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Asymmetric transfer hydrogenation of a new *N*-tosyltetrahydrocarbazole-1-one ester with the Noyori-Ikariya catalyst

Ömer Dilek [§] **and Erkan Ertürk** [*]

TÜBITAK Marmara Research Center, 41470 Gebze, Kocaeli, Türkiye

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Abstract: Enantioselective reduction of a new 1-oxotetrahydrocarbazole compound (ethyl 2-(1-oxo-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate) through asymmetric transfer hydrogenation by using the commercially available Noyori–Ikariya ruthenium catalyst and HCO_2H/Et_3N or HCO_2H/DABCO as the hydrogen source have been investigated. High enantiomeric excesses (up to 96% *ee*) and moderate to good yields (24–72%) for corresponding alcohol and lactone compounds have been achieved. Structures of all compounds have been characterized by spectroscopic techniques.

Keywords: Asymmetric transfer hydrogenation; Noyori–Ikariya ruthenium catalyst; chiral tetrahydrocarbazoles; *N*-tosyltetrahydrocarbazolone; enantioselective lactone synthesis.

1. Introduction

Natural products have had a special place in the synthetic and medicinal chemistry due to their significant biological activities.[1,2] The cyclohexane-fused indole unit, tetrahydrocarbazole (THC), is encountered in numerous indole alkaloids, such as uleine, gilbertine, tubifolidine, kopsihainanine, as well as natural product-like drug molecules.[3–5] The majority of those molecules contain a chiral THC moiety. Thus, their asymmetric syntheses by catalytic enantioselective transformations have become an important endeavor in recent years.[6–13] In conjunction with our special interest in the synthesis of indole alkaloids,[14–18] we were also involved in the enantioselective synthesis of their intermediates recently (Scheme 1).[16] In this context, when the THC-1-one ester (±)-**1** was subjected to asymmetric transfer hydrogenation with the Noyori–Ikariya ruthenium catalyst **3** (Ru-ATH) in the presence of HCO_2H–DABCO (11:6) mixture as the hydrogen source, and followed by the treatment with aqueous HCl, the corresponding lactone **2** was obtained in 45% yield and 97% *ee*. This conversion likely proceeds through a unique mechanism that includes (i) formation of the primary alcohol product **4**, (ii) formation of a vinylogous iminium cation (**5**) via water elimination, and (iii) *syn*-selective 1,6-addition of the ester nucleophile to the vinylogous iminium cation to give **2**.[16] It was also disclosed that *N*-tosyl-1- or 4-oxo-THCs can be reduced to corresponding alcohols with high yields and enantioselectivities (98–99% yields, 99% *ee*) through Ru-ATH in the presence of HCO_2H–Et_3N azeotrope as the hydrogen source.

[*] Corresponding author: E-Mail: erkan.erturk@tubitak.gov.tr

[§]Present address: Isparta University of Applied Sciences, Central Research Laboratory Application and Research Center, 32200 Isparta, Türkiye

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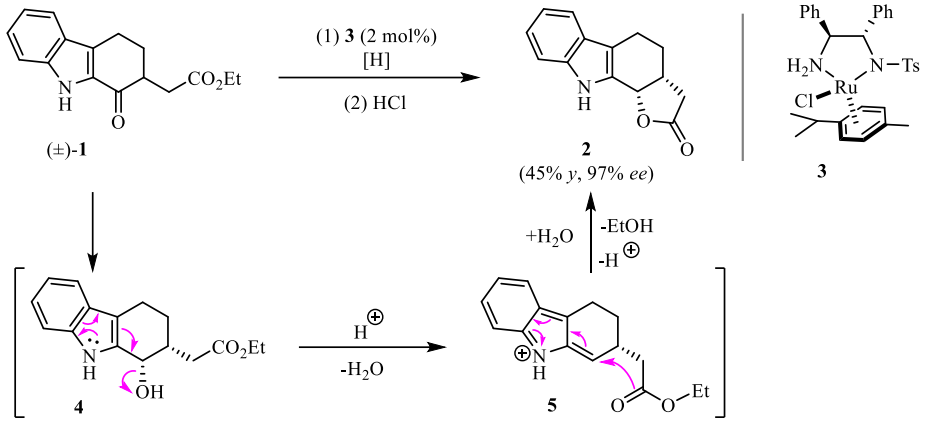
Notably, recent works have proven that the enantioselective reduction of ketones through asymmetric transfer hydrogenation with Noyori–Ikariya-type ruthenium catalysts is one of the most established technique to create a chiral framework efficiently and enantioselectively.[19–25] In this respect, the recent work of Ding and co-workers on the synthesis of (+)-alsmaphorazine and (+)-strictamine is one of the most significant examples.[8] Considering that *N*-tosyl-tetrahydrocarbazole-1-one ester (±)-**6** would be a useful intermediate for the enantioselective synthesis of chiral THCs, we studied its enantioselective reduction by Ru-ATH. Herein, we would like to report the results obtained throughout the study.



