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AN IMPROVED SYNTHESIS OF C_2 SYMMETRIC CHIRAL BIPYRIDINE-PINENE LIGANDS

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ABSTRACT
This communication depicts a short and improved synthesis of Pinene-based C_2-symmetric chiral bipyridine ligands. These ligands are very suitable catalysts for high enantioselectivity towards various asymmetric reactions. Synthesis of the chiral ligand (15) was achieved in only five steps with improved yield as compared to the earlier synthesis, which involves a total of eleven steps with lower yield. The novel synthetic route will endorse the large-scale synthesis of the ligand and, in turn, will help explore more asymmetric reactions in modern synthetic and pharmaceutical chemistry.
Keywords: Synthesis, Pinene, Bipyridine, Chiral, Ligand, Catalyst, Enantioselective
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INTRODUCTION

Pinene-based chiral pyridine ligands are very important precursors for the development of asymmetric reactions in modern synthetic and pharmaceutical chemistry.[1-5] Chen[6] *et al.* have developed a innovative C_2-symmetric ligand (10) containing a central bipyridine-pinene derived core and two functionalized diphenylmethanol subunits, i.e. Salen-TADDOL-like ligand.[7,8] The ligand (10) forms a strong complex with Ti-metal and showed very promising enantioselectivity for various asymmetric reactions like alkylation of substituted benzaldehyde using diethylzinc[9], trimethylsilylcyanation of various benzaldehyde[10], ring-opening reaction of meso-epoxides with ArSH[11] and Strecker-type reaction of phosphinoyl ketimines.[12] Herein, we have developed an improved synthetic route for the synthesis of a similar ligand (15) useful for the medicinal chemistry.

EXPERIMENITAL

Materials and Methods

TLC (Thin Layer Chromatography) analysis was carried out on silica gel 60 F254 precoated glass sheets and detected under UV light. ^{1}H, ^{13}C NMR (Nuclear Magnetic Resonance) and ^{19}F spectra were recorded on Bruker AVANCE DPE-400 and chemical shifts (δ) are in ppm relative to $CDCl_3$ (7.26 ppm or 77 ppm) as internal standard. High resolution mass spectra (HR-MS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Specific Optical Rotation (SOR) was measured on a JASCO P-1010 polarimeter at the indicated temperature with a sodium lamp (D line, 589 nm). All chemicals and solvents were purchased either from Aldrich Chemical Co., Fisher Scientific, or Lancaster. Analytical data of all known compounds were in agreement with the literature value; for all new compounds, analytical data are summarized along with their synthesis procedure in the laboratory.

Experimental Procedure

Compound 14a

To a stirred solution of 5 ml of dry tetrahydrofuran (THF) and dry N, N-Diisopropylethylamine (DIPEA) (1.46 g, 0.014 mol) at -5 °C was added n-Butyl lithium (n-BuLi) (9.0 ml, 0.014 mol, 1.6*M* in hexane) over 5 min under Argon atm. The Lithium diisopropylamide (LDA) was generated after 1h of stirring at 0 °C. The flask was cooled to -40 °C, and Chloro compound (13) (2.0g, 0.009 mol) in 10 ml dry THF was

added dropwise over 10 min. The cooling bath was switched off and allowed the temp to rise to -10 °C (~2.5 h required). The reaction mass was cooled back to -78 °C, and to this, Benzophenone (2.52 g, 0.011 mol) (predried over Phosphorus pentoxide [P_2O_5] in desiccator) in 20 ml of dry THF was added dropwise over 15 min. Reaction mass was further stirred for 3h at the same temp. and then turn off the cooling bath for overnight. Silica gel thin layer chromatography (TLC) and workup in the usual manner, followed by silica gel column chromatography, gave compound (14_a) (2.63 g, 70%).

^{1}H-NMR ($CDCl_3$, δ): -0.142 to -0.116 (*d*, 1H, *J* =10.3 Hz), 0.85 (*s*, 3H), 1.38 (*s*, 3H), 2.05-2.09 (*m*, 1H), 2.52-2.59 (*m*, 2H), 4.35 (*s*, 1H), 7.06-7.13 (*m*, 7H), 7.31-7.37 (*m*, 5H), 8.77 (*s*, 1H, OH).

