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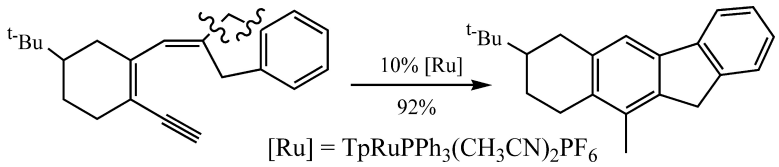

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Ruthenium-Catalyzed Regioselective 1,3-Methylene Transfer by Cleavage of Two Adjacent σ-Carbon−Carbon Bonds: An Easy and Selective Synthesis of Highly Subsituted Benzenes

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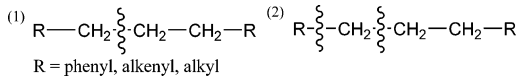
Metal-catalyzed cleavage of a σ-carbon−carbon bond is an interesting and useful method in organic reactions.[1] Reported examples of such reactions focus exclusively on the activation of strained[2] or functionalized carbon−carbon bonds.[3] Although there has been significant advancement in the metal-catalyzed activation of carbon−carbon double and triple bonds,[4,5] catalytic cleavage of a σ-carbon−carbon bond of the aliphatic type (Scheme 1, eq 1) has attained less progress.[2a,3a] One perspective method involves the use of electrophilic metals to activate functionalized alkynes and generates carbocations or carbene species to facilitate the cleavage of adjacent carbon−carbon bonds.[6,7] This approach is applicable to reactions of the metathesis type[7] and 1,2-alkyl shift.[8c,8d] In this study, we report a ruthenium-catalyzed 1,3-regioselective methylene transfer in the cycloisomerization of 3,5-dien-1-ynes, which involves cleavage of two σ-carbon−carbon bonds of the aliphatic type (eq 2).

Cyclization of 3,5-dien-1-ynes to benzene derivatives has been implemented by metal complexes via formation of metal−vinylidene intermediates.[8] We sought to apply this method to the synthesis of highly substituted benzenes,[9] which is an important subject in catalytic reactions.[10] As shown in Scheme 2, heating 6,6-disubstituted 3,5-dien-1-yne **1** in hot toluene (100 °C, 10 h) with 10% $TpRuPPh_3(CH_3CN)_2PF_6$[8c,9] catalyst gave 6-propyl-1,2,3,4-tetrahydronaphthalene **2** in 42% yield. Under similar conditions, the cyclopropylidenyl and cyclobutylidenyl derivatives **3** and **4** preferably gave benzene products **5** and **6**, resulting from a regioselective 1,2-alkyl shift, in yields of 23% and 68% respectively. In such cyclizations, we observed a 1,2-shift of the alkynyl proton of species **d-4**, indicative of a vinylidene intermediate.[8] To our astonishment, the catalytic transformation on the cyclopentylidene analogue **7** gave tricyclic benzene **8** in 87% yield; this product contained an unexpected methyl group. The structure of benzene **8** was determined by the proton-NOE effect.[11] This transformation involves not only a regioselective 1,2-alkyl shift, but also a transfer of the methylene group. We prepared a ^{13}C-labeled sample **7**, in which the C(5) carbon (8 atom ^{13}C %) migrated only to the C(6)H carbon of benzene **8** (eq 3). This information suggests that formation of benzene **8** arises from the 6-*endo-dig* cyclization[12] of dienyne **7**, with one methylene group of the cyclopentylidene ring 1,3-migrating to the C(2)-alkyne carbon. Such a 1,3-methylene transfer involves cleavage of two adjacent σ-carbon−carbon bonds. The yields of benzene **8** are highly dependent on the solvents: benzene (57%, 80 °C, 7 h), DMF (71%, 100 °C, 6 h), DMSO (87%, 100 °C, 6 h), 1,4-dioxane (65%, 100 °C, 4 h), dichloroethane (61%, 80 °C, 8 h).