Scheme 1. Enantioselective synthesis of lactone **2** through asymmetric transfer hydrogenation by the Noyori-Ikariya catalyst **3**.[16]

2. Experimental

2.1. Chemical Materials and Apparatus

All chemicals were supplied by Sigma Aldrich or Merck companies. The solvents utilized in column chromatography were used as received without further purification. An oven-dried glassware was used to carry out all air-sensitive reactions under N_2. Gas-tight syringe and cannula techniques were used to transfer all of the chemicals and solvents under N_2. Thin layer chromatography (TLC) was performed using aluminum sheets pre-coated with silica gel SIL G/UV254 from MN GmbH & Co. The spots were made visible in UV light (254 nm), and/or by staining with phosphomolybdic acid solution in EtOH (10%, w/v). Using silica gel (MN-silicagel 60, 230–400 mesh), chromatographic separations were carried out. Using a BÜCHI Melting Point B-540 apparatus, all melting points were measured in an open glass capillary tube. The values are not corrected. PerkinElmer Spectrum One FT-IR spectrometer was used to record infrared (FT-IR) spectra. Broad (br), strong (s), medium (m), and weak (w) are the four different types of bands. A 500 MHz NMR spectrometer was used to record the ^{1}H and ^{13}C NMR spectra. Chemical shifts are expressed as parts per million (ppm) in relation to the solvent's residual protons ($CHCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm) and carbon resonance ($CDCl_3$: 77.00 ppm, DMSO-d_6: 39.52 ppm). The NMR peak multiplicities were as follows: s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet, and br for broad. Tetrahydrofuran (THF) was used to obtain high resolution electrospray ionization mass spectra (HR-ESI-MS) using a Bruker micrOTOF-Q. The specific rotations ([α]) were measured using a 1.0 dm path length, 1 mL cell, and Optical Activity Ltd. AA-65 polarimeter, and the sample concentrations are reported in g/100 mL units. Organic extracts were dried over anhydrous sodium sulphate and were evaporated using a rotatory evaporator operating at reduced pressure of about 10–20 Torr. Prior to use under a nitrogen atmosphere, THF was freshly distilled from sodium/benzophenone under N_2. Chromatographic separation of enantiomers were performed using an Agilent 1200 HPLC spectrometer equipped with a DAD detector at 25 °C, on a Daicel-Chiralcel OD-H column (column length: 250 mm, column internal diameter: 4.6 mm, column material: silica gel coated with cellulose-tris(3,5-dimethylphenylcarbamate) with a particle size (diameter of 5 µm).

2.2. Chemistry

*2.2.1. Synthesis of ethyl 2-(1-oxo-9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate ((±)-**6**)*

