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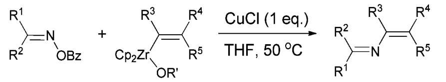
Copper-mediated electrophilic imination of alkenylzirconocenes with *O*-benzoyl ketoximes and aldoximes†

Hailan Liu,[ab] Xiaoyu Yan,[b] Chao Chen,[b] Qingbin Liu*[a] and Chanjuan Xi*[b]

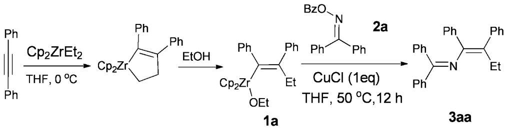
Copper-mediated electrophilic imination of alkenylzirconocenes generated *in situ* from alkynes and zirconocenes is accomplished under mild reaction conditions. The reaction can be used to prepare various 2-azadienes.

Nitrogen-substituted alkenes probably represent the most versatile class of olefinic compounds. The electron-donating ability of nitrogen strongly polarizes the double bond, which allows for an exceptionally high level of reactivity together with a strong differentiation of the two sp^2 carbon atoms.[1–3] Consequently, a number of reactions have been developed for the synthesis of N-substituted alkenes, for example, condensation of a secondary amine with a carbonyl compound[4] or hydroaminations of alkynes afforded enamines.[5] Although significant contributions have been made, these methods still remain rather limited, which is most certainly due to their harsh reaction conditions, low functional group tolerance, and low selectivity. On the other hand, in recent years, metal-promoted olefinic C–N cross-coupling reactions provided a powerful and convenient approach to the abovementioned N-substituted alkenes. Among them, Pd- or Cu-catalyzed cross-coupling reaction of electrophilic alkenyl halides with nucleophilic amides provided a straightforward method for the formation of N-substituted alkenes.[6–8] Meanwhile, an umpolung,[9] electrophilic amination of organometals using a reagent of type R_2N^+ such as chloro- and hydroxylamines has also provided a significant complement to the formation of C–N bonds.[10] Our group also focused on this type of transformation and succeeded in the copper-catalyzed electrophilic aminations of alkenylzirconocenes to obtain a wide range of enamines.[11] In the course of this study, we envisioned that the umpolung strategy using oxime esters as the electrophilic nitrogen reagents could be applied to the imination of alkenylzirconocenes, which would provide a useful method for the synthesis of 2-azadienes that are often used for the synthesis of various heterocycles[3] and are generally prepared by aza-Wittig reaction or enolization of *N*-acyl imines.[12] A few related cross-coupling reactions were studied by Narasaka[13] and Liebeskind[14] and their co-workers using oxime reagents and alkenyl Grignard reagents or alkenylboronic acids or alkenylstannanes. Herein, we describe a copper-mediated electrophilic imination of alkenylzirconocenes with *O*-benzoyl oximes (Scheme 1). This reaction affords a convenient method for the synthesis of 2-azadienes in one-pot from alkynes.



Scheme 1 Cu-mediated imination of alkenylzirconocenes with *O*-benzoyl oximes.

Alkenylzirconocenes are useful intermediates in a number of organic syntheses,[15] since they are easily prepared from available alkynes or alkenyl halides with zirconocene species.[16,17] As part of our ongoing project on alkenylzirconocene chemistry, our initial investigation explored the cross-coupling of alkenylzirconocene derivatives with benzophenone *O*-benzoyloxime **2a**. A typical procedure is as follows. To a solution of alkenylzirconocene **1a**,[18] which was produced by alcoholysis of the corresponding zirconacyclopentene prepared from diphenylacetylene and Cp_2ZrEt_2,[16d] CuCl (1 equiv.) and *O*-benzoyloxime **2a** (1.5 equiv.) were added. 2-Azadiene **3aa** was formed at 50 °C for 12 h (Scheme 2). After workup, 2-azadiene **3aa** was isolated in 76% yield. In this case, benzophenone and diphenylmethanimine were also detected as by-products using GC-MS, and benzophenone was isolated in 11% yield, which is readily separated with the desired product using flash chromatography.



