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Highly enantioselective synthesis of chiral 3,4-dihydro-2*H*-pyran-5-carbonitrile via tandem Michael addition/asymmetric transfer hydrogenation/cyclization reactions catalyzed by a bifunctional Noyori-Ikariya type catalyst

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ABSTRACT

Tandem catalytic reaction in one-pot possesses remarkable advantages and is a powerful methodology for the synthesis of high value chemicals. Asymmetric transfer hydrogenation catalyzed by Ru-TsDPEN type catalysts, developed Noyori and Ikariya, is a useful strategy for constructing chiral alcohols and amines. Herein, a novel bifunctional Noyori-Ikariya type catalyst was developed, which displays good catalytic efficiency for Michael addition/ATH/cyclization tandem reaction. A series of chiral 3,4-dihydro-2*H*-pyran-5-carbonitriles were synthesized in good yield (up to 79%) and with excellent enantioselectivity (up to 97%) via this one-pot reaction under mild conditions.

1. Introduction

Tandem catalytic reactions refer to the synthetic strategies of sequential catalytic reaction without purification of intermediates, which could complete in one-pot with simple operation and minimum workup [1–3]. This enables to greatly reduce the operation of purification and the generation of waste and save time, energy and labor [4,5]. Since its remarkable advantages, tandem catalytic reactions have been attracted much attention and well developed in the past few decades [6–15].

Asymmetric catalysis is a powerful and common synthetic strategy for the synthesis of optical pure compounds, and it has been also well developed in the past few years [16–20]. Among these methods, asymmetric transfer hydrogenation (ATH) is a useful strategy to reduce prochiral ketones and imines providing enantioselective alcohol and amines [21–25]. Noyori, Ikariya and the coworkers developed an efficient chiral catalyst, Ru-TsDPEN (*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamin), which displayed excellent catalytic efficiency for the asymmetric reduction of ketones [26,27]. Because of its simple operation, mild reaction conditions, high yield and enantioselectivity, Noyori-Ikariya type catalyst gained much attention and developed rapidly with different metals (Ru, Rh and Ir) and modified ligands [28–31].

Since both strategies of tandem reaction and asymmetric transfer hydrogenation have admired advantages, ATH-based tandem reactions are becoming a research hotspot [32–38]. Using Noyori-Ikariya type catalyst, Lin and colleagues synthesized 3-substituted phthalides through ATH/cyclization reactions.[12] Gong group prepared a serial of optical amines via hydroamination/ATH under relay catalysis of gold complex and chiral Brønsted acid binary addition/ATH tandem process for the synthesis of chiral γ-secondary amino alcohols [32]. As the synthetic and biological importance of 3,4-dihydro-2*H*-pyran-5-carbonitrile, we reported a process for the access to chiral 3,4-dihydro-2*H*-pyran-5-carbonitrile via ATH/cyclization (as shown in Scheme 1a) [35]. We also tried to proceed this reaction through Michael addition/ATH/Cyclization with the starting materials of unsaturated ketone and malononitrile. Unfortunately, very bad conversion was observed. Wang and coworkers realized a similar Michael reaction with unsaturated ketone and malononitrile and cyclization tandem reaction using chiral organic base as a catalyst (Scheme 1b) [39]. However, this process needs a very long reaction time. Herein, we prepared a bifunctional chiral catalyst by combining an organic base and Noyori-Ikariya type catalyst. This catalyst showed good catalytic efficiency for the synthesis of chiral 3,4-dihydro-2*H*-pyran-5-carbonitrile via a Michael addition/ATH/cyclization tandem reaction.

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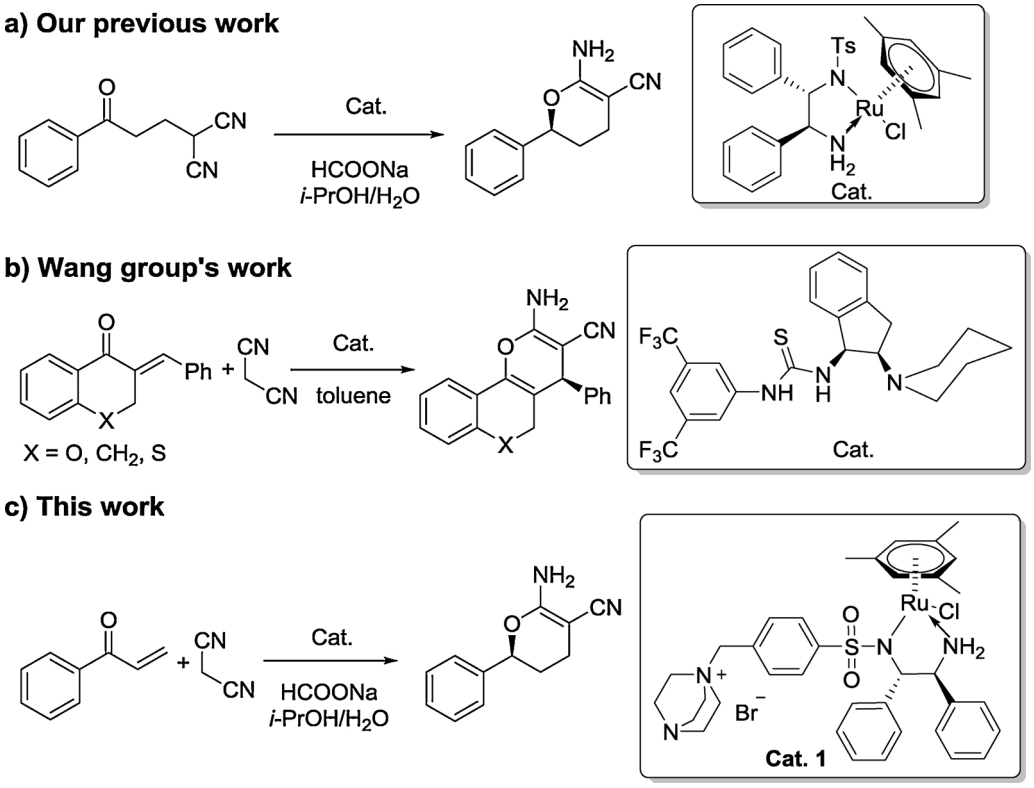

