Applications of Cross-linked Poly(4-vinylpyridine/styrene) Copolymer-supported Ytterbium(III) Triflate in Mannich-type Reaction: Three Component One-pot Synthesis of β-Aminoketones

Sang-Hyeup Lee[*] and Byoung Se Lee[†,*]

Department of Life Chemistry, Catholic University of Daegu, Gyeongsan 712-702, Korea. [*]E-mail: leeshh@cu.ac.kr
[†]Department of Chemistry, Inha University, Incheon 402-751, Korea. [*]E-mail: flagon11d@inha.ac.kr
Received May 21, 2008, Accepted July 15, 2008

The ytterbium catalyst immobilized on the cross-linked poly(4-vinylpyridine/styrene) copolymer (P/S-Yb) was applied in the Mannich-type, three component one-pot synthesis of β-aminoketones. This catalytic system showed excellent catalytic activity and selectivity which resulted in the exclusive formation of β-aminoketone. The applicability of this immobilized catalyst system was shown by the reusability test and again highlighted by the synthesis of a β-aminoketone library using a broad range of substrates.

Key Words: Polymer-supported catalyst, Poly(4-vinylpyridine/styrene), Ytterbium(III) triflate, Mannich-type reaction

Introduction

In the modern syntheses of chemical libraries, drugs, natural products, fine chemicals, and etc., the use of polymer-supported reagents, catalysts, and scavengers have provided several advantages such as simplification of product work-up and recovery/reuse of polymer-bound species.[1] One particular interest lies on the immobilization of organometallic species on solid matrix. A variety of transition metal or rare earth metal catalyzed reactions has been already established and also will take an important part of the synthetic chemists' arsenal.[2] From practical, economical, and environmental standpoints, heterogeneous metal catalysts immobilized on polymers or other insoluble matrix clearly have benefits since immobilized catalysts can be recovered from reaction mixtures by simple filtration to be recycled. In addition, safety issues such as product contamination by the catalyst are far less of a concern than when homogeneous catalysts are used, especially in the pharmaceutical industry.[3]

In the last two decades, rare earth metal triflates (RE(OTf)$_3$) have been developed as mild, water-stable Lewis acids in a wide range of organic transformations including aldol, Diels-Alder, Michael addition, aziridination, oxidation/reduction, rearrangement, and protection/deprotection reactions.[2] The most characteristic features of lanthanide triflates (Ln(OTf)$_3$) are that they are stable in the presence of water and most polar functional groups, and catalytically active even in the presence of Lewis bases containing nitrogen, oxygen, phosphorous and sulfur atoms. So far, these catalysts have been mainly utilized as homogeneous catalysts in most applications.[4] Although they could be recovered by aqueous extraction and reused,[4a] the use of immobilized catalysts on solid supports is more desirable to achieve improved recycling and facile use in given synthetic schemes. Accordingly, preparation methods of immobilized RE(OTf)$_3$ catalysts using different immobilization techniques and/or different insoluble matrixes have been reported.[5,6] Polymer supported scandium catalyst, polyallylscandium trifylamide ditriflate (PA-Sc-Tad), in which the scandium was immobilized onto solid supports by complexation, has been reported by Kobayashi group.[5] Recently, the same research group also developed microencapsulated RE(OTf)$_3$ using soluble polystyrene and lightly cross-linked polystyrene as supports.[6] Although these catalysts were recycled without any loss of catalytic activity, there are some drawbacks. For example, in spite of the excellent stabilities of PA-Sc-Tad, the activity of the catalyst are rather lower than that of its soluble counterpart, Sc(OTf)$_3$.[5] In addition, there are some difficulties in the intricate multi step preparation of both aforementioned catalysts and/or in its use which requires precipitation of the polymer for recovery of catalysts.[5,6]

One of our research programs has been focused on the development of the novel polymer-supported catalysts and reagents, more specifically the immobilization of metallic species to polymer matrix for various purposes. Recently, we found that the lanthanide triflates, in particular, Yb(OTf)$_3$ can be easily immobilized on the series of cross-linked poly(4-vinylpyridine/styrene) copolymer (^{x}P/S, where superscript x equates to % pyridine content)[7] as well as on the series of ionic polymers prepared by quaternization of parent ^{x}P/S resins.[8] We also reported that both the immobilized ytterbium catalysts showed excellent catalytic activity and reusability in a Lewis acid-catalyzed model reaction, two component reaction of preformed imine and vinyl silyl-ether yielding β-aminoketones.

