

Copper-Catalyzed Electrophilic Amination of Alkenylzirconocenes with O-Benzoylhydroxylamines: An Efficient Method for Synthesis of Enamines

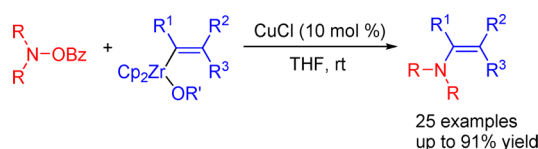
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ABSTRACT



Copper-catalyzed electrophilic amination of alkenylzirconocenes is accomplished under mild reaction conditions. The reaction tolerates a wide range of functional groups and can be used to prepare some hindered enamines.

Enamines are versatile functional groups capable of partaking in a variety of important transformations including regioselective alkylations and acylations, cycloadditions, and a range of heterocycle forming processes.¹ Recently, enamines have received more attention since they can be asymmetrically hydrogenated into chiral amines² or hydroborated into N–B frustrated Lewis pairs.³ The traditional approach for the synthesis of enamines is the condensation of a secondary amine with a carbonyl compound under mineral or Lewis acid catalysis.⁴ While this approach is fairly general, it presents

several limitations, such as harsh reaction conditions and low functional group tolerance. Furthermore, no real control of regiochemistry and stereochemistry have been achieved. Alternative methods for the synthesis of enamines are hydroaminations of alkynes⁵ and methylenation of amides.⁶ Although significant contributions have been made, this method exhibits poor performance for dialkylamine and internal alkynes.⁷ On the other hand, in recent years,

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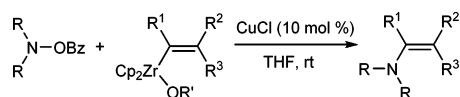
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the Pd- or Cu-catalyzed formation of enamines from electrophilic alkenyl halides and nucleophilic secondary amines is a hallmark reaction in this field.^{8,9} This coupling with dialkylamine is often inefficient; in particular, the amination with secondary acyclic alkylamines or hindered amines is rarely reported. An umpolung strategy, reaction of an electrophilic nitrogen source with a nucleophilic organometallic reagent,^{10,11} would provide a complementary method for the construction of a C–N bond under mild conditions. Although electrophilic amination of arylmetallic and alkylmetallic reagents has been reported,¹² the electrophilic amination of alkenylmetallic reagents has been rarely reported.^{10b,c} As part of an ongoing program in our laboratory to systematically study zirconocene chemistry, we herein describe a copper-catalyzed amination of alkenylzirconocenes with *O*-benzoylhydroxylamines to afford a wide range of enamines (Scheme 1) in a reverse coupling mode under mild conditions.

Scheme 1. Cu-Catalyzed Amination of Alkenylzirconocenes with Hydroxylamines



Alkenylzirconocenes are useful intermediates in organic synthesis,¹³ since they can be easily prepared from

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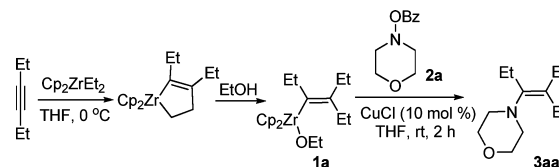
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available materials *via* (i) hydrozirconation of alkynes with the Schwartz's reagent,¹⁴ (ii) zirconacycle-mediated carbocyclization of alkynes,¹⁵ or (iii) oxidative addition of alkenyl halides to Cp₂Zr(II).¹⁶ Reactions of alkenylzirconocenes with *O*-benzoylhydroxylamines could provide a general route to various enamines. Herein, we report details of the synthesis of enamines *via* the reaction of alkenylzirconocenes with *O*-benzoylhydroxylamines.

Scheme 2. Amination of **1a** with **2a**



A typical procedure is as follows. To a solution of alkenylzirconocene **1a**, which was produced by alcoholysis of the corresponding zirconacyclopentene prepared from 3-hexyne and Cp₂ZrEt₂,^{15a} were added CuCl (10 mol %) and 4-benzoyloxymorpholine **2a**. Enamine **3aa** was formed exclusively after the reaction was stirred at rt for 2 h (Scheme 2). After simple extraction workup, enamine **3aa** was isolated in 83% yield with about 95% purity determined by GC analysis. This isolation process is elegant since most enamines are sensitive to air and unsuitable for common column chromatography. In the absence of CuCl, the enamine **3aa** was only detected in a trace amount.

