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Synthesis of 1,2-Disubstituted Cyclopentadienes from Alkynes Using a Catalytic Haloallylation/Cross-Coupling/Metathesis Relay

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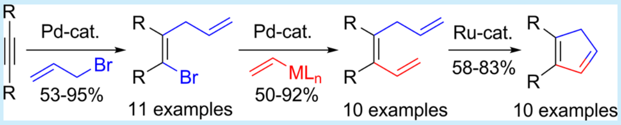
S *Supporting Information*

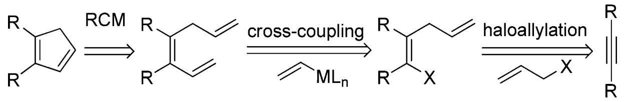


ABSTRACT: A three-step method based on Pd-catalyzed haloallylation of alkynes, Pd-catalyzed cross-coupling, and Ru-catalyzed ring-closing metathesis constitutes a new and short approach to variety of 1,2-substituted cyclopentadienes. The scope of the method is broad with respect to different substituents (alkyl, aryl, metallocenyl, and other substituents as well as their combinations are tolerated), and all steps proceeded with sensible yields. As a demonstration of product utility, several of the prepared cyclopentadienes were converted into the corresponding ferrocenes.

Cyclopentadienes are versatile organic compounds that have found application in two major areas. First, they are convenient substrates in organic synthesis,[1] and second, they can be used as ligands in transition metal complexes.[2] The transition metal complexes bearing various cyclopentadienyl ligands constitute an important class of compounds that have found numerous applications in catalytic and stoichiometric reactions.[3] Although a number of processes enabling the synthesis of variously substituted cyclopentadienes have been developed, there is a lack of any general synthetic strategy allowing the preparation of certain types. One class of such compounds are 1,2-disubstituted cyclopentadienes and their corresponding metallocenes, which have been shown to catalyze various reactions such as polymerization of alkenes,[4] cyclotrimerization of alkynes,[5] C−H activation of arenes,[6] and cycloisomerization[7] of enynes. Although methods for the preparation of 1,2-disubstituted cyclopentadienes based on Pauson−Khand[8] or retro-Diels−Alder[9] reactions (to name a few) have been reported, the development of a more general approach is of considerable interest because of their current and potential applications in catalysis.

A retrosynthetic analysis of the 1,2-disubstituted cyclopentadiene framework is depicted in Scheme 1. The cyclopentadiene should be available via ring-closing metathesis of a 1,3,6-triene. The triene should be accessible through cross-coupling of a *cis*-1-halo-1,4-diene with a vinylmetal, and finally, the halodiene should be obtainable by Pd-catalyzed haloallylation of an alkyne. In such a manner, cyclopentadienes should be accessible in just three steps.

Scheme 1. Retrosynthetic Analysis of 1,2-Disubstituted Cyclopentadienes



As far as the access to haloallylated alkynes is concerned, one option is to carry out allylations of silylated alkynes[10] or allylstannylations of alkynes[11] to furnish the corresponding silylated or stannylated pentadienes, followed by halogenation. Another one could rely on haloallylation as exemplified by Pd(II)-catalyzed chloroallylation of alkynes giving rise to *cis*-1-halo-1,4-dienes, as first described by Kaneda et al.[12] Recently, regioselective haloallylations of activated alkynes have been reported as well.[13] Also worth noting is the formation of *trans*- or *cis*-1-halo-1,4-dienes by Pd(II)-catalyzed allylation of alkynes with allylic alcohols in the presence of CuX$_2$ salts or ionic liquids.[14] Haloallylation followed by further transformation of the formed 1-halo-1,4-dienes was reported as well, and it encompassed subsequent Suzuki cross-coupling,[15] Wacker−Tsuji oxidation, or Sonogashira reaction.[16] The importance of haloallylation is also demonstrated by its application in a synthesis of the natural products (−)-haterumalide and (−)-oocydin A.[17]