Prompted by these results, we decided to examine the catalytic activity and reusability of P/S supported ytterbium(III) triflate (P/S-Yb) in Mannich-type, three component one pot synthesis of β-aminoketones which is much more robust than the previously mentioned two component synthesis. Herein we wish to report the results.

Results and Discussion

Recently, we reported the two component synthesis of β-aminoketones from preformed imines and silyl enol ether using ytterbium catalyst immobilized on two different kinds of solid matrixes. Significant improvement of reactivity and reusability was not observed by employing ytterbium immobilized on ionic liquid-based polymeric supports than that on the parent P/S resins, in spite of the rather tedious, multi-step modification of the former from the latter. Accordingly, we decided to use P/S resins as supports for the immobilization of ytterbium and, among a series of P/S resins embedding different quantities of pyridine functionality, we chose ^{30}P/S resin which displayed the best catalytic activity and reusability.[7]

The optimized solvent system (CH_3CN:CH_2Cl_2 = 3:1) worked efficiently in this Mannich-type three component reaction using 1-naphthaldehyde, aniline, and silyl enol ether **3** as model substrates (Scheme 1). The preferential coordination/activation ability of the immobilized ytterbium catalysts to aldimine over aldehyde resulted in the exclusive formation of desired β-aminoketone **4a** (R^1 = 1-naphthyl, R^2 = phenyl) in the yield over 90%, and no appreciable amount of potential side products, such as β-hydroxyketone or its dehydrated product, was observed. In addition, even without the employment of dehydrating additives such as molecular sieves or magnesium sulfate, which are in many cases utilized to accelerate the process, the reaction proceeded in a rate comparable to that observed in two component reaction. The immobilized ytterbium catalyst is not sensitive to air and moisture upon storage and much easier to handle than its soluble counterpart, $Yb(OTf)_3$. In addition, the catalyst was not influenced by water formed and not altered during the reaction, confirmed by the reusability and leaching test of ^{30}P/S-Yb using the same substrates for the ten successive cycles. The recovered catalyst by filtration could be reused more than ten times without the loss of catalytic activity. During the 10 runs, any considerable retardation of reaction was not observed and all the reactions were completed within two hours with yields constantly over 90% after isolation (1st, 5th, and 10th run). No significant leaching of the catalyst was observed *via* IR experiments of recovered catalysts (Figure 1). The result was further confirmed through ICP-AES analysis; no detectable amount of ytterbium (detection limit corresponded to 0.2% of total ytterbium on the catalyst) was monitored in each filtrate.

Encouraged by these results, we then synthesized a small set of β-aminoketone library **4** using a combination of aromatic, aliphatic, and α,β-unsaturated aldehydes **1**, aromatic amines **2**, and silyl enol ether **3** (Table 1). It should be noted that each reaction was achieved using the recovered catalysts from the previous reaction. As reported in Table 1, all the members of library **4** were synthesized in high yields proving that the catalyst was successfully reusable at least for fifteen runs without the appreciable loss of catalytic activity, as exemplified by the isolated yields obtained in the 1st and 15th reaction cycles for the same product **4** (entries 1 and 15 where R^1 = R^2 = phenyl).

