

ALDOL CONDENSATION REACTIONS EFFECTIVELY CATALYSED BY LEWIS ACID

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Abstract: A complex of manganese (III) and *R,R*-1,2-Diaminocyclohexane linked ketopinic acid ligand was synthesized and utilised as catalyst in the aldol condensation reactions of benzaldehyde with various aliphatic ketones to furnish products with excellent yield of >99%.

Keywords: Lewis acid, ketopinic acid, manganese, catalysis, aldol condensation

Introduction

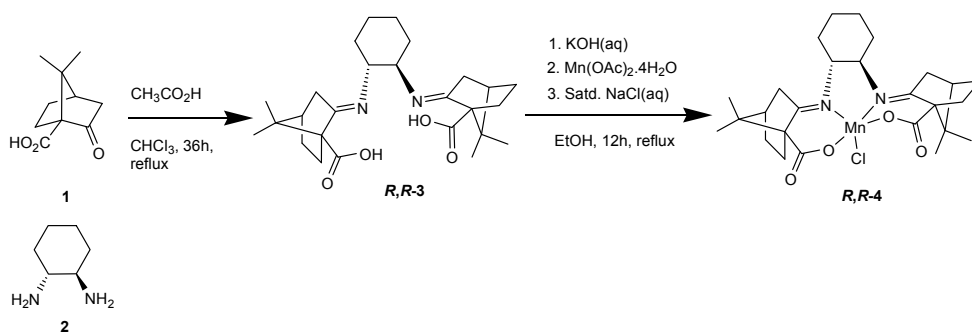
Aldol condensation reaction as C-C bond formation reaction continued to provide opportunity for the synthesis of valuable intermediates, natural products, and biologically important compounds.¹⁻³ One of the major concern with some of the reported methodologies has always been the issue of atom economy.^{4,5} Although a number of attempts which employ catalysts was made to improve the condition, it however usually incorporates the use of harsh temperature.⁶⁻¹⁰ In this work, a new organic-metal complex

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based on ketopinic acid scaffold and manganese was constructed and tested as catalyst in the aldol condensation of various aliphatic substrates at a mild temperature.

Results and Discussion

The ligand ***R,R*-3** reported by Yang et al¹¹ was synthesized using the standard procedure, followed by the complexation step (Scheme 1) to obtain the new Mn(III) complex ***R,R*-4**.¹² Thus, the synthesis was carried out by refluxing ketopinic acid **1** with the *R,R*-1,2-Diaminocyclohexane **2** in the presence of a catalytic amount of glacial acetic acid, using chloroform as solvent (Scheme 1). Condensation of ketopinic acid (2 equiv.), with the *R,R*-1,2-Diaminocyclohexane as a linker enabled the generation of the C-2 symmetry and expand the space occupied by the ligand on each face of the final complex. Several attempts were made to obtain a single crystal for x-ray crystallography but without success. Therefore density functional theory (DFT) calculation was performed using B3LYP/LanL2DZ method implemented in Gaussian 03.¹³ The method was therefore used with the Dunning and Huzinaga valence double- ζ basis functions for first-row elements, while efficient core-potential functions were employed for chlorine and manganese.¹⁴⁻¹⁷ The result indicates that ***R,R*-4** adopts a square pyramidal geometry (Figure 1). It is hoped that the position of the manganese atom tightly situated at the center of the ketopinic acid moieties would enhance the coordination of the electrophilic centers of the substrates in the course of the reaction.

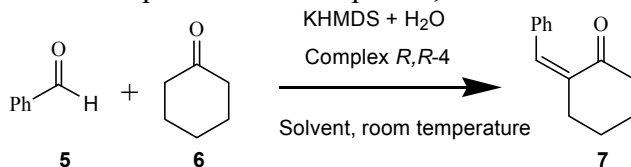


Scheme 1. Synthesis of ketopinic acid-derived complex.



