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Ytterbium(III) triflate-catalyzed asymmetric nucleophilic addition of functionalized lithium (α -carbalkoxyvinyl)cuprates to chiral *p*-toluenesulfinimines (thiooxime *S*-oxides)

Guigen Li,* Han-Xun Wei and Jason D. Hook

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

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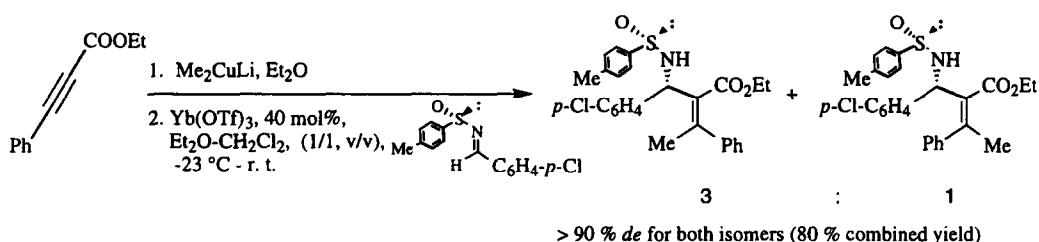
Abstract

Ytterbium(III) triflate has been found to catalyze anionic additions of functionalized lithium (α -carbalkoxyvinyl)cuprates to chiral *p*-toluenesulfinimines (thiooxime *S*-oxides) in a cosolvent system ($\text{Et}_2\text{O}-\text{CH}_2\text{Cl}_2$). This new system has made it possible to utilize those *p*-toluenesulfinimines of low solubility in Et_2O as the electrophiles to react with anionic (α -carbalkoxyvinyl)cuprates for the asymmetric synthesis of the corresponding β -mono and β,β -disubstituted Baylis–Hillman adducts. Modest yields (51.0–64.4% yield) and good to excellent diastereoselectivities (>90% *de*) were obtained. © 1999 Elsevier Science Ltd. All rights reserved.

Chiral *p*-toluenesulfinimines (thiooxime *S*-oxides) pioneered by Davis^{1,2} have been extensively utilized as electrophilic acceptors to react with various anionic species for the stereoselective synthesis of many organic compounds, such as α - and β -amino acids,³ *N*-sulfinyl *cis*-aziridine 2-carboxylic acids,⁴ and amines,⁵ etc. These organometallic species include Grignard reagents (RMgX), alkylaluminum cyanides (Et_2AlCN) and enolates [$\text{CH}_2=\text{C}(\text{OLi})\text{OMe}$]. Recently, we developed a novel tandem vicinal difunctionalization method by reacting chiral *p*-toluenesulfinimines (thiooxime *S*-oxides) with functionalized lithium (α -carbalkoxyvinyl)cuprates, which were derived from Michael-type addition of R_2CuLi to α,β -acetylenic esters, for the asymmetric synthesis of unusual Baylis–Hillman adducts. This asymmetric carbon–carbon bond formation is promoted by a stoichiometric amount of Et_2AlCl in a diethyl ether solution.⁶ During our efforts to study the scope of this reaction by using various chiral *p*-toluenesulfinimines substrates, we encountered a solubility problem, i.e. some thiooxime *S*-oxides (e.g. *para*-chlorine and fluorine derivatives) are insoluble in diethyl ether. Furthermore, the Lewis acid Et_2AlCl cannot effectively promote the reaction in several cosolvent systems. In this report, we would like to describe a new ytterbium(III) triflate-catalyzed anionic addition of (α -carbalkoxyvinyl)cuprates to thiooxime *S*-oxides.