^{13}C-NMR ($CDCl_3$, δ): 21.12, 26.27, 28.88, 41.40, 42.88, 45.33, 48.44, 81.77, 121.46, 126.56, 127.06, 127.17, 127.97, 128.10, 128.39, 136.33, 142.54, 145.36, 145.78, 146.33, 158.17. SOR $[\alpha]^{24}$ = - 333.0 ° (*c* 0.5, Dichloromethane [DCM]).

Compound 14b

To a stirring solution of 5 ml of dry THF and DIPEA (1.46 g, 0.014 mol) at -5 °C was added *n*-BuLi (9.0 ml, 0.014 mol, 1.6 M in hexane) over 5 min in a 100 ml round-bottom flask (RBF). under Argon atm. The LDA was generated after 1h of stirring at 0 °C. The round-bottom flask was cooled to -40 °C, and Chloro compound (13) (2.0 g, 0.009 mol) in 10 ml dry THF was added dropwise over 10 min. The cooling bath was switched off and allowed the temperature to rise to -10 °C (~2.5 h required). The reaction mass was cooled back to -78 °C, and to this bis(4-fluorophenyl)methanone (2.52 g, 0.011 mol) (predried over P_2O_5 in desiccators for 12h) in 20 ml of dry THF was added dropwise over 15 min. The reaction mass was for further stirred for 3h at the same temperature, and then the cooling bath was turned off overnight. Checked TLC and workup in usual manner, followed by silica gel column chromatography, gave the required compound (14_b) (2.95g, 72%).

^{1}H-NMR ($CDCl_3$, δ): -0.059 to -0.033 (d, 1H, *J* =10.3 Hz), 0.84 (*s*, 3H), 1.38 (*s*, 3H), 2.09- 2.15 (*m*, 1H), 2.49-2.57 (*m*, 2H), 4.28 (*s*, 1H), 6.82-6.87 (*m*, 2H), 7.03-7.10 (*m*, 5H), 7.16-7.18 (*d*, 1H, *J* =6 Hz), 7.30-7.34 (*m*, 2H), 8.75 (*s*, 1H, OH).

^{13}C-NMR ($CDCl_3$, δ): 21.14, 26.34, 29.05, 41.37, 42.89, 45.90, 48.15, 81.17, 113.66, 113.86, 114.78, 114.99, 121.39, 129.66, 129.74, 129.95, 130.03, 133.88, 141.52, 142.48, 143.69, 144.15, 157.27, 160.52, 162.99.

^{19}F-NMR: -115.357 (1F) and -116.3027 (1F).

HR-MS (FAB+) (M.F. $C_{25}H_{22}ClF_2NO$), Exact mass: 425.1358, Observed m/z: 426.4772.

SOR, $[\alpha]^{24}$ = - 308.0 ° (*c* 0.5, DCM).

Ligand 15

To a mixture of Zinc powder (0.80 g, 0.012 mol), $NiCl_2.6H_2O$ (6.15 g, 0.009 mol), and Triphenyl phosphine (PPh_3) (5.90 g, 0.023 mol), degassed Dimethylformamide (DMF) (25 ml) was added using a syringe pump under Argon atm. The mixture was heated at 60°C for 2 h, during which period the colour changed from blue to red (Ni^0). Then a solution of compound (14_b) (2.00 g, 0.005 mol) in degassed DMF (10 ml) was added dropwise. The reaction mass was heated for a further 22-24 h (Checked TLC) and then poured into 10% aqueous ammonia (100 ml) solution. The resulting suspension was extracted with DCM (4×75 ml), the combined organic layers were washed with brine (20 ml), dried over anhydrous magnesium sulfate, and evaporated in vacuum to give a crude mass. Followed by silica gel (pretreated with 0.5% Triethylamine in n-Hexane) column chromatography, gave Ligand (15) (2.20 g, 41%).