Ethyl 2-(1-oxo-2,3,4,9-tetrahydro-*1H*-carbazol-2-yl)acetate[16,17] ((±)-**1**, 2.17 g, 8.0 mmol, 1.00 equiv), 4-dimethylaminopyridine (DMAP; 97.7 mg, 0.8 mmol, 0.10 equiv), triethylamine (1.39 mL, 1.01 g, 10.0 mmol, 1.25 equiv), *p*-toluenesulfonyl chloride (3.36 g, 17.6 mmol, 2.2 equiv) and 32 mL of CH_2Cl_2 were added into the 100 mL flask that was equipped with magnetic stirring bar. The mixture were stirred until the solids were dissolved. Then 16 mL 50% $NaOH_{(aq)}$ and $^nBu_4N(HSO_4)$ (0.11 g, 0.32 mmol, 0.04 equiv) were added into the flask and the flask was capped with glass stopper. The mixture was vigorously stirred at room temperature for 16 h. The conversion was followed by TLC. But the conversion was not completed. Then pH value of mixture was adjusted to 5–6 with 2.0 M HCl and the organic components was extracted with $CHCl_3$ (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. The residue was then purified by column chromatography to afford 2.04 g (4.8 mmol, 60%) of the title compound ((±)-**6**) as a white solid. Mp: 148–150 °C. TLC: R_f = 0.31 (silica gel; Hexanes/EtOAc, 8:2, v/v). FTIR(KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3443 (w), 2988 (w), 2920 (w), 1780 (s), 1677 (s), 1598 (s), 1557 (s), 1451 (s), 1402 (s), 1367 (s), 1347 (s), 1277 (s), 1260 (s), 1206 (s), 1177 (s), 1139 (s), 980 (s), 960 (s, 942 (s), 880 (w), 863 (w), 810 (s), 750 (s), 743 (s), 669 (s), 578 (s), 535 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.9 Hz, 1H), 7.54 (ddd, J = 8.5, 7.2, 1.2 Hz, 1H), 7.33 (dt, J = 12.4, 2.6 Hz, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.08 (dddd, J = 29.2, 16.5, 10.3, 4.5 Hz, 3H), 3.00 – 2.90 (m, 1H), 2.40 (s, 3H), 2.39 – 2.30 (m, 2H), 2.08 – 1.91 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 125 MHz, $CDCl_3$) δ 188.05 (C=O), 172.24 (C=O), 144.39 (C), 139.82 (C), 137.08 (C), 136.99 (C), 131.99 (C), 129.31 (CH), 129.07 (CH), 127.58 (CH), 127.07 (C), 123.63 (CH), 121.10 (CH), 116.05 (CH), 60.55 (CH_2), 45.06 (CH), 34.58 (CH_2), 29.78 (CH_2), 21.61 (CH_3),21.18 (CH_2), 14.17 (CH_3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{23}NO_5SNa$, 448.1195; Found: 448.1140.

*2.2.2. Synthesis of racemic cis-ethyl 2-(1-hydroxy-9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate ((±)-**7**), trans-ethyl trans-2-(1-hydroxy-9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate ((±)-**8**), and 10-tosyl-3,3a,4,5,10,10b-hexahydro-2H-furo[2,3-a]carbazol-2-one ((±)-**9**)*

An oven dried 50 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was charged with ethyl 2-(1-oxo-9-tosyl-2,3,4,9-tetrahydro-*1H*-carbazol-2-yl)acetate ((±)-**6**, 425.5 mg, 1.00 mmol, 1.00 equiv). The tube was evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Solid particles were dissolved by adding dry THF (10 mL) and dry MeOH (10 mL). Then, $NaBH_4$ (66.2 mg, 1.75 mmol, 1.75 equiv) was added in portions. The conversion was followed by TLC. After the conversion was completed, the mixture was poured into the beaker containing 10 mL 10% HCl and stirred 1 h at room temperature. THF and MeOH were removed by rotary evaporation under reduced pressure and the remaining residue was mixed with distilled water (20 mL). The organic components were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was then purified by column chromatography to afford (±)-**7** (43.0 mg, 0.1 mmol, 10%), (±)-**8** (171 mg, 0.4 mmol, 40%) and (±)-**9** (152.0 mg, 0.4 mmol, 40%). (±)-**7:** TLC: R_f = 0.36 (silica gel; Hexanes/EtOAc, 8:2, v/v). FTIR(KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3516 (w), 2926 (w), 1777 (s), 1729 (s), 1596 (w), 1452 (s), 1369 (s), 1291 (w), 1174 (s), 1089 (s), 1023 (w), 965 (s), 927 (w), 813 (w), 746 (s), 667 (s), 583 (s), 537 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.25 – 7.18 (m, 3H), 5.22 (s, 1H), 4.21 (qd, J = 7.1, 1.2 Hz, 2H), 3.23 (d, J = 2.7 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.64 – 2.47 (m, 2H), 2.37 – 2.27 (m, 4H), 1.90 (qd, J = 12.7, 5.5 Hz, 1H), 1.77 (ddd, J = 12.9, 3.7, 2.1 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 125 MHz, $CDCl_3$) δ 173.05 (C), 144.84 (C), 136.73 (C), 136.33 (C), 135.75 (C), 129.89 (CH), 129.25 (C), 126.42 (CH), 125.22 (CH), 123.44 (CH), 120.56 (C), 119.21 (CH), 114.41 (CH), 63.02 (CH), 60.40 (CH_2), 37.39 (CH), 36.77 (CH_2), 22.81 (CH_2), 21.52 (CH_3), 21.30 (CH_2), 14.27 (CH_3). HPLC: Chiralcel OD-H; *n*-