* Corresponding author. E-mail: qeggli@ttu.edu

It has been shown that lithium (α -carbalkoxyvinyl)cuprates cannot undergo nucleophilic reactions with thiooxime *S*-oxides when THF was employed as the solvent and various Lewis acids as promoters.⁶ Therefore, lithium (α -carbalkoxyvinyl)cuprates were generated in a diethyl ether solution via the conjugate addition of organocopper lithium reagents to α,β -acetylenic esters as described in the literature.^{7-9a,b,c} To solve the solubility problem of some *p*-toluenesulfinimines in diethyl ether, CH_2Cl_2 was employed to dissolve the thiooxime *S*-oxides. Unfortunately, less than 20% yields were obtained even when a stoichiometric amount of Et_2AlCl was used as the Lewis acid promoter. Among several other Lewis acids that we examined, it was found that ytterbium(III) triflate can catalyze this anionic addition reaction in the $\text{Et}_2\text{O}-\text{CH}_2\text{Cl}_2$ cosolvent system represented in Scheme 1 with the results summarized in Table 1.



Scheme 1. $\text{Yb}(\text{OTf})_3$ -catalyzed asymmetric addition of lithium (α -carbalkoxyvinyl)cuprates to thiooxime *S*-oxides

The present ytterbium(III) triflate-catalyzed carbon–carbon bond forming process is much slower at low temperatures than the Et_2AlCl -promoted process which was performed at $-23-0^\circ\text{C}$ in pure Et_2O solution. Less than 10% of the starting *p*-toluenesulfinimine was consumed at 0°C even after several hours. The reaction had to be carried out at room temperature for more than 10 h to achieve complete conversion in all seven cases as shown in Table 1. The typical procedure is demonstrated by entry 1 in Table 1. Into a dry, nitrogen flushed flask was added purified cuprous iodide (0.210 g, 1.10 mmol) and freshly distilled diethyl ether (5 mL). The resulting solution was cooled to -23°C using a CCl_4 /dry ice bath and a solution of phenyllithium in cyclohexane–diethyl ether (1.8 M, 1.22 mL, 2.20 mmol) was added dropwise via syringe. The resulting homogeneous black solution was stirred for 30 min at 23°C before a solution of ethyl phenylpropiolate (0.213 g, 1.20 mmol) in Et_2O (2 mL) was added in ca. 10 min. The reaction mixture was stirred at -23°C for 2 h, and then a solution of (*S*)-(+)-benzylidene-*p*-toluenesulfinamide (0.243 g, 1.0 mmol) in CH_2Cl_2 (2 mL) and a solution of $\text{Yb}(\text{OTf})_3$ (0.248 g in CH_2Cl_2 , 8.0 mL, 0.40 mmol, 40 mol%) were added in order via a syringe. The CCl_4 /dry ice bath was removed and the resulting mixture was stirred at rt for 16 h. The reaction was finally quenched by the dropwise addition of sat. aqueous NH_4Cl solution (2 mL). The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with 10% aqueous ammonia and brine, dried over anhydrous magnesium sulfate and concentrated to dryness. Purification by flash chromatography (EtOAc :hexane, 1:10, v/v) provided product 1 (0.317 g, 64.0% yield) as colorless oil. ^1H and ^{13}C NMR spectra of the major isomer are identical to the one from the known procedure.⁶ ^1H NMR (200 MHz, CDCl_3): δ 7.60 (d, $J=8.23$ Hz, 2H), 7.52 (d, $J=6.94$ Hz, 2H), 7.36–7.13 (m, 15H), 5.82 (d, $J=10.36$ Hz, 1H), 5.51 (d, $J=10.36$ Hz, 1H), 3.71 (q, $J=7.22$ Hz, 2H), 2.37 (s, 3H), 0.62 (t, $J=7.22$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 169.5, 151.4, 142.8, 142.3, 140.9, 140.7, 139.7, 131.3, 129.4, 128.9, 128.8, 128.4, 128.3, 127.9, 127.8, 127.4, 126.5, 125.7, 60.4, 60.3, 21.3, 13.1.

