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Polymer Scandium-Catalyzed Three-Component Reactions Leading to Diverse Amino Ketone, Amino Ester, and Amino Nitrile Derivatives

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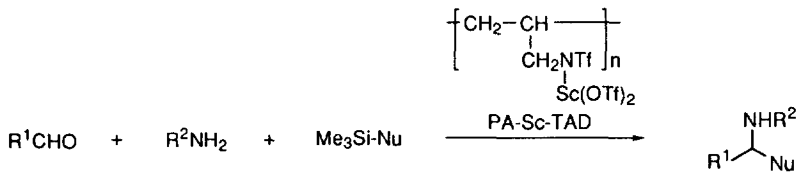
Abstract: *In the presence of a polymer-supported scandium catalyst (PA-Sc-TAD), three-component reactions between aldehydes, amines, and silylated nucleophiles proceeded smoothly to afford β-amino ketones, β-amino esters, and α-amino nitriles in high yields. These reactions provide a useful route to large numbers of structurally distinct amino group-containing compounds of high quality and quantity.*

Development of efficient new methods for the synthesis of large numbers of structurally distinct molecules is becoming one of the most important tasks in organic synthesis. Combinatorial synthesis[1] may provide a new way to the goal, however, methods using polymer-supported reagents (solid phase synthesis) have some limitations such as low reactivities and low loading levels of polymer-supported substrates, which prevent large-scale syntheses, etc. In order to overcome these problems, we have developed a new method for the preparation of libraries using a polymer catalyst.[2] By exploiting active polymer catalysts,[3] low reactivity would be improved and large-scale synthesis would become possible. Actually, a new method for the preparation of a quinoline library using a novel polymer-supported scandium catalyst has been developed recently.[2b] According to this method, a number of quinoline derivatives can be rapidly prepared in more than hundreds of milligrams quantities. We have further examined the catalyst ability of the polymer in other synthetic reactions. In this paper, we report polymer-catalyzed three-component reactions between aldehydes, amines, and silylated nucleophiles, leading to amino ketone, amino ester, and amino nitrile derivatives.



We have already shown that three-component reactions[4] between aldehydes, amines, and silyl enolates proceed smoothly in the presence of a catalytic amount of lanthanide triflate ($Ln(OTf)_3$).[5] When benzaldehyde, aniline, and the silyl enol ether of propiophenone (**1**) were combined in the presence of polyallylscandium trifylamide ditriflate (PA-Sc-TAD),[2b] it was found that the reaction proceeded a little slower compared to that using $Ln(OTf)_3$ as a catalyst, but that the clean reaction proceeded smoothly at room temperature to afford the corresponding β-amino ketone in a 91% yield (after column chromatography on silica gel). In this reaction, the molar ratio of aldehyde : amine : **1** was 1 : 1 : 1.1, and no side reaction was observed. After the reaction was completed, the catalyst was filtered and the filtrate was concentrated *in vacuo* to afford the almost pure β-amino ketone.[6] Other examples are shown in Table 1 (entries 1-12). Heterocyclic and aliphatic aldehydes and a glyoxal also worked well with various amines and **1** to give β-amino ketone derivatives in high yields.

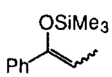
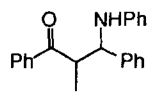
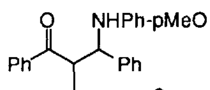
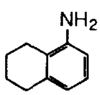
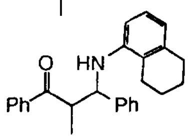
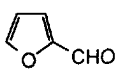
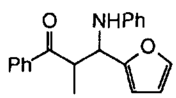
We then examined the reactions using the ketene silyl acetal of methyl isobutylate (**2**) as a silylated nucleophile. It was expected that a β-amino ester could be produced by the reaction of cyclohexanecarboxyaldehyde, p-chloroaniline, and ketene silyl acetal **2** under standard conditions. However, only a trace amount of the product was obtained after 19 h at room temperature. It was assumed that water was produced in the formation of the imine from the aldehyde and the amine, and that the ketene silyl acetal was decomposed by this water leading to the low yield. We then added magnesium sulfate ($MgSO_4$) as a dehydrating agent and the yield was dramatically improved to afford the desired adduct in a 74% yield. Under these reaction conditions, several β-amino ester derivatives were obtained in high yields (Table 1, entries 13-18).

