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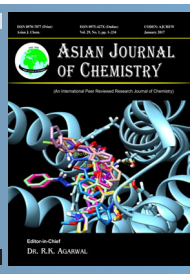

Polymer-Supported Ruthenium(II)/Phenyloxazoline Complex: Reusable and Highly Selective Catalyst for N-H Insertion Reactions

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A group of functionalized β-amino esters were successfully synthesized in excellent yields (> 99 %) *via* NH-insertion of ethyldiazoacetate into various amines catalyzed by porous-polymer-supported ruthenium(II)-pheox catalyst. The catalyst was readily recovered and reused at least five times without loss of its catalytic activity.

Keywords: Polymer-support, Ruthenium, N-H insertion, Recyclability.

INTRODUCTION

The N-H insertion reactions catalyzed by metal-complexes are of great importance for the formation of amino acids precursor to be used for preparation of natural products and other pharmaceuticals [1-3]. Over the past decades, several transition-metal complexes such as rhodium [4-8], copper [9,10] and iron [3] were emerged as effective catalysts for N-H insertion reactions [11-14]. Recently, ruthenium(II) showed remarkable catalytic activity in inter- and intra-molecular N-H insertion reactions with diazo-compounds [15]. Immobilization of the ruthenium(II)-catalyst onto polymeric support presented an interesting area of research. Especially, this polymeric catalyst can easily recovered and recycle again. Herein, we report a new polymer-supported ruthenium(II)-pheox which incorporated with a new ruthenium(II)-pheox catalyst and we evaluated its catalytic activity in N-H insertion of ethyldiazoacetate (EDA) with different amines and afforded excellent reactivities with ability to be reused five times keeping its catalytic activity.

EXPERIMENTAL

Reactions were performed under argon atmosphere. Dichloro methane (CH_2Cl_2) and dimethyl formamide (DMF) dehydrated from Kanto Chemical Co., Inc. Acetonitrile and diethyl ether dehydrated from Wako Pure Chemical Industries, Ltd. Ethyldiazoacetate was purchased from Sigma-Aldrich, Co. All the reactions were registered by thin layer chromatography (TLC). The starting materials were used after purification. The products were visualized by irradiation with UV light. ^{1}H NMR (400 MHz or 300 MHz) and ^{13}C NMR (100 MHz or 75 MHz) spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shifts are reported as δ values (ppm) compare to internal TMS (0.00 ppm) in $CDCl_3$.

Synthesis of ruthenium(II)-pheox complex 7 (Monomer): A mixture of compound **6** (100 mg, 0.16 mmol), 4-dimethyl aminopyridine (DMAP) (4 mg, 0.03 mmol) and N,N'-dicyclohexylcarbodiimide (DCC) (100.6 mg, 0.48 mmol), were mixed in a two necked flask with a magnetic stirring bar. The flask was evacuated and filled with argon. Acetonitile (4 mL) was injected, the flask was cooled in ice and acrylic acid (0.033 mL, 0.48 mmol) was slowly injected from the side arm. At room temperature the reaction was continued for 3 h and the product was determined by UV light. After evaporation of the solvent the product was purified by column chromatograrhy using silica gel with CH_2Cl_2/CH_3CN [20/1 (v/v)] to give a yellow solid product **cat. A** in 70 % yield (69.0 mg, 0.10 mmol). R_f = 0.8 (CH_2Cl_2/CH_3CN = 5/1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 6H), 2.16 (s, 6H), 2.52 (s, 3H), 2.55 (s, 3H), 4.39 (s, 2H), 5.27 (s, 2H), 5.87 (dd, *J* = 1.7, 10.5 Hz, 1H), 6.22 (dd, *J* = 10.5, 17.3 Hz, 1H), 6.48 (dd, *J* = 1.6, 17.3 Hz, 1H), 6.94 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.4 (d, *J* = 7.7 Hz, 1H), 7.8 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 4.0, 4.5, 27.6, 66.0, 66.2, 81.6, 121.2, 121.3, 121.9, 125.5, 134.8, 136.7, 141.5, 172.2, 185.6.