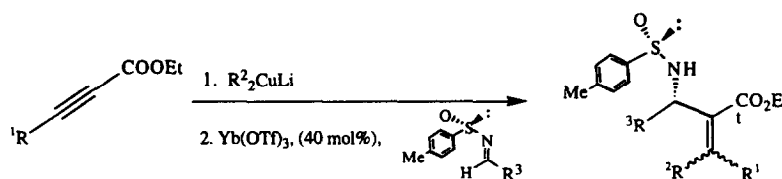
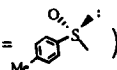
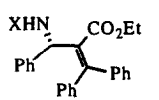
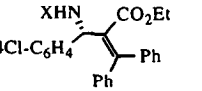
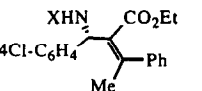
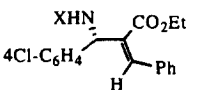

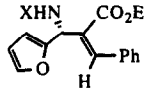
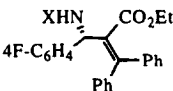

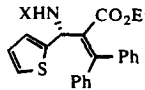


Table 1
Results of Yb(OTf)₃-catalyzed anionic additions of vinylcuprates to sulfinimines

R ¹	R ²	R ³	Product (X = )	Yield (%) ^a	% <i>de</i> ^b (Z/E)
Ph	Ph	Ph		64.0	88.0
Ph	Ph	4-Cl-C ₆ H ₄ -		62.2	64.1
Ph	Me	4-Cl-C ₆ H ₄ -		54.0 ^c	>90 (3:1)
H	Ph	4-Cl-C ₆ H ₄ -		51.0 ^c	>90 (1.8:1)
H	Ph			52.4	>90
Ph	Ph	4-F-C ₆ H ₄ -		61.0	84.2
Ph	Ph			64.4	>90

^a The purified yields after column chromatography; ^b Determined by ¹H-NMR for the purified products, >90 means only one diastereoisomer was observed; ^c The yield of the mixture containing two isomers which were difficult to separate by column chromatography.

Ytterbium(III) triflate and its derivatives have already been used as catalysts or promoters in many asymmetric reactions^{10,11} including the Baylis–Hillman reaction¹² and hydrophosphonylation^{13,14} in several solvent systems (e.g. THF, MeCN and CH₂Cl₂). However, ytterbium(III) triflate is insoluble in diethyl ether even at room temperature. Fortunately, it can be dissolved in Et₂O–CH₂Cl₂ cosolvent system, and therefore can efficiently catalyze the present anionic addition reaction.

The yields of the present process are comparable to those of the Et₂AlCl-promoted system. It is interesting to note that the present room temperature condition can result in high diastereoselectivities (>90% *de*) for several substrates (3–4, 5, 7) and some *Z/E* selectivities (1.8:1 and 3:1 for 3 and 4,

respectively). *Z/E* Selectivities were usually controlled by stereo effects of olefinic terminal groups⁶ in nucleophiles such as alkenylcuprates and allenolates. Both alkenylcuprates and allenolates could exist in equilibrium in the cosolvent system of Et₂O–CH₂Cl₂ with different nucleophilic reactivities toward *p*-toluenesulfinimines. Many factors, such as reagent, starting material, solvent, temperature, etc., could effect the formation and reactivities of alkenylcuprates and allenolates.¹² Further modifications on this new system will be made in the future to achieve higher *Z/E* and diastereoselectivities.

In conclusion, a new Yb(OTf)₃-catalyzed anionic addition of functionalized lithium (α-carbalkoxyvinyl)cuprates to chiral *p*-toluenesulfinimines has been developed. This process can be utilized for the asymmetric synthesis of both β-monosubstituted and β,β-disubstituted α-(aminoalkyl)acrylates, the unusual Baylis–Hillman adducts. The Et₂O–CH₂Cl₂ cosolvent system can overcome the disadvantage of the Et₂AlCl-promoted process in which some thiooxime *S*-oxides with poor solubility in Et₂O do not work well.

Acknowledgements

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