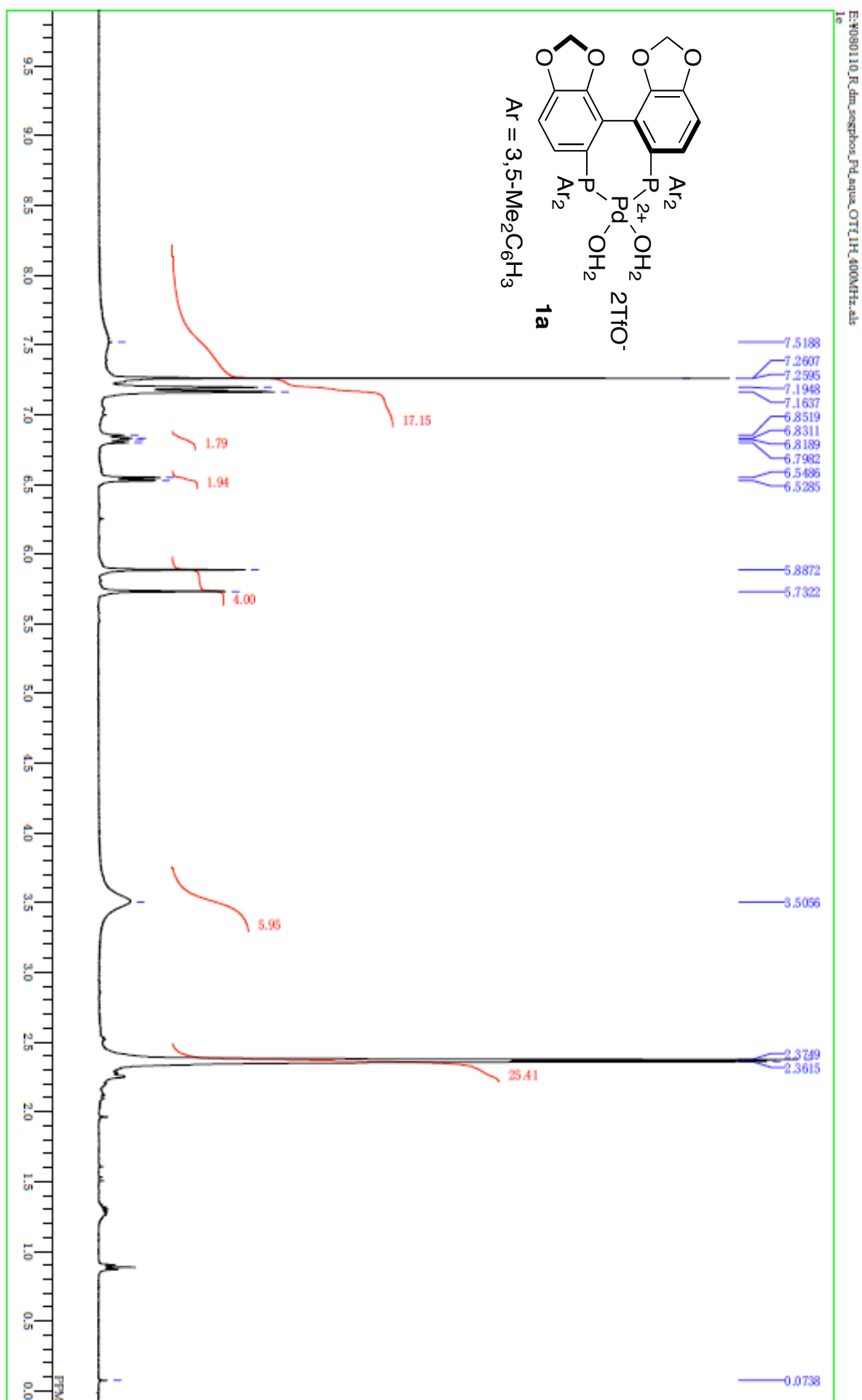
(C) X-Ray Crystal Structure Analysis of 23:

Crystal data: $C_{16}H_{19}NO_5$, *FW* = 305.32, monoclinic *P*2$_1$, *a* = 8.675(2), *b* = 15.232(4), *c* = 11.263(3) Å, β = 99.373(4)°, *V* = 1468.5(6) Å^3; D_X = 1.381 Mg m^{-3}; *Z* = 4; μ(Mo Kα) = 0.103 mm^{-1}, *T* = 100 K. Plate shaped colorless crystals were grown from a methanol solution of **23**. A single crystal with the dimensions of 0.42 x 0.21 x 0.03 mm was mounted on a MicroMount^{TM} (MiTeGen, LLC) and set on a Rigaku AFC-8 diffractomter with a Saturn70 CCD detector. The diffraction data were collected using MoKα radiation, which was monochromated by a multi-layered confocal mirror. The unit cell dimensions were determined using 5690 reflections with $3.66 \le 2\theta \le 65.03°$. The diffraction data of 8921 within $3.66 \le 2\theta \le 60.14°$ were collected. The data were merged, including Friedel pairs, to give 8921 unique reflections with the R_{int} of 0.0403. The structure was solved by a direct method and refined on F^2 by a least-squares method by the programs SIR2004[3] and SHELXL97,[2] respectively. The imaginary part of the anomalous dispersion term of each atom was set to zero on the refinements. The final *R* values against 3455 unique reflections ($2\theta_{max}$ = 60.14°) with $I > 2\sigma(I)$ are 0.0489 and 0.0970 for the *R*(*F*) and the *wR*(*F*^{2}), respectively.
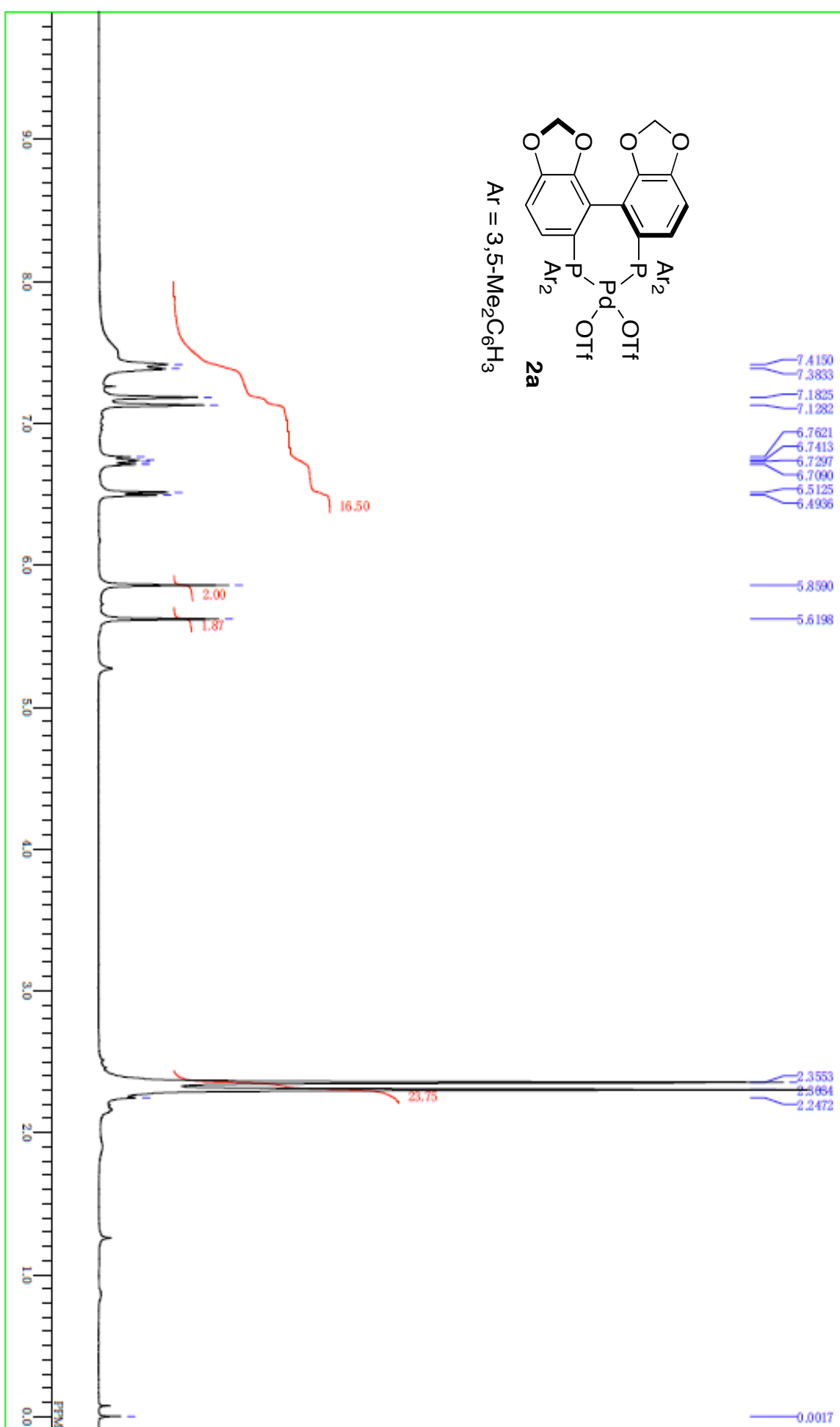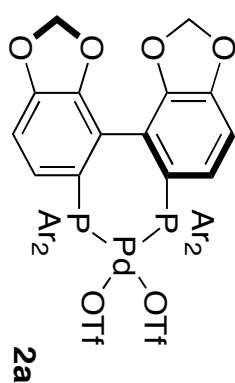
(1) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435.

(2) SHELXL97: Sheldrick, G. M., University of Göttingen, Germany, 1997.

(3) Burla, M. C.; Caliandro, R.; Camalli, M.; , Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R., *J. Appl. Cryst.* **2005**, 38, 381-388.

(D) NMR spectra of the Pd complexes

Ar = 3,5-Me₂C₆H₃

1a

Ar = 3,5-Me$_2$C$_6$H$_3$

2a

7.4150
7.3833
7.1825
7.1282
6.7621
6.7413
6.7297
6.7090
6.5125
6.4936
5.8590
5.6198
2.3553
2.3684
2.2472
0.0017

16.50
2.00
1.87
23.75

PPM

(E) NMR spectra of the new compounds

18

7.2627

6.5837
6.5226

6.1697
6.1343
6.0793
6.0512
6.0463
6.0158

1.00

2.12

1.5595
9.60

0.0024

PPM

7.2686
7.0355

6.5930

5.4632
5.1788
5.1629
5.1471
5.1312
5.1153
4.6997
4.6838
4.6679
4.6527
4.6368
4.5648
4.5349

3.8531
3.8061
2.8747
2.8454
2.8168
2.8052
2.7691
2.7399
2.6483
2.6196
2.5954
2.5879
2.5598
2.5433
2.5311
2.4731
2.4621
2.4335
2.3932
2.3816
2.3694
2.3608
2.3480
1.6846
1.2903
1.2744
1.2567
1.2408
1.0406
1.0254
0.7611
0.7452

0.0000

1.00
0.94
0.91
0.95
1.91
5.82
2.17
3.21
2.34
6.31
3.60
3.31

22

24