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PAPER

Pd-Catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)-indoles†

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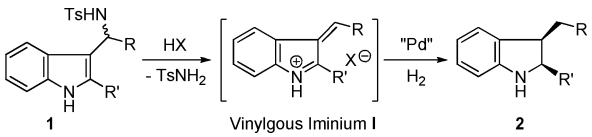
A series of 2-substituted 3-(toluenesulfonamidoalkyl)indoles was synthesized by application of $(EtO)_2POH$ or iodine as the catalyst, and was hydrogenated using chiral Pd catalyst, giving the 2,3-disubstituted indolines with up to 97% ee.

Introduction

Homogeneous catalytic asymmetric hydrogenation has emerged to be a powerful tool for constructing enantiomerically pure architectures, such as chiral alcohols and amines.[1] Due to the simple operation and convenient after-treatment, great progress has been made in asymmetric hydrogenation. However, the asymmetric hydrogenation of aromatic and heteroaromatic compounds is still a challenge because of their aromaticity as well as the severe conditions needed to overcome this stability.[2,3] To overcome these difficulties, some groups have devoted to searching for effective approaches to activate aromatic rings.[4,5] Recently, our group developed a novel strategy for highly enantioselective Pd-catalyzed hydrogenation of unprotected indoles with Brønsted acid as the activator.[6] Based on this strategy, we also documented the dehydration triggered asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles[7] and consecutive Brønsted acid/Pd-complex promoted tandem reactions of simple indoles and aldehydes for the rapid synthesis of chiral 2,3-disubstituted indoline derivatives.[8]

The 3-(toluenesulfonamidoalkyl)indole structural motif, **1**, is embedded in synthetic indole derivatives and numerous alkaloids.[9] Reaction of indole derivatives, **1**, with a Brønsted acid or a Lewis acid would produce an elimination of toluenesulfonamide ($TsNH_2$),[10] leading to vinylogous iminium intermediate, **I** (Scheme 1),[11] which was also involved in many other transformations.[12] Considering palladium complexes have been successfully applied to asymmetric hydrogenation of indoles,[6–8] we envisioned that 3-(toluenesulfonamidoalkyl)indoles **1** would be hydrogenated in the presence of Brønsted acid using chiral Pd catalyst, affording the chiral 2,3-disubstituted indolines. Herein, we report a series of 2-substituted 3-(toluenesulfonamidoalkyl)indoles that was synthesized and hydrogenated, giving the 2,3-disubstituted indolines with up to 97% ee.



Scheme 1 The process for Pd-catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)indoles **1**.

Results and discussions

Although indoles are known to undergo Friedel–Crafts reactions with *N*-tosyl imines under both Lewis acidic and Brønsted acidic conditions, affording 3-(toluenesulfonamidoalkyl)indoles,[10b,10g,13] the Friedel–Crafts reactions between 2-substituted indoles **3** and imines **4** are rarely reported.[14] When we followed the standard procedure of You's work,[13b] only the bisindole product was isolated with racemic phosphoric acid (*rac*-1,1′-binaphthalene-2,2′-diyl phosphoric acid) as the catalyst. Considering the relatively strong acidity of phosphoric acid, thereafter, we tried weaker acidity diethyl phosphonate $(EtO)_2POH$ as the catalyst. Gratifyingly, several substrates were synthesized with low to excellent yields.[15] In this process, at least 3.0 equivalents of 2-substituted indoles were needed, along with bisindole by-products, and the yields varied with the steric effect of *N*-tosyl imines (Table 1, entries 1, 3–6). In addition, for the aliphatic aldehyde derived *N*-tosyl imines, no desired product was obtained (Table 1, entries 2, 10 and 11). After screening several other catalysts, fortunately, molecular iodine (I_2) was found to be a good catalyst to promote this reaction.[16] Although the mechanism of the reaction catalyzed by I_2 was not clear, I_2 showed its robust action in this reaction. Both aliphatic and aromatic aldehyde derived imines reacted well with only 1.0 equivalent of 2-substituted indoles in 5 min to give 3-(toluenesulfonamidoalkyl)indoles **1** in moderate to good yields (Table 1, entries 2, 5, 6, 8, and 10–14). By comparison with diethyl phosphonate, I_2 displayed its generality in the synthesis of 3-(toluenesulfonamidoalkyl)indoles.