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

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[a] *Institute of Chemistry and Chemical Engineering, Hebei Normal University, Shijiazhuang 050091, China*

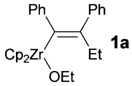
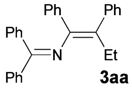
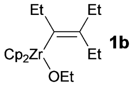
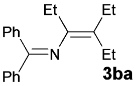
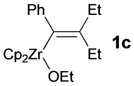
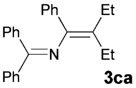
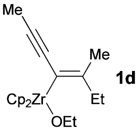
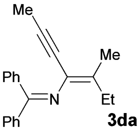
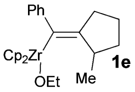
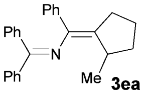
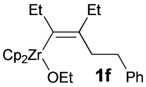
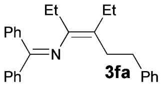
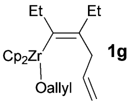
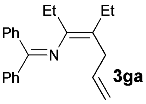
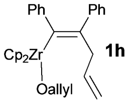
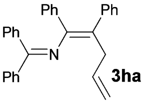
[b] *Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China. E-mail: cjxi@tsinghua.edu.cn*

† Electronic supplementary information (ESI) available: Experimental procedures, full characterization including ^{1}H NMR and ^{13}C NMR data for all new compounds and NOESY of compound **3hc**. See DOI: 10.1039/c3cc41574k

In the absence of CuCl, the 2-azadiene **3aa** was only detected in a trace amount using GC-MS. Use of a catalytic amount of CuCl (10%) afforded the product **3aa** in 8% yield. Replacement of THF with toluene or dichloromethane after formation of alkenylzirconocenes from alkynes and zirconocenes did not allow this reaction to proceed either and the starting materials remained. Other cuprous salts such as CuBr, CuI, and CuOAc afforded the product **3aa** in 47%, 28%, and 35% yields, respectively. Transitioning from *O*-benzoyl to *O*-pentafluorobenzoyl (used by Narasaka[13] and Liebeskind[14] in their studies) did not improve the yield of product **3aa**. Thus, we use the *O*-benzoyloximes as electrophilic nitrogen reagents.

The imination with **2a** was performed with a number of alkenylzirconocene species, including alkyl, aryl, allyl, and alkynyl substituents. The representative results are summarized in Table 1. Alkenylzirconocenes **1a**–**1f** (generated *in situ* by carbozirconation of alkynes)[11,16d] were treated with *O*-benzoyloxime **2a** under the optimized conditions and the corresponding 2-azadienes **3aa**–**3fa** were formed in 48% to 76% isolated yields (entries 1–6). Alkenylzirconocenes **1g** and **1h**, which were prepared by reaction of zirconacyclopentenes with diallyl ethers,[16g] were employed, skipped dienimines **3ga** and **3ha** were formed in 55% and 85% yield, respectively (entries 7 and 8).

Table 1 Electrophilic imination of various alkenylzirconocenes[a]

Entry	Alkenylzirconocene	2-Azadiene	Yield[b] (%)
1	 **1a**	 **3aa**	76 (63)[c]
2	 **1b**	 **3ba**	54 (45)[c]
3	 **1c**	 **3ca**	48 (38)[c]
4	 **1d**	 **3da**	69
5	 **1e**	 **3ea**	51
6	 **1f**	 **3fa**	62
7	 **1g**	 **3ga**	55
8	 **1h**	 **3ha**	85

[a] Reaction conditions: alkenylzirconocene **1** prepared *in situ* from alkynes (0.5 mmol) with zirconocenes in 3 mL of THF solution, *O*-benzoyloxime **2a** (0.75 mmol), CuCl (0.5 mmol), N_2, 50 °C, 12 h. [b] Isolated yield based on alkynes. [c] Reaction was run on a 10 mmol scale.

