

Lewis Acid-Promoted Radical Carbon-Carbon Bond Forming Reactions with *N*-Ethylpiperidine Hypophosphite

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Construction of carbon-carbon bonds is one of the most important tasks in organic synthesis, and the well-developed radical reactions have become important synthetic tools for forming carbon-carbon bonds of biologically important molecules.¹ In the process, organotin hydrides have played a major role. Although organotin hydrides give high yields, they have several drawbacks. Their toxicity prevents them from being used on a practical scale, and it is difficult to eliminate toxic by-products from the desired products. Therefore, organotin hydrides are not acceptable in an industrial process of manufacturing drugs and medicines. Consequently, various alternatives to organotin hydrides have been reported.² Among them, hypophosphorous acid and its salts have shown to be suitable alternatives to organotin hydrides in radical reactions.³ Hypophosphorous acid and its salts have advantages over organotin hydrides in cost-effectiveness, non-toxicity and easy work-up process.

Electron-deficient alkenes are generally employed in radical carbon-carbon bond forming reactions because of the nucleophilic character of alkyl radicals which are the most frequently used radical donors in organic synthesis.^{1d,4} However, it is not easy to accomplish the radical carbon-carbon bond forming reactions with β -substituted alkenes even though β -substituted alkenes have an electron-withdrawing group.⁵ Therefore, a general method for the radical carbon-carbon bond forming reactions with β -substituted alkenes is highly appreciated.

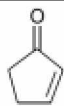

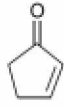
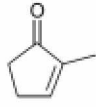
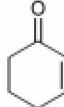
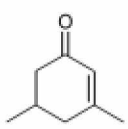
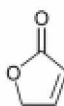
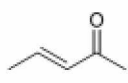

Our recent studies on the radical addition reactions with *N*-ethylpiperidine hypophosphite (EHP) showed that β -substituted alkenes are hardly radical acceptors.³ Recently,

Table 1. Effect of Lewis acids on radical addition reaction to methyl crotonate (10 equiv) in dioxane

Entry	Lewis acid	Yield (%)
1	none	0
2	BF ₃ ·OEt ₂	51
3	ZnCl ₂	47
4	AlCl ₃	32
5	InCl ₃	25
6	Yb(OTf) ₃	66
7	Sc(OTf) ₃	64

Lewis acids are frequently employed in radical reactions, especially for stereoselective radical reactions.⁶ We anticipated that use of Lewis acids in radical addition reactions

Table 2. Reaction of cyclohexyl iodide and various β -substituted alkenes (10 equiv) with EHP (7 equiv) in the presence of Yb(OTf)₃ in dioxane

Entry	Substrate	Yb(OTf) ₃ (equiv)	AIBN (equiv)	Time (h)	Yield (%)
1		1	0.5	1	86
2		0	0.5	1	50
3		1	1.0 ^a	1	57 (25) ^b
4		1	0.5	3	92
5		1	0.5	3	80
6		1	1.0	6	0
7		1	0.5	3	54
8		1	0.5	3	75
9		1	0.5	3	60

^aEt₃B·O₂ was used as initiator at room temperature. ^b3-Ethylpentanone.

with EPHP would improve the reactivity of the radical acceptor by increasing the electron-withdrawing nature of an olefinic linkage via complexation of a Lewis acid. Herein, we report on Lewis acid-promoted radical carbon-carbon bond forming reactions of β -substituted alkenes with EPHP.

The first system chosen for this study was the reaction of cyclohexyl iodide and methyl crotonate with a series of Lewis acids to determine which were most effective at promoting addition reactions (Table 1). In the absence of a Lewis acid, no addition product was detected. Lewis acids in lanthanide family, Yb(OTf)₃ and Sc(OTf)₃ proved to be highly effective promoters for the radical addition reactions of β -substituted alkenes with EPHP, while common Lewis acids such as BF₃·OEt₂, ZnCl₂, AlCl₃ and InCl₃ enhanced the yields of the addition product moderately.

Yb(OTf)₃ is the choice of Lewis acid for the addition reactions. The reactivity of various β -substituted alkenes was surveyed under reaction conditions, and the results are summarized in Table 2. The reaction of 2-cyclopentenone under the standard reaction conditions produced an 86% yield of the addition product (entry 1). A blank experiment was carried out without using Yb(OTf)₃, which gave a low yield of the addition product (entry 2). Although the reaction proceeded smoothly at room temperature using Et₃B as initiator, 3-ethylcyclopentanone, ethylated by-product was also produced along with the desired addition product (entry 3). Cyclic enones afforded high yields of the addition products (entries 4 and 5). However, β -substituted cyclic enones remained intact (entry 6). Unsaturated lactone, acyclic ketone and nitrile gave the addition products in moderate yields under reaction conditions (entries 7-9).

In conclusion, we have shown that Lewis acids promote EPHP-mediated radical addition reactions. Our method may be used as a process of forming carbon-carbon bonds with β -substituted alkenes in synthetic chemistry.

Typical procedure: A solution of cyclohexyl iodide (0.043 mL, 0.333 mmol), 2-cyclopentenone (0.28 mL, 3.33 mmol), Yb(OTf)₃ (207 mg, 0.333 mmol) and EPHP (2.21 mL, 2.33 mmol, 1.05 M solution in dioxane) in dry dioxane (3 mL) under argon was treated with AIBN (28 mg, 0.167 mmol) twice (30 min interval) during reflux. The reaction was followed by TLC. When the reaction was completed, the reaction mixture was washed with saturated NH₄Cl and

brine. The organic layer was dried over anhydrous MgSO₄. After filtration, the solvent was removed in vacuum and the residue was separated by flash column chromatography on silica gel (eluent: hexanes/EtOAc, 10:1) to afford 3-cyclohexylcyclopentanone (48 mg, 86%).

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