The reactions with 4-benzoyloxymorpholine-derived electrophile **2a** could be performed with a number of alkenylzirconocene species, including alkyl, aryl, alkenyl, and alkynyl substituents. The representative results are summarized in Table 1. Alkenylzirconocenes **1a–1m**, which were prepared by alcoholysis of in situ prepared zirconacyclopentenes,¹⁷ were treated with 4-benzoyloxymorpholine **2a** in the presence of 10 mol % of CuCl, and the corresponding enamine **3aa–3ma** was formed in 78% to 91% isolated yields (entries 1–13). In all the cases above, the reaction afforded only one single isomer. To confirm the structure of the product, yellow single crystals of **3da** suitable for X-ray diffraction analysis were obtained by recrystallization in *n*-hexane. The structure of **3da** clearly shows that two phenyl groups were located in *cis*-form to each other (see Supporting Information), which was consistent with the parent alkenylzirconocene **1d**. It means that the double bond configuration was retained during

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Table 1. Scope of Electrophilic Amination of Various Alkenylzirconocenes^a

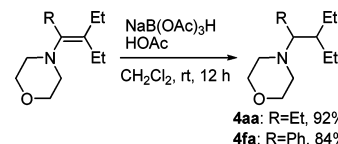
entry	alkenylzirconocene	enamine	yield (%) ^b	entry	alkenylzirconocene	enamine	yield (%) ^b
1			83%	9			86%
2			86%	10			82%
3			85%	11			78%
4			91%	12			87%
5			88%	13			85%
6			85%	14			83%
7			78%	15			81%
8			75%	16			74%

^a Reaction conditions: alkenylzirconocene **1** (0.5 mmol) prepared in situ in 3 mL of THF solution, 4-benzoyloxymorpholine **2a** (0.55 mmol), CuCl (0.05 mmol), N₂, rt, 2 h. ^b Isolated yield based on alkyne.

the amination. This is important for a well-defined preparation of multisubstituted enamines. It is also noteworthy that products **3ea–3ka**, dependent upon three different substituents in the enamines, were successfully obtained (entries 5–11). Notably, products **3ja** and **3ka** are *E/Z* isomers prepared by the different configuration of alkenylzirconocenes (entries 10–11). When alkenylzirconocenes **1n** and **1o**, which were prepared by reaction of the zirconacyclopentenes with diallyl ether,^{15c,d} were employed, skipped dienamines **3na** and **3oa** were formed in 83% and 81% yield, respectively (entries 14–15). In addition, dienylyl zirconocene complex **1p** generated by the alcoholysis of the corresponding zirconacyclopentadiene^{15e} can also be used as a nucleophile to afford dienamine **3pa** (entry 16), which is a particularly interesting type of electron-rich diene for [4 + 2] cycloaddition reactions.¹⁷ All the aminations of alkenylzirconocenes were accomplished in less than 2 h at rt. Hydrozirconation of alkynes with Schwartz's reagent could afford mono- and disubstituted chloroalkenylzirconocenes,¹⁴ which were expected to react with *O*-benzoylhydroxylamine to afford mono- and disubstituted enamines in the presence of CuCl. However, the expected enamines were not observed in such a

reaction; instead, *O*-benzoylhydroxylamine acted as an oxidant and 1,3-diene was isolated.^{18,19} In other words, the reaction is not convenient for the preparation of mono- and disubstituted enamines.

Scheme 3. Reduction of Enamine to Amines by NaB(OAc)₃H

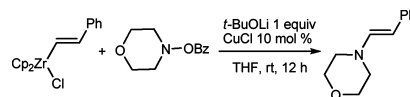


The enamines could be reduced to amines. Here, as examples, the enamines **3aa** and **3fa** were directly reduced with NaB(OAc)₃H/HOAc to isolate **4aa** and **4fa** in 92% and 84% yield, respectively (Scheme 3). This result indirectly indicates efficiency in the synthesis of amines and the purity of the parent enamines.

