

Selective preparation of benzene derivatives from three different alkynes and pyridine derivatives from two different alkynes and a nitrile*

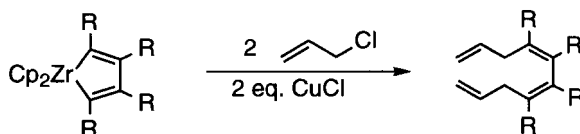
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Abstract: Selective preparation of benzene derivatives from three different alkynes and pyridine derivatives from different alkynes and a nitrile were developed.

C–C BOND FORMATION OF ZIRCONACYCLOPENTADIENES

Since the first zirconacyclopentadiene was prepared by coupling of 2 equiv of diphenylacetylene on zirconocene in 1970 [1], many groups have reported the formation of zirconacyclopentadienes [1]. Surprisingly, for more than 20 years almost no carbon–carbon bond formation reactions have been reported for zirconacyclopentadienes. Only one paper appeared in 1983 to show the insertion reaction of the third alkyne into a zirconacyclopentadiene to form a zirconacycloheptatriene [2]. However, unfortunately, the zirconacyclopentadienes we prepared did not show such insertion reactions. Therefore, we decided to develop general carbon–carbon bond formation of zirconacyclopentadienes, since various zirconacyclopentadienes could be conveniently prepared.



Scheme 1 The first example of transmetalation of zirconacyclopentadienes to Cu for C–C bond formation.

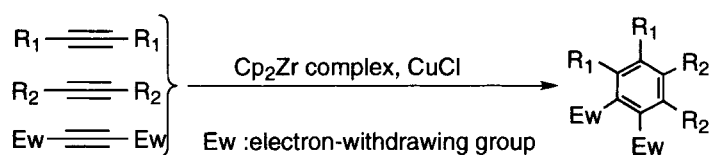
During the course of our study, we found the first example of transmetalation of zirconacyclopentadienes to Cu using CuCl [3]. In this reaction we found double allylation of zirconacyclopentadienes in the presence of allyl chloride to afford 1,4,6,9-tetraenes in high yields (Scheme 1).

SELECTIVE BENZENE FORMATION FROM THREE DIFFERENT ALKYNES

This prompted us to investigate various reactions of zirconacyclopentadienes in the presence of CuCl, and we developed a highly selective benzene formation reaction by intermolecular coupling of three different alkynes. This was the first example of the selective coupling of three different alkynes in high yield in one-pot (Scheme 2) [4].

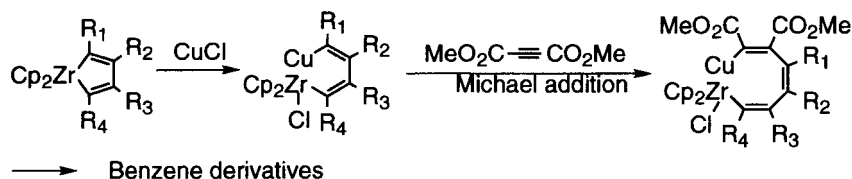
This procedure had a limitation regarding the third alkyne. At least one electron-withdrawing group was required for the third alkyne as a substituent for the formation of benzene derivatives. One

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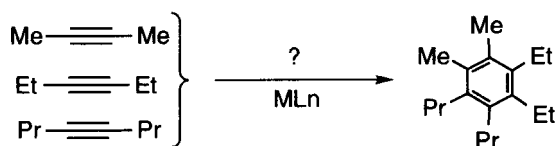
Scheme 2 First example of selective benzene formation from three different alkynes in one-pot.

reason is that the transmetallation product from zirconacyclopentadiene to Cu is an organocopper species that undergoes Michael addition-type reaction to conjugated olefin or alkynes (Scheme 3). Therefore, alkynes with electron-donating groups did not react with zirconacyclopentadienes in the presence of CuCl.



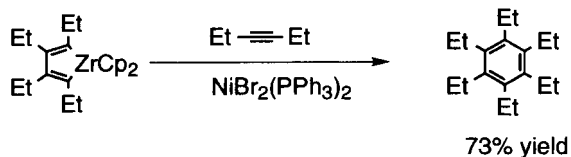
Scheme 3 Copper(I)-mediated benzene formation reaction which requires a third alkyne with an electron-withdrawing group.

Functional group-dependent selective reaction is relatively easy, but it is not a general reaction. We believe that when we can control the formation of benzene derivatives from three different alkynes with similar alkyl-substituents, it can be a general procedure. In order to develop such general procedure, we turned our attention from CuCl to late transition metals which can lead to an insertion reaction of the carbon-carbon triple bond of an alkyne into the metal-carbon bond. Nickel complexes were chosen as the late transition-metal compounds [5].



Scheme 4 New challenge: Selective coupling of three different alkynes with alkyl-substituents.

Fortunately, when we used NiX₂(PPh₃)₂ (X = Cl or Br) as the nickel complex, zirconacyclopentadienes reacted with the alkyl-substituted third alkyne to give benzene derivatives (Scheme 5). It is interesting to note that not only electron-donating group but also electron-withdrawing group-substituted alkynes could be used as the third alkyne in this reaction. We tried the coupling of three different alkynes with alkyl-substituents, and benzene derivatives were obtained selectively as shown in Table 1 [5].