^{1}H-NMR ($CDCl_3$, δ): 0.094-0.119 (*d*, 2H, *J*=10.2 Hz), 0.87 (*s*, 3H), 1.41 (*s*, 3H), 2.14-2.2 (*m*, 2H), 2.51-2.54 (*m*, 2H), 2.63-2.66 (*m*, 2H), 4.40 (s, 2H), 6.84-6.88 (*m*, 4H), 7.07-7.12 (*m*, 8H), 7.31-7.33 (*d*, 2H, *J*=6 Hz), 7.39-7.42 (*m*, 4H), 7.94-7.96 (*d*, 2H, *J*=6 Hz), 9.58 (*s*, 2H, OH).

^{13}C-NMR ($CDCl_3$, δ): 21.21, 26.33, 28.91, 41.65, 42.88, 45.74, 48.24, 81.21, 114.05, 114.25, 114.94, 115.15, 118.36, 129.41, 129.49, 129.55 129.63, 135.32, 141.37, 144.34, 150.58, 156.64, 160.57, 163.02.

HR-MS (FAB+) (M.F. $C_{50}H_{44}F_4N_2O_2$), Exact mass: 780.3339, Observed m/z: 780.3338.

SOR, $[\alpha]^{24}$ = - 468.0 ° (*c* 0.5, DCM).

Compound 16_b

It was isolated by silica gel column chromatography (0.25 g, 15%) during the isolation of Ligand-15.

^{1}H-NMR ($CDCl_3$, δ): -0.119 to -0.094 (d, 1H, *J* =10.2 Hz), 0.84 (*s*, 3H), 1.39 (*s*, 3H), 2.05- 2.12 (*m*, 1H), 2.53-2.54 (*d*, 2H, *J* =7.8 Hz), 4.30 (*s*, 1H), 6.78-6.83 (*m*, 2H), 7.03-7.08 (*m*, 5H),7.18-7.21 (*m*, 1H), 7.33-7.36 (*m*, 2H), 8.35-8.37 (*dd*, 1H, *J* =1.64 Hz each), 9.97 (*s*, 1H).

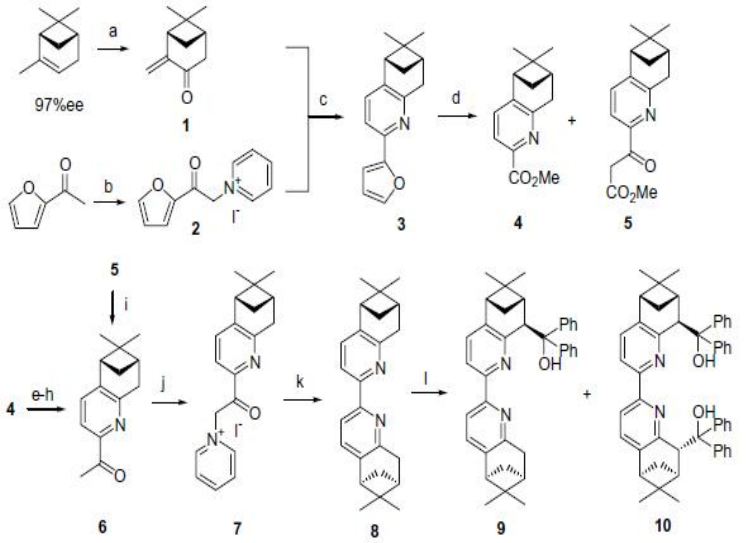
^{19}F-NMR: -115.694 (1F) and -116.782 (1F).

HR-MS (FAB+) (M.F. $C_{25}H_{23}F_2NO$), Exact mass: 391.1748, Observed m/z: 392.4548.

SOR, $[\alpha]^{24}$ = - 239.2 ° (*c* 0.5, DCM).

