A Highly Efficient Catalytic System for C-H Activation: A Practical Approach to Angiotensin II Receptor Blockers

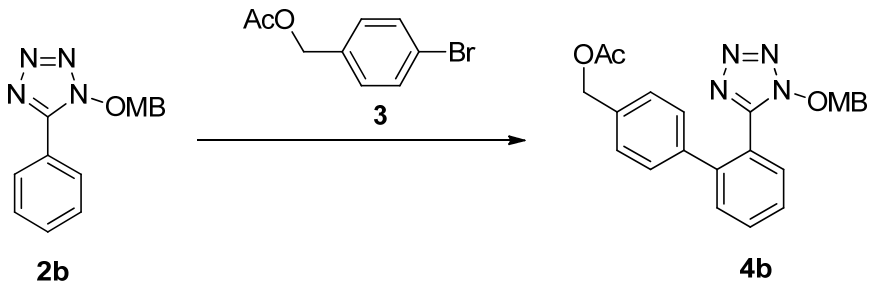
Masahiko Seki

Healthcare Business Division
Process Research & Development Laboratory
API Corporation
1-1, Shiroishi, Kurosaki, Yahatanishi-ku, Kitakyushu,
Fukuoka 806-0004, Japan
E-mail: seki.masahiko@mm.api-corp.co.jp

Supporting Information

Experimental

General: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm pre-coated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol-heat or visualized by UV light where feasible. Ruthenium catalysts **6a**-**6e** were purchased from Johnson Matthey and Sigma Aldrich All solvents and reagents were used as received.



2b **4b**

A mixture of $RuCl_3 \cdot xH_2O$ (**6d**) (Ru 40.01%, 5.7 mg, 23 μmol), PPh_3 (10.4 mg, 40.3 μmol), **2b** (481 mg, 1.81 mmol), K_2CO_3 (499 mg, 3.61 mmol), **3** (455 mg, 1.99 mmol) and NMP (1.9 mL) was stirred under N_2 atmosphere at 140^{o}C for 12 h. The mixture was cooled to 20^{o}C and it was diluted with AcOEt (10 mL) and washed twice with water, dried over $MgSO_4$ and evaporated. The residue contained **4b** (607 mg, 81%) as assayed by HPLC (Cadenza CD-C18, 3 μm, 4.6 x 150 mm, CH_3CN/30 mM KH_2PO_4 (3:2), 225 nm, 40^{o}C). The authentic sample of **4b** was obtained by purification with silica-gel column chromatography using a mixture of *n*-hexane and AcOEt (4/1).

mp 117-118^{o}C.

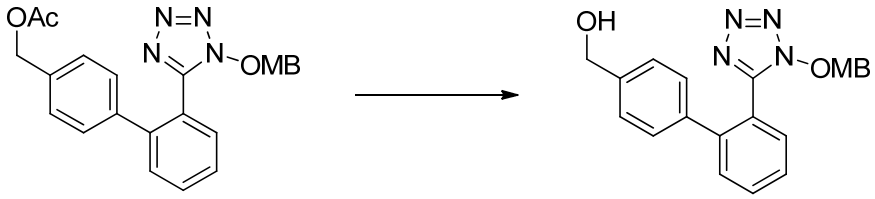
IR (KBr): ν_{max} = 1735, 1603 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.74 (td, *J* = 7.7, 1.4 Hz, 1H), 7.61-7.58 (m, 3H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.27 (td, *J* = 7.4, 1.4 Hz, 1H), 7.00 (d, 2H, *J* = 8.2 Hz, 2H), 6.91 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.81 (t, *J* = 7.4 Hz, 1H), 5.06 (s, 2H), 4.98 (s, 2H), 3.51 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 170, 156, 154, 141, 138, 136, 131, 131, 130, 130, 128, 128, 128, 122, 121, 120, 111, 65, 55, 46, 21.

MS: *m/z* = 415 (MH^{+}).

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52; Found: C, 69.55; H, 5.11; N, 13.45.



4b **7**

To a solution of **4b** (1.01 g, 2.44 mmol) in MeOH (5.0 mL), was added MeONa in MeOH (28 wt %) (24 μL, 23 mg, 0.12 mmol) and the mixture was stirred for 9 h. The mixture was evaporated and the residue was dissolved in $CHCl_3$ and washed, dried over $MgSO_4$ and evaporated. The solids formed were collected by adding *n*-hexane to provide **7** (820 mg, 90%) in colorless crystals.

mp 139-141^{o}C.

IR (KBr): ν_{max} = 3398, 1605 cm^{-1}.

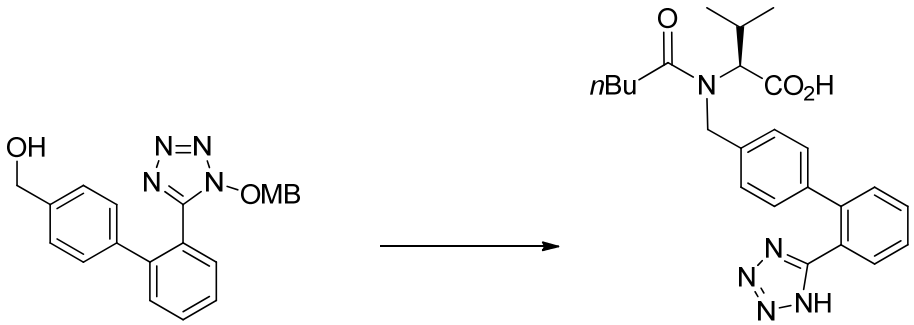
^{1}H NMR (DMSO-d_6): δ = 7.73 (td, *J* = 7.8, 2.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.59-7.55 (m, 2H), 7.26 (td, *J* = 7.9, 1.6 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* =

8.2 Hz, 2H), 6.91 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.81 (t, *J* = 7.9 Hz, 1H), 5.22 (t, *J* = 5.9 Hz, 1H), 4.93 (s, 2H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.50 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 157, 154, 142, 141, 137, 131, 131, 130, 128, 128, 127, 122, 121, 120, 111, 62, 55, 46.