Scheme 5

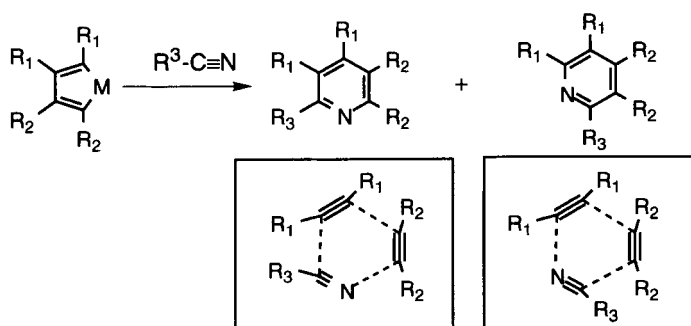
Table 1 Formation of benzenes from three different alkynes.

$R_1 \text{---} R_1'$	$R_2 \text{---} R_2$	$R_3 \text{---} R_3'$	Product	Yield (%) ^a
$\text{Ph} \text{---} \text{Ph}$	$\text{Me} \text{---} \text{Me}$	$\text{Pr} \text{---} \text{Pr}$		80 (62)
$\text{Bu} \text{---} \text{Bu}$	$\text{Me} \text{---} \text{Me}$	$\text{Et} \text{---} \text{Et}$		65 (44)
$\text{Pr} \text{---} \text{Pr}$	$\text{Me} \text{---} \text{Me}$	$\text{Et} \text{---} \text{Et}$		63 (55)

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

SELECTIVE PYRIDINE FORMATION FROM TWO DIFFERENT ALKYNES AND A NITRILE

It is well known that pyridine derivatives can be prepared by the coupling of two alkynes and a nitrile using transition metals such as cobalt [6]. According to the reaction mechanism, a cobaltacyclopentadiene is formed first, and then it reacts with a nitrile. In this method using cobalt, the coupling reaction of two different alkynes and a nitrile fundamentally gives two isomers of pyridine as shown in Scheme 6. This difficulty comes from the two possible orientations of the nitrile in its coupling with the unsymmetrical cobaltacyclopentadienes. Therefore, so far a pyridine formation from two different alkynes and a nitrile has not been useful in organic synthesis because of the lack of a selective and general method [6].

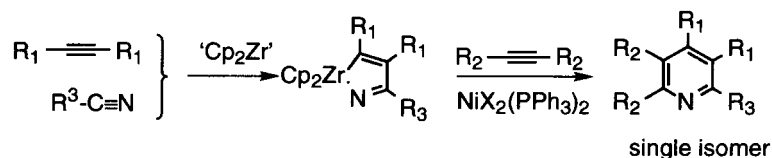


Scheme 6 Pyridine formation as a mixture of isomers from metallacyclopentadienes.

When we checked the literature for the formation of pyridine using transition-metal complexes, we thought this problem could be solved if one alkyne and a nitrile could couple together first on the metal. It is surprising to note that even in the reaction of α,ω -cyanoalkynes with an alkyne, intermolecular coupling of the alkyne moieties occurs first in the case of cobalt according to the mechanism. Therefore, consequently selective and general preparation of pyridine derivatives from two different alkynes and a nitrile using cobalt complexes is not easy.

Recently, we have reported that the selective coupling reaction of an alkyne and a nitrile via β,β' bond cleavage of zirconacyclopentenes afforded azazirconacyclopentadienes [7]. Reaction of the

azazirconacyclopentadienes with the second alkyne in the presence of $\text{NiX}_2(\text{PPh}_3)_2$ gave pyridine derivatives in high yields (Scheme 7) [8].



Scheme 7

The results of pyridine formation from two different alkynes and a nitrile are shown in Table 2. It is noteworthy that in all cases only one isomer was obtained. In the case of a pyridine prepared from 4-octyne and 3-hexyne, two isomers could be completely controlled and prepared as single products. This is the first example to provide a general and selective preparative method of pyridine from two different alkynes and a nitrile [8].

Table 2 $\text{NiCl}_2(\text{PPh}_3)_2$ -mediated reaction of zirconacyclopentadienes with alkynes.

Azazirconacyclopentadiene	Alkyne	RT/h	Product	Yields/% ^a
	$\text{Pr}-\text{C}\equiv\text{C}-\text{Pr}$	9		86 (66)
	$\text{Et}-\text{C}\equiv\text{C}-\text{Et}$	9		58 (41)
	$\text{Pr}-\text{C}\equiv\text{C}-\text{Pr}$	6		86 (52)

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

REFERENCES

- G. W. Watt, F. O. Drummond, Jr. *J. Am. Chem. Soc.* **92**, 821 (1970). For other examples, see Z. Xi, R. Hara, T. Takahashi. *J. Org. Chem.* **60**, 4444 (1995) and referenced therein.
- A. Famili, M. F. Farona, S. Thanedar. *J. Chem. Soc. Chem. Commun.* 435 (1983).
- T. Takahashi, M. Kotora, K. Kasai, N. Suzuki. *Organometallics* **13**, 4183 (1994).
- T. Takahashi, M. Kotora, Z. Xi. *J. Chem. Soc. Chem. Commun.* 361 (1995); T. Takahashi, Z. Xi, A. Yamazaki, Y. Liu, K. Nakajima, M. Kotora. *J. Am. Chem. Soc.* **120**, 1672 (1998).
- T. Takahashi, F.-Y. Tsai, Y. Li, K. Nakajima, M. Kotora. *J. Am. Chem. Soc.* **121**, 11093 (1999).
- For a review, see N. E. Schore. *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming (Eds.), Vol. 5, p. 1129, Pergamon, Oxford (1991).
- T. Takahashi, C. Xi, Z. Xi, M. Kageyama, R. Fischer, K. Nakajima, E. Negishi. *J. Org. Chem.* **63**, 6802 (1998).
- T. Takahashi, F.-Y. Tsai, M. Kotora. *J. Am. Chem. Soc.* **122**, 4994 (2000).