Figure 1. DFT optimized structure of R,R-4 obtained using Gaussian 03.

The catalytic activity of complex R,R-4 was investigated in accordance with the procedure reported by Yoshikawa et al. with modification¹⁸. Hence benzaldehyde was reacted with cyclohexanone in different ethereal solvents and at three catalyst loadings (Table 1). The results shows that THF is the most efficient solvent as it allows the formation of the aldol product in >99% yield at relatively shorter time. Attempt to reduce the catalyst loading result in longer duration of the reaction. Although not included in Table 1, but the method development reveals that any attempt to reduce the cyclohexanone equivalent furnish the corresponding aldol in negligible amount. In fact it could only be detected in the ^1H NMR spectroscopic analysis of the reaction mixture.

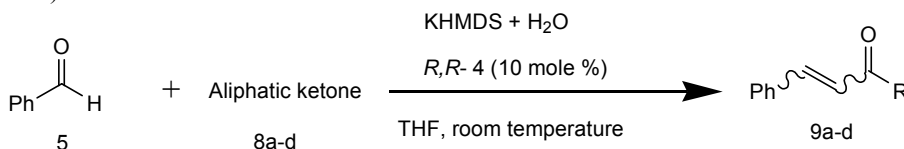
Table 1. Aldol condensation of benzaldehyde with cyclohexanone in three different solvents in the presence of complex **R,R-4**^a.

Solvent	R,R-4 (mole %)	Time (h)	Yield (%) ^b
THF	1	18	>99
	5	13	>99
	10	4	>99
EtOAc	1	24	>99
	5	24	>99
	10	24	>99
Dioxane	1	24	trace
	5	20	trace
	10	1	trace

^aBenzaldehyde (1.5 mmol), cyclohexanone (15 mmol). *Cis* assignment for **7** was determined using DFT calculation of the lowest-energy isomer;

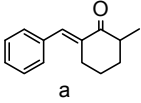
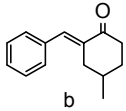
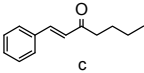
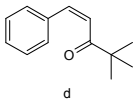
^bDetermined by ¹H NMR spectroscopic analysis of the reaction mixture.

Based on the catalyst performance, other substrates were explored to further ascertain its efficacy. The results (Table 2) demonstrate that the catalyst has relatively wide spectrum of activity.

Table 2. Aldol condensation of various aliphatic substrates in the presence of **R,R-4** (10 mole %)^a.

	Aliphatic ketone
a	2-Methylcyclohexanone
b	4-Methylcyclohexanone
c	2-Hexanone
d	Pinacolone

Table 2. Continued

Aldol products, 9 ^b	Time (h)	Yield (%) ^c
 a	4.2	>99
 b	4.4	>99
 c	4.7	>99
 d	5	>99

^aBenzaldehyde (1.5 mmol), Ketone (15 mmol);

^bGeometrical assignment for **9a** and **9b** was determined using DFT calculation of the lowest-energy isomers;

^cDetermined by the ¹H NMR spectroscopic analysis of the reaction mixture.

Experimental

Reagent-grade ethanol was used as received from commercial source, tetrahydrofuran was distilled from benzophenone/ketyl solutions and chloroform was passed through a column of basic alumina. Analytical thin-layer chromatography was performed on ALUGRAM XTRA silica gel 0.2 mm (containing a fluorescent indicator at 254 nm). Flash chromatography was carried out on MN Kieselgel 60 0.063-0.2 mm/ 70-230 mesh. All other reagents were purchased from Aldrich and used as received. NMR spectra were recorded on Bruker Avance III HD spectrometer (400 and 600 MHz). All signals were expressed as ppm down field from TMS, referenced to the residual protonated solvent signals in ¹H NMR (7.26 ppm) and to the deuterated carbon signals in ¹³C NMR (77.36 ppm). IR spectral measurements were carried out on a Perkin Elmer spectrum 400 FT-IR spectrometer (ATR). Elemental analyses were conducted using an

Elementar Vario micro cube. Melting points were determined by means of a Reichert apparatus and are uncorrected.

