

Metalative Reppe Reaction. Organized Assembly of Acetylene Molecules on Titanium Template Leading to a New Style of Acetylene Cyclotrimerization

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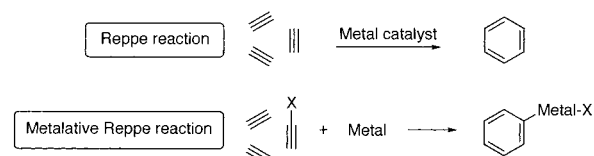
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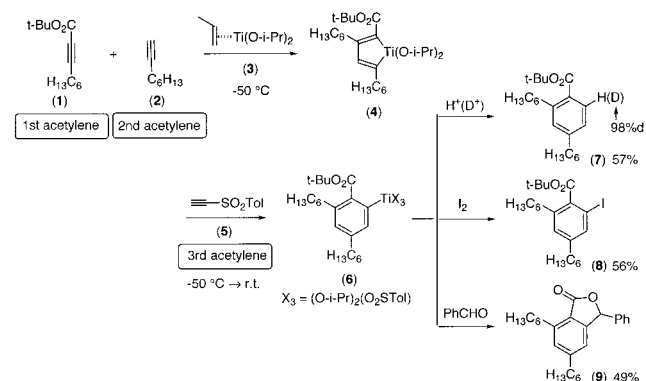
Cyclotrimerization of acetylenes as illustrated in the upper equation of Scheme 1, which was first developed by Reppe et al. in 1948,¹ has recently attracted much attention as a method for the preparation of aromatic compounds.² However, in practice, when this method is to be applied to the preparation of substituted aromatic compounds from three different, unsymmetrical acetylenes, 38 homo- and cross-coupling products possibly may be produced. Thus, the assembly of such acetylenes to strictly one single aromatic compound is a formidable challenge.³

Considering the importance of organometallic compounds in organic synthesis together with the aforementioned Reppe-type reactions, we show herein a new and perfect style of acetylene cyclotrimerization. Thus, *three different, unsymmetrical acetylenes and one molecule of a certain metallic species, which is a titanium in the present case, are combined together in a highly controlled manner to give directly aromatic organometallic compounds as a single isomer.* As this new cyclotrimerization of acetylenes

Scheme 1. Conventional and New Styles of the Reppe Reaction



Scheme 2. The Metalative Reppe Reaction



affords arylmetal compounds, it should be called the metalative Reppe reaction as shown in the lower equation of Scheme 1.

Experimental operation of the metalative Reppe reaction, which can be carried out in one pot, is very simple as illustrated in Scheme 2 and entries 1–3 of Table 1.⁴ Dialkoxytitanacyclopentadiene **4**⁵ was first prepared from two different, unsymmetrical acetylenes **1** and **2** (as the first and second acetylenes) and a divalent titanium alkoxide reagent, (η^2 -propene)Ti(O-*i*-Pr)₂ (**3**),⁶ at -50 °C. Ethynyl tolyl sulfone (**5**)^{7,8} was then added as the third acetylene and the reaction temperature was raised to room temperature to give a single aryltitanium compound **6**, the presence of which was confirmed by the subsequent reactions with electrophiles to give single adducts **7–9**. Thus, simple hydrolysis afforded the aromatic product **7**, the structure of which was unambiguously assigned by standard analyses and comparison with an authentic sample prepared independently by a different route. More importantly, deuteriolysis gave the single deuterated aromatic compound **7-d**. Moreover, the treatment of the aryltitanium compound **6** with iodine or an aldehyde furnished an aromatic iodide **8** or a homologated aromatic compound **9**, demonstrating the advantageous feature of the metalative Reppe reaction over the conventional version. It should be emphasized that the asymmetry of the third acetylene **5** was preserved in the products **7-d**, **8**, and **9** through the regioselective generation of the carbon–titanium bond in **6**.

(4) For the details of experimental procedures and physical properties of products, see the Supporting Information.

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(7) Commercially available ethynyl tolyl sulfone (**5**) is the reagent of choice in laboratories due to its easy handling and storage. While the corresponding sulfoxide also underwent the same reaction, but with lower efficiency (17% yield of **7**), ethynyl sulfide or ethynyl ethyl ether did not afford the aromatic compound. Both the strong electron-withdrawing nature of the sulfonyl group, which should promote the [4+2] addition or insertion in Scheme 3, and its character as a good leaving group appear essential for the success of this transformation.

(8) For a review on synthetic application of sulfones, see: Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

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(1) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104–116.

(2) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 741–770. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1129–1162. Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556. Müller, E. *Synthesis* **1974**, 761–774.

(3) A portion of this work was orally presented at the 79th Annual Meeting of the Chemical Society of Japan, March 29, 2001, Kobe; Abstract 2H405. Quite recently, after we completed the preparation of this manuscript, the following report on the selective cyclotrimerization of three different, unsymmetrical acetylenes by taking advantage of palladium catalysis appeared. (a) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835–2841. Other cyclotrimerization methods of acetylenes to aromatic compounds reported recently are so far limited to the homo-coupling of an acetylene (ref 3b–h), cross-coupling involving at least one symmetrical acetylene (ref 3i–l), or cross-coupling of tethered acetylenes (i.e., diynes or triynes) (ref 3m–r). (b) Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 796–802. (c) Ozerov, O. V.; Patrick, B. O.; Ladipo, F. T. *J. Am. Chem. Soc.* **2000**, *122*, 6423–6431. (d) Ozerov, O. V.; Ladipo, F. T.; Patrick, B. O. *J. Am. Chem. Soc.* **1999**, *121*, 7941–7942. (e) Chio, K. S.; Park, M. K.; Han, B. H. *J. Chem. Res.* (S) **1998**, 518–519. (f) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911–2924. (g) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1615–1618. (h) Jhinguan, A. K.; Maier, W. F. *J. Org. Chem.* **1987**, *52*, 1161–1165. (i) Mori, N.; Ikeda, S.; Odashima, K. *Chem. Commun.* **2001**, 181–182. (j) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5231–5234. (k) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093–11100. (l) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672–1680. (m) Kohta, S.; Mohanraj, K.; Durani, S. *Chem. Commun.* **2000**, 1909–1910. (n) Wituski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965–1966. (o) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549–550. (p) Wituski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426–2430. (q) Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 5035–5038. (r) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253–3256.

