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Copper-Mediated Amidation of Alkenylzirconocenes with Acyl Azides: Formation of Enamides

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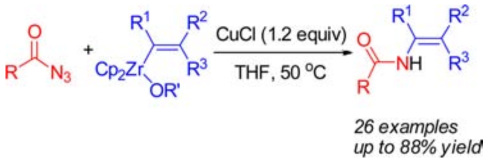
ABSTRACT



Copper-mediated amidation of alkenylzirconocenes generated in situ from alkynes and zirconocenes with acyl azides is accomplished under mild conditions. The reaction can be used to prepare various enamides.

Enamides contain an electron-withdrawing acyl group on the nitrogen atom, and they display an exceptionally fine balance of stability and reactivity of nitrogen-substituted alkenes. Therefore, the enamides provide various insertions into organic molecules as nitrogen-based functional compounds and are widely useful in organic synthesis.[1,2] The traditional synthetic route to enamides is the thermal decomposition of alkylidenebisamides.[3] However, the synthetic method involves rather harsh reaction conditions such as high temperature and/or the use of strong acids and bases. In recent years, metal-promoted olefinic C–N bond formation reactions provided a powerful and convenient approach to the nitrogen-substituted alkenes.[4−7] Among them, Pd- or Cu-catalyzed amidation of alkenyl halides with amides provided a straightforward method for the formation of enamides.[4,5] Meanwhile, copper-promoted amidation of alkenylmetalloids with amides has been also received attention.[8]

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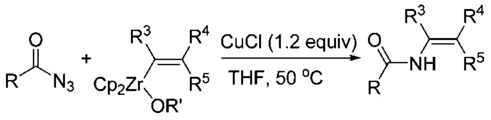
In addition to the use of amides in amidation reactions, other N-atom reagents have been rarely reported in the reaction. Acyl azides are readily accessible and have participated in a wide range of reactions that constructed new carbon−nitrogen bonds.[9] Moreover, molecular nitrogen is released as a byproduct from reactions that is also very attractive from an environmental perspective. However, acyl azides as nitrenoid precursors in the amidation reactions have been far less attention. Our group has succeeded in the copper-mediated aminations and iminations of alkenylzirconocenes to obtain a wide range of enamines[10] and enimines,[11] respectively. As part of our ongoing project on alkenylzirconocene chemistry,[12−14] we envisioned that use of acyl azides as nitrenoid precursors could be applied to the amidation reaction, which would provide a useful method for the synthesis of enamides. Herein, we describe a copper-mediated amidation of alkenylzirconocenes with acyl azides to afford a wide range of enamides under mild conditions (Scheme 1).

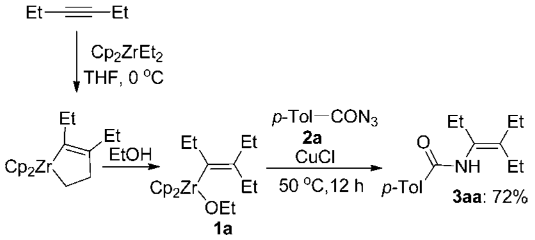
Scheme 1. Cu-Mediated Amidation of Alkenylzirconocenes with Acyl Azides



As an example, alkenylzirconocene **1a**,[15] which was generated by ethanolysis of the corresponding diethylzirconacyclopentene prepared from 3-hexyne and Cp_2ZrEt_2 in THF,[13c] reacted with 4-methylbenzoyl azide **2a** in the presence of CuCl to afford enamide **3aa** in 72% isolated yield (Scheme 2).

The extensive amidation reaction with **2a** was conducted with variously fresh alkenylzirconocenes **1a**−**l**[13c,f] and individually to form their corresponding enamides **3aa**−**la** in the isolated yields between 45% to 88%, indicating the wide scope of various substituents as alkyl, aryl, allyl, and TMS. The representative results are summarized in Table 1. In all cases, one product was solely observed. To confirm their molecular structures, single crystals of the representative **3da** were obtained by the recrystallization in *n*-hexane. Its structure revealed the *cis*-fashion of its phenyl and methyl groups (see the Supporting Information), which was consistent with its substance of the alkenylzirconocene **1d**, maintaining the configuration of the double bond during the amidation reaction. Therefore, such a reaction would be potentially used for a highly substituted enamides.