After accomplishing the synthesis of 3-(toluenesulfonamidoalkyl)indoles **1**, their asymmetric hydrogenation was also explored. Initially, 3-(toluenesulfonamidoalkyl)indole **1a** was chosen

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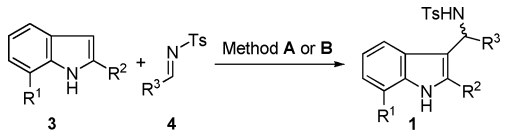
Table 1 The synthesis of 3-(toluenesulfonamidoalkyl)indoles **1**[a]



Method **A**: $(EtO)_2POH$, Toluene, 0 °C-rt, 12 h
Method **B**: I_2, CH_2Cl_2, 0 °C, 5 min

Entry	$R^1/R^2/R^3$	Method	Yield (%)[b]
1	H/Me/Ph	**A**	90 (**1a**)
2[c]	H/Me/Cy	**B**	50 (**1b**)
3	H/Me/4-FC_6H_4	**A**	64 (**1c**)
4	H/Me/4-MeC_6H_4	**A**	79 (**1d**)
5	H/Me/3-MeC_6H_4	**B (A)**	79 (15) (**1e**)
6	H/Me/2-MeC_6H_4	**B (A)**	82 (30) (**1f**)
7	H/n-Bu/Ph	**A**	85 (**1g**)
8	H/phenethyl/Ph	**B**	74 (**1h**)
9	Me/Me/Ph	**A**	99 (**1i**)
10[c]	Me/Me/Cy	**B**	54 (**1j**)
11[c]	Me/Me/*i*-Pr	**B**	47 (**1k**)
12	Me/Me/4-MeC_6H_4	**B (A)**	70 (25) (**1l**)
13	Me/Me/3-MeC_6H_4	**B (A)**	71 (29) (**1m**)
14	Me/Me/2-MeC_6H_4	**B**	71 (**1n**)

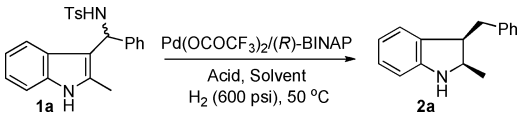
[a] Reaction conditions: Method **A**: **3** (3 equiv.), **4** (0.25 mol L^{-1}) in toluene, $(EtO)_2POH$ (10 mol%), 12 h, 0 °C–rt; Method **B**: **3** (1 equiv.), **4** (0.25 mol L^{-1}) in CH_2Cl_2, I_2 (10 mol%), 5 min, 0 °C. [b] Isolated yields. [c] No desired product was isolated by method **A**.

as the model substrate, and $Pd(OCOCF_3)_2$/(*R*)-BINAP/$TsOH{\cdot}H_2O$ were used to begin conditions screening. No desired product was observed when the reaction was performed in toluene and THF (Table 2, entries 1 and 2). To our delight, moderate to good enantioselectivities and conversions were obtained in TFE and DCM (Table 2, entries 3 and 4). Full conversions and good to excellent ee values were achieved when the mixed solvent was applied and DCM/TFE (1/1) delivered the best result with 85% ee (Table 2, entries 5–7). However, other Brønsted acids did not improve the enantioselectivity (Table 2, entries 8–12). Next, the effect of some bisphosphine ligands on the reactivity and enantioselectivity was explored, and (*R*)-H8-BINAP **L3** was found to be the best one (Table 2, entries 13–15). Therefore, the optimal conditions were established as the following: $Pd(OCOCF_3)_2$/(*R*)-H8-BINAP/$TsOH{\cdot}H_2O$/DCM-TFE(1 : 1)/H_2 (600 psi)/50 °C.