Scheme 1. Tandem catalytic reactions for the synthesis of chiral pyrancarbonitrile analogues.

2. Experimental

2.1. Chemicals and instruments

Compounds **4** was synthesized according to the reported literatures [40]. All other chemicals and solvents were of analytic grade and used as received except as specified. NMR spectra were measured on a Bruker DRX-400 spectrometer. HRMS data were recorded on a GC–TOF instrument using the EI technique. Analytical HPLC was carried out with a Waters® Chromatography setup consisting of: Waters® 717plus Autosampler, Waters® 1525 Binary HPLC Pump, and Waters® 2478 Dual λ Absorbance Detector. The enantiomeric excesses (*ee*) were determined using a Daicel Chiralpak® column AD-H or Daicel Chiralcel® column OJ-H with the above HPLC setup.

2.2. The synthesis of 3

To a solution of (*S,S*)-1,2-diphenylethane-1,2-diamine (424 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in CH_2Cl_2 (10 mL), 4-(bromomethyl)phenylsulfonyl chloride **1** (525 mg, 1.96 mmol) in dichloromethane (10 mL) were added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h. After removal of solvents under reduced pressure, the residue was purified by silica gel column chromatography. The product **3** was obtained as white solid (0.45 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 2H), 7.27–6.98 (m, 12H), 4.50 (s, 2H), 4.45 (d, J = 5.1 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.0, 136.9, 129.0, 128.6, 128.3, 128.2, 127.7, 127.5, 127.5, 127.4, 63.0, 60.0, 31.7. HRMS (ESI): *m/z* calculated for $C_{21}H_{21}N_2O_2SBr$ $[M + H]^+$: 445.0580; found: 445.0583.

2.3. The synthesis of 2

A mixture of 1, 4-diazabicyclo[2.2.2]octane (DABCO, 69 mg, 0.7 mmol), sulfonamide **3** (222 mL, 0.5 mmol), and AcOEt (10 mL) was stirred at room temperature for 5 h. The ligand **2** were obtained by filtration as white solid (0.45 g, 95%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.16–7.03 (m, 7H), 6.96–6.86 (m, 3H), 6.85–6.77 (m, 2H), 4.47 (d, J = 9.0 Hz, 1H), 4.43 (s, 2H), 4.01 (d, J = 9.0 Hz, 1H), 3.29–3.21 (m, 6H), 3.21–3.10 (m, 6H). ^{13}C NMR (100 MHz, Methanol-d_4) δ 133.3, 130.2, 127.9, 127.5, 127.4, 127.3, 127.2, 126.5, 66.4, 65.1, 60.8, 52.2, 45.4, 44.7. HRMS (ESI): *m/z* calculated for $C_{27}H_{33}BrN_4O_2S$ $[M\text{-}Br]^+$: 477.2319; found: 477.2333.

2.4. The synthesis of catalyst 1

$[RuCl_2(Mesitylene)]_2$ (0.5 mmol) and ligand **2** (1 mmol) were dissolved in MeOH (7 mL), and the mixture was stirred for 5 h at room temperature. Then, the solvent was removed under reduced pressure, providing catalyst **1** as a red solid, which was directly used for the catalysis.

2.5. General procedure for synthesis of chiral 3,4-dihydro-2H-pyran-5-carbonitriles [35]

The catalyst **1** (1.6 mg, 2 μmol), **4** (0.10 mmol), malononitrile (7.9 mg, 0.12 mmol), HCOONa (68.0 mg, 1.0 mmol), and *i*-PrOH/H_2O (4 mL, v/v = 3/1) were added in a 10 mL round bottom flask in turn. The mixture was stirred at 60 °C for 3–7 h. The reaction was monitored constantly by TLC. After completion of the reaction, the solvent was removed by evaporation. Water (2 mL) was added to the residue, and then the mixture was extracted by ethyl acetate (3.0 mL × 3). The combined ethyl acetate was washed with brine and dehydrated with Na_2SO_4. After the evaporation of ethyl acetate, the residue was purified by silica gel flash column chromatography to afford the desired product. The *ee* value was determined by a Daicel Chiralcel AD–H or OJ–H column.

5a: (*S*)-6-amino-2-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitrile. White solid, yield 72%, 97% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5H), 5.02 (dd, J = 10.4, 2.4 Hz, 1H), 4.40 (br, 2H), 2.54–2.39 (m,