Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 60 (2004) 1345–1352

Tetrahedron

Zr-promoted ‘pair’-selective and regioselective synthesis of penta-substituted benzene derivatives

Yves R. Dumond and Ei-ichi Negishi*

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA

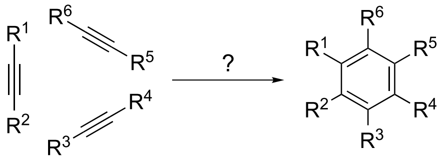
Received 22 August 2003; accepted 2 September 2003

Abstract—Tetra-substituted zirconacyclopentadiene derivatives, obtainable via in situ generation of zirconacyclopropenes and their cyclic carbozirconation with alkynes, can be treated with alkynyllithiums to induce 1,2-migration accompanied by aromatization and protonolysis, leading to the formation of penta-substituted benzene derivatives, in which all five substituted may be different.

---

1. Introduction

Synthesis of benzenes via cyclotrimerization of three molecules of alkynes is a thermodynamically favorable process reported as early as 1866.[1] Almost a century later, Reppe reported what appears to be the first transition metal-catalyzed cyclooligomerization of alkynes producing benzenes and cyclooctatetraenes.[2] Since then, most, if not all, of the d-block transition metals have been shown to catalyze cyclotrimerization of alkynes.[3] In cases where unsymmetrically substituted alkynes and/or two or three different alkynes are employed, synthetically unattractive mixtures of products are generally obtained. Thus, random cyclotrimerization of three different alkynes can, in principle, produce 10 different products, each of which can exist as two or more regioisomers. These reactions can still be very attractive for the synthesis of compounds of material chemical interest but not of fine chemicals. Development of ‘pair’-selective[4] and regioselective synthesis of benzenes from three different unsymmetrically substituted alkenes, as represented by Scheme 1, has indeed been very difficult.



Scheme 1.

One of the notable earlier investigations of pair-selective and regioselective synthesis of benzene derivatives is the Co-catalyzed alkyne cyclotrimerization developed by Vollhardt,[5] which has been successfully applied to the synthesis of natural products including estrone (**1**) and protoberberine alkaloids (**2**). However, satisfactory results have been obtained mostly with tethered α,ω-diynes and a large excess of symmetrical $Me_3SiC{\equiv}CSiMe_3$ requiring subsequent differentiation of the two Me_3Si groups. The strategy of tethering alkynes has been further extended by the use of tethered triynes, as exemplified by a Rh-catalyzed synthesis of a tricyclic precursor to calomelanolactone (**3**).[6] Although only one alkyne molecule is incorporated into a benzene ring, the Dötz benzannulation[7] via Cr-carbene addition to alkynes is another noteworthy example of transition metal-mediated selective synthesis of arenes.

Although no systematic historical presentation is intended here, various pair-selective and regioselective procedures involving other late transition metals have also been developed. In particular, considerable efforts have been expended in the development of Pd-catalyzed procedures with the use of tethered triynes,[8a] haloenynes[8b] and halodienes[9] by Negishi, haloendiynes also by him[8a] and de Meijere,[10] and haloarenediynes by Grigg.[11] Recent investigations of Pd-catalyzed benzannulation of enynes and diynes by Yamamoto and Gevorgyan are also noteworthy.[12]

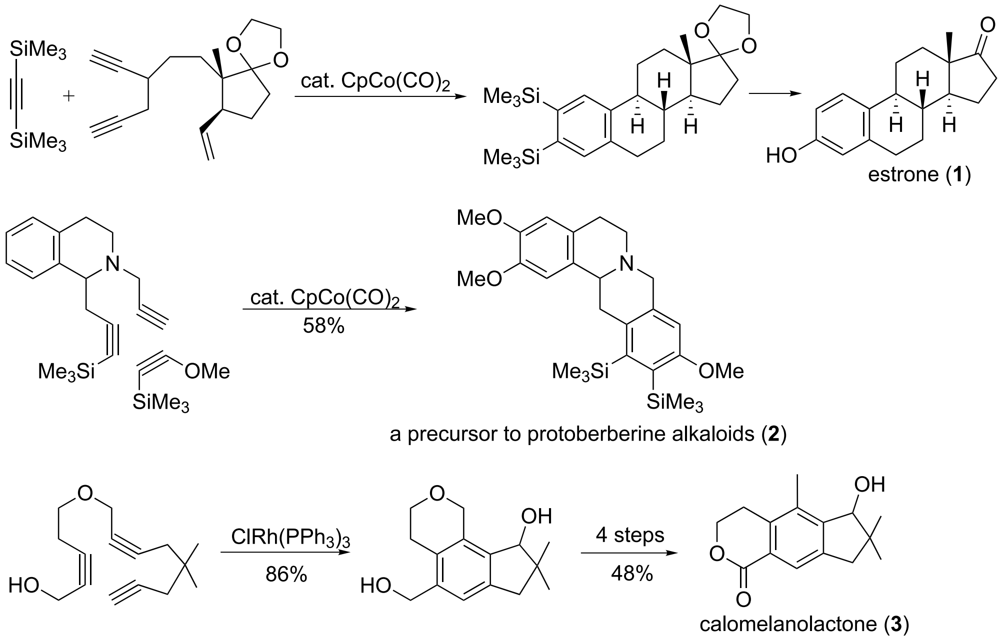
Until recently, the use of early transition metals in the alkyne-based selective arene synthesis had been less well-developed. However, conversion of zirconacyclopentadienes to benzene derivatives in a pair-selective manner was reported by Takahashi in 1995[13] and has since been further developed.[14,15] Even so, those procedures that permit regiocontrolled syntheses of benzene derivatives had not been developed at the time of our unexpected

---

Keywords: Zr-Promoted; ‘Pair’-and regioselective synthesis; Penta-substituted benzenes; Zirconacyclopentadienes; Alkynylzirconate migratory insertion.