hexane/^{i}PrOH (90:10), 1.0 mL/min; 254 nm (UV−vis); t_R = 9.9 min (5), t_R = 16.2 min (*ent*-5). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{25}NO_5SNa$, 450.1351; Found: 450.1347. (±)-**8:** Mp: 110–112 °C. TLC: R_f = 0.30 (silica gel; Hexanes/EtOAc, 8:2, v/v). FTIR(KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3545 (w), 2927 (s), 1730 (s), 1597 (w), 1452 (s), 1368 (s), 1284 (s), 1089 (s), 1025 (s), 813 (w), 754 (s), 669 (s), 584 (s), 546 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.31 (ddd, *J* = 8.4, 7.4, 1.3 Hz, 1H), 7.24 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.01 (d, *J* = 2.9 Hz, 1H), 4.23 – 4.09 (m, 2H), 3.68 (d, *J* = 2.2 Hz, 1H), 2.70 (dt, *J* = 17.0, 5.4 Hz, 1H), 2.64 – 2.52 (m, 2H), 2.46 (dd, *J* = 15.3, 6.5 Hz, 1H), 2.36 – 2.23 (m, 4H), 2.19 (dddd, *J* = 11.4, 8.6, 5.6, 3.2 Hz, 1H), 1.80 – 1.62 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, $CDCl_3$) δ 172.46 (C), 144.88 (C), 136.62 (C), 135.85 (C), 135.23 (C), 129.80 (CH), 129.47 (C), 126.45 (CH), 125.29 (CH), 123.69 (CH), 121.22 (C), 119.19 (CH), 114.75 (CH), 66.48 (CH), 60.46 (CH_2), 38.23 (CH), 36.15 (CH_2), 23.32 (CH_2), 21.52 (CH_3), 18.76 (CH_2), 14.24 (CH_3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{25}NO_5SNa$, 450.1351; Found: 450.1347. (±)-**9:** Mp: 199–200 °C. TLC: R_f = 0.18 (silica gel; Hexanes/EtOAc, 8:2, v/v). FTIR(KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436 (w), 3053 (w), 2947 (w), 2919 (s), 1920 (w), 1782 (s), 1598 (w), 1451 (s), 1381 (s), 1370 (s), 1291 (w), 1237 (s), 1179 (s), 1164 (s), 1152 (s9, 1087 (s), 1023 (w), 964 (s), 935 (s), 888 (w), 811 (w), 738 (s), 702 (w), 665 (s), 579 (s), 547 (w), 536 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.31 – 7.20 (m, 3H), 6.02 (d, *J* = 5.0 Hz, 1H), 2.94 (dd, *J* = 17.1, 7.5 Hz, 1H), 2.86 (ddd, *J* = 16.9, 5.1, 2.8 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.65 (ddd, *J* = 16.6, 11.3, 5.1 Hz, 1H), 2.43 (dd, *J* = 17.1, 1.4 Hz, 1H), 2.33 (s, 3H), 1.97 (ddd, *J* = 12.4, 7.4, 4.7 Hz, 1H), 1.72 (m, 1H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, $CDCl_3$) δ 175.69 (C), 144.90 (C), 136.41 (C), 135.50 (C), 129.79 (C), 129.65 (CH), 128.05 (C), 127.62 (CH), 126.15 (CH), 123.33 (CH), 123.30 (C), 119.51 (CH), 114.48 (CH), 72.39 (CH), 36.28 (CH_2), 35.57 (CH), 24.20 (CH_2), 21.55 (CH_3), 19.79 (CH_2). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (80:20), 1.0 mL/min; 254 nm (UV−vis); t_R = 14.5 min (7), t_R = 21.5 min (*ent*-7). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{19}NO_4SNa$, 404.0933; Found: 404.0961.