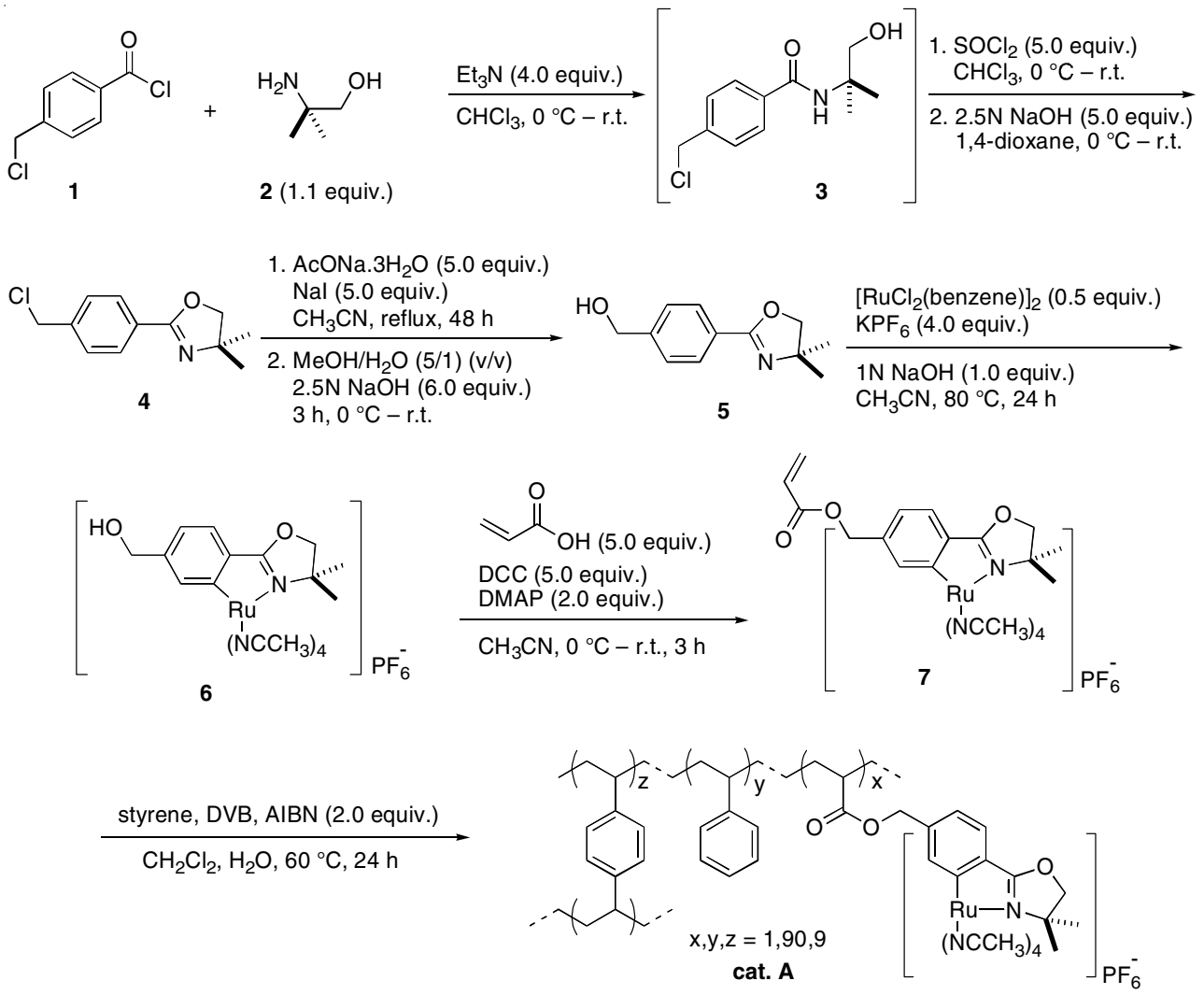
Cross-linking polymerization of ruthenium(II)-pheox complex 7 to give cat. A as a microporous polymer: The ruthenium(II)-complex **7** (52 mg, 0.078 mmol) was inserted in a two necked round flask containing a magnetic stirring bar and a reflux condenser. After charging with argon, dichloro-