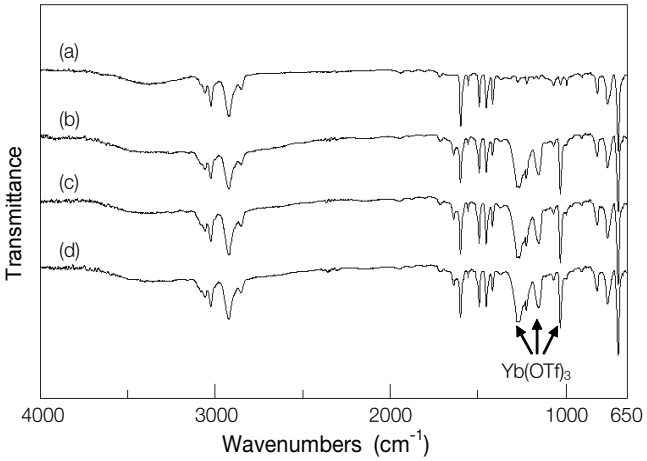
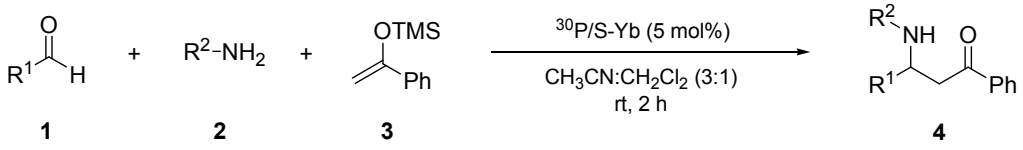


Figure 1. FT-IR spectra of (a) ^{30}P/S, (b) ^{30}P/S-Yb freshly prepared, (c) ^{30}P/S-Yb recovered after 5th cycle (d) ^{30}P/S-Yb recovered after 10th cycle.

Table 1. Three-component synthesis of β-aminoketones **4** catalyzed by ytterbium immobilized on ^{30}P/S resin (^{30}P/S-Yb)[a]

Entry	R^1	R^2	Yield[b] (%)
1	Ph	Ph	**4b**, 92
2	1-Naphthyl	Ph	**4a**, 94
3	3-NO_2-Ph	Ph	**4c**, 90
4	4-Cl-Ph	Ph	**4d**, 96
5	(*E*)-2-phenylethenyl	Ph	**4e**, 90
6	4-MeO-Ph	Ph	**4f**, 94
7	3,4-Methlenedioxy-Ph	Ph	**4g**, 89
8	2-CN-Ph	Ph	**4h**, 97
9	Cyclohexyl	Ph	**4i**, 88
10	4-MeO-Ph	4-Br-Ph	**4j**, 90
11	4-MeO-Ph	4-Cl-Ph	**4k**, 94
12	4-MeO-Ph	4-F-Ph	**4l**, 88
13	4-MeO-Ph	4-MeO-Ph	**4m**, 90
14	4-MeO-Ph	4-HO-Ph	**4n**, 84
15	Ph	Ph	**4b**, 94

[a]All reactions were carried out with aldehyde **1** (1.0 mmol), amine **2** (1.0 mmol) and silyl enol ether **3** (1.5 mmol) employing the catalyst recovered from the previous runs. [b]Isolated yield.



Scheme 1. Mannich-type, three component synthesis of β-aminoketone **4** catalyzed by ^{30}P/S-Yb.

Conclusions

The ytterbium catalyst immobilized on the cross-linked poly(4-vinylpyridine/styrene) copolymer was applied in the Mannich-type three component one pot β-aminoketone synthesis. This catalyst showed good catalytic activity and can be reused several times without a loss of its catalytic activity. It also demonstrated excellent selectivity for aldimine towards the nucleophilic attack which resulted in the formation of the desired β-aminoketones exclusively; contamination of potential side products raised from the aldehyde activation was not observed. To show the broad applicability of the catalyst system, a small set of β-aminoketone library was successfully synthesized by using a combination of a variety of aromatic/aliphatic aldehydes and aromatic amines. In the construction of the library, the reusability of the catalyst was again highlighted by synthesizing each library member using a catalyst recovered from the previous reaction.

Immobilization of other kinds of organometallic species possessing Lewis acid catalytic activities as well as their application in other kinds of Lewis acid catalyzed reactions to construct small organic molecule libraries is currently in progress and will be reported in due course.