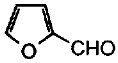
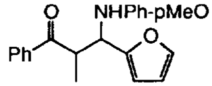
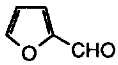
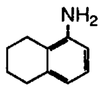
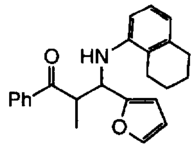
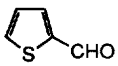
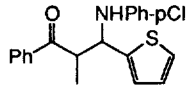
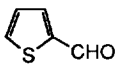
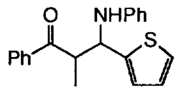
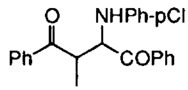
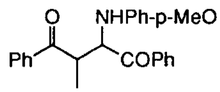
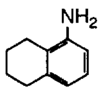
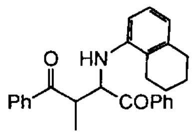
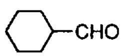
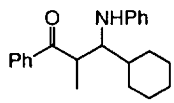
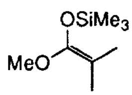
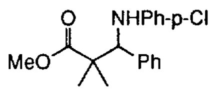
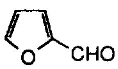
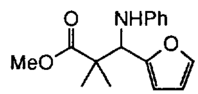
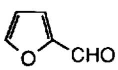
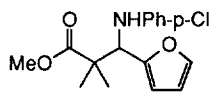
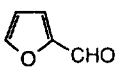
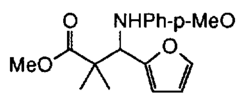
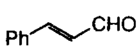
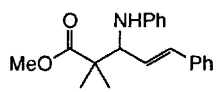
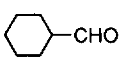
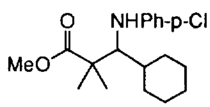
Finally, we used cyanotrimethylsilane (TMSCN) as a silylated nucleophile. The three component reactions between aldehydes, amines, and TMSCN proceeded smoothly in the presence of PA-Sc-TAD to afford various α-amino nitrile derivatives (Table 1, entries 19-24).[7,8]

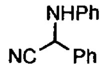
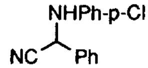
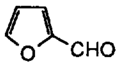
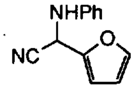
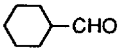
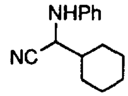
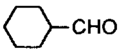
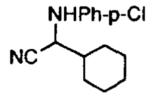
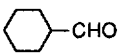
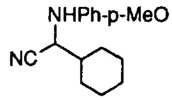
A typical experimental procedure is described as follows: In the presence of PA-Sc-TAD (56.0 mg), an aldehyde (0.40 mmol), an aromatic amine (0.40 mmol), and a silylated reagent (0.44 mmol) were mixed in CH_2Cl_2-CH_3CN (2:1, 2.4 ml). When ketene silyl acetals were used, $MgSO_4$ (125 mg) was added beforehand. The mixture was stirred at room temperature for 19 h and hexane (20 ml) was added. The catalyst was filtered and the filtrate was concentrated *in vacuo* to afford a crude adduct. After purification by column chromatography (silica gel), the desired adduct was obtained in a high yield.

In summary, three-component reactions between aldehydes, amines, and silylated nucleophiles have been successfully carried out by using a polymer scandium catalyst to afford β-amino ketones, β-amino esters, and α-amino nitriles in high yields. The reactions are very clean and the procedure is very easy; simply mixing the catalyst (PA-Sc-TAD) and almost equimolar amounts of an aldehyde, an amine, and a silylated nucleophile. After filtration, the filtrates are concentrated to give almost pure products in most cases. It is noted that PA-Sc-TAD can be easily recovered and that continuous use is possible without any loss of activity. These reactions provide a useful route to large numbers of structurally distinct amino group-containing compounds of high quality and quantity.

Table 1. Three-Component Reactions Using a Polymer Scandium Catalyst[a)]

Entry	Aldehyde	Amine	Silyl Nucleophile	Product	Yield/%[b)]
1	PhCHO	$PhNH_2$	 1		91 (1.1:1)[c)]
2	PhCHO	p-MeO-$PhNH_2$	1		87 (1.2:1)
3	PhCHO		1		92 (2.2:1)
4		$PhNH_2$	1		84 (1.2:1)

5		*p*-MeO-PhNH2	1		85 (1.2:1)
6			1		91 (4.0:1)
7		*p*-Cl-PhNH2	1		91 (1.2:1)
8		PhNH2	1		87 (1.1:1)
9	PhCOCHO	*p*-Cl-PhNH2	1		95 (2.6:1)
10	PhCOCHO	*p*-MeO-PhNH2	1		91 (1.9:1)
11	PhCOCHO		1		84 (1.6:1)
12		PhNH2	1		77 (2.1:1)
13	PhCHO	*p*-Cl-PhNH2	 2		88
14		PhNH2	2		89
15		*p*-Cl-PhNH2	2		87
16		*p*-MeO-PhNH2	2		85
17		PhNH2	2		73
18		*p*-ClPhNH2	2		74

19	PhCHO	$PhNH_2$	Me_3SiCN **3**		86
20	PhCHO	*p*-Cl-$PhNH_2$	**3**		94
21		$PhNH_2$	**3**		83
22		$PhNH_2$	**3**		96
23		*p*-$ClPhNH_2$	**3**		99
24		*p*-$MeOPhNH_2$	**3**		96

a) All the reactions were carried out at room temperature. Magnesium sulfate was added when **2** was used (see the text). b) Isolated yields. c) Diastereomer ratio determined by ^1H and/or ^{13}C NMR. Relative stereochemical assignment was not made.

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(5) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773-5776.

(6) A small excess of **1** was removed under reduced pressure.

(7) For synthesis of α-amino nitrile, *Review*: Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148-162.

(8) We have found that the reactions of imine with TMSCN or three-component reactions of aldehydes, amines, and TMSCN are efficiently catalyzed by $Ln(OTf)_3$. Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett in press.*

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