methane (3 mL) was inserted from the side arm. Styrene (0.8 mL, 7.02 mmol), 1,4-divinyl benzene (DVB) (0.1 mL, 0.70 mmol) and distilled H_2O (1.5 mL) were supplied *via* syringe. (AIBN) (25 mg, 0.156 mmol) was added and the reaction was refluxed for 24 h. The polymeric product was washed with hexane, ether and acetonitrile respectively until the filtrate becomes clear under U.V. and dried under vacuum to give a solid product (yellow) **cat. A** in a quantitative yield (1000 mg). Anal. Found: C, 85.48 %; H, 7.36 %; N, 0.98 % (loading 0.14 mmol/g).

General procedure for NH insertion of diazo compound (EDA) into amines catalyzed by cat. A: A definite amount of polymer-supported ruthenium(II)-pheox complex **cat. A** was evacuated and backfilled with argon. The reaction flask was charged with (0.3 mmol) of amines dissolved in CH_2Cl_2 (3 mL) by injection through the side arm of the flask and the reaction flask was cooled in ice bath. Ethyldiazoacetate (0.035 mL, 0.33 mmol) was slowly inserted and the reaction was stirred for 15 min at room temperature. The reaction product was isolated by centrifugation and the catalyst was separated by washing with acetonitrile and hexane respectively and dried under vacuum to be ready for the next use. The product in the filtrate was concentrated to afford the desired product in a pure form without further purification.

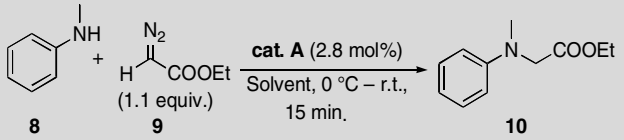
RESULTS AND DISCUSSION

In the presence of AIBN, the ruthenium(II)-pheox catalyst **7**, styrene and 1,4-divinyl benzene (DVB) was successfully polymerized. As a new protocol in this polymerization reaction, water was added for getting the microporous polymer-supported ruthenium(II)-pheox **cat. A** as shown in **Scheme-I**. The exact loading of the complex inside the polymer was evaluated from the elemental analysis of nitrogen. To evaluate the catalytic activity of **cat. A** in an NH insertion reaction of diazo compound into an mine, we started to optimize the reaction conditions by selecting the better solvents and by using the commercially available ethyl diazoacetate (EDA) **9** with *N*-methylaniline (**8**) to avoid the dimerization product and the results are summarized in Table-1. The insertion of EDA into *N*-methylaniline N-H bond was effectively catalyzed by **cat. A** in the presence of CH_2Cl_2 as a good swelling solvent compared with the other solvents to afford ethyl 2-(N-methyl-N-phenyl-amino)acetate (**10**) in > 99 % yield within 15 min and without any further purification (Table-1, entry 1). In case of the protic solvents, there is a considerable decrease in the yield (Table-1, entries 5 and 6); probably, this is due to the non-swelling ability and instability of the ruthenium catalyst and diazo compound



Scheme-I: Synthesis of polymer-supported ruthenium dimethyl phenyloxazoline complex

TABLE-1
SOLVENT SCREENING FOR **cat. A** CATALYZED INSERTION OF EDA INTO *N*-METHYLANILINE[a]

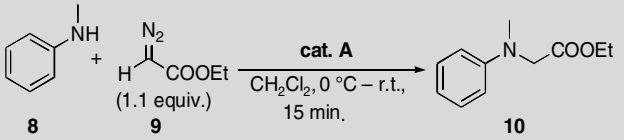


8 9 10

Entry	Solvent	Yield (%)[b]
1	CH_2Cl_2	> 99
2	THF	80
3	CH_3CN	52
4	Toluene	52
5	MeOH	40
6	*t*-BuOH	30

[a]Reaction conditions: **cat. A** loading (0.14 mmol/g) (60 mg, 0.0084 mmol), *N*-methylaniline (0.3 mmol) dissolved in solvent (3.0 mL) and injected at 0 °C, then EDA (3.3 mmol) was injected and the reaction was sired at room temperature for 15 min.
[b]Isolated yield pure enough (no need for further purification).