Experimental Section

General. All chemicals were obtained from commercial suppliers and were used without further purification. All of the glassware used in the solid-phase reactions was silanized by treating with Sigmacote® or 10% dichlorodimethylsilane in toluene followed by dry MeOH. Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh) using ethyl acetate/hexanes as eluents. FT-IR spectra were recorded using a JASCO 4100 spectrometer equipped with a diamond single-reflection attenuated total reflectance (ATR) accessory. Inductively coupled plasma-atomic emission spectrometry (ICP-AES) was performed using a Perkin-Elmer/Optima-4300 DV. ^{1}H and ^{13}C NMR spectra were recorded using a Varian INOVA-399 (400 MHz) and calibrated using tetramethylsilane as an internal reference. Mass spectra were obtained using a Varian 1200L instrument (Quadrupole MS).

Preparation of ytterbium catalyst immobilized on cross-linked poly(4-vinylpyridine/styrene) copolymer with 30% pyridine functionality (^{30}P/S-Yb). In brief, cross-linked poly(4-vinylpyridine/styrene) copolymer with 30% pyridine functionality (^{30}P/S) was prepared by the radical suspension copolymerization of 4-vinylpyridine (30 mol%), styrene (70 mol%) and 1 mol% of the 1,4-bis(4-vinylphenoxy)butane as a flexible cross-linker. Yb(OTf)$_3$ was then loaded on this cross-linked ^{30}P/S copolymer using a mixture of CH_2Cl_2/MeOH (1:1) as a solvent to provide title catalyst, ^{30}PS-Yb (loading level: 0.146 mmol Yb/g resin). For the detailed experimental procedure and full characterization of the catalyst, see the precedent literature reported.[7]

Typical experimental procedure for the three-component synthesis of β-aminoketones 4 catalyzed by ^{30}P/S-Yb. ^{30}P/S-Yb (342 mg, equivalent to 5 mol% Yb) was suspended in a mixture of CH_3CN/CH_2Cl_2 (3/1, 10 mL). To the mixture of aldehyde **1** (1 mmol), amine **2** (1 mmol) and silyl enol ether **3** (1.5 mmol) were added and the resultant suspension was shaken vigorously at room temperature. The progress of the reaction was monitored by TLC. After two hours, the reaction mixture was filtered through a plastic syringe equipped with a polyethylene frit and then washed with CH_3CN/CH_2Cl_2 (3/1, 10 mL × 3) and CH_2Cl_2. (10 mL × 3). The combined filtrate was evaporated and the residue was purified by flash chromatography on silica gel to afford the corresponding β-aminoketone **4**. The recovered catalyst was dried under nitrogen stream, transferred back to flask, and reused in the next experiment.

Reusability and leaching test of 1-naphthaldehyde, aniline and silyl enol ether **3** as model substrates were performed by employing recovered ^{30}P/S-Yb catalysts for successive ten cycles. All the reactions in the Table 1 were also performed in the same manner as described above by employing ^{30}P/S-Yb catalysts recovered from the previous synthesis. All the products were characterized by NMR (^{1}H and ^{13}C) and mass spectroscopy.

Compound **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 8.0 Hz, 1H), 7.88-7.98 (m, 3H), 7.79 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.54-7.66 (m, 3H), 7.38-7.48 (m, 3H), 7.04-7.12 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.54-6.60 (m, 2H), 5.86 (dd, J = 4.2, 8.2 Hz, 1H), 4.68 (br s, 1H), 3.65 (dd, J = 4.2, 16.6 Hz, 1H), 3.55 (dd, J = 8.2, 16.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5, 147.1, 137.9, 136.9, 134.4, 133.7, 130.7, 129.5, 129.3, 128.9, 128.4, 128.1, 126.7, 126.0, 125.8, 123.7, 122.5, 117.9, 113.9, 50.8, 45.2; MS (EI) *m/z* M^+ for $C_{25}H_{21}NO$ calc. 351, found 351 (M^+, 55), 257 (22), 232 (100), 153 (23), 105 (51).