At the outset, bromoallylation of various alkynes using a modified version of Kaneda's protocol was performed. We found that the best results were obtained when the reaction was carried out in pure allyl bromide in the presence of PdCl$_2$(PhCN)$_2$ (5 mol %) at 10 °C (Scheme 2). In the first set, bromoallylation of variously substituted diphenylacetylenes was carried out. In general, bromoallylation proceeded in a *syn* manner to give the desired products having a *cis* configuration with respect to the positions of the bromo and allyl groups. Formation of the *trans* isomer—the product of *anti* bromoallylation—was observed in minor amounts and never exceeded 5% yield judging from ^{1}H NMR spectra. Thus, reactions with **1a**−**c** proceeded uneventfully to give the desired 1-bromo-1,4-dienes **2a**−**c** in high isolated yields of 89%, 98%, and 95%. The reaction with bis(4-trifluoromethylphenyl)-acetylene (**1d**) was sluggish and gave rise to two isomers,

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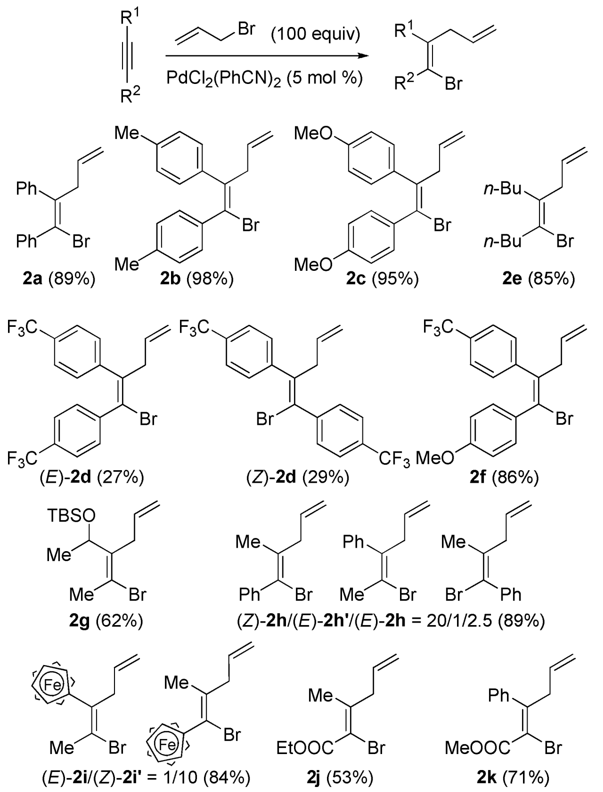
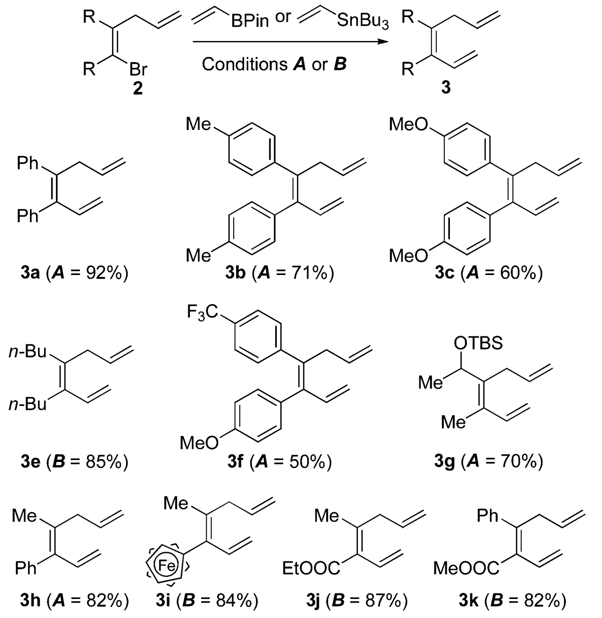
Scheme 2. Bromoallylation of Alkynes 1: Formation of 1-Halo-1,4-dienes 2



(*Z*)-**2d** and (*E*)-**2d**, that were isolated in 29% and 27% yield, respectively. Bromoallylation of 5-decyne (**1e**), a representative of bisalkylated alkynes, again proceeded smoothly to give **2e** in a very nice isolated yield of 85%.

