

Ln(OTf)₃- or Sc(OTf)₃-Catalyzed Three Components Coupling Reactions between Aldehydes, Amines, and Dienes or Alkenes. Efficient Syntheses of Pyridine and Quinoline Derivatives

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Three components coupling reactions between aldehydes, amines, and dienes or alkenes were catalyzed by lanthanide or scandium triflate to afford pyridine and quinoline derivatives in high yields. The Lewis acid catalysts were stable and kept their activity even in the presence of water and amines.

The imino Diels-Alder reaction is among the most powerful synthetic tools for constructing N-containing six-membered heterocycles, such as pyridines and quinolines.¹ Although Lewis acids often promote these reactions, more than stoichiometric amounts of the acids are required due to the strong coordination of the acids to nitrogen atoms.¹ Another problem is instability of imines (Schiff bases) employed in these reactions, especially under the influence of Lewis acids. It is desirable that the imines activated by Lewis acids are immediately trapped by dienes or dienophiles.² In 1989, Weinreb et al. reported a convenient procedure for imino Diels-Alder reaction of an aldehyde and a 1,3-diene with N-sulfinyl p-toluenesulfonamide via N-sulfonyl imine produced *in situ*, by using a stoichiometric amount of BF₃·OEt₂ as a promoter.³

In this report, we describe that three components coupling reactions between aldehydes, amines, and alkenes via imine formation and imino Diels-Alder-type reactions are performed by using lanthanide triflate (Ln(OTf)₃) or scandium triflate (Sc(OTf)₃) as a catalyst (5-10 mol% use), to afford pyridine and quinoline derivatives in high yields. Unique reactivities of imines which are prepared *in situ* and work as both dienophiles and azadienes under certain conditions are also reported.

Recently, we found that Ln(OTf)₃ and Sc(OTf)₃ were stable in water and realized Lewis acid catalysis in aqueous solutions.^{4,5} We also demonstrated that these triflates efficiently activated not only aldehydes but also imines.^{4,6} Bearing in mind the usefulness and efficiency of one-pot procedures, we tested use of Ln(OTf)₃ and Sc(OTf)₃ as catalysts in imine formation and successive imino Diels-Alder-type reactions.

First, in the presence of 10 mol% of ytterbium triflate (Yb(OTf)₃, a representative of lanthanide triflate) and magnesium sulfate, benzaldehyde was treated with aniline and 2-trimethylsiloxy-4-methoxy-1,3-butadiene (Danishefsky's diene, **1**)⁷ successively in acetonitrile at room temperature. The three components coupling reaction proceeded smoothly to afford the corresponding tetrahydropyridine derivative in an 80% yield. It is noteworthy that Yb(OTf)₃ kept its activity and effectively catalyzed the reaction even in the coexistence of water and the amine.⁸ Use of Sc(OTf)₃ slightly improved the yield. Other examples of the three components coupling reactions are shown in Table 1.⁹ Phenylglyoxal monohydrate reacted with p-anisidine and **1** to give the corresponding tetrahydropyridine derivative in a 76% yield. The imine derived from phenylglyoxal is known to be highly hygroscopic and that its purification by distillation or chromatography is very difficult due to its instability.¹⁰ In the reaction of 2,3-dimethylbutadiene, a moderate yield was obtained.

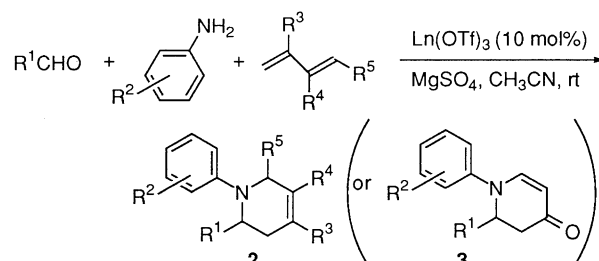


Table 1. Ln(OTf)₃-Catalyzed Three Components Coupling Reactions (1). Intermediate Imines As Dienophiles

| R ¹ | R ² | Diene | Product | Ln | Yield /% |
|----------------|----------------|----------|----------|----|----------|
| Ph | H | | 3 | Yb | 80 |
| Ph | H | 1 | 3 | Sc | 83 |
| Ph | p-MeO | 1 | 3 | Yb | 83 |
| PhCO | p-MeO | 1 | 3 | Yb | 76 |
| PhCO | p-MeO | | 2 | Sc | 44 |

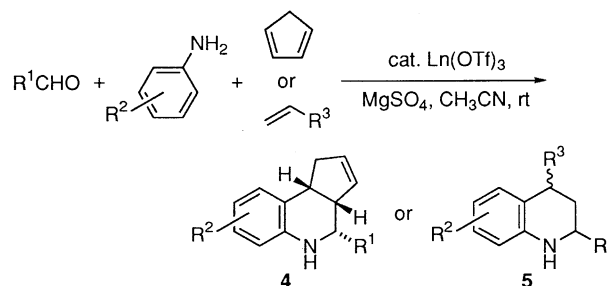
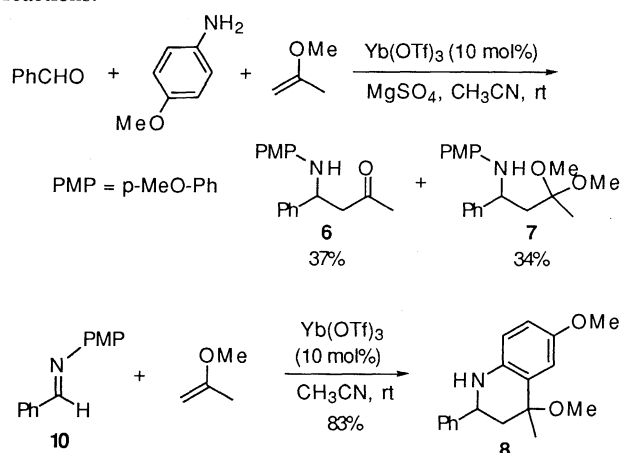