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



To establish the full scope of the amidation reaction, we further explored a range of acyl azide substrates (Figure 1) with the alkenylzirconocenes. Aryl acyl azides **2b**, **2c**, and **2d** derived from benzoyl chloride, *p*-anisoyl chloride, and *p*-chlorobenzoyl chloride[16] were also used in the reaction to give the corresponding enamides (Scheme 3, **3ab**, **3cc**, **3jc**, **3ad**, and **3cd**). If the substituent group was electron-withdrawing group or electron-donating on the benzene ring, the reactions could afford the desired products in good yields. When heteroaryl acylazides **2e**−**j** derived from the corresponding acyl chloride, such as 2-pyridinecarbonyl chloride,[17] 2-thiophenecarbonyl chloride,[18] and 2-furancarbonyl chloride,[19] were used, the corresponding products **3ae**−**cg** were obtained in moderate yields. When alkylacyl azide **2h** and benzylacyl azide **2i** derived from heptanoyl chloride[19] and phenylacetyl chloride[19] were employed in the reaction, the expected enamides were not obtained and starting materials remained. Cinnamoyl

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[15] Compound **1a** (generated in situ) was obtained in 95% yield, which was detected by ^1H NMR using mesitylene as an internal standard.

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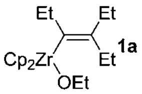
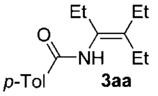
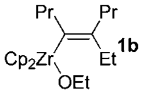
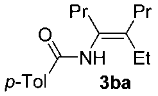
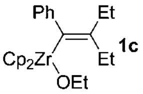
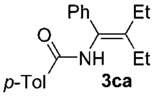
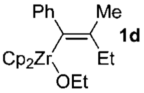
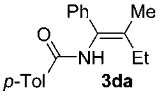
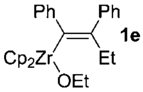
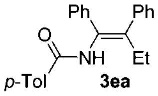
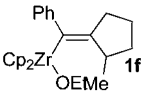
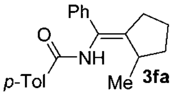
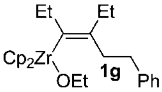
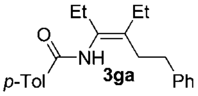
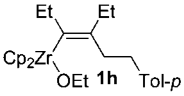
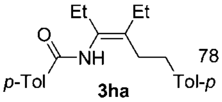
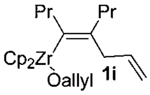
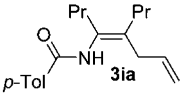
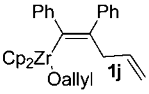
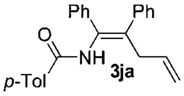
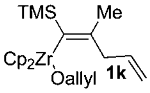
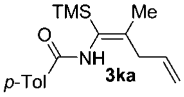
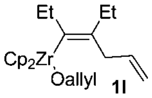
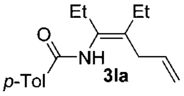
Table 1. Amidation of Various Alkenylzirconocenes[a]

entry	alkenylzirconocene	enamides	yield(%)[b]
1	 **1a**	 **3aa**	72
2	 **1b**	 **3ba**	55
3	 **1c**	 **3ca**	55
4	 **1d**	 **3da**	62
5	 **1e**	 **3ea**	45
6	 **1f**	 **3fa**	59
7	 **1g**	 **3ga**	65
8	 **1h**	 **3ha**	78
9	 **1i**	 **3ia**	81
10	 **1j**	 **3ja**	42
11	 **1k**	 **3ka**	88
12	 **1l**	 **3la**	84

[a] Reaction conditions: alkenylzirconocene **1** prepared in situ from alkyne (0.5 mmol) with zirconocene in 3 mL of THF solution, acyl azide **2a** (0.45 mmol), CuCl (0.55 mmol), N_2, 50 °C, protected from light, 12 h. [b] Isolated yield based on acyl azide.

azide **2j** derived from cinnamoyl chloride[17] was used in the reaction to afford the corresponding enamides **3cj** and **3dj** in 66% and 44% yield, respectively. Sulfonyl azide **2k**[17] could also offer the corresponding enamide **3ck** in 44% yield.