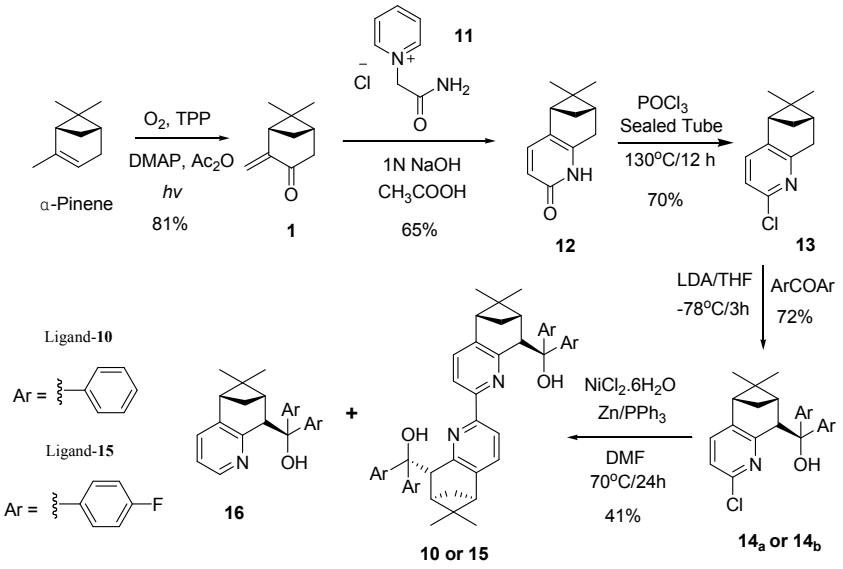
RESULTS AND DISCUSSION

Scheme-I shows the synthesis of ligand (10) from commercially available α-pinene through 11 steps, including the last step, which yields only 8% of the required ligand (10) and unrequired compound (9) with 82% yield.[6] The compound (9) was converted to ligand (10) by treatment with LDA followed by electrophile benzophenone (ArCOAr), again with poor yield. Since the ligand (10) was required in >10 mol% scale, it was necessary to overcome the hurdles involved in the large-scale synthesis of ligand (10), which in turn will reduce the cost of the synthesis of ligand as well as the time involved in the scale-up project. From the literature search, it was revealed that bipyridyl ligands are generally synthesized by using Nickel (Ni) catalyzed homo coupling reaction.[13] The compound 8 can be synthesized by following the literature process[14]; however, if the last step (conversion of 8 to 10) ends up with only 8% yield, then it will not benefit cost reduction in the scale-up process. Hence, we planned to do the LDA reaction before the homo coupling step. Scheme-II describes a short and improved synthetic route for the synthesis of Ligand (15), useful for the medicinal chemistry.



Scheme 1. Reagents and conditions: (a) O_2, TPP, DMAP, Ac_2O, pyridine, CH_2Cl_2, Na-lamp (400 W), 50%; (b) I_2, pyridine, 100-110 °C, 56%; (c) NH_4OAc, AcOH, 100–110 °C, 84%; (d) O_3, CH_2Cl_2–CH_3OH (2:1), −78 °C; CH_2N_2, Et_2O, 0 °C, **4** (42%), **5** (21%); (e) $LiAlH_4$, THF, rt, 72%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 91%; (g) CH_3MgI, Et_2O, rt, 77%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 100%; (i) H_2SO_4, AcOH, H_2O, reflux, 88%; (j) I_2, pyridine, 100–110 °C; (k) **1**, NH_4OAc, AcOH, 100–110 °C, 39%; (l) *n*-BuLi, Et_2O, 0 °C to rt, benzophenone, Et_2O, −78 °C, **9** (82%), **10** (8%).

Scheme-I: Synthesis of Ligand (10) as Reported by C.P. Chen *et al*.[6]



Scheme-II: A Short and Improved Synthesis of Ligand (10 & 15)