Compound **4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.96 (m, 2H), 7.54-7.62 (m, 1H), 7.42-7.50 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.22-7.30 (m, 1H), 7.06-7.16 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.54-6.63 (m, 2H), 5.03 (dd, J = 5.6, 7.2 Hz, 1H), 4.57 (br s, 1H), 3.53 (dd, J = 5.2, 16.0 Hz, 1H), 3.44 (dd, J = 7.6, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5, 147.2, 143.2, 136.9, 133.6, 129.3, 129.0, 128.9, 128.4, 127.6, 126.6, 118.0, 114.0, 55.0, 46.5; MS (EI) *m/z* M^+ for $C_{21}H_{19}NO$ calc. 301, found 301 (M^+, 6), 182 (100), 105 (34), 77 (31).

Compound **4c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (t, J = 1.8 Hz, 1H), 8.05-8.10 (m, 1H), 7.86-7.92 (m, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.54-7.60 (m, 1H), 7.40-7.50 (m, 3H), 7.06-7.14 (m, 2H), 6.69 (t, J = 7.4 Hz, 1H), 6.48-6.56 (m, 2H), 5.10 (t, J = 6.2 Hz, 1H), 4.66 (br s, 1H), 3.51(d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.5, 148.9, 146.5, 145.7, 136.5, 134.0, 133.2, 130.0, 129.5, 129.0, 128.4, 122.7, 121.7, 118.7, 114.1, 54.3, 46.0; MS (EI) *m/z* M^+ for $C_{21}H_{18}N_2O_3$ calc. 346, found 346 (M^+, 21), 227 (100), 181 (42), 105 (46).

Compound **4d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88-7.96 (m, 2H), 7.54-7.64 (m, 1H), 7.44-7.50 (m, 2H), 7.36-7.43 (m, 2H), 7.27-7.34 (m, 2H), 7.06-7.16 (m, 2H), 6.66-6.74 (m, 1H), 6.52-6.58 (m, 2H), 5.00 (t, J = 6.2 Hz, 1H), 4.58 (br s, 1H), 3.49 (dd, J = 5.4, 16.2 Hz, 1H), 3.43 (dd, J = 7.6, 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.1, 146.9, 141.7, 136.7, 133.8, 133.2, 129.4, 129.2, 129.0, 128.4, 128.0, 118.3,

114.0, 54.4, 46.3; MS (EI) *m/z* M^+ for $C_{21}H_{18}ClNO$ calc. 335, found 335 (M^+, 9), 242 (7), 216 (100), 105 (29).

Compound **4e**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92-7.98 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.23-7.34 (m, 4H), 7.12-7.22 (m, 3H), 6.60-6.74 (m, 4H), 6.31 (dd, *J* = 6.0, 16.0 Hz, 1H), 4.64-4.74 (m, 1H), 4.27 (br s, 1H), 3.39 (d, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 147.1, 137.1, 136.8, 133.6, 130.9, 130.8 129.5, 128.9, 128.7, 128.4, 127.8, 126.6, 118.1, 114.1, 52.4, 44.1; MS (EI) *m/z* M^+ for $C_{23}H_{21}NO$ calc. 327, found 327 (M^+, 18), 234 (10), 208 (100), 105 (52).

Compound **4f**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.96 (m, 2H), 7.54-7.62 (m, 1H), 7.42-7.50 (m, 2H), 7.34-7.40 (m, 2H), 7.06-7.16 (m, 2H), 6.84-6.90 (m, 2H), 6.64-6.72 (m, 1H), 6.56-6.62 (m, 2H), 4.99 (dd, *J*= 5.8, 7.0 Hz, 1H), 4.53 (br s, 1H), 3.51 (dd, *J* = 5.2, 18.0 Hz, 1H), 3.42 (dd, *J* = 7.2, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 159.0, 147.2, 137.0, 135.1, 133.6, 129.3, 128.9, 128.4, 127.7 117.9 114.4, 114.0, 55.5, 55.4, 54.44, 54.39, 46.6; MS (EI) *m/z* M^+ for $C_{22}H_{21}NO_2$ calc. 331, found 331 (M^+, 10), 238 (8), 212 (100), 168 (6), 105 (81).