*2.2.3. Enantioselective synthesis of **7** and **9** via asymmetric transfer hydrogenation of (±)-**6***

Table 1, entries 1–3: An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (**3**, 12.60 mg, 0.02 mmol, 2 mol%) and ethyl 2-(1-oxo-9-tosyl-2,3,4,9-tetrahydro-*1H*-carbazol-2-yl)acetate ((±)-**6**, 425.5 mg, 1.00 mmol, 1.00 equiv). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry N_2. Then 2.4 mL of a freshly prepared HCO_2H/Et_3N(5:2) azeotropic mixture and 5 mL of dry THF were successively added into the reaction tube. After stirring the reaction mixture for the time and temperature specified in Table 1 under N_2, the reaction mixture was treated with 10% aqueous HCl (5 mL) for 30 min or it was directly subjected to rotary evaporation under reduced pressure. The residue was treated with water (20 mL) and extracted with DCM (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of residue by flash column chromatography on silica gel afforded the chiral alcohol **7** and the lactone **9**. The reaction conditions, quenching procedures of the reactions, yields, enantiomerical excesses, and optical rotation values of enantiomerically enriched compounds **7** and **9** are given in Table 1.

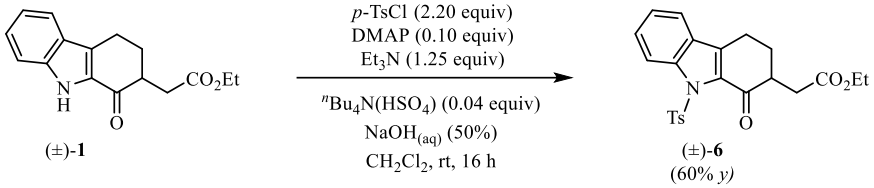
Table 1, entry 4: An oven-dried 25 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was charged with ethyl 2-(1-oxo-9-tosyl-2,3,4,9-tetrahydro-*1H*-carbazol-2-yl)acetate ((±)-**6**, 425.5 mg, 1.00 mmol, 1.00 equiv) and RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (**3**, 12.60 mg, 0.02 mmol, 2 mol%). The Schlenk tube was evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Solid particles were dissolved by the addition of 5 mL dry THF. Another oven-dried 10 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was charged with DABCO (673 mg, 6.0 mmol, 6.00 equiv). It was evacuated for 15 min, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Solid particles were dissolved by adding dry THF (5 mL). The tube was cooled down to 0 °C in an ice bath and HCO_2H (377 μL, 460 mg, 10.0 mmol, 10.00 equiv) was dropwise added into the tube. The resulting solution containing HCO_2H/DABCO (10:6) mixture was then stirred for 30 minutes while the temperature was

allowed to rise to room temperature. Then, it was transferred into the 25 mL Schlenk tube containing the catalyst and the substrate ((±)-**6**) by the cannula technique. The reaction mixture was then stirred at 35 °C for 6 days under N_2. The mixture was then poured into a beaker containing 10 mL of distilled water. The organic components were extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave the enantiomerically enriched compounds **7** in 48% yield and **9** in 24% yield as white solids.