2,2'-(1R,2R)-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)bis(7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid) **R,R-3**

Ketopinic acid (382 mg, 2.096 mmol) was dissolved in CHCl_3 (5 mL) followed by the addition of *R,R*-1,2-Diaminocyclohexane (126 μL , 1.05 mmol) and acetic acid (0.1 mL) at room temperature. The mixture was refluxed for 36 h and the reaction quenched with H_2O (5 mL). The resulting biphasic solution was extracted with CH_2Cl_2 (10 mL), and the layers were separated. The organic layer was washed with brine (5 mL), dried over anhydrous MgSO_4 , and concentrated. The crude product was purified by column chromatography on silica gel using 4/1 EtOAc/ CH_2Cl_2 as eluent to obtain the product as a white solid (0.48 g, 40%); m.p. 159-163 °C; δ_{H} (400 MHz; CDCl_3) 0.83 (s, 6H), 1.23 (s, 6H), 1.24-1.25 (m, 2H), 1.27-1.65 (m, 10H), 1.83 (d, $J = 6.6$ Hz, 2H), 1.92-2.11 (m, 6H), 2.35 (td, $J = 12.1, 4.6$ Hz, 2H), 2.54 (t, $J = 3.8$ Hz, 1H), 2.61 (t, $J = 3.0$ Hz, 1H), 3.43 (dd, $J = 5.2, 3.2$ Hz, 2H); δ_{C} (100 MHz; CDCl_3) 19.9, 20.3, 24.1, 28.0, 30.9, 32.1, 35.2, 43.6, 49.6, 60.5, 64.5, 173.2, 183.4. IR (neat, cm^{-1}) 2892, 2503, 1760, 1554

2,2'-(1R,2R)-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)bis(7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylato) manganese (III) chloride **R,R-4**

Solution of the ligand **R,R-3** (119 mg, 0.268 mmol) containing KOH (0.5M, 8 mL) in ethanol was allowed to reflux under nitrogen atmosphere with $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (138 mg, 0.563 mmol) for 12 h. The reaction mixture was cooled to room temperature and brine (8 mL) was added to give a biphasic solution. The resulting solution was filtered, concentrated *in vacuo* and redissolved in dichloromethane. After concentration, the water layer was removed using a separating funnel and the solution was again concentrated till dryness. The complex was recrystallized from acetonitrile

and obtained as brown amorphous powder (71 mg, 50% yield). Anal. Calcd for $C_{26}H_{36}ClMnN_2O_4$ % : C, 60.75; H, 8.50; N, 4.72. Found: C, 60.75; H, 8.51; N, 4.74. IR (neat, cm^{-1}): 1738 (C=O), 1687 (C=N).

Procedure for the aldol condensation reactions

A solution of potassium hexamethyldisilazide (KHMDs, 43.2 μ l, 0.0216 mmol, 0.5M in toluene) and water (48 μ l, 0.048 mmol, 1M in THF) were stirred for 20 min, and then ketone (15 mmol) was added. The mixture was stirred for another 10 min followed by the addition of the solution of catalyst **R,R-4** (66 mg, 10 mole %) and aldehyde (1.5 mmol) in THF (0.5 mL). Stirring was continued with regular monitoring by 1H NMR until no starting materials are detected. The reaction mixture is quenched by addition of 1M HCl, and the oily layer separated. The aqueous solution was extracted twice with ether. The oily layer and the ether extracts were combined and dried over anhydrous sodium sulphate.

