Heterocyclized Carbometalation of Alkynes: Unexpected Formation of Eight-Membered Oxazirconacycles with an Intramolecularly Coordinated Isoquinoline Moiety

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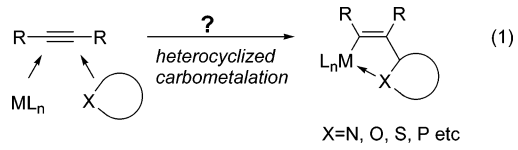
Summary: The isoquinolyl-zirconation of various unactivated alkynes was investigated by a one-pot, three-component reaction of two different alkynes with a nitrile in the presence of 1 equiv of CuCl. The true nature of the resulting products of novel eight-membered oxazirconacycles containing an intramolecular Zr−N coordination was established using X-ray crystallography.

Reaction processes that can provide a significant amplification of molecular complexity from simple building blocks occupy a special place in organic synthesis. In this sense, carbometalation of alkynes would be a powerful method for generating alkenyl organometallics, which represents an important access to stereodefined C=C double bonds.[1] Functionalized carbometalations such as allyl-, acyl-, dienyl-, vinyl-, and alkynylmetalation[2] of alkynes are of particular interest, as they provide synthetically useful functionalized di-, tri-, and tetrasubstituted alkenes. There are few reports, however, of heterocycle-incorporated carbometalation as shown in eq 1, in which a heterocycle group is directly



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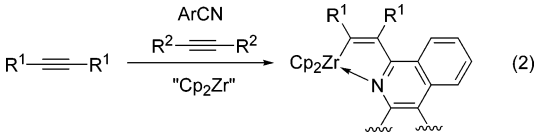
introduced into a C−C double-bond unit. Although by utilization of heteroaryl halides, palladium-catalyzed heterocyclized carbopalladation of alkynes followed by trapping with oxygen or nitrogen nucleophilic reagents has been reported,[3] the metal-containing intermediate of carbometalation has not been examined.

In this paper, we report novel zirconium-mediated heterocyclized carbometalation of unactivated alkynes in the presence of CuCl to afford air-stable isoquinolyl-zirconation products by a one-pot, three-component reaction of two different alkynes with a nitrile (eq 2).



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This reaction provides a versatile procedure for the synthesis of functionalized isoquinoline derivatives after hydrolysis. We also report the unique X-ray structure of the zirconium-containing complex.

The synthesis of isoquinoline ring systems has received considerable attention, since they widely occur in natural alkaloids and have pharmacological activities.[4] During our studies of new processes for heterocycle formation, we found that azazirconacyclopentadienes[5] derived from highly selective coupling of an alkyne and *o*-halobenzonitrile reacted with DMAD (dimethyl acetylenedicarboxylate) in the presence of 1 equiv of CuCl to afford the novel eight-membered oxazirconacycles **2** with

(1) For reviews on carbometalation of alkynes, see: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, 2002; pp 1123−1651. (b) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 865−911. (c) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841−870. (d) Marek, I.; Normant, J. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 271−337. (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. See also: (f) Liu, Y. H.; Shen, B. H.; Kotora, M.; Takahashi, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 949−952. (g) Xi, C.; Kotora, M.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2000**, *65*, 945−950. (h) Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, F. J. *J. Am. Chem. Soc.* **1998**, *120*, 4865.