3. Results and Discussion

3.1. Chemistry

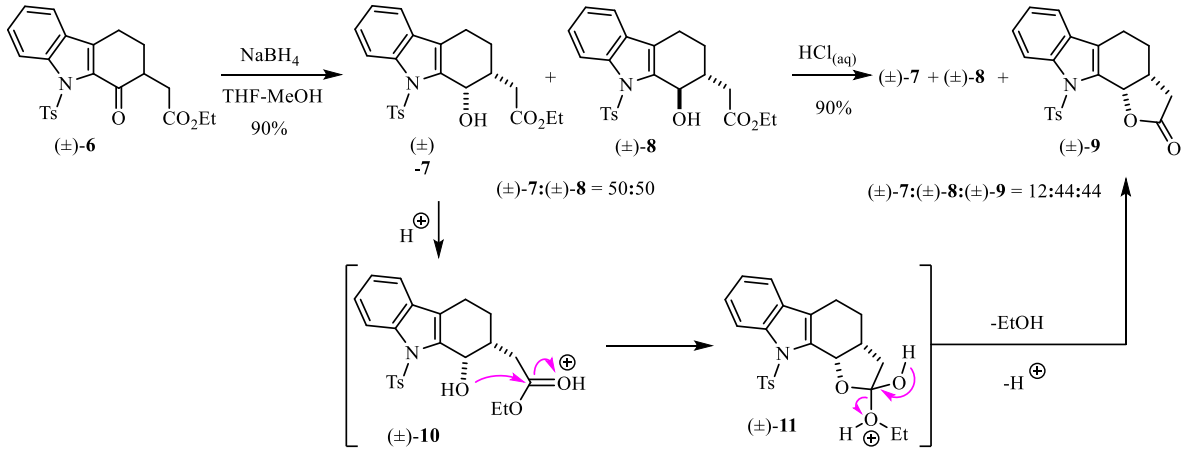
The racemic starting material ((±)-**1**) was first prepared by the procedure described in the literature.[16,17] Then, it was converted to (±)-**6** in 60% yield by the reaction of *p*-TsCl in the presence of $^{n}Bu_4N(HSO_4)$ in dichloromethane–aqueous NaOH medium (Scheme 2). Note that (±)-**6** is unknown in the literature.



Scheme 2. Preparation of *N*-tosyl-tetrahydrocarbazole-1-one ester (±)-**6**.

While reduction of (±)-**6** with $NaBH_4$ in MeOH/THF gave only the diastereomers (±)-**7** and (±)-**8** in 50:50 molar ratio, *in-situ* quenching of the reaction mixture with 18% HCl delivered a mixture consisting of (±)-**7**, (±)-**8** and (±)-**9**, in 12:44:44 molar ratio respectively (Scheme 3). Thus, the alcohols (±)-**7** and (±)-**8** could not be completely converted to the lactone (±)-**9**. This result, the decrease in proportion of (±)-**7** molar ratio from 50% to 12%, indicates that only the *cis*-alcohol (±)-**7** undergoes cyclization giving the lactone (±)-**9** and which recalls that a *Brønsted*-acid-catalyzed transesterification reaction takes place. Consequently, conversion of (±)-**7** to (±)-**9** through *Brønsted*-acid-catalyzed transesterification entails formation of the intermediates (±)-**10** and (±)-**11** (Scheme 3), a different mechanism from that proposed for the formation of **2** in Scheme 1. At this point, it should be mentioned once more that the *N*-unprotected derivative of (±)-**6** ((±)-**1**, Scheme 1) was converted to the corresponding lactone ((±)-**2**) completely in our previous report, when it was subjected to the reduction with $NaBH_4$ and quenching with aqueous HCl.[16] Accordingly, when the nitrogen atom of THC-1-one ester is substituted with tosyl group, which is an electron withdrawing group, 1-oxo or 1-hydroxycarbazoles exhibit entirely different chemical properties. (±)-**7**, (±)-**8** and (±)-**9** were separated from each other by flash column chromatography and characterized by spectroscopic techniques such as NMR, FTIR, HRMS. The enantiomeric separation of (±)-**7** and (±)-**9** were performed by HPLC using chiral column as well.

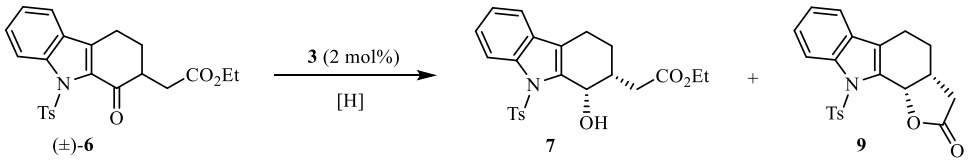
Asymmetric transfer hydrogenation with the Noyori-Ikariya catalyst



Scheme 3. Synthesis of (±)-**7**, (±)-**8**, and (±)-**9** through the reduction of (±)-**6** with $NaBH_4$.