Then our attention turned to unsymmetrically substituted alkynes such as 1-(4-trifluoromethylphenyl)-2-(4-methoxyphenyl)acetylene (**1f**), 4-(TBSO)-pent-2-yne (**1g**) propynylbenzene (**1h**), propynylferrocene (**1i**), ethyl butynoate (**1j**), and methyl 3-phenylpropynoate (**2k**). Bromoallylation of **1f** proceeded with full conversion and furnished only one regioisomer **2f** in a high isolated yield of 86%. The formation of the opposite regioisomer was not detected. The observed regioselectivity is in agreement with the generally accepted reaction mechanism of halopalladation outlined by Kaneda et al.[12] and supported by observations of Bäckvall et al.[18] On the basis of haloallylation reactions with differently substituted allyl halides, halopalladation of the triple bond is assumed to be the first step. In this respect it not surprising that the halide anion should attack the carbon atom with a lower electron density (an electrophilic carbon atom) whereas the palladium cation should attack the carbon atom with a higher electron density (a nucleophilic carbon atom). (The electron density is also in agreement with resonance structures of the corresponding alkynes.) The observed regioselectivity is in accordance with the data observed for carbometalation or hydrostannation[19] of disubstituted alkynes. A similar trend was observed also with **1g**, bromoallylation of which gave rise to **2g** in 62% yield. A somewhat different course of the reaction was observed during bromoallylations of **1h** and **1i**. Bromoallylation of the former yielded a mixture of 3 products: (*Z*)-**2h**, (*E*)-**2h′**, and (*E*)-**2h** in a 20:1:2.5 ratio and 89% yield. Bromoallylation of the latter furnished (*E*)-**2i** and (*Z*)-**2i′** in a 1:10 ratio and 84% yield. On the other hand, in the case of **2j** and **2k** only one regioisomer was formed.

Scheme 3. Cross-Coupling Reactions of 1-Bromo-1,4-dienes 2 with Vinylmetals To Give 1,3,6-Trienes 3[a]

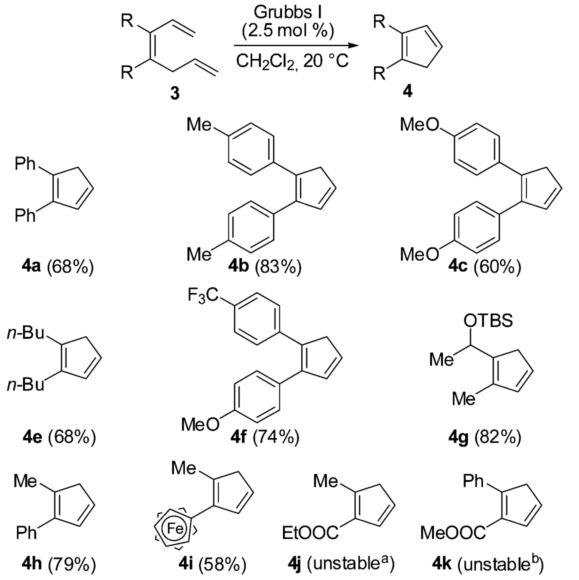


[a] Conditions: *A* (Suzuki coupling): PEPPSI-*i*-Pr (5 mol %), Cs_2CO_3,THF/H_2O (9/1), 50 °C; *B* (Stille coupling): PEPPSI-*i*-Pr (5 mol %), CsF, THF, 4 Å MS, 50 °C. Isolated yields are shown.

With bromodienes **2** in hand, cross-coupling with vinylmetals ensued (Scheme 3). Initially, cross-coupling under Suzuki conditions with potassium vinyltrifluoroborate in the presence of a catalytic amount of $PdCl_2$ (5 mol %) and PPh_3 (10 mol %) at