Compound **4g**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.95 (m, 2H), 7.55-7.62 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.08-7.16 (m, 2H), 6.90-6.98 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.54-6.62 (m, 2H), 5.90-5.96 (m, 2H), 4.93 (dd, *J* = 5.4, 7.4 Hz, 1H), 4.53 (br s, 1H), 3.48 (dd, *J* = 5.4, 16.2 Hz, 1H), 3.39 (dd, *J* = 7.8, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.4, 148.2, 147.1, 146.9, 137.3, 136.9, 133.7, 129.3, 128.9, 128.4, 119.7, 118.0, 114.0, 108.7, 107.0, 101.2, 54.8, 46.7; MS (EI) *m/z* M^+ for $C_{22}H_{19}NO_3$ calc. 345, found 345 (M^+, 21), 252 (21), 226 (100), 148 (8), 105 (81).

Compound **4h**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.95 (m, 2H), 7.79 (t, *J* = 1.6 Hz, 1H), 7.70-7.75 (m, 1H), 7.56-7.63 (m, 1H), 7.40-7.55 (m, 4H), 7.10-7.16 (m, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.53-6.58 (m, 2H), 5.07 (t, *J* = 6.2 Hz, 1H), 4.69 (br s, 1H), 3.50 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.6, 146.6, 145.0, 136.6, 134.0, 131.5, 131.3, 130.4, 129.8, 129.5, 129.1, 128.4, 119.1, 118.6, 114.0, 113.0, 54.2, 46.1; MS (EI) *m/z* M^+ for $C_{22}H_{18}N_2O$ calc. 326, found 326 (M^+, 42), 234 (17), 207 (100), 156 (8), 105 (71).

Compound **4i**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.95 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.08-7.18 (m, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 2H), 3.76-4.00 (m, 2H), 3.24 (dd, *J*= 5.6, 16.8 Hz, 1H), 3.12 (dd, *J* = 5.4, 16.6 Hz, 1H), 1.90-2.02 (m, 1H), 1.54-1.84 (m, 5H), 1.00-1.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.7, 147.9, 137.4, 133.3, 129.5, 128.8, 128.3, 117.2, 113.4, 54.9, 42.2, 40.5, 30.0, 29.6, 26.7, 26.52, 26.50; MS (EI) *m/z* M^+ for $C_{21}H_{25}NO$ calc. 307, found 307 (M^+, 11), 224 (100), 188 (17), 119 (6), 105 (76).

Compound **4j**: ^1H NMR (DMSO-d_6, 400 MHz) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 7.2 Hz, 1H), 4.91 (dd, *J* = 7.6, 12.4 Hz, 1H), 3.69 (s, 3H), 3.59 (dd, *J*= 8.4, 16.8 Hz, 1H), 3.28 (dd, *J* = 4.4, 16.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 198.0, 158.8, 147.8, 137.4, 135.9, 133.9, 131.9, 129.4, 128.7, 128.4, 115.5, 114.4, 107.1, 55.7, 55.6, 52.9, 47.1; MS (EI) *m/z* M^+ for $C_{22}H_{20}BrNO_2$ calc. 409, found 409 (M^+, 6), 290 (53), 238 (36), 171 (30), 161 (17), 134 (8), 105 (100).

Compound **4k**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88-7.94 (m, 2H), 7.54-7.62 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H),7.00-7.06 (m, 2H), 6.82-6.90 (m, 2H), 6.45-6.52 (m, 2H), 4.91 (dd, *J* = 5.2, 7.2 Hz, 1H), 4.60 (br s, 1H), 3.78 (s, 1H), 3.48 (dd, *J* = 5.4, 16.2 Hz, 1H), 3.40 (dd, *J* = 7.4, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5, 159.1, 145.8, 136.9, 134.6, 133.7, 129.1, 128.9, 128.4, 127.6, 122.6, 115.2, 114.5, 55.49, 55.45, 54.58, 54.53, 46.5; MS (EI) *m/z* M^+ for $C_{22}H_{20}ClNO_2$ calc. 365, found 365 (M^+, 7), 246 (79), 161 (6), 127 (11), 105 (100).