MS: *m/z* = 373 (MH^+).

Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04; Found: C, 70.76; H, 5.27; N, 15.01.



7 **1a**

A mixture of **7** (1.00 g, 2.69 mmol) and TMSBr (0.711 mL, 822 mg, 5.37 mmol) in CH_3CN (5.0 mL) was stirred at 50°C for 4.5 h. The mixture was cooled to 20°C and to the mixture were added *i*Pr_2EtN (1.57 g, 12.1 mmol) and L-valine benzyl ester *p*-toluenesulfonate (1.53 g, 4.03 mmol) and CH_3CN (4.0 mL). The mixture was stirred at 50°C for 2 h. After cooling the mixture to 20°C, it was diluted with AcOEt (20 mL) and water (1.7 mL). The aqueous phase was extracted with AcOEt and combined organic phases were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The residue was dissolved in $CHCl_3$ and 84.1% portion of this material was evaporated. Into the residue were added toluene (6.4 mL), pyridine (0.275 mL, 0.269 g, 3.40 mmol) and *n*-pentanoyl chloride (0.376 mL, 0.382 g, 3.17 mmol) and the mixture was stirred at 20°C for 4 h and at 40°C for 2 h. Pyridine (92.8 mg, 1.17 mmol) and *n*BuCOCl (141 mg, 1.17 mol) were added and it was stirred at 40°C for 3 h. The mixture was cooled down to 20°C and 1M HCl (5 mL) and AcOEt (20 mL) were added. The aqueous phase was extracted with AcOEt and the combined extracts were washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The

residue was purified by silica-gel column chromatography using a mixture of toluene/AcOEt = 50:1 to 5:1 to afford *n*-pentanoyl derivative (1.47 g). It was dissolved in 2-propanol (4.53 g). To a portion (800 mg) of the solution were added Pd/C (5%Pd, water: 58.8 wt%, 128 mg), ammonium formate (96.2 mg, 1.53 mmol) and water (0.51 mL) and the mixture was stirred at 20°C for 14 min and at 45°C for 6 h. The mixture was filtered by adding 2-propanol (10 mL). The filtered solids were washed with 2-propanol (5 mL) and the combined solution was evaporated. Into the residue were added 0.5M NaOH (2.0 mL), water (7 mL) and TBME (5 mL). The aqueous phase was washed with TBME and treated with 1N HCl (1.7 mL) and AcOEt (40 mL). The aqueous phase was extracted twice with AcOEt and the combined extracts were washed with sat. aq. NaCl, dried over $MgSO_4$ and evaporated. The solids formed were collected by adding a mixture of cyclohexane and AcOEt to afford **1a** (99.5 mg, 76%) in colorless crystals.

mp 70-95°C (Valsartan **1a** is known to exist in several crystalline forms (P. Bühimayer, F. Ostermayer, T. Schmidlin (Ciba-Geigy), EP0443983A1 (priority date: February 19, 1990)). Control of the polymorph was not examined in this study.
IR (KBr): ν_{max} = 1730, 1619 cm^{-1}.
^{1}H NMR (DMSO-d_6)(C_M: major rotamer; C_m: minor rotamer): δ = 16.3 (brs, 1H), 12.6 (brs, 1H), 7.70-7.63 (m, 2H, C_M, C_m), 7.58-7.53 (m, 2H, C_M, C_m), 7.20 (d, *J* = 8.2 Hz, 1H, C_M), 7.08 (d, *J* = 8.2 Hz, 1H, C_m), 7.07 (d, *J* = 8.2 Hz, 1H, C_M), 6.97 (d, *J* = 8.2 Hz, 1H, C_m), 4.62 (s, 2H, C_M), 4.48 (d, *J* = 15.2 Hz, 1H, C_m), 4.46 (d, *J* = 10.3 Hz, 1H, C_M), 4.43 (d, *J* = 15.2 Hz, 1H, C_m), 4.08 (d, *J* = 10.5 Hz, 1H, C_m), 2.53-2.45 (m, 2H, C_m), 2.22-2.12 (m, 1H, C_M, C_m), 2.21 (dt, *J* = 15.8, 7.9 Hz, 1H, C_M), 2.03 (dt, *J* = 15.8, 7.9 Hz, 1H, C_M), 1.54 (quint, *J* = 6.9 Hz, 2H, C_m), 1.41 (dquint, *J* = 14.1, 7.9 Hz, 1H, C_M), 1.37 (dquint, *J* = 14.1, 7.9 Hz, 1H, C_M), 1.31 (sext, *J* = 6.9 Hz, 2H, C_m), 1.15 (sext, *J* = 7.9 Hz, 2H, C_M), 0.93 (d, *J* = 6.9 Hz, 3H, C_m), 0.93 (d, *J* = 7.9 Hz, 3H, C_M), 0.88 (t, *J* = 6.9 Hz, 3H, C_m), 0.76 (t, *J* = 7.9 Hz, 3H, C_M), 0.75 (d, *J* = 7.9 Hz, 3H, C_M), 0.70 (d, *J* = 6.9 Hz, 3H, C_m).
HRMS: Calcd for $C_{24}H_{29}N_5O_3$, 435.2270. Found 435.2267.