Table 2. Ln(OTf)₃-Catalyzed Three Components Coupling Reactions (2). Intermediate Imines As Azadienes

| R ¹ | R ² | Alkene | Product | Ln | Yield /% |
|----------------|----------------|--------|----------|----|----------|
| Ph | H | | 4 | Yb | 56 |
| PhCO | p-MeO | | 4 | Yb | 94 |
| MeOCO | p-MeO | | 4 | Yb | 80 |
| Ph | H | | 5 | Sc | 83 |
| Ph | o-MeO | | 5 | Yb | 86 |
| Ph | p-MeO | | 5 | Yb | 60 |

Next, we performed the reaction between benzaldehyde, anisidine, and cyclopentadiene under the same reaction

conditions. It was found that the reaction course changed in this case and that a tetrahydroquinoline derivative was obtained in a 56% yield. In this reaction, an imine produced *in situ* worked as an azadiene toward one of double bonds of cyclopentadiene as a dienophile.^{10,11} Other examples are shown in Table 2. A vinyl sulfide and a vinyl ether worked well as dienophiles to afford tetrahydroquinoline derivatives in high yields.¹² On the other hand, the three components coupling reaction between benzaldehyde, anisidine, and 2-methoxypropene did not give tetrahydroquinoline derivative **8** but β -amino ketone **6** and its dimethylacetal **7**. A possible mechanism for the formation of **6** and **7** is shown in Scheme 1. Intermediate **9** is quenched by water and methanol generated *in situ* to afford **6** and **7**, respectively. Very interestingly, imine **10** reacted with 2-methoxypropene in the presence of 10 mol% of Yb(OTf)₃ under anhydrous conditions to produce tetrahydroquinoline derivative **8** in an 83% yield.¹³ It is noted that these results suggest a stepwise mechanism in these types of imino Diels Alder reactions.¹⁴

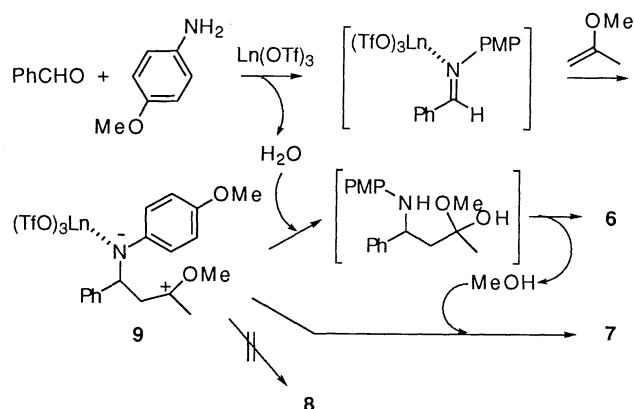


Further studies to clarify the precise mechanism of these reactions as well as to develop new synthetic reactions using the properties of Ln(OTf)₃ and Sc(OTf)₃ are now actively in progress.

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Scheme 1. A Possible Mechanism for the Formation of **6** and **7**

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- When typical Lewis acids such as BF₃·OEt₂ and ZnCl₂ (100 mol%) were used instead of the rare earth metal triflates under the same reaction conditions, lower yields were observed (23% and 12%, respectively).
- A typical experimental procedure is described for the three components coupling reactions between benzaldehyde, aniline, and **1**. To a suspension of Yb(OTf)₃ (0.05 mmol, 10 mol%) and magnesium sulfate (400 mg) in acetonitrile (0.5 ml) was added benzaldehyde (0.5 mmol) and aniline (0.5 mmol) in acetonitrile (1.5 ml), and then **1** (1.5 mmol) in acetonitrile (0.5 ml) at 0 °C. After the mixture was stirred for 20 h at this temperature, water was added and the product was extracted with dichloromethane. After a usual work up, the crude product was chromatographed on silica gel to afford **3** (R¹ = Ph, R² = H) in an 80% yield. When other lanthanide triflates than Yb(OTf)₃ were used, **3** was also obtained in good yields.
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- As for the reactions of vinyl ethers, see Y. S. Cheng, E. Ho, P. S. Mariano, and H. L. Ammon, *J. Org. Chem.*, **56**, 5678 (1985); T. Joh and N. Hagihara, *Tetrahedron Lett.*, **1967**, 4199, and references cited therein. As for the reactions of vinyl sulfides, see K. Narasaka and T. Shibata, *Heterocycles*, **35**, 1039 (1993).
- In this reaction, small amounts of quinoline derivative **11** (3%) and acetal **7** (2%) were obtained. We also found that isolated **8** were converted to **11** under acidic conditions. Cf. T. Shindo, Y. Taniguchi, K. Takaki, Y. Fujiwara, *Abstracts of Papers*, the 67th Annual Meeting of the Chemical Society of Japan, Tokyo, March 1994; 4J234, p 1071.
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