* Corresponding author. Tel.: +1-765-494-5301; fax: +1-765-494-0239; e-mail address: negishi@purdue.edu

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.102

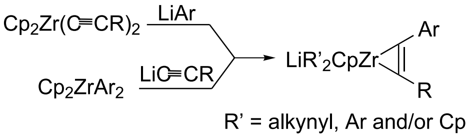


Scheme 2.

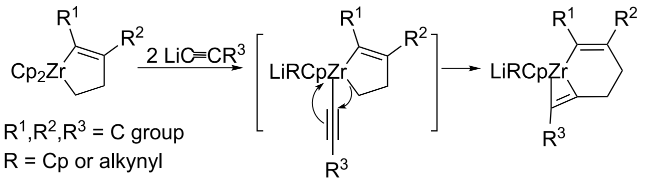
discovery of arene formation by the reaction of zirconacyclopentadienes with alkynyllithiums that has led to the results described below. We report herein a Zr-promoted synthesis of benzene derivatives containing up to five different non-hydrogen groups in the predetermined positions with or without the use of tethering. It may well represent the first demonstration of transition metal-mediated alkyne-based synthesis of such benzene derivatives without two or more of one kind of substituent (Scheme 2).

2. Results and discussion

We have previously discovered a novel migratory insertion reactions of zirconates containing alkynyl and/or aryl groups shown in Scheme 3.[16] During the course of our investigation of related reactions of alkenylzirconates, a similar migratory insertion reaction shown in Scheme 4 was also discovered.[17] In this reaction, an alkyl group rather than an alkenyl group preferentially migrated from Zr to an alkynyl C atom.



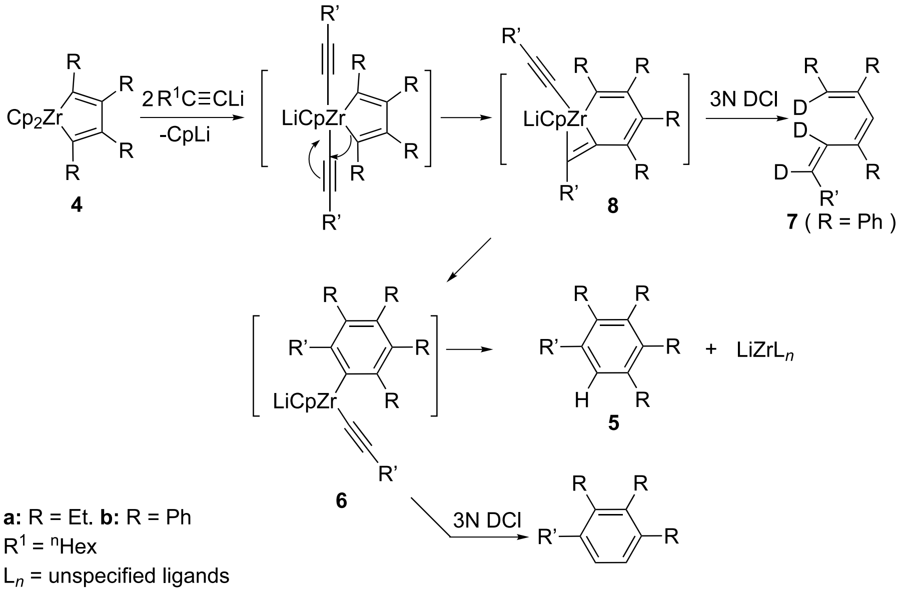
Scheme 3.



Scheme 4.

To further explore the scope of these migratory insertion reactions, a zirconacyclopentadiene (**4a**, generated in situ from ^{n}Bu$_2$ZrCp$_2$ and 2 equiv. of 3-hexyne,[18] was treated with 2 equiv. of 1-octynyllithium in THF at 23 °Cs for 2 h. After quenching the reaction mixture with 3 N HCl, 1-(n-hexyl)-2,3,4,5-tetralthylbenzene (**5a**) was produced in 65% NMR yield rather than the expected acyclic, conjugated triene. As a penta-substituted arylzirconium derivative (**6a**) was suspected as the organometallic precursor to the product (**5a**), the reaction mixture was quenched with 3 N DCl. However, the extent of D incorporation at the C-6 position was only 5%. When only 1 equiv. of ^{n}HexC$\equiv$CLi was used, the yield of **5a** was 30%. Examination of the reaction mixture before quenching by NMR spectroscopy revealed the following. Firstly, **5a** had already been formed in about 30% yield before quenching, indicating that one H atom was internally supplied and transferred to the product. Secondly, about 50% of the starting **4a** remained unreacted. Addition of the 2 equiv. of ^{n}HexC$\equiv$CLi to this mixture consumed essentially all of **4a**, and the yield of **5a** increased to about 60%, thereby establishing the 2:1 stoichiometry between ^{n}HexC$\equiv$CLi and **4a**. Thirdly, examination of the 2:1 reaction mixture by ^{1}H NMR spectroscopy revealed the presence of nearly 1 equiv. of LiCp (δ 6.30 ppm).[19] This has provided a plausible explanation for the requirement of 2 equiv. of ^{n}HexC$\equiv$CLi.