Compound **4l**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.80 (t, *J* = 8.8 Hz, 2H), 6.46-6.55 (m, 2H), 4.89 (dd, *J* = 5.4, 7.4 Hz, 1H), 4.40 (br s, 1H), 3.79 (s, 3H), 3.48 (dd, *J* = 5.2, 16.0 Hz, 1H), 3.39 (dd, *J* = 7.6, 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 159.1, 156.2 (d, J_{cf} = 234.3 Hz), 143.6 (d, J_{cf} = 2.2 Hz), 136.9, 134.9, 133.7, 128.9, 128.4, 127.6, 115.7 (d, J_{cf} = 22.3 Hz), 115.1 (d, J_{cf} = 6.7 Hz), 114.4, 55.5, 55.4, 55.13, 55.08, 44.6; MS (EI) *m/z* M^+ for $C_{22}H_{20}FNO_2$ calc. 349, found 349 (M^+, 15), 239 (14), 186 (7), 122 (11), 105 (87).

Compound **4m**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88-7.96 (m, 2H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 2H), 4.90 (dd, *J* = 5.6, 7.2 Hz, 1H), 4.26 (br s, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.47 (dd, *J* = 5.4, 16.2 Hz, 1H), 3.40 (dd, *J* = 7.4, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.7, 159.0, 152.5, 141.5, 137.0, 135.4, 133.6, 128.9, 128.4, 127.7, 115.6, 114.9, 114.4, 55.93, 55.88, 55.48, 55.43, 55.36, 55.31, 46.7; MS (EI) *m/z* M^+ for $C_{23}H_{23}NO_3$ calc. 361, found 361 (M^+, 12), 242 (99), 226 (36), 161 (9), 134 (14), 123 (24), 105 (100).

Compound **4n**: ^1H NMR (DMSO-d_6, 400 MHz) δ 8.38 (s, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 6.36 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 8.4 Hz, 1H), 4.83 (dd, *J*= 8.0, 13.2 Hz, 1H),3.68 (s, 3H), 3.52 (dd, *J*= 8.4, 16.4 Hz, 1H), 3.23 (dd, *J* = 5.2, 16.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 198.6, 158.6, 149.0, 141.3, 137.6, 136.8, 133.8, 129.4, 128.7, 128.4, 116.1, 115.2, 114.2, 55.62, 55.59, 54.3, 47.3; MS (EI) *m/z* M^+ for $C_{22}H_{21}NO_3$ calc. 347, found 347 (M^+, 12), 238 (28), 227 (100), 183 (8), 161 (14), 120 (21), 105 (89).

Acknowledgments. This research was supported by research grants from Catholic University of Daegu in 2008.

References

1. (a) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320-336. (b) For a comprehensive review of polymer-supported reagents, see: Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, *23*, 3815-4195.
2. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L.

Chem. Rev. **2002**, *102*, 2227-2302.
3. (a) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121,* 11229-11230. (b) Kwueon, E. K.; Choi, D. S.; Choi, H. Y.; Lee, Y. J.; Jo, C. H.; Hwang, S. H.; Park, Y. S.; Song, C. E. *Bull. Korean Chem. Soc.* **2005**, *26*, 1839-1842.
4. (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nahayama, S.; Hachiya, I. *Synlett* **1995**, 233-234. (b) Lee, S.-g.; Park, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1367-1368.
5. (a) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256-2257. (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8911-8978. (c) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron Lett.* **1996**, *37*, 9221-9224.
6. (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985-2986. (b) Nagayama, S.; Kobyashi, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 567-569.
7. Lee, B. S.; Mahajan, S.; Janda, K. D. *Tetrahedron* **2005**, *61*, 3081-3086.
8. Lee, B. S.; Mahajan, S.; Janda, K. D. *Tetrahedron Lett*. **2005**, *46*, 807-810.