(Z)-2-benzylidenecyclohexanone **7**

Yellow oil; >99% yield, δ_H (600 MHz; $CDCl_3$) 1.50 (q, $J = 2.0$ Hz, CH_2), 1.55 (q, $J = 2.3$ Hz, CH_2), 1.57 (t, $J = 3.1$ Hz, CH_2), 1.63 (t, $J = 3.1$ Hz, CH_2), 6.88 (s, 2H), 7.32-7.33 (m, 2H), 7.40 (s, 1H), 7.61 (s, 1H), δ_C (100 MHz; $CDCl_3$) 22.2, 24.3, 35.0, 128.2, 128.3, 128.4, 133.1, 134.0, 139.5, 198.3. IR (neat, cm^{-1}) 3038, 1671, 1638, 1450.

(E)-2-benzylidene-6-methylcyclohexanone **9a**

Yellow oil; >99% yield; δ_H (600 MHz; $CDCl_3$) 1.22 (d, $J = 1.2$ Hz, CH_3), 1.23-1.24 (m, 2H), 1.32-1.36 (m, 2H), 2.10-2.12 (m, 2H), 2.22-2.32 (m, 2H), 6.89 (s, 2H), 7.41-7.43 (m, 2H), 7.54 (s, 1H), 7.81 (s, 1H). δ_C (100 MHz; $CDCl_3$) 16.2, 26.3, 29.2, 30.6, 40.6, 133.2, 136.3, 136.7, 134.2, 134.8, 140.1, 199.3. IR (neat, cm^{-1}) 3045, 1674, 1632, 1447.

(E)-2-benzylidene-4-methylcyclohexanone **9b**

Yellow oil; >99% yield, δ_H (600 MHz; $CDCl_3$) 0.99 (d, $J = 0.5$ Hz, CH_3), 1.62-1.68 (m, 2H), 1.85-1.93 (m, 2H), 2.33-2.80 (m, 2H), 2.86-2.93

(m, 1H), 3.20-3.52 (m, 1H), 3.62-3.72 (m, 1H), 7.02 (s, CH), 7.61-7.68 (m, 2H), 7.72 (s, 1H), 7.84 (s, 1H). δ_C (100 MHz; $CDCl_3$) 16.2, 26.3, 29.2, 30.6, 40.3, 133.2, 136.3, 136.7, 134.2, 134.8, 140.1, 199.5. IR (neat, cm^{-1}) 3044, 1675, 1632, 1447.

trans-1-phenylhept-1-en-3-one **9c**

Yellow oil; >99% yield, δ_H (600 MHz; $CDCl_3$) 0.96 (t, $J = 0.9$ Hz, 3H), 1.52-1.59 (m, 4H), 3.20 (t, $J = 3.1$ Hz, 2H), 6.53 (d, $J = 12.0$ Hz, 1H), 6.66 (d, $J = 12.0$ Hz, 1H), 6.83 (d, $J = 6.5$, 2H), 7.66-7.68 (m, 3H). δ_C (100 MHz; $CDCl_3$) 12.3, 23.4, 28.6, 40.2, 128.3, 129.0, 131.1, 135.1, 140.1, 147.2, 199.5. IR (neat, cm^{-1}) 3051, 1668, 1646, 1510.

Cis-4,4-dimethyl-1-phenylpent-1-en-3-one **9d**

Yellow oil ; >99% yield, δ_H (600 MHz; $CDCl_3$) 1.51 (s, 9H), 6.93 (d, $J = 6.0$ Hz, 1H), 7.43 (d, $J = 6.0$ Hz, 1H), 7.66-7.68 (m, 2H), 7.72-7.75 (m, 3H). δ_C (100 MHz; $CDCl_3$) 33.2, 43.1, 127.3, 129.1, 129.8, 133.10, 138.0, 140.2, 198.5. IR (neat, cm^{-1}) 3055, 1671, 1644, 1525.

Conclusions

The synthesis of a complex based on the scaffold of ketopinic acid was successfully achieved, and its subsequent application in the catalytic aldol condensation reactions of benzaldehyde with various aliphatic ketones. It is quite remarkable that irrespective of the structure of the aliphatic ketone, the yield of the products was apparently excellent within short duration.

Acknowledgements

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