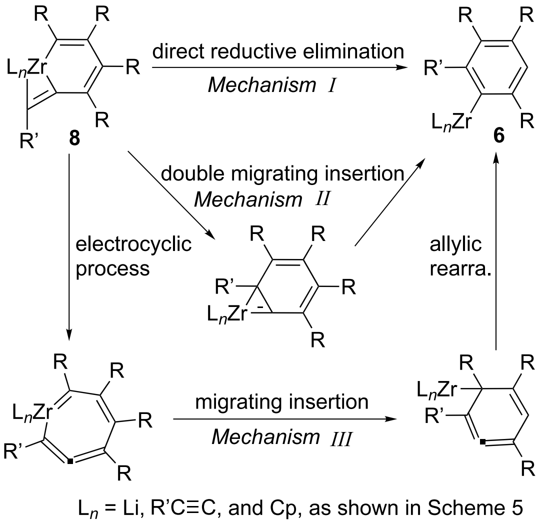
When PhC$\equiv$CPh was used in place of EtC$\equiv$CEt, the aromatization process must have been significantly slowed down. Upon quenching the reaction mixture with 3 N DCl, examination of the complex product mixture by ^{1}H NMR spectroscopy revealed the formation of the expected benzene derivative (**5a**) and its monodeuterated derivative with an aromatic ring-bound D as well as 1,5,6-trideuterio-1,2,3,4-tetraphenyl-1,3,5-dodecatriene (**7**). The above results have supported our interpretation that the reaction must have proceeded via a bicyclic zirconate (**8**) similar to that identified in the previously reported reaction of



Scheme 5.

zirconacyclopentenes.[17] All of the results presented above may be summarized as shown in Scheme 5.

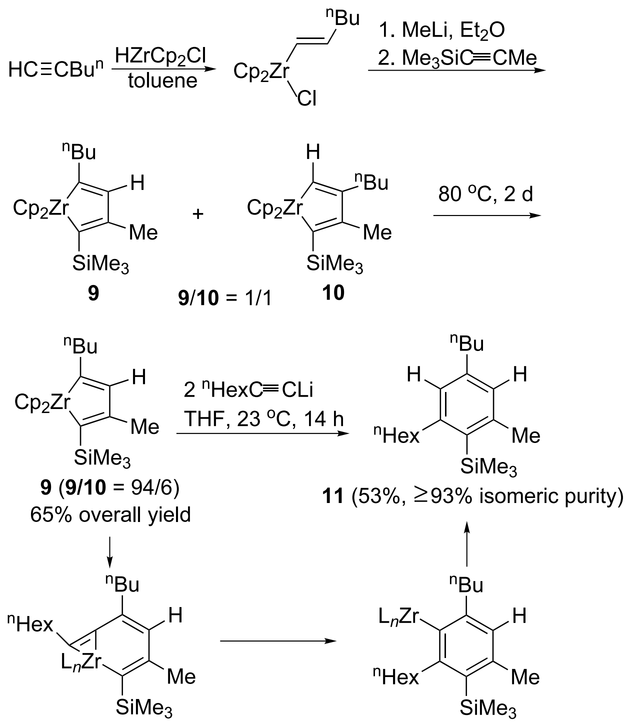
At this point, the mechanism for the conversion of the bicyclic zirconate (**8**) into **6** still remains to be clarified, although the following three alternatives may be considered as being plausible (Scheme 6). Mechanism I involving direct formation of **6** from **8** via reductive elimination is simple and attractive, and a similar reductive elimination process for the formation of cyclobutenes has been proposed.[20] However, the direct C–C bond formation from diorganylzirconocenes via reductive elimination is essentially unknown, and a more indirect path of lower energy barriers involving active participation of π-bonds and other strained bonds are likely to be operative. With this rationalization in mind, two indirect paths, i.e., Mechanisms II and III, are also proposed for the conversion of **8** into **6**. In Mechanism II, a series of two 1,2-migratory insertion processes are thought to take place to effect an overall reductive elimination, while a six-electron electrocyclic process to generate a seven-numbered zirconcycle may then be followed by a migratory insertion and aromatization via allylic rearrangement in Mechanism III. At this moment, it is not possible to choose one over the others, but it would be interesting and important to pursue the question of whether or not direct reductive elimination of diorganylzirconocenes without the involvement of π-bonds is feasible.



Scheme 6.

One important mechanistic issue that remained to be clarified was the source of H for converting **6** into **5**. As stated earlier, quenching the reaction mixture derived from **4a** and ⁿHexC≡CLi gave the expected monodeuterated derivative of **5a** only in 5% yield. So, the putative intermediate **6a** either was not actually formed or was indeed formed but converted into **5a** by abstraction of H from one or more compounds present in the reaction mixture before quenching with HCl or DCl. Irrespective of what the correct mechanism might be, the source of the majority of H must be one or more of the compounds in the reaction mixture. Accordingly, some deuterated compounds were used in place of their non-deuterated counterparts. No D incorporation was observed when THF-d_8 was used in place of THF. On the other hand, incorporation of D to the extent of 14% was observed above and beyond 5% from DCl quenching, when cyclopentadiene-d_5 of 96% D was used for the preparation of Cl_2ZrCp_2-d_{10}. Although cleaner D incorporation was never achieved, it was clear that there were more than one source of H and that the organozirconium precursor to **5a**, be it **6a** or not, must have been competively quenched by internal H sources.