Next, we investigated enantioselective reduction of (±)-**6** by Ru-ATH (Table 1). Upon the treatment of (±)-**6** with HCO_2H-Et_3N (5:2) in the presence of 2 mol% of the ruthenium complex (**3**) and HCO_2H-Et_3N (5:2) at 40 °C for 24 h, only the formation of **7** was observed in 25% yield and 96% *ee* (Table 1, entry 1). At this point, it should be stated that Ru-ATH of racemic cyclic ketones delivers only the *cis*-substituted (alcohol) product.[21–25] Extending the time from 1 day to 5 days increased the total yield from 25% to 46%, while causing the enantiomeric excess to decrease from 96% to 85% along with the concomitant formation of the lactone **9** (entry 2). Similarly, when the reaction time was increased from 1 day to 3 days and 10% HCl was used for quenching the reaction, the total yield increased from 25% to 45%; thus, **7** was isolated in 31% yield and 75% *ee* and **9** in 14% yield and 74% *ee* (entry 3). Enantiomeric excesses of compounds **7** and **9** were determined to be actually the same and it dropped as the reaction time and the temperature increased (entries 1–3). When the hydrogen source was switched from HCO_2H-Et_3N to HCO_2H-DABCO, the overall yield increased from 46 to 72%, whereas the enantiomeric excess decreased from 84% *ee* to 72% *ee* (entries 2 and 4).

Table 1. Asymmetric Transfer Hydrogenation of (±)-**6** with the Noyori-Ikariya Catalyst **3**[a]



Entry	[H][b]	Reaction Conditions	Quenching	Conversion	Yield (%)[d]	7:9[e]	7 *ee*[f] (%) [$[\alpha]_D^{27}$ (c = 0.5, $CHCl_3$)][g]	9 *ee*[f] (%) [$[\alpha]_D^{27}$ (c = 0.5, $CHCl_3$)][g]
1	HCO_2H/Et_3N (5/2)	THF 40 °C, 1 d	–	nfc[c]	25	25:0	96 [–138]	-
2	HCO_2H/Et_3N (5/2)	THF 35 °C, 5 d	–	nfc	46	36:10	84 [–120]	85 [–226]
3	HCO_2H/Et_3N (5/2)	THF 40 °C, 3 d	$HCl_{(aq)}$ (10%)	nfc	45	31:14	75 [–108]	74 [–197]
4	HCO_2H/DABCO (10 / 6)	THF 35 °C, 6 d	–	nfc	72	48:24	78 [–112]	57 [–152]

[a] Reaction conditions: (±)-**6** (1.0 mmol, 1.0 equiv), catalyst (**3**, 2 mol%), THF (5 mL), N_2, then 10% HCl (5 mL) for entry 1; (±)-**6** (1.0 mmol, 1.0 equiv), catalyst (**3**, 2 mol%), THF (10 mL), N_2, for entries 2, 3 and 4.
[b] Hydrogen source
[c] No full conversion
[d] Isolated yield
[e] The **7:9** ratio was determined gravimetrically after isolation of **7** and **9** by flash column chromatography.
[f] Determined by HPLC on a chiral column
[g] Value of optical rotation

4. Conclusion

In this study, enantioselective reduction of a new 1-oxotetrahydrocarbazole compound, *N*-tosyl-1-oxotetrahydrocarbazolyl-2-acetate ester ((±)-**6**), through asymmetric transfer hydrogenation by using the commercially available Noyori–Ikariya ruthenium catalyst have been investigated. The corresponding *cis*-alcohol **7** and the lactone **9** have been obtained in mediocre to good yields and enantioselectivities (24–72% yield, up to 96% *ee*). Both **7** and **9** could be separated from each other by column chromatography. The mechanism of the lactone formation seems to proceed through a *Brønsted*-acid-catalyzed transesterification as only the *cis*-alcohol product (±)-**7** undergoes to cyclization giving the corresponding lactone. We hope that the chemistry disclosed herein will be helpful to researchers involved in the enantioselective synthesis of chiral tetrahydrocarbazole analogues.

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Supporting Information

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ORCID
Ömer Dilek: 0000-0003-1409-782X
Erkan Ertürk: 0000-0001-5746-5683

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