

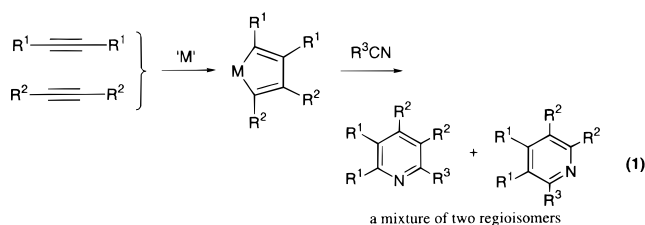
Selective Formation of Substituted Pyridines from Two Different Alkynes and a Nitrile: Novel Coupling Reaction of Azazirconacyclopentadienes with Alkynes

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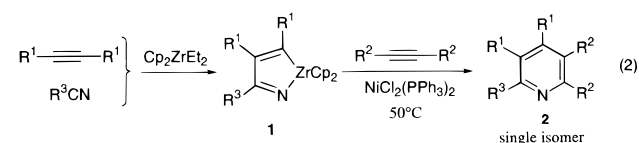
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Cocycloaddition of two alkynes and a nitrile using transition metals is a straightforward and attractive method for the preparation of pyridines.^{1–6} Cobalt complexes have been extensively used for this process, and the mechanistic aspect of the reaction has been intensively investigated.^{2,3} It is generally accepted that metallacyclopentadienes formed by coupling of two alkynes are intermediates for the formation of pyridines in catalytic and stoichiometric reactions and even in the case of cocycloaddition of α,ω -cyanoalkynes with alkynes.¹ However, there is a critical problem as regards the selectivity in the pyridine formation by the *intermolecular* coupling of two different alkynes and one nitrile as shown in eq 1. Reaction of metallacyclopentadienes prepared from two different alkynes with a nitrile affords a



mixture of two regioisomers due to the orientation of the nitrile molecule. Consequently, therefore, there has been no general preparative method which could control the selectivity of the *intermolecular* coupling of two different alkynes and one nitrile, although the orientation of the nitrile was controlled when alkynes bearing a COOR group were used as Wakatsuki et al. reported.^{2d}

We would like to report a novel coupling reaction of azazirconacyclopentadienes, which were in situ prepared from an alkyne and a nitrile, with a different alkyne to afford only single isomers of pyridines as shown in eq 2.



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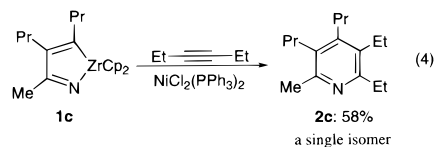
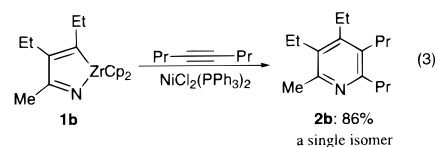
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Recently, we have developed highly selective coupling of an alkyne and a nitrile using Cp₂ZrEt₂ which gave azazirconacyclopentadienes **1**.⁷ Initially, we investigated the coupling reaction of the azazirconacyclopentadienes **1** with an alkyne in the presence of 2 equiv of CuCl,⁸ since the direct reaction of **1** with alkynes did not proceed. However, no formation of pyridine was observed in the presence of CuCl. Very recently, we have developed transmetalation reaction of zirconacyclopentadienes to Ni using NiCl₂(PPh₃)₂.⁹ In the presence of 1 equiv of NiCl₂(PPh₃)₂, the coupling reaction of triethylazazirconacyclopentadiene **1a** (R¹ = R³ = Et) with 3-hexyne proceeded and pentaethylpyridine **2a** was obtained in 71% yield.

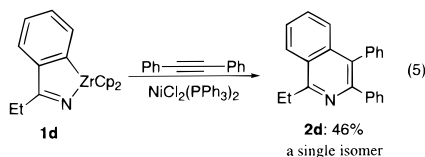
The typical procedure is as follows. To a solution of triethylazazirconacyclopentadiene **1a** in situ prepared from 1 mmol of 3-hexyne, 1 mmol of Cp₂ZrEt₂, and 1 mmol of propionitrile in 10 mL of THF were added 3-hexyne (2.5 mmol) and NiCl₂(PPh₃)₂ (1.0 mmol) at room temperature. The mixture was warmed to 50 °C, stirred for 9 h, quenched with 20% NaHCO₃, and extracted with diethyl ether. GC analysis showed that the pentaethylpyridine was formed in 71% yield. After workup, column chromatography on silica gel afforded pentaethylpyridine in 55% isolated yield.

This novel reaction could be used for the coupling of azazirconacyclopentadienes with a second different alkyne. It is noteworthy that the reaction of **1b**, which was prepared from 3-hexyne and acetonitrile, with 4-octyne gave **2b** in 86% yield as a single product. On the other hand, azazirconacyclopentadiene **1c** which was prepared from 4-octyne and acetonitrile reacted with 3-hexyne to give **2c** as a single product. In both cases the pyridines were

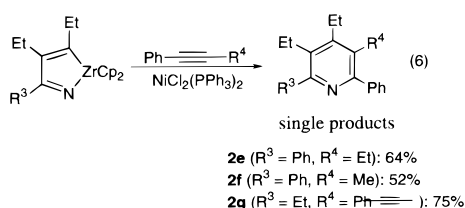


prepared from the same combination of alkynes and a nitrile such as 3-hexyne, 4-octyne and acetonitrile. However, the different order afforded the different isomers as single products cleanly.