It then occurred to us that, if **6** or an alternate precursor to **5** could be either stabilized or competitively protonated by an added protonating agent to give **5** without interfering with the desired process, **5** would be produced in higher yields. Accordingly, various Lewis bases as election pair donors and proton acids as protonating agents were added to the reaction mixture. However, addition of Et_3N, 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), dppp, and dppe had no detectable effect, while that of PMe_3 totally inhibited the reaction.



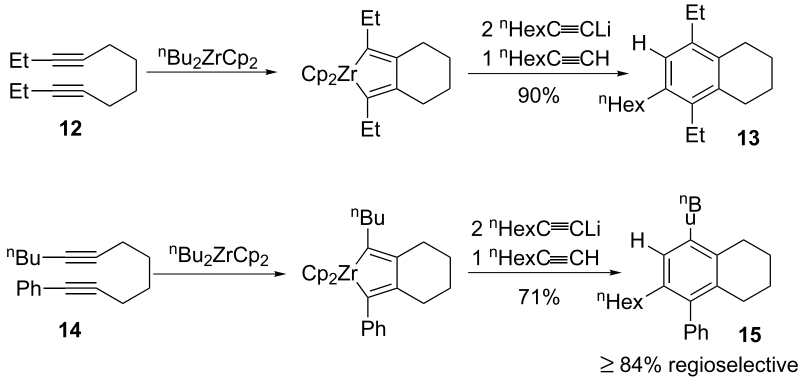
Scheme 7.

Fortunately, addition of proton acids was much more fruitful. The best proton source proved to be the same terminal alkyne as that used for the preparation of the alkynyllithium. Thus, addition of 1 equiv. of 1-octyne to the mixture of the reaction of **4a** with 2 equiv. of ^{n}HexC≡CLi at 23 °C for 3 h led to the formation of **5a** in 90% yield. When ^{n}HexC≡CD was used, D incorporation in the expected position took place to the extent of 86%. These results have not only provided a much superior procedure for the conversion of **4** into **5** but also strongly supported the intermediacy of **6** as the immediate precursor to **5**. Other proton acids were less effective. Methanol was evidently too acidic, as no desired product was formed. Presumably, ^{n}HexC≡CLi was prematurely quenched by MeOH. Indene and *t*-butanol did produce the desired product **5a**, but with no improvement.

As stated earlier, any methods for the synthesis of benzene derivatives that must necessarily incorporate two or more of one kind of substituent are of very limited utility for the synthesis of fine chemicals, even though they may be very useful in the synthesis of oligomers and polymers of material chemical interest. For the former objective, it was essential to be able to synthesize zirconacyclopentadienes containing four different non-hydrogen groups, one or more of which may be replaced with H and/or some other groups, such as SiMe$_3$, that can be differentiated later. Of various methods thus far developed for the synthesis of zirconacyclopentadienes,[21] two of them often referred to as the Erker–Buchwald protocol[22] and the Negishi–Takahashi protocol[23] have been most widely used. A more recently developed method of Rosenthal[24] and its modification by Tilley[25] as well as earlier contributions by Farona[26] and Nugent[27] are also noteworthy. For the purpose of developing pair-selective synthesis of benzene derivatives, modifications of the Negishi–Takahashi protocol through the use of Et$_2$ZrCp$_2$ have proved to be useful.[28] At the time of this investigation, however, there was only one reported procedure by Buchwald[29] for the pair-selective and regioselective synthesis of zirconacyclopentadienes with four different groups in the predetermined positions, as exemplified by the process shown in Scheme 7.

Accordingly, we generated **9** in about 65% yield as a 94:6 regiosomeric mixture of **9** with **10**. Under non-optimized conditions, the 94:6 mixture of **9** and **10** was treated with 2 equiv. of ^{n}HexC≡CLi. One regioisomer of >93% regiosomeric purity thus obtained was identified as **11** (Scheme 7). Thus, the conjugated diene moiety containing ^{n}Bu, H, Me, and Me$_3$Si groups retained its regiochemistry throughout the reaction. Noteworthy is the nearly 100% regioselectivity observed for the incorporation of 1-octyne in the conversion of **9** to **11**. The results indicate that the migratory insertion of 1-octyne took place almost exclusively on the side of ^{n}Bu or away from Me$_3$Si (Scheme 7). These results were obtained before the development of an improved procedure involving addition of a 1-alkyne, and its application to this case has not yet been performed.

As has been amply demonstrated (vide supra), the use of tethered diynes substantially reduced the level of difficulty in controlling regioselectivity. Some preliminary results along this line are summarized in Scheme 8. In cases where unsymmetrically substituted diynes were used, the reaction proceeded in approximately 85% regioselectivity. When Zr was flanked with ^{n}Bu and Ph, the ^{n}Bu side migrated preferentially. In addition to steric factors, electronic



Scheme 8.

factors, such as the well-documented benzylic, allylic, and propergylic interaction with Zr, appears to be significant. Although only one symmetric tether, i.e., tetramethylene, was used in this study, a variety of unsymmetric tethers including those containing heteroatoms can, in principle, be used in the reaction described herein, and efforts are being made along this line.