(2) For allyl-metalation of alkynes, see: (a) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587. (b) Bernardou, F.; Miginiac, L. *J. Organomet. Chem.* **1977**, *125*, 23. (c) Suzuki, N.; Kondakov, D. Y.; Kageyama, M.; Kotora, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519−4540. (d) Yamanoi, S.; Imai, T.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 3031−3034. (e) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221−10222. For acyl-metalation of alkynes, see: (f) Hoberg, H.; Schaefer, D.; Burkhart, G.; Krüger, C.; Romao, M. J. *J. Organomet. Chem.* **1984**, *266*, 203 and references therein. (g) DeShong, P.; Sidler, D. R.; Rybczynski, P. J.; Slough, G. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2575. (h) DeShong, P.; Sidler, D. R. *J. Org. Chem.* **1988**, *53*, 4892. (i) Takai, K.; Kataoka, Y.; Yoshizumi, K.; Oguchi, Y.; Utimoto, K. *Chem. Lett.* **1991**, 1479−1482. For alkenyl- or dienyl-metalation of alkynes: (j) Furber, M.; Taylor, R. J. K.; Burford, S. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809−1815. (k) Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871−5872. (l) Chinkov, N.; Majumbar, S.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 13258−13264. For alkynyl-metalation, see: (m) Shirakawa, E.; Yoshida, H.; Kurahashi, T.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 2975−2976. (n) Liu, Y. H.; Zhong, Z.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451−7456. For haloamidation, see: (o) Li, Y.; Matsumura, H.; Yamanaka, M.; Takahashi, T. *Tetrahedron* **2004**, *60*, 1393−1400. For metalloesterification, see: (p) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228−3229.

(3) (a) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823. (b) Kartens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *J. Organomet. Chem.* **2001**, *624*, 244. (c) Finch, H.; Pegg, N. A.; Evans, B. *Tetrahedron Lett.* **1993**, *34*, 8353.

(4) (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; Vol. 1. (b) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.

(5) For the formation of azazirconacyclopentadienes, see: (a) Takahashi, T.; Xi, C. J.; Xi, Z. F.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802−6808. (b) Negishi, E.; Holms, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336−3346. (c) Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310−2312. (d) Quntar, A. A.; Melman, A.; Srebnik, M. *J. Org. Chem.* **2002**, *67*, 3769−3772.

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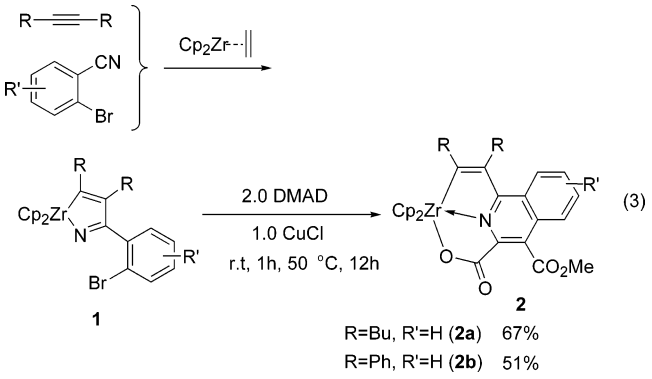
Table 1. Isoquinolyl-Zirconation of Alkynes: Formation of Eight-Membered Oxazirconacycles

entry	first alkyne	ArCN	second alkyne	yield of **2** (%)[a]
1	PrC≡CPr	2-BrC_6H_4CN	DMAD	50 (**2c**)
2	PrC≡CPr	2-BrC_6H_4CN	DEAD	61 (**2d**)
3	PhC≡CBu	2-BrC_6H_4CN	DMAD	44[b] (**2e**)
4	PrC≡CPr	2,6-Cl_2-C_6H_3CN	DMAD	56 (**2f**)
5	PrC≡CPr	2,6-Cl_2-C_6H_3CN	DEAD	61 (**2g**)
6	PhC≡CPh	2,6-Cl_2-C_6H_3CN	DMAD	60 (**2h**)
7	PhC≡CPh	2-Cl-C_6H_4CN	DMAD	30 (**2b**)
8	BuC≡CBu	2-F-C_6H_4CN	DMAD	67 (**2a**)
9	PrC≡CPr	2,6-F_2-C_6H_3CN	DEAD	63[c] (**2i**)

[a] Isolated yields. Unless noted, all the reactions were carried out using CuCl at room temperature for 1 h and 50 °C for 12 h. [b] Two isomers were obtained in a ratio of 1:1. [c] Reaction was done at room temperature for 12 h.