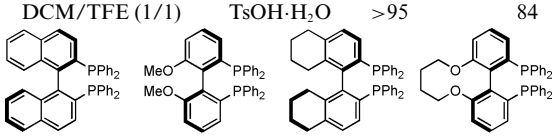
With optimized conditions in hand, the reaction scope was examined, and the results are summarized in Table 3. Excellent yields and enantioselectivities were obtained with 3-(toluenesulfonamidoalkyl)indoles **1** bearing various substituted patterns. The electronic character of R^3 had little impact on reactivities and enantioselectivities (Table 3, entries 3 and 4). In general, when R^3 were alkyl groups, slightly higher enantioselectivities were obtained than R^3 as aromatic groups (Table 3, entries 2, 10 and 11). For 2-butyl and 2-phenethyl substituted 3-(toluenesulfonamidomethyl)indoles, 92% and 91% ee were achieved, respectively (Table 3, entries 7 and 8). Notably, excellent ee values were obtained with substrates bearing a methyl group at the 7-position of the indole motif (Table 3, entries 9–14), which might be ascribed to steric hindrance.

Inspired by the previous work,[8] we also attempted the tandem reaction (Friedel–Crafts/asymmetric hydrogenation) of indoles **3** and *N*-tosyl imines **4**. First, Friedel–Crafts reaction products **1** formed in the presence of Brønsted acid. Then, $TsNH_2$ dropped out to give the intermediate vinylogous iminium **I**. Finally, an asymmetric hydrogenation process was used to give the products.

Table 2 Optimization of the asymmetric hydrogenation of **1a**[a]

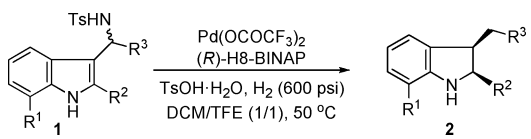


Entry	Solvent	Acid	Conv. (%)[b]	ee (%)[c]
1	Toluene	$TsOH{\cdot}H_2O$	—[d]	—
2	THF	$TsOH{\cdot}H_2O$	—[d]	—
3	TFE	$TsOH{\cdot}H_2O$	79	71
4	DCM	$TsOH{\cdot}H_2O$	92	66
5	DCM/TFE (1/2)	$TsOH{\cdot}H_2O$	>95	83
6	DCM/TFE (1/1)	$TsOH{\cdot}H_2O$	>95	85
7	DCM/TFE (2/1)	$TsOH{\cdot}H_2O$	>95	80
8	DCM/TFE (1/1)	CF_3SO_3H	76	74
9	DCM/TFE (1/1)	TFA	78	41
10	DCM/TFE(1/1)	$PhCO_2H$	—[d]	—
11	DCM/TFE (1/1)	L-CSA	>95	81
12	DCM/TFE (1/1)	D-CSA	>95	76
13[e]	DCM/TFE (1/1)	$TsOH{\cdot}H_2O$	>95	81
14[f]	DCM/TFE (1/1)	$TsOH{\cdot}H_2O$	>95	87
15[g]	DCM/TFE (1/1)	$TsOH{\cdot}H_2O$	>95	84



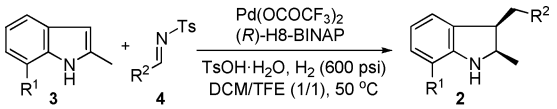
[a] Reaction conditions: $Pd(OCOCF_3)_2$ (2 mol%), **L1** (2.4 mol%), **1a** (0.25 mmol), H_2 (600 psi), acid (0.25 mmol), solvent (3 mL), 50 °C, 16–20 h. [b] Determined by ^1H NMR. [c] Determined by HPLC analysis. [d] 2-Methyl-3-benzylindole was obtained. [e] Ligand **L2** was used. [f] Ligand **L3** was used. [g] Ligand **L4** was used.