It is interesting to note that azazirconacyclopentadiene **1d**¹⁰ prepared from diphenylzirconocene and a nitrile reacted with diphenylacetylene to produce a substituted isoquinoline derivative **2d** in 46% yield (eq 5).

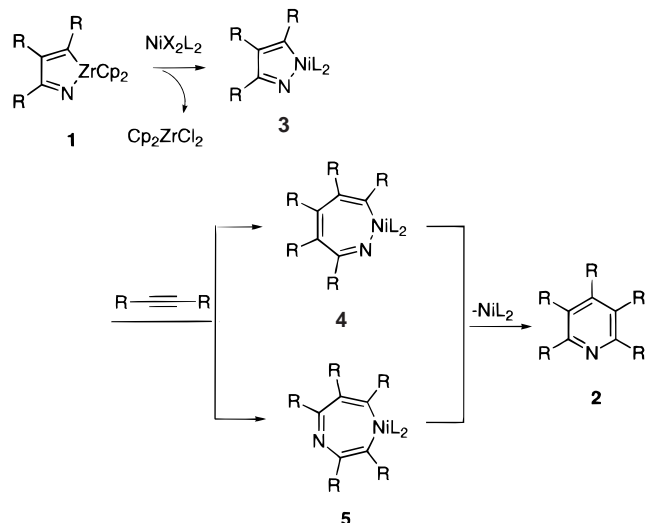


When unsymmetrical alkynes such as 1-phenyl-1-propyne, 1-phenyl-1-butyne, and diphenylbutadiyne were used as the second alkyne, the coupling reaction proceeded with high regioselectivity¹ and only single products were obtained (eq 6).



The reaction mechanism is not clear yet. However, as we reported in the selective benzene formation,⁹ reaction of NiCl₂(PPh₃)₂ with azazirconacyclopentadienes **1** to give azanickelacyclopentadienes **3** is plausible, although the formation of azanickelacyclopentadienes **3** has not yet been observed during the reactions. The formation of Cp₂ZrCl₂ was detected (>98% NMR yield). One possible path from **3** to **2** is insertion of the second alkyne into **3**. There are two pathways for insertion of the second alkyne into azanickelacyclopentadienes as shown in Scheme 1.

Scheme 1



When the second alkyne inserts into the Ni–C bond of **3**, the azanickelacycloheptatrienes **4** is formed. On the other hand, when the insertion occurs in the Ni–N bond of **3**, the corresponding complex **5** is produced. Intramolecular reductive coupling of **4** or **5** affords the substituted pyridine derivatives **2**. Although there is no strong evidence for the intermediate **4** or **5**, the insertion of the second alkyne into the Ni–C bond is more likely.

Combination of azazirconacyclopentadiene formation using Cp₂ZrEt₂ and its coupling with an alkyne provided an efficient

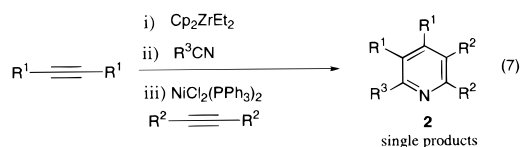
Table 1. One-Pot Preparation of Substituted Pyridine Derivatives from Two Different Alkynes and a Nitrile Using Zirconocene and Nickel Complexes

First Alkyne	Nitrile	Second Alkyne	Time/h	Product	Yields/% ^a
Et—C≡C—Et	MeCN	Pr—C≡C—Pr	9		86 (66)
Pr—C≡C—Pr	MeCN	Et—C≡C—Et	9		58 (41)
Et—C≡C—Et	PhCN	Ph—C≡C—Et	12		64 (53)
Et—C≡C—Et	PhCN	Ph—C≡C—Me	12		52 (42)
Et—C≡C—Et	EtCN	Ph—C≡C—C≡C—Ph	12		75 (44)
Me—C≡C—Me	PhCN	Pr—C≡C—Pr	6		86 (52)
Et—C≡C—Et	PhCN	Pr—C≡C—Pr	6		73 (57)
Pr—C≡C—Pr	PhCN	Et—C≡C—Et	6		63 (49)
Et—C≡C—Et	MeCN	Ph—C≡C—Ph	36		89 (65)
Ph—C≡C—Ph	EtCN	Pr—C≡C—Pr	12		77 (58)

^a GC yields. Isolated yields are given in parentheses.

one-pot procedure to produce substituted pyridine derivatives with high selectivities. The results of the one-pot reaction are shown in Table 1.

One-pot procedure



Clarification of the reaction mechanism of the formation of pyridines from azazirconacyclopentadienes await further investigations.

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Supporting Information Available: Experimental details and spectroscopic characterization of compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.