All of the reactions discussed above employed Cp_2ZrCl_2, but we also used $(Ind)_2ZrCl_2$, where Ind is indenyl, and Cp_2HfCl_2 for the synthesis of **5a** from 3-hexyne. Without the benefit of added 1-octyne, **5a** was obtained in 60 and 35% yields, respectively. Prior to the experiments described thus far in this paper, we briefly investigated the reaction of dialkynylzirconocoenes with alkenyllithiums. The reaction of $(PhC{\equiv}C)_2ZrCp_2$ with (*E*)-PhC≡CLi gave, upon treatment with I_2, a rather complex mixture containing (*E*)-PhCH=CHC≡CPh and (*E*,*E*)-PhCH=CHCH=CHPh among others. In no case was a clean reaction observed. More recently, Hirao[30] reported the reaction of alkenylzirconocene chlorides with 2 equiv. of alkynyllithiums to give (*E*,*Z*)-conjugated dienes in good yields, thereby further extending the scope of migratory insertion reactions of alkynylzirconates.

3. Conclusions

The migratory insertion reaction of alkynylzirconates, generated in situ by treating zirconacyclopentadienes with 2 equiv. of alkynyllithiums, unexpectedly produced the corresponding benzene derivatives rather than the expected conjugated trienes. Evidently, the expected migratory insertion reaction took place to give bicyclic zirconacycles (**8**), which then underwent reductive C–C bond formation by an as yet unclear mechanism to produce arylzirconates (**6**) Their protonolysis provided benzene derivatives (**5**). Protonolysis can be best achieved in situ by the addition of alkynes corresponding to the alkynyllithium used, since the precursors to **5**, i.e., **6**, are unstable, and they tend to undergo further complex reactions before full consumption of the starting compounds. This novel synthesis of benzene derivatives is, in principle, applicable to pair-selective and regioselective synthesis of benzene derivatives containing up to five different non-hydrogen groups. As such, it appears to represent the first demonstration of transition metal-mediated pair-selective and regioselective synthesis of benzene derivatives from three different and untethered alkynes.

4. Experimental

4.1. General

All manipulations were conducted under an atmosphere of dry argon, unless otherwise noted. Flash chromatographic separations were carried out on 230–400 mesh silica gel 60. Gas chromatography was performed on a HP 6890 Gas Chromatograph using HP-5 capillary column (30 m× 0.32 mm, 0.5 μm film) with mesitylene as an internal standard. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer. NMR yields were determined using mesitylene as an internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum 2000 FTIR spectrometer. THF was distilled from sodium benzophenone ketyl.

4.2. Preparation of symmetrically tetra-substituted zirconacyclopentadienes

Zirconacyclopentadienes containing four Et groups (**4a**) and four Ph groups (**4b**) were prepared by the reaction of $^nBu_2ZrCp_2$[18] with 2 equiv. of 3-hexyne and diphenylethyne, respectively, according to the previously reported procedure,[18] as described below for the synthesis of **5a**.

4.2.1. Preparation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraethylzirconacyclopentadiene (4a). To a solution of Cl_2ZrCp_2 (584 mg. 2.0 mmol) in THF (6 mL) were added dropwise at −78 °C via syringe ^nBuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol) and 3-hexyne (0.33 g, 0.45 mL, 4 mmol). After stirring for 10 min at −78 °C, the reaction mixture was warmed to 23 °C and stirred further for 2 h. After addition of mesitylene (240 mg, 0.28 mL, 2 mmol), clean quantitative formation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraethylzirconacyclopentadiene (**4a**) was observed by GLC and ^1H NMR (C_6D_6, THF) Cp signal at 5.94 ppm.

4.2.2. Preparation of 1,1-bis(η^5-cyclopentadienyl)-2,3,4,5-tetraphenylzirconacyclopentadiene (4b). This compound was prepared as above in 94% NMR yield[31] by using 0.71 g (4 mmol) of diphenylethyne in place of 3-hexyne: ^1H NMR(C_6D_6, THF) Cp signal at 6.22 ppm.

4.3. Reaction of zirconacyclopentadienes (4) with alkynyllithiums

This reaction was carried out as detailed below for the conversion of **4a** into **5a**.

4.3.1. Conversion of 4a into 1-(*n*-hexyl)-2,3,4,5-tetraethylbenzene (5a). Representative procedure. 1-Octynyllithium, prepared in THF at −78 °C from 1-octyne (0.44 g, 0.59 mL, 4 mmol) and ^nBuLi (2.5 M in hexane, 1.6 mL, 4 mmol), was added dropwise at −78 °C via cannula to the reaction mixture containing **4a** described in Section 4.2.1, and the resultant mixture was stirred at −78 °C for 1 h, warmed to 23 °C, but the zirconacyclopentadiene **2a** was observed unchanged by ^1H NMR (C_6D_6/THF=6/1) (Cp signal at 5.94 ppm). The reaction mixture was stirred for an additional 1 h to generate the title compound (**5a**) observed in the reaction mixture by ^1H NMR (C_6D_6/THF=6/1) (aromatic proton signal at δ 6.91 ppm, 50% NMR yield). Formation of CpLi (δ 6.30 ppm) up to 100% was also observed. The reaction mixture was quenched with 3 N HCl, extracted with pentane, washed with $NaHCO_3$ dried over $MgSO_4$, and concentrated. GLC and ^1H NMR examination using mesitylene as an internal standard indicated about 65% yields of the title compound over several runs. After filtration on a silica gel pad and evaporation in vacuo, the title compound was isolated in 51% yield (279 mg): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, J=5.7 Hz, 3H), 1.15–1.4 (m, 20H), 2.55–2.7 (m, 10H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.13, 15.59 (2C), 15.68, 15.92, 21.71, 21.79, 22.03, 22.69, 25.60, 29.83, 31.77, 31.82, 33.10, 127.23, 137.32, 137.40, 138.36, 139.27, 139.77; HRMS (FAB KIPEG) calcd for $C_{20}H_{34}$ (M+1) 275.2739, found 275.2737.