To establish the full scope of the amination reaction of alkenylzirconocenes, we further explored a range of *O*-benzoylhydroxylamines (Figure 1). *O*-Benzoylhydroxylamine **2b** derived from piperidine was used in the reaction to afford the corresponding enamines (Scheme 4, **3bb** and **3eb**). *O*-Benzoylhydroxylamines **2c–2e** derived from common acyclic amines or hydroxylamines, such as diethylhydroxylamine, *N*-methylbutan-1-amine, and *N*-methylcyclohexanamine, were also used in the reaction to give the corresponding enamines (**3bc**, **3ec**, **3fd**, and **3fe**). Furthermore, *O*-benzoyl-*N,N*-diallylhydroxylamine **2f** was employed in the reaction to give the corresponding enamine **3bf**. Both cyclic and acyclic *O*-benzoylhydroxylamines afforded the corresponding products in excellent yield. Hindered enamines are usually difficult to prepare by traditional methods. When *O*-benzoyl-*N,N*-diisopropylhydroxylamine **2g** was employed, the reaction did not occur at rt. When the reaction mixture was heated to 50 °C for 2 h, enamines **3bg** and **3eg** were obtained in excellent yields. When 1-benzoyloxy-2,2,6,6-tetramethylpiperidine

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(19) LiCl was often used to activate chloroalkenylzirconocenes in the presence of CuCl;¹⁸ however LiCl was not effective in this reaction. When *t*-BuOLi was added, the reaction proceeded to afford enamine in 30% NMR yield. 1,4-Diphenyl-1,3-diene was observed as another product.



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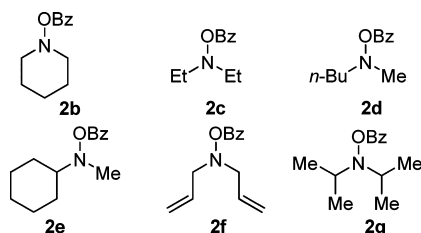
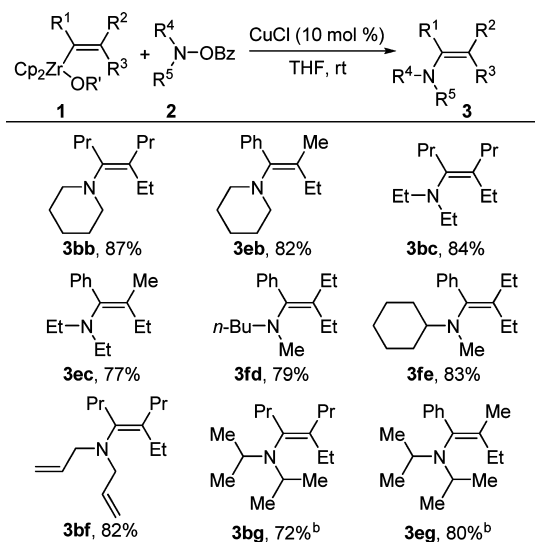


Figure 1. *O*-Benzoylhydroxylamines employed in the reaction.

Scheme 4. Scope of Electrophilic Amination of Various Hydroxylamines^a

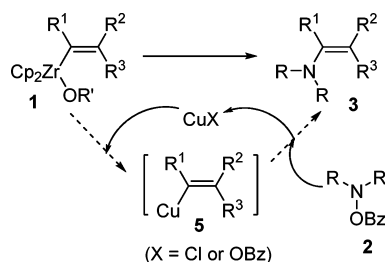


^a Reaction conditions: alkenylzirconocenes **1** (0.5 mmol) prepared in situ in 3 mL of THF solution, *O*-benzoylhydroxylamines **2** (0.55 mmol), CuCl (0.05 mmol), N₂, rt, 2 h, the isolated yield based on alkyne.
^b 50 °C, 2 h.

was used, the corresponding enamine was detected by GC-MS in low yield.

Transmetalations of the C–Zr bond to the C–Cu bond have been extensively observed.²⁰ In combination with

Scheme 5. Possible Reaction Pathway



known facts, a plausible mechanism is shown in Scheme 5. In the first step, alkenylzirconocene **1** is transmetalated with CuCl to give alkenylcopper intermediate **5**. Then subsequent electrophilic amination^{12c} of the alkenylcopper intermediate **5** with hydroxylamine affords enamine **3** with regeneration of the Cu(I) salt.

In summary, we have developed an efficient method for the preparation of enamines *via* copper-catalyzed electrophilic amination of alkenylzirconocene reagents with *O*-benzoylhydroxylamines. The reaction proceeds under mild conditions in high yields with a wide range of functional groups. The products can be efficiently isolated from the reaction mixture by simple extraction. The configuration of enamines is retained during this reaction.

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Supporting Information Available. Experimental procedures, full characterization including ¹H NMR and ¹³C NMR data for all new compounds and X-ray crystal structure of **3da**, and X-ray data for **3da** (CIF). These materials are available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.