We prepared various 6,6-cycloalkylidenyl-3,5-dien-1-ynes **9**−**17** to examine the generality of this cyclization using the same catalyst (10 mol %). The reactions worked well for 3,5-dien-1-ynes **9**−**12** (entries 1−4), and gave substituted benzenes **18**, **8**, and **19**−**20** in 63−93% yields. The cyclization evidently proceeded more efficiently for cyclopentylidenyl derivatives **9** and **12** than their cyclohexylidenyl analogues **10** and **11**. In the cyclization of 3,5-dien-1-ynes **13** and **14** (entries 5−6), the resulting benzenes **21**−**22** have the methyl group located at the phenyl C(3)-carbon according to the proton-NOE spectra.[11] This observation is consistent with our observed 1,3-methylene transfer in the ^{13}C-labeling experiment (Scheme 2, eq 3). The value of this cyclization is reflected by the selective 1,2-shift of the cycloalkylidene alkyl groups, and the examples are manifested by 3,5-dien-1-ynes **15**−**17** (entries 7−9). According to proton-NOE effects,[11] the resulting products **23**−**25** show no shift for the phenyl substituent, a 1,2-shift for the uncleaved benzyl group, and a 1,3-shift for the methyl (or methylene) group. This structural rearrangement is amazing because the phenyl and its cleaved methyl group are in the remote meta position. The synthetic value of this cyclization is evident from its reaction generality shown in Table 1, which provides an easy and selective synthesis of highly substituted benzenes[10] as represented by compound **25** bearing six unequivalent phenyl substituents.

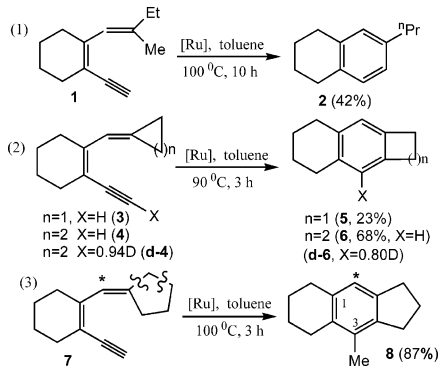
We prepared deuterated dienyne **d-7** to understand better this novel 1,3-methylene transfer. The results shown in Scheme 3 (eq 1, entry 1, Z = H) confirm that the $C(1)X_2$(X = 0.94 D) fragment of the cyclopentylidene group is cleaved. The corresponding cyclized product **d-8** has a fused cyclopentyl ring with the CH_2 and the CX_2 (X = 0.91 D**)** units respectively linking to the phenyl C(5) and C(4) carbons, whereas the CHY_2 methyl (Y = 0.90 D) is located at the C(3) carbon without loss of deuterium content. This structural arrangement is identical to those of benzenes **23**−**25**. One of the methyl protons of species **d-8** (entry 2) arises mainly from the alkynyl deuterium **d-7**. A similar phenomenon is also observed

Scheme 1 [a]



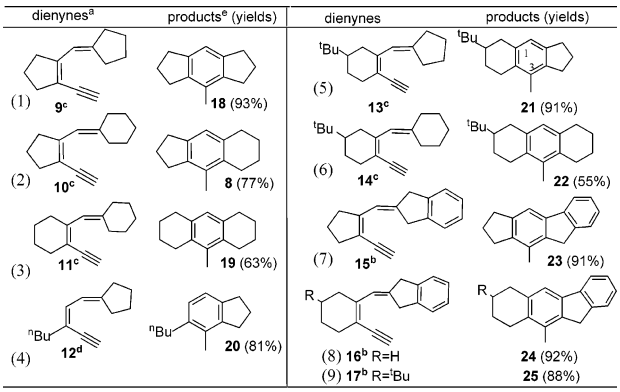
[a] * means C = 13% ^{13}C. [Ru] = $TpRuPPh_3(CH_3CN)PF_6$.

Scheme 2



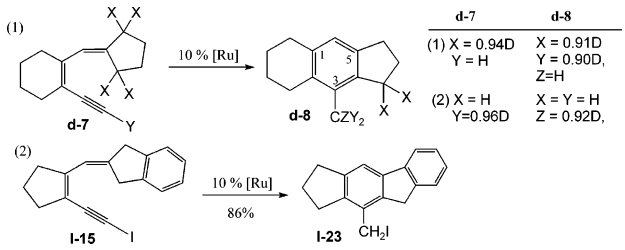
10.1021/ja0504901 CCC: $30.25

Table 1. Ruthenium-Catalyzed Regioselective Methylene Transfer Reaction

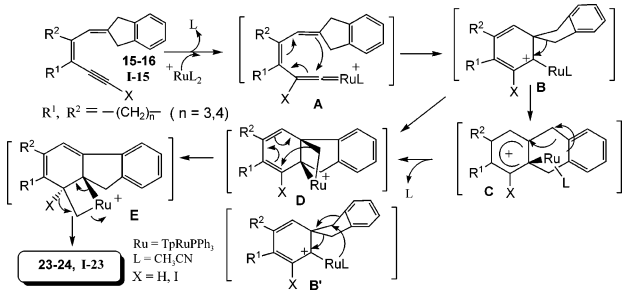


[a] 10 mol % catalyst, [substrate] =1.0 M, 100 °C, toluene. [b] 1.5 h. [c] 4.0 h. [d] 8.0 h. [e] Yields were reported by separation from a silica column.