4.3.2. 1-(*n*-Hexyl)-2,3,4,5-tetraphenylbenzene (5b). To the reaction mixture containing **4b** prepared in Section 4.2.2 was added 1-octynyllithium, prepared in THF at −78 °C from 1-octyne (0.44 g, 0.59 mL, 4 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4 mmol), at −78 °C via cannula, and the reaction mixture was stirred at −78 °C for 1 h and warmed to 23 °C. The reaction mixture was further stirred for 3 h, quenched with 3 N HCl, extracted with pentane, washed with $NaHCO_3$ dried over $MgSO_4$, and concentrated. GLC and GC/MS examination showed the formation of the title compound (**5b**) and 1,2,3,4-tetraphenyl-1,3,5-dodecatriene. In case of quenching with 3 N DCl, GLC and GC/MS examination showed the formation of the benzene derivative (**5b**) and **7** containing three deuterium atoms, supporting the proposed structure of **8**.

4.3.3. Preparation of 1,1-bis(η^5-cyclopentadienyl-2-trimethylsilyl-3-methyl-5-(*n*-butyl)zirconacyclopentadiene(9) and its conversion to 1-trimethylsilyl-2-(*n*-hexyl)-4-(*n*-butyl)-6-methylbenzene(11). To $HZrCp_2Cl$ (1.40 g, 5.43 mmol) in 16 mL of toluene was added at 23 °C 1-hexyne (0.45 g, 0.62 mL, 5.43 mmol). After 10 h at 23 °C, MeLi (1.4 M in Et_2O, 3.88 mL, 5.43 mmol) was added at 0 °C. One hour later, 1-trimethylsilyl-1-propyne (0.61 g, 0.80 mL, 5.43 mmol) was added. The reaction mixture was then heated at 80 °C for 2 days to afford regioisomerically 94% pure **9** in 42% yield, only other regiosomer produced being the 3-(*n*-butyl) isomer (6%).

To the mixture containing **9** obtained above was added at −78 °C 1-octynyllithium, prepared in THF from 1-octyne (1.32 g, 1.77 mL, 12.0 mmol) and ^{n}BuLi (2.5 M in hexane, 4.8 mL, 12.0 mmol). After stirring at 23 °C overnight, the standard workup as in Section 4.3.1 afforded **11** in 53% yield based on **9** as a >93% regioisomerically pure substance: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.49 (s, 9H), 1.0–1.1 (m, 6H), 1.4–2.35 (m, 15H), 2.61 (t, J=7.7 Hz, 2H), 2.78 (t, J=8.0 Hz, 2H), 6.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 3.82 (3C), 14.10 (2C), 22.62, 22.68, 24.84, 29.56, 31.92, 33.41, 33.82, 35.31, 36.98, 127.40, 128.52, 132.69, 143.30, 144.08, 149.60; HRMS calcd for $C_{20}H_{36}Si$ (M+) 304.2586, found 304.2588.

4.4. Investigation of the proton source

Following the same procedure as in Section 4.3.1 for the preparation of **5a**, the reaction mixture was quenched with 3 N DCl and <5% D incorporation was observed by LRMS. Following the same procedure as above for the preparation of **5a** but using THF-d_8, 0% D incorporation was obtained. By using Cp_2ZrCl_2-d_{10} (>96% D incorporation) for the synthesis of **5a**, 14% D incorporation was recorded by ^{13}C NMR and LRMS.

4.5. Effects of added bases

The reaction of **4a** with 2 equiv. of ^{n}HexC$\equiv$CLi was run in the presence of various tertiary amines and phosphines. Addition of 12 equiv. of Et_3N or DMAP, 6 Mequiv. of 2,2′-bipyridyl or dppp, or 1.6 Mequiv. of dppe did not detectably change either the rate of formation or the yield of **5a**, the latter of which ranged 50–70%. Addition of $(MeOCH_2)_2$ or TMEDA (6 equiv.) merely slowed down the reaction, and addition of either PMe_3 (12 equiv.) or 1,10-phenanthroline (6 Mequiv.) inhibited the desired benzene formation. In all cases, ^{1}H NMR examination of the reaction mixture in C_6D_6–THF (6:1) showed the displacement of up to 1 equiv. of CpLi (δ 6.30 pm).

4.6. Reactions of zirconacyclopentadienes with alkynyllithiums in the presence of the corresponding 1-alkynes. An improved synthesis of benzene derivatives

These reactions were run in the same manner as described in Section 4.3.1 except that 1-alkyne (1 equiv. relative to Zr) was added at the beginning of the reaction of zirconacyclopentadienes with 1-alkynyllithium (2 equiv.).