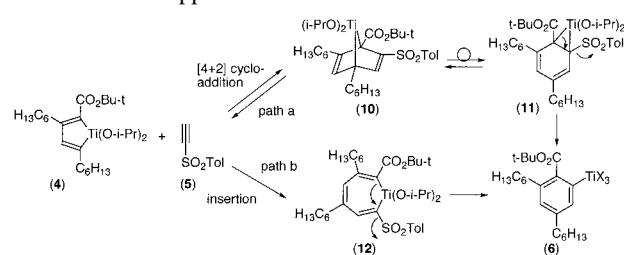
Table 1. Preparation of Various Aromatic Compounds by the Metalative Reppe Reaction

Entry	Acetylenes			Aryltitanium compound generated in situ ^a	Electrophile	Product	Isolated yield (%)
	1st	2nd	3rd				
1					H ⁺ (D [*])		57 98% ^d (77-d)
2	"	"	"	"	I ₂		56 (8)
3	"	"	"	"	PhCHO		49 (9)
4	"		"		H ⁺ (D [*])		46 94% ^d
5			"		H ⁺ (D [*])		65 80% ^d
6			"		H ⁺ (D [*])		50 78% ^d
7			"		H ⁺ (D [*])		56 98% ^d
8		"	"		H ⁺ ^c		74
9		"	"		H ⁺ ^c		88
10			"		H ⁺ (D [*])		74 91% ^d

^a Based on the results of deuteration in the right column. For entries 8 and 9, the structures are tentatively shown. X refers to O-*i*-Pr, Cl, and/or SO₂Tol. ^b Lower incorporation of deuterium as compared to other entries should be attributable to the use of a larger amount of the sulfonylacetylene, as its acidic acetylenic proton may protonate the aryltitanium compound during the reaction. ^c Only protonation is shown, because ¹H NMR analysis hardly determined the position and/or the degree of the deuteration.

Path a or b in Scheme 3 most likely accounts for the incorporation of the third acetylene.⁹ Thus, in path a, the [4+2] cycloaddition of the titanacyclopentadiene **4** and the sulfonylacetylene **5** took place to furnish the bicyclic titanacycle **10**, at least in an equilibrium concentration. The regioselectivity as well as the high regioselectivity of this cycloaddition is the key to the later formation of the aryl-titanium bond of **6** at the defined position. Then, the carbon-titanium bond of the titanacycle **10**

(9) The mechanism of metal-catalyzed cyclotrimerization of acetylenes has been explained in terms of [4+2] cycloaddition or insertion of the third acetylene to the metallacyclopentadiene, followed by the reductive elimination of the metal (refs 2, 3c, 3f, 3l). However, the present case apparently consists of the elimination of the sulfonyl group rather than the reductive elimination of the metal at the final step.

Scheme 3. Proposed Reaction Course for the Final Step of the Metalative Reppe Reaction

rearranges to a suitable position such as **11** where the 1,2-elimination of the sulfonyl group is feasible. Finally, the sulfonyl group was eliminated to shift the equilibrium to the formation of the aryltitanium compound **6**. Alternatively, path b involves regioselective insertion of the third acetylene **5** to the titanacycle **4** followed by the elimination of the sulfonyl group at the sp² carbon with inversion of configuration to give **6**. However, in any event, as we could not so far identify any of the important intermediates in Scheme 3, a conclusion on the exact reaction path should await further study.

The above preparation of aromatic compounds appears reasonably general in that the alkyl and ester groups in the first acetylene, the alkyl group in the second acetylene, and the electrophiles are arbitrarily selected depending upon the synthetic purpose. Another example to substantiate this point is shown in entry 4 in Table 1. Needless to say, two of the three acetylenes may be of the same kind as the reactions which are listed in entries 5–7. Even though two molecules of the sulfonyl acetylene were employed as the second and third acetylenes in entries 5 and 6, they behaved as quite different acetylenes, because one molecule was incorporated as such to form a sulfonyl substituent, while the other molecule was transformed to the titanated C=C unit in a regioselective manner. The issue, namely, which sulfonyl group of the two in the intermediate (such as **10** in Scheme 3) is preferably eliminated in entry 6, may be highly dependent on the structure of titanacycle, but the single aromatic product was obtained in this case. The metalative Reppe reaction could also be applied to the generation of various bicyclic aromatic titanium compounds from tethered diynes as shown in entries 8–10. In general, it should also be noted that functional groups such as an ester, amide, sulfonyl, or alkoxide groups in the starting acetylenes survive the reaction conditions to permit the preparation of functionalized aryltitanium compounds. In summary, we have reported herein the first metalative Reppe reaction, which realized the direct preparation of aryltitanium compounds¹⁰ from three acetylenes in a highly organized manner.

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Supporting Information Available: Experimental procedures and physical properties of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) For synthetic application of organotitanium compounds, see: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139–172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 195–282.