Scheme 3



Scheme 4



for the alkynyl iodide species **I-15** (eq 2)**,** which transfers its iodide to the benzyl methylene group of product **I-23**.

Shown in Scheme 4 is our proposed mechanism, in which the initial step involves formation of a ruthenium−vinylidene species **A**[8] via 1,2-shifts of hydrogen and iodo groups.[8b] 6-*endo-dig* Electrocyclization[12] of species **A** gives cyclohexadienyl cation **B**. We envisage that cationic charge of species **B** resides mainly on the Ru−C carbon[8c,13] and induces a selective 1,2-alkyl shift to give cationic intermediate **C.** This species is stabilized by a cationic pentadienyl resonance. Attack of the ruthenium center of species **C** at the remote benzyl CH_2 carbon induces 1,2-phenyl shift, and gives cyclobutylruthenium species **D**; the driving force for this transformation is the formation of an extra Ru−C bond. For species **D**, the 1,5-sigmatropic alkyl shift[14] (via suprafacial retention) leads to intermediate **E,** and ultimately gives the observed products **23** and **24**. We do not exclude the possibility that species **B** can be directly transformed into species **D** through a "push−pull" mechanism, as shown by structure **B′**. In this pathway, the ruthenium attacks at the benzyl carbon simultaneously when the Ru−C carbocation induces a 1,2-shift of the other benzyl group. The proposed mechanism[15,16] rationalizes the observed alkynyl ^{2}H and iodide shifts of starting 3,5-die-1-nynes **d-7** and **I-16** (Scheme 3).

In summary, we report a new ruthenium-catalyzed 6-*endo-dig* cyclization of 6,6-cycloalkylidenyl-3,5-dien-1-ynes[17] that produces highly substituted benzenes with atom economy. In this structural reorganization, we observe a regioselective 1,3-methylene migration via extrusion from a cycloalkylidenyl ring, in addition to a regiocontrolled 1,2-alkyl migration.

Acknowledgment. We thank the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: NMR spectra, spectral data of compounds **1-25, I-15**, and **I-23**, NMR spectra of ^{2}H- and ^{13}C-labeled **d-7** and **d-8**, and ^{1}H NOE of **8**, **21**, **23**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Cyclization of 2′,2′-disubstituted (*o*-ethynyl)styrenes by $TpRuPPh_3(CH_3CN)_2PF_6$ followed 5-*endo-dig* mode and gave 2-alkenyl indenes exclusively. The preference for this cyclization is because the corresponding 6-*endo-dig* mode leads to dearomatization of the reaction intermediate. See: Madhushaw, R.-J.; Lo, C.-Y.; Huang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560.

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(11) The ^{1}H-NOE spectra of benzene derivatives **8**, **21**, **23**, **24**, and **25** are provided in Supporting Information.

(12) Cyclization of 3,5-dien-1-ynes to benzene products by this catalyst can be achieved by the 5-*endo-dig* pathway, but the C(5)-carbon of starting 3,5-dien-1-yne shows a 1,2-shift. Our ^{13}C(5)-labeling experiment in Scheme 2 (eq 3) is characteristic of 6-*endo-dig* cyclization. See ref 8c.

(13) The cationic charge in structure **B** should reside mainly on the Ru−C carbon because the TpRu fragment is an electron-rich center, which stabilizes the adjacent carbocation more efficiently.

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(15) The behavior of 3,5-dien-1-yne **1** is distinct from its cycloalkylidene analogues. We envisage that its elongation product **2** (Scheme 2, eq 1) arises from the C−H activation of either the methyl or the CH_2CH_3 group by ruthenium via intermediate **B**. Such C−H activations are unlikely to occur for cycloalkylidene analogues because of their restricted ring conformations. The mechanism will be characterized in future studies.

(16) Benzene products **5** and **6** (Scheme 2, eq 2) are proposed to arise from an intermediate such as species **C** (Scheme 4) which will not undergo ring contraction to yield an intermediate like **D**.

(17) This 1,3-methylene reaction is not applicable to common internal alkynes except for iodoalkynes.

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