4.6.1. Improved synthesis of 1-(*n*-hexyl)-2,3,4,5-tetraethylbenzene (5a). Improved representative procedure. To the reaction mixture containing **4a** (Section 4.2.1), were added ^{n}HexC$\equiv$CLi, prepared from 1-octyne (0.44 g, 0.59 mL, 4.0 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol), and 1-octyne (0.22 g, 2.0 mmol) at −78 °C. After stirring first at −78 °C for 1 h and then at −23 °C for several hours, **5a** was produced in 90% yield by NMR. Its spectral data are presented in Section 4.3.1.

4.6.2. 1-(*n*-Octyl)-6-deuterio-2,3,4,5-tetraethylbenzene. This reaction was carried out as described in Section 4.6.1 except that 1-decyne (0.55 g, 4.0 mmol) was used to prepare ^{n}OctC$\equiv$CLi and that 1-deuterio-1-decyne (95% D, 0.28 g, 2.0 mmol) was added as a D source The title compound was obtained in 90% yield with incorporation of D to the extent of 86%: ^{1}H NMR($CDCl_3$, Me_4Si) δ 0.90 (t, J=5.7 Hz, 3H), 1.15–1.4 (m, 24H), 2.55–2.7 (m, 10H), 6.87 (s, 14% of 1H); ^{13}C NMR ($CDCl_3$) δ 13.91, 15.47 (2C), 15.54, 15.79, 21.58, 21.66, 21.90, 22.58, 25.47, 28.89, 29.39, 31.53, 31.73, 32.95, 33.75, no peak at 127 because of D on the benzene ring, 137.07, 137.17, 138.04, 138.98, 139,50; LRMS calcd (M+) 303, found 303 (86%).

4.6.3. Preparation of 3,9-dodecadiyne (12) and its conversion to 5,8-diethyl-6-(*n*-hexyl)-1,2,3,4-tetrahydronaphthalene (13). 3,9-Dodecadiyne (**12**) was prepared in 70% yield by successively treating 1,7-octadiyne (5.3 g, 6.64 mL, 50 mmol) in THF (100 mL) with ^{n}BuLi (2.5 M in hexane, 42 mL, 105 mmol, −78 °C, 1 h) and iodoethane (17.9 g, 9.2 mL, 115 mmol) in DMPU (150 mL): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.11 (t, J=7.5 Hz, 6H), 1.57 (broad t, J=6.5 Hz, 4H), 2.1–2.2 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.35 (2C), 14.28 (2C), 18.26 (2C), 28.19 (2C), 79.02 (2C), 81.75 (2C).

3,9-Dodecadiyne (**12**) (0.324 g, 2.0 mmol) prepared above was treated with $^n Bu_2ZrCp_2$ generated in THF (6 mL) from Cp_2ZrCl_2 (0.584 g, 2.0 mmol) and ^{n}BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol) as described in Section 4.2.1. After confirming the formation of a zirconabicycle in nearly quantitative yield by ^{1}H NMR spectroscopy, ^{n}HexC$\equiv$CLi generated in situ from 1-octyne (0.44 g, 4.0 mmol) and an additional 2.0 mmol (0.22 g) of 1-octyne were added at −78 °C, and the reaction mixture was stirred overnight at 23 °C to produce **13** in 90% NMR yield: ^{1}H NMR ($CDCl_3$, Me_4Si) 0.89 (t, J=6.8 Hz, 3H), 1.11 (t, J=6.7 Hz, 3H), 1.19 (t, J=7.6 Hz, 3H), 1.2–1.55 (m, 12H), 1.8–2.8 (m, 10H), 6.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.99, 14.23, 14.36, 21.21, 22.91, 23.28, 25.47, 26.46, 26.94, 29.72, 31.57, 31.80, 32.00, 33.03, 126.41, 132.54, 134.87, 137.41, 137.61, 139.29; HRMS calcd for $C_{20}H_{32}$ (M+) 272.2504, found 272.2501.

4.6.4. Preparation of 1-phenyl-1,7-dodecadiyne (14) and its conversion to 5-phenyl-6-(*n*-hexyl)-8-(*n*-butyl)-1,2,3,4-tetrahydronaphthalene (15). 1,7-Octadiyne (10.6 g, 13.3 mL, 100 mmol) was mono-butylated by using ^{n}BuLi (100 mmol), ^{n}BuI (22.1 g, 13.7 mL, 120 mmol), and DMPU (90 mL). After the usual workup, distillation afforded 1,7-dodecadiyne in about 35% yield. Successive treatment of 1,7-dodecadiyne (0.45 g, 2.8 mmol) in THF with ^{n}BuLi (3.36 mmol −78 °C), dry $ZnBr_2$ (4.2 mmol, −78 °C for 1 h and then 23 °C for 0.5 h), iodobenzene (0.86 g, 0.47 mL, 4.2 mmol), and $Pd(PPh_3)_4$ (65 mg, 0.056 mmol, 14 h, 23 °C).[32] The reaction mixture was successively treated with 3 N HCl, pentane, aqueous $NaHCO_3$, and $MgSO_4$ to give **14** in 91% yield: ^{1}H NMR ($CDCl_3Me_4Si$) δ 0.97 (t, J=7 Hz, 3H), 1.45–1.55 (m, 4H), 1.7–1.8 (m, 4H), 2.2–2.3 (m, 4H), 2.49 (t, J=6.8 Hz, 2H), 7.3–7.35 (m, 3H), 7.45–7.5 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.59, 18.30, 18.39, 18.92, 21.90, 27.79, 28.22, 31.18, 79.54, 80.52, 80.74, 89.89, 123.94, 127.43, 128.11 (2C), 131.47 (2C).