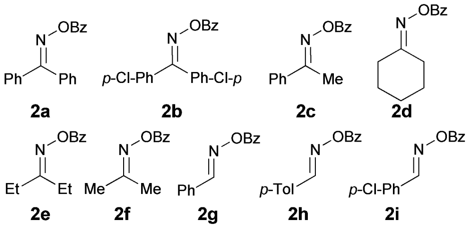
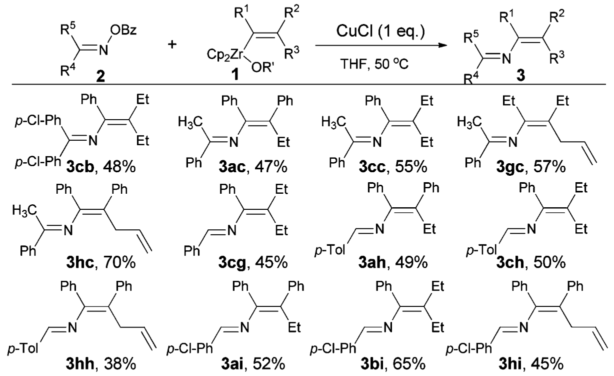


Fig. 1 Range of *O*-benzoyloxime substrates.

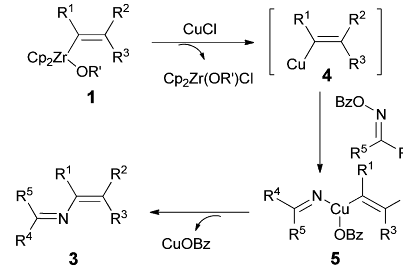


Reaction conditions: alkenylzirconocene **1** prepared in situ from alkyne (0.5 mmol) with zirconocene in 3 mL of THF solution, *O*-benzoyloxime **2** (0.75 mmol), CuCl (0.5 mmol), N_2, 50 °C, 12 h, isolated yield based on alkyne.

Scheme 3 The scope of electrophilic imination.

To establish the full scope of the imination reaction, we further explored a range of *O*-benzoyloximes (Fig. 1) with alkenylzirconocenes **1**. *O*-Benzoyloxime **2b** derived from bis(4-chloropehnyl)methanone[14] was used in the reaction to afford the corresponding 2-azadiene **3cb** in 48% isolated yield (Scheme 3). (*E*)-1-Phenyl-ethanone *O*-benzoyloxime **2c** derived from acetophenone[19] was used in the reaction to give the corresponding 2-azadienes **3ac**, **3cc**, **3gc**, and **3hc** in good yields. The stereochemistry of **3hc** was determined using 2-D NMR. The NOESY spectra (see ESI†) revealed that the methyl group and the vinyl group were in a *cis*-fashion, which is consistent with **2c**. When *O*-benzoyloximes **2d**–**2f** derived from alkyl–alkyl ketones such as cyclohexanone, pentan-3-one, or acetone[19] were employed in the reaction, the expected 2-azadienes were detected using GC-MS in a trace amount and the starting materials remained. *O*-Benzoylaldoximes **2g**–**2i** derived from aldehydes such as benzaldehyde, *p*-tolualdehyde, and *p*-chlorobenzaldehyde[19] were used, the corresponding products **3cg**, **3ah**–**3hh**, and **3ai**–**3hi** were obtained in moderate to good yields. In Liebeskind's work, utilization of aldoxime *O*-carboxylates did not give the desired aldimines, rather they underwent β-elimination to give the corresponding nitrile products under their reaction conditions.[14] It is worth mentioning that abovementioned products are stable and could be purified using flash chromatography on alumina (for details of purification, see ESI†).

Transmetalation of the C–Zr bond to the C–Cu bond has been extensively observed.[20] Oxidative additions to N–O bonded



Scheme 4 Possible reaction pathway.

species are precedented.[14,21] In combination with known facts, a plausible mechanism is shown in Scheme 4. In the first step, alkenylzirconocene **1** is transmetalated with CuCl to give intermediate **4**. Then oxidative addition of *O*-benzoyloximes to N–O bonds forms the intermediate **5**. Finally, subsequent reductive elimination affords 2-azadiene **3**.

In summary, a general copper-mediated electrophilic imination of alkenylzirconocene reagents with *O*-benzoyl ketoximes and aldoximes has been developed. This reaction represents an interesting entry to the synthesis of 2-azadienes within one-pot reaction from alkynes. Further studies on the use of 2-azadienes will be reported in due course.

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