an intramolecular Zr−N coordination (eq 3). Remark-



(3)

ably, **2** proved to be stable to air and water in its solid state, surviving an aqueous alkali−hydrolysis workup and allowing a convenient separation through column chromatography on silica gel. It is noteworthy that air-stable, C−Zr σ-bond-containing complexes are rare.[6]

A typical procedure for the preparation of **2** is as follows: to a solution of azazirconacyclopentadiene **1a** (1 mmol), prepared by cross-coupling of 1 mmol of alkyne and 1 mmol of 2-bromobenzonitrile assisted by a low-valent zirconocene−ethylene complex in THF, were added DMAD (2 mmol) and CuCl (1 mmol) sequentially at 0 °C. The reaction mixture was warmed to room temperature for 1 h and kept at 50 °C for 12 h, quenched with 20% $NaHCO_3$ solution. Purification by column chromatography on silica gel afforded **2a** in 67% isolated yield. The representative reactions of various *o*-halonitriles with alkynes are listed in Table 1. To investigate the generality of this reaction, chloro-substituted nitriles such as *o*-chlorobenzonitrile and 2,6-dichlorobenzonitrile were used in the reaction; the corresponding products were obtained in 30−61% isolated yields (entries 4∼7). Selective C−F bond activation is of current interest in organometallic chemistry.[7] Very surprisingly, here even the fluoro-substituted nitriles, namely *o*-fluorobenzonitrile and 2,6-difluorobenzonitrile, worked well in this chemistry and afforded oxazirconacycles **2a** and **2i** in 67% and 63% yield, respectively. These results indicated the ease of cleavage of stronger

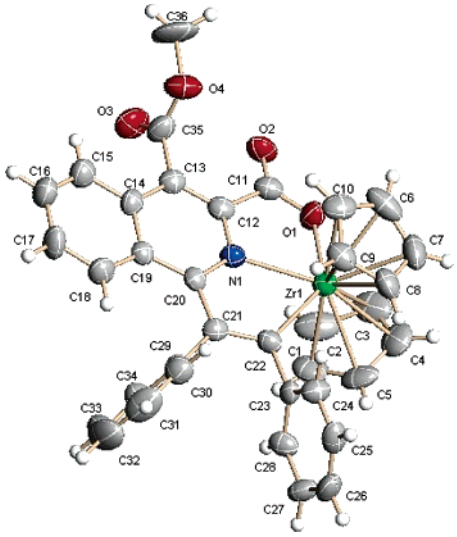
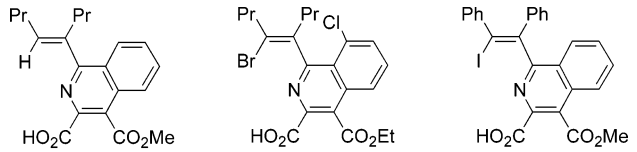


Figure 1. Structure of one of the two crystallographically independent **2b**. Selected bond lengths (Å): Zr(1)−O(1) = 2.152(4), Zr(1)−N(1) = 2.336(4), Zr(1)−C(22) = 2.365(5), O(1)−C(11) = 1.261(6), O(2)−C(11) = 1.225(6); C(11)−C(12) = 1.518(8).

C−Cl and C−F bonds during the reaction. It is noteworthy that employing DEAD (diethyl acetylenedicarboxylate) also works well in this reaction (entries 2, 5, and 9). However, using other activated alkynes such as phenyl- or alkyl-substituted alkynyl esters or ketones resulted in the formation of a complicated reaction mixture. On the other hand, hydrolysis of **2c** afforded the 3-isoquinolyl acid **3** in 93% isolated yield. Bromi-



nation of **2g** or iodination of **2b** with 1 equiv of bromine or iodine afforded the corresponding halogenated products **4** and **5** in 84% and 67% yields, respectively.