1-Phenyl-1,7-dodecadiyne (**14**) (0.476 g, 2.0 mmol) was converted to **15** in 71% NMR yield by its reaction with ^{n}HexC≡CLi (4.0 mmol) and 1-octyne (2.0 mmol) as described in Section 4.6.3. The product (**15**) yielded the following spectral data: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J=6.7 Hz, 6H), 125–1.6 (m, 16H), 1.8–2.75 (m, 8H), 6.93 (s, 1H), 7.1–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.92 (2C), 22.28, 23.12, 26.37, 26.84, 28.77, 28.87, 29.07, 29.33, 31.71, 31.84, 32.41, 32.61, 126.19, 126.66, 127.99 (2C), 129.55 (2C), 132.06, 134.92, 137.53, 139.00, 139.70, 141.06; HRMS calcd for $C_{26}H_{36}$ (M+) 348.2817, found 348.2816.

4.7. Use of Ind_2ZrCl_2 and Cp_2HfCl_2 in the synthesis of 5a from 3-hexyne and 1-octyne

Following the non-optimized procedure described in Section 4.3.1, the use of Ind_2ZrCl_2 and Cp_2HfCl_2 led to the formation of **5a** in 60 and 35% yields, respectively.

4.8. Reaction of bis(phenylethynyl)zirconocene with (*E*)-2-phenylethenyllithium

Bis(phenylethynyl)-zirconocene was generated by treating Cp_2ZrCl_2 (2.0 mmol) with PhC≡CLi prepared from 4 mmol each of PhC≡CH and ^{n}BuLi in THF (75% NMR yield, Cp signal at δ 6.15 ppm). Its treatment with *(E)*-2-phenylethenyllithium (4 mmol) at 23 °C for 1 d followed by addition of I_2 (2.5 equiv.) let to a complex mixture containing 1,4-diphenyl-1-buten-3-yne and 1,4-diphenyl-1,3-butadiene. This reaction was not further investigated.

Acknowledgements

The authors thank the National Science Foundation (CHE-0309613) and Purdue University for support of this research. Y. R. D. was a Purdue Research Foundation Graduate Fellow (1997–1998). Generous assistance in the procurement of Zr compounds by Boulder Scientific Co. is gratefully acknowledged. We also thank Professor T. Takahashi for sharing unpublished results and Professor V. Gegorgyan for providing us with useful information. Technical assistance provided by Ms Q. Hu is gratefully acknowledged.

References and notes

1. Berthelot, M. C. R. *Acad. Sci.* **1866**, 905.
2. Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Liebigs Ann. Chem.* **1948**, *560*, 1.
3. See, for example Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. Principles and Applications of Organotransition Metal Chemistry; 2nd ed. University Science Books: Mill Valley, CA, 1987; p 989.
4. In place of 'pair'-selective, copuloselective (copulo in Latin= to pair) has been proposed. See Anastasia, A.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 311.
5. Vollhardt, K. P. C. *Angew Chem. Int. Ed.* **1984**, *23*, 539, and references therein.
6. Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239.
7. For a review, see (a) Wulff, W. D. *Comprehensive Organometallic Chemistry II*, Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, p 469. (b) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187.
8. (a) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. (b) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471.
9. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
10. Meyer, F. E.; de Meijere, A. *Synlett* **1999**, 777.
11. Grigg, R.; Rasul, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825.
12. (a) Saito, S.; Yamamoto, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 1635–1646 Chapter IV.10.2. (b) Gevorgyan, V.; Yamamato, Y. *J. Organomet. Chem.* **1999**, *576*, 232.
13. Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361.
14. Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154.
15. Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672.
16. Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440.
17. Dumond, Y.; Negishi, E. *J. Am. Chem. Soc.* **1999**, *121*, 11223.
18. (a) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
19. (a) Kondakov, D.; Negishi, E. *Chem. Commun.* **1996**, 963.

(b) See also Razuvaev, G.; Vyshinskaya, L.; Vasil'eva, G.; Malysheva, A. *Dokl. Akad. Nauk. SSSR* **1978**, *243*, 1212.

20. Liu, Y.; Sun, W.; Nakajima, K.; Takahashi, T. *Chem. Commun.* **1998**, 1133.
21. For a review, see Negishi, E.; Takahashi, T. *Houben-Weyl Science of Synthesis*, Imamoto, T., Ed.; Thieme: Stuttgart, 2003; Vol. 2, pp 739–774 Sect. 2.11.5.
22. For a review, see Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.
23. For a review, see Takahashi, T.; Li, Y. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 50–85 Chapter 2.
24. For a review, see Rosenthal, V.; Burlakov, V. V. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 355–389 Chapter 10.
25. Nitschke, J. R.; Zürcher, S.; Tilley, D. T. *J. Am. Chem. Soc.* **2000**, *122*, 10345.
26. Thanedar, S.; Farona, M. F. *J. Organomet. Chem.* **1982**, *235*, 65.
27. Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788.
28. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444.
29. (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870.
30. Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Organomet. Chem.* **1999**, *575*, 76.
31. Ref. 21, p 753.
32. King, A. O.; Negishi, E.; Villani, Jr. F. J.; Silveira, Jr. A. *J. Org. Chem.* **1978**, *43*, 358.