Table 3 Pd-Catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)indoles **1**[a]



Entry	**1** ($R^1/R^2/R^3$)	Yield[b]	ee (%)[c]
1	**1a** (H/Me/Ph)	89 (**2a**)	87
2	**1b** (H/Me/Cy)	97 (**2b**)	92
3	**1c** (H/Me/4-FC_6H_4)	81 (**2c**)	86
4	**1d** (H/Me/4-MeC_6H_4)	84 (**2d**)	84
5	**1e** (H/Me/3-MeC_6H_4)	97 (**2e**)	87
6	**1f** (H/Me/2-MeC_6H_4)	93 (**2f**)	89
7	**1g** (H/n-Bu/Ph)	97 (**2g**)	92
8	**1h** (H/phenethyl/Ph)	95 (**2h**)	91
9	**1i** (Me/Me/Ph)	94 (**2i**)	95
10	**1j** (Me/Me/Cy)	90 (**2j**)	97
11	**1k** (Me/Me/*i*-Pr)	88 (**2k**)	94
12	**1l** (Me/Me/4-MeC_6H_4)	87 (**2l**)	94
13	**1m** (Me/Me/3-MeC_6H_4)	97 (**2m**)	94
14	**1n** (Me/Me/2-MeC_6H_4)	97 (**2n**)	94

[a] Reaction conditions: $Pd(OCOCF_3)_2$ (2 mol%), (*R*)-H8-BINAP (2.4 mol%), **1** (0.25 mmol), H_2 (600 psi), DCM/TFE = 1 : 1 (3 mL), $TsOH{\cdot}H_2O$ (0.25 mmol), 50 °C, 16–20 h. [b] Isolated yields. [c] Determined by HPLC.



Entry	R^1 of **3**	R^2 of **4**	Ee (%)	Yield (%)
1	H	Ph	90	89 (**2a**)
2	H	Cy	93	93 (**2b**)
3	Me	4-MeC_6H_4	95	82 (**2l**)

Scheme 2 Tandem reactions of indoles **3** and *N*-tosyl imines **4**.

Gratifyingly, the reaction proceeded smoothly without losing the enantioselectivity (Scheme 2).

Conclusions

In summary, we have synthesized a series of 2-substituted 3-(toluenesulfonamidoalkyl)indoles **1** by using $(EtO)_2POH$ or iodine as the catalyst, and their asymmetric hydrogenation reactions were also explored using the chiral palladium catalyst in the presence of Brønsted acid, giving the chiral 2,3-disubstituted indolines with up to 97% ee. In addition, the tandem reactions of 2-substituted indoles and *N*-tosyl imines under the standard reaction conditions can also perform well with similar ee values. The readily accessible starting materials, high enantioselectivity and high yields make this method very useful for the synthesis of chiral 2,3-disubstituted indolines.

Experimental section

General procedure for the synthesis of 3-(toluenesulfonamidoalkyl)indoles 1

3-(Toluenesulfonamidoalkyl)indoles **1a–n** were synthesized from the corresponding 2-substituted indoles and *N*-tosyl imines according to either method **A** or **B**.

Method **A**: In a dry Schlenk tube, *N*-tosyl imines **4** (1 mmol) and $(EtO)_2POH$ (0.1 mmol) were dissolved in toluene (4 mL) under nitrogen. The solution was stirred for 10 min at room temperature and then for another 5 min at 0 °C. Subsequently, 2-substituted indoles **3** (3 mmol) were added in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature naturally. After the reaction was complete (monitored by TLC), 10% $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine (10 mL), separated, and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1/5) to afford the product.

Method **B**: In a dry Schlenk tube, 2-substituted indoles **3** (1 mmol) and I_2 (10 mol%) were dissolved in 4 mL dry CH_2Cl_2. Then the resulting mixture was stirred at 0 °C for 2 min before *N*-tosyl imines **4** (1 mmol) was added. Finally, a saturated solution of sodium subsulfite was not added to quench the reaction until the starting materials were consumed as indicated by TLC (about 5 min). The mixture was extracted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (10 mL), separated, and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1/5) to afford the product.