The ^1H NMR spectrum of **2a** in $CDCl_3$ showed a singlet peak at 6.0 ppm assigned to Cp protons. Integration of a singlet at 4.1 ppm (methyl protons of the $-CO_2Me$ moiety) indicated only one ester group existed and the C−O bond of the other ester group was cleaved during the reaction. Additionally, the ^{13}C NMR spectrum of **2a** showed peaks at 109.86 and 230.58 ppm assignable to the Cp and =CZr moieties, respectively.[8] To confirm spectroscopic assignments and to have a deep insight into the molecular structure of **2**, an X-ray diffraction study was carried out and shown in Figure 1. The ORTEP plot clearly shows the eight-membered oxametallacyclic structure of the product. The Zr−C distance of 2.365(5) Å is comparable to that found for other Zr^{IV}−C(sp^2)-containing oxametallacycles,[8] while the Zr−N(1) distance of 2.336(4) Å[9] suggests a dative interaction between the isoquinolyl nitrogen and the

(6) (a) Luker, T.; Whitby, R. J.; Webster, M. *J. Organomet. Chem.* **1995**, *492*, 53−57. (b) Mohamadi, F.; Spees, M. M. *Organometallics* **1992**, *11*, 1398−1400.

(7) Deck, P. A.; Konate, M. M.; Kelly, B. V.; Slebodnick, C. *Organometallics* **2004**, *23*, 1089−1097 and references therein.

(8) Sun, H.; Burlakov, V. V.; Spannenberg, A.; Baumann, W.; Arndt, P.; Rosenthal, U. *Organometallics* **2002**, *21*, 3360−3366.

(9) Kempe, R. Brenner, S.; Arndt, P. *Organometallics* **1996**, *15*, 1071−1074.

metal. The O(C=O) group was found to assume the expected ester-type structure, where one oxygen atom, O(1), links to the metal while the other is bent away from the metal. This orientation causes the metal center to be pentacoordinate and results in an 18-electron complex. The bite angle (136.68°) defined by O(1)−Zr(1)−C(22) is the largest among the oxazirconacycle family: for example, 121.2° for the seven-membered σ, syn-η^3-allyl-type species $Cp^*_2Zr[C_4H_6C(=O)O]$,[10] and 96.85° for *rac*-(ebthi)$ZrOCMe{=}CHCH_2C(SiMe_3){=}C(SiMe_3)$.[9]

Recently, Takahashi et al. reported a novel coupling reaction of azazirconacyclopentadienes with alkynes to form pyridines in the presence of $NiCl_2(PPh_3)_2$, in which transmetalation of azazirconacycles to give azanickelacycles is suggested.[11] Although the mechanism of the reaction presented here is not clear yet, one plausible reaction pathway may involve the following steps: selective transmetalation of the Zr−N bond to a Cu−N bond since the Zr−C(sp^2) bond of azazirconacyclopentadienes remains intact, subsequent conjugate addition/cyclization concomitant with demethylation of DMAD, and formation of a Zr−O bond. A similar demethylation was observed in *o*-MeO-containing benzyl-substituted cyclopentadienyltitanium complexes.[12]

In summary, a novel isoquinolyl-zirconation of unactivated alkynes to produce new air-stable oxazirconacycles has been described. This method enhances the synthetic utility of five-membered azazirconacycles by providing products of highly functionalized isoquinoline derivatives. Clarification of the reaction mechanism and further application of this chemistry are in progress.

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Supporting Information Available: Text and figures giving experimental details and spectroscopic characterization data for all isolated compounds and a CIF file giving crystallographic data for **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Yasuda, H.; Okamoto, T.; Matsuoka, Y.; Nakamura, A.; Kai, Y.; Kanehisa, N.; Kasai, N. *Organometallics* **1989**, *8*, 1139−1152.

(11) (a) Takahashi, T.; Tsai, F.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994. (b) Takahashi, T.; Tsai, F.; Li, Y. Z.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059−5067.

(12) Qian, Y. L.; Huang, J. L.; Yang, J. M.; Chan, A. S. C.; Chen, W. H.; Chen, X. P.; Li, G. S.; Li, B. H.; Jin, X. L.; Yang, Q. C. *J. Organomet. Chem*. **1997**, *547*, 263.