TABLE-2
EFFECT OF **cat. A** LOADING CATALYZED INSERTION OF EDA INTO *N*-METHYLANILINE[a]



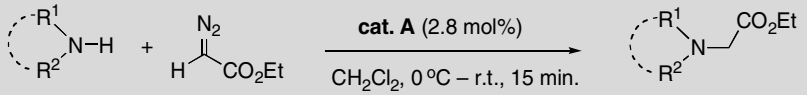
8 9 10

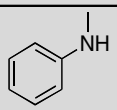
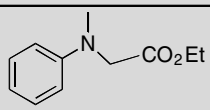
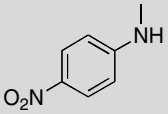
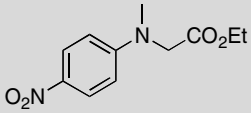
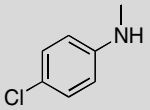
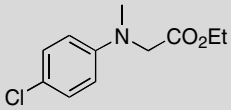
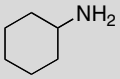
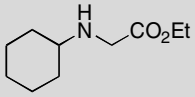
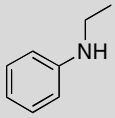
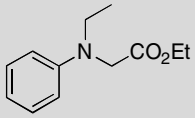
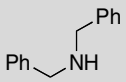
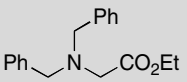
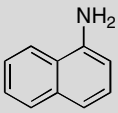
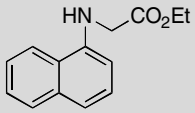
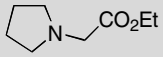
Entry	**cat. A** (mol %)	Yield (%)[b]
1	1.4	66
2	2.8	> 99
3	4.2	92
4	8.0	72

[a]Reaction conditions: **cat. A** loading (0.14 mmol/g), *N*-methylaniline (0.3 mmol) dissolved in solvent (3.0 mL) and injected at 0 °C, then EDA (3.3 mmol) was injected and the reaction was sired at room temperature for 15 min.
[b]Isolated yield pure enough (no need for further purification).

in this medium. For further investigation, we studied the effect of the polymeric catalyst (**cat. A**) loading as shown in Table-2. It is found that 2.8 mol % of **cat. A** offered a remarkable yield > 99 % in contrast with the high and low mol %. Under the optimized conditions, a variety of amines underwent reaction with ethyldiazoacetate in presence of 2.8 mol % of **cat. A** to give the corresponding *N*- substituted glycine ethyl esters in excellent yields (Table-3). Interestingly, **cat. A** easily and quantitatively recovered by centrifugation, decantation of the product and washing the polymeric catalyst with acetonitrile, hexane and dichloromethane until nothing detected under U.V to submit to the next run. **cat. A** presented recycability until

TABLE-3
INSERTION OF EDA INTO N-H OF VARIOUS AMINE DERIVATIVES CATALYZED BY **cat. A**[a]



Entry	Amines	Cycle	Product	Yield (%)[b]
1		1-5		> 99
2		1		> 99
3		1		92
4		1		74
5		1		88
6		1		97
7		1		79
8		1		93

[a]Reaction conditions: **cat. A** loading (0.14 mmol/g) (60 mg, 0.0084 mmol), amine (0.3 mmol) dissolved in CH_2Cl_2 (3.0 mL) and injected at 0 °C, then EDA (3.3 mmol) was injected and the reaction was sired at room temperature for 15 min.
[b]Isolated yield pure enough (no need for further purification).

five times in the case of *N*-methylaniline (Table-3, entry 1) to afford > 99 % yield of ethyl 2-(N-methyl-N-phenylamino)-acetate. Additonally, no leaching ability was detected during the progress of the reactions.

Conclusion

We have successfully designed and synthesized a porous polymer-supported ruthenium(II)-pheox incorporated with the active ruthenium(II)-pheox catalyst and this heterogeneous polymeric catalyst afforded high catalytic activity in N-H insertion of ethyldiazoacetate with different types of amines as well as it has ability to recyclable five times with the same catalytic activity. Polymer-supported ruthenium(II)-pheox (**cat. A)** has many potential applications in the medicinal and pharmaceutical industries.

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