N-(Cyclohexyl(2-methyl-1*H*-indol-3-yl)methyl)-4-methyl-benzenesulfonamide (**1b**). White solid, m.p. 94–95 °C; ^{1}H NMR (400 MHz, d^6-acetone) δ 9.61 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.82 (dd, J = 18.3, 7.6 Hz, 4H), 6.53 (d, J = 8.3 Hz, 1H), 4.29 (t, J = 9.2 Hz, 1H), 2.34–2.25 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H), 2.08–1.97 (m, 1H), 1.76 (dd, J = 9.2, 4.8 Hz, 1H), 1.56 (dd, J = 19.4, 11.5 Hz, 2H), 1.42–0.95 (m, 6H), 0.87–0.77 (m, 1H). ^{13}C NMR (100 MHz, d^6-acetone) δ 142.03, 136.75, 133.63, 128.83, 127.24, 126.80, 120.95, 119.64, 119.17, 111.04, 110.71, 57.46, 42.54, 31.85, 30.93, 27.11, 26.81, 26.66, 21.24, 11.79. HRMS calculated for $C_{24}H_{30}N_2O_2NaS$ $[M+Na]^+$ 419.1769, found 419.1769; IR (KBr) ν 3386, 2924, 2857, 1307, 1156, 670 cm^{-1}.

General procedure for Pd-catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)indoles

(*R*)-H8-BINAP (3.8 mg, 0.006 mmol) and $Pd(OCOCF_3)_2$ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone 1 mL was added. The mixture was stirred at room temperature for 1 h, and then solvent was removed under vacuum to give the catalyst. In a glovebox, $TsOH·H_2O$ (0.25 mmol) and substrate **1** (0.25 mmol) were stirred in 1 mL solvent (DCM and TFE were mixed in ratio of 1 : 1 prior to use) at room temperature for 5 min. Subsequently, the above catalyst together with 2 mL solvent was added to the reaction mixture. The hydrogenation was performed at 50 °C under H_2 (600 psi) in a stainless steel autoclave for 16–20 h. After carefully releasing the hydrogen, the resulting mixture was concentrated under vacuum and dissolved in saturated aqueous $NaHCO_3$ (5 mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and dried over Na_2SO_4. After purification by silica gel chromatography using petroleum ether/EtOAc (10/1) as eluent, the enantiomeric excess of the products were determined by HPLC with chiral columns (OJ-H, OD-H or AD-H).

(2*R*,3*R*)-(−)-2-Methyl-3-benzylindoline (**2a**). 89% yield, 87% ee, $[\alpha]_D^{27}$ −68.0 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, J = 6.5 Hz, 3H), 2.87 (dd, J = 13.8, 8.9 Hz, 1H), 2.97 (dd, J = 13.9, 7.2 Hz, 1H), 3.53 (dd, J = 15.9, 7.8 Hz, 1H), 3.71 (br s, 1H), 3.96–4.03 (m, 1H), 6.54–6.65 (m, 3H), 7.00 (t, J = 7.4, 1H), 7.17–7.31 (m, 5H); HPLC (OJ-H, elute: hexanes/*i*-PrOH = 80/20, detector: 254 nm, flow rate: 1.0 mL min^{-1}), t_1 = 10.4 min, t_2 = 11.6 min (maj.).

General procedure for Pd-catalyzed tandem reactions of 2-substituted indoles and *N*-tosyl imines

(*R*)-H8-BINAP (3.8 mg, 0.006 mmol) and $Pd(OCOCF_3)_2$ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at rt for 1 h, then the solvent was removed under vacuum to give the catalyst. In a glovebox, acid (0.25 mmol) and indole (0.25 mmol) were stirred in 1 mL DCM/TFE at room temperature for 1 min. Subsequently, *N*-tosyl imine (0.25 mmol) was added to the solution. Finally, the above catalyst together with 2 mL DCM/TFE was added to the reaction mixture. The hydrogenation was performed at 50 °C under H_2 (600 psi) in a stainless steel autoclave for 16 h. After carefully releasing the

hydrogen, the resulting mixture was concentrated under vacuum and dissolved in saturated aqueous $NaHCO_3$ (5 mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and dried over Na_2SO_4. After purification by silica gel chromatography using petroleum ether/EtOAc (10/1) as eluent, the enantiomeric excess of the products were determined by HPLC with chiral column.

Acknowledgements

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