The pinocarvone (1) was synthesized with 81% yield by photooxidation of commercially available α-pinene (97% enantiomeric excess) with some modification in Mihelich and Eickhoff's process.[15] Pinocarvone (1) was converted into pyridone (12) by following Malkov[16] *et al.* protocol (11, ammonium acetate, piperidine, ethanol (EtOH), 80 °C, 10 h; then formamide, 200°C, 1h) with only 20-39% yield. However, we have used much milder condition[17] using aqueous sodium hydroxide followed by acetic acid at 100°C, to synthesize pyridone (12) with 65% yield. By using phosphorus oxychloride ($POCl_3$) and Phosphorus pentachloride (PCl_5), the pyridone (12) was converted to a chloro compound (13) with a moderate 40% yield. After performing several experiments, we have developed a sealed tube reaction condition using only $POCl_3$ to synthesize 13 with a very good 70% yield. To convert compound (13) to compound (14_b), we have tried several reaction conditions as summarized in Table-1. We found that anion generation temperature -40 °C to -10 °C and cooling back to -78 °C before adding the electrophile ArCOAr, are the critical conditions to get 72% yield.

Table-1: Various Reaction Conditions Followed for the Synthesis of 14_b from 13

Reagent (equi.)	Drying of ArCOAr	Solvent	Anion Temperature	Reaction Temperature	%Yield[a]
DIPEA (1.1) *n*-BuLi (1.1)	High Vacuum (6h)	Dry Ether	-78 °C (45 min.)	-78 °C (45 min.) to 25°C/ 12 h	5
DIPEA (1.5) *n*-BuLi (1.5)	High Vacuum (8h)	Dry THF	-78 °C (2 h)	-78 °C (1.5 h) to 25°C/ 12 h	8
DIPEA (1.1) *n*-BuLi (1.1) [b]HMPA (20 mol%)	Toluene Azeotrope	Dry THF	-40 °C (2 h)	-40 °C (2.5 h) to 25°C/ 12 h	0
t-BuLi (1.2)	Toluene Azeotrope	Dry THF	-78 °C (1.5 h) to -35 °C (2 h)	-78 °C (1.5 h) to 25°C/ 12 h	0
[c]LiHMDS (1.5)	P_2O_5 overnight in Desiccator	Dry THF	-40 °C to -10 °C (2.5 h)	-78 °C (2 h) to 25°C/ 12 h	0
DIPEA (1.5) *n*-BuLi (1.5)	P_2O_5 overnight in Desiccator	Dry THF	-40 °C to -10 °C (2.5 h)	-78 °C (3 h) to 25°C/ 12 h	72

[a] Isolated yield by silica gel column chromatography, [b] Hexamethylphosphoramide,
[c] Lithium bis(trimethylsilyl)amide

For the homo coupling reaction, Zinc (Zn) metal powder was activated by stirring with Trimethylsilyl chloride TMSCl (Catalytic amount). We have explored (Table-2) the homo coupling reaction of chloro compound (14_b) by using Nickel(II) chloride hexahydrate ($NiCl_2 \cdot 6H_2O$) catalyst to get the best possible yield of the required ligand (15). However, we could only attend 41% yield of ligand (15) since the deschloro compound (16) was the side product along with unreacted starting material, chloro compound (14_b).

Table-2: Homo-Coupling Reaction Conditions

$NiCl_2.6H_2O$ (equivalence)	Activated Zn (equi.)	PPh_3 (equi.)	Degassed Solvent	Temp./Time	% Yield[a]
1.04	1.3	4.14	DMF	60°C/ 16 h	A = 8, B= 35, C= 40
1.6	1.6	6.4	DMF	55 °C/ 24 h	A= 0, B= 51, C= 35
Anhydrous $NiCl_2$(0.05)	1.5	0.3	Dry Pyridine	Reflux/ 12 h	Only C (No reaction)
1.2	1.5	4.2	Dry THF	60°C/ 24 h	Only C (No reaction)
2.2	2.2	8.2	DMF	70°C/ 24 h	A= 10, B= 40, C= 15
2.0	2.6.	4.8	DMF	70°C/ 24 h	A= 41, B= 15, C= 10

[a]A= Ligand (15), B= Reduced Product (16), C= Chloro compound (14_b)

CONCLUSION

Thus, we have successfully achieved the synthesis of ligand (15) with a much better yield than previously reported by C.P. Chen *et al*.[6] for the similar ligand (10). Further studies for the application of Ligand (15) for various asymmetric reactions of medicinal chemistry will be a very useful and interesting field of research.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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