The plausible mechanism is proposed in Scheme 4. On the base of the known transmetalation from the C−Zr to C−Cu bond,[20] the alkenylzirconocene **1** is first transmetalated with CuCl to form an intermediate as the alkenylcopper **4**. Then coordination of acyl azide[10c] to **4** forms the intermediate **5**. Rearrangement of **5** and a release of N_2 forms the intermediate **6**, which is hydrolyzed to afford product **3**.

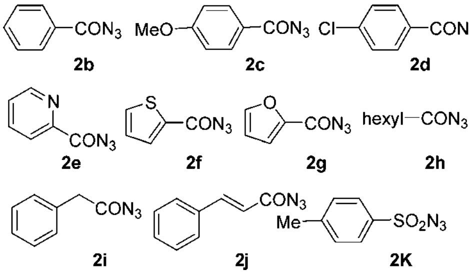
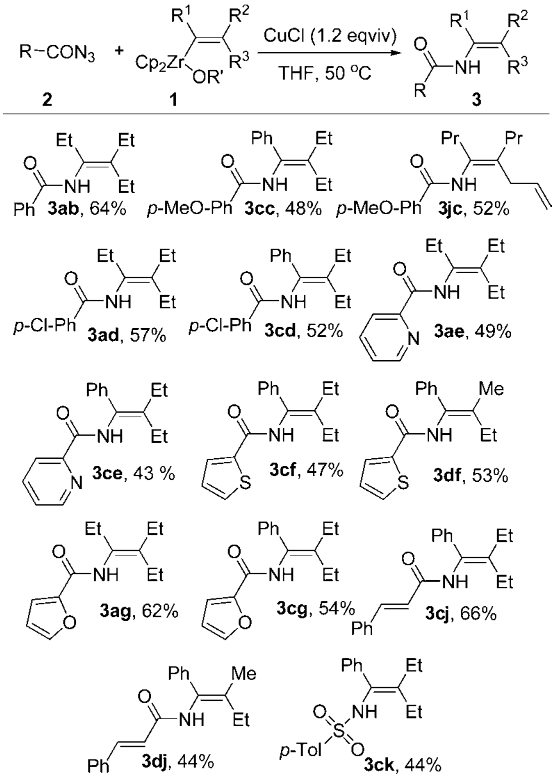


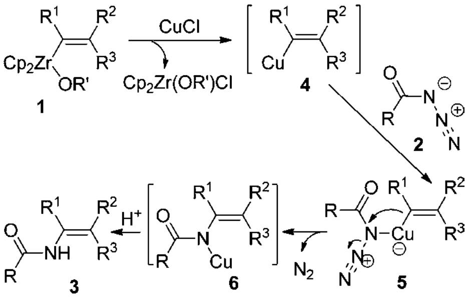
Figure 1. Range of azide substrates.

Scheme 3. The Scope of Amidation with various Acyl Azides[a]



[a] Reaction conditions: alkenylzirconocene **1** prepared in situ from alkyne (0.5 mmol) with zirconocene in 3 mL of THF solution, acyl azide **2** (0.45 mmol), CuCl (0.55 mmol), N_2, 50 °C, protected from light, 12 h, isolated yield based on acyl azide.

Scheme 4. Possible Reaction Pathway



In summary, a general copper-mediated amidation of alkenylzirconocenes with acyl azides has been developed. This reaction represents an interesting entry to the synthesis of enamides within a one-pot reaction from alkynes.

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Supporting Information Available. Experimental procedures, full characterization including ^{1}H NMR and ^{13}C NMR data and IR data for all new compounds, copies of spectra for all compounds, and the X-ray structure of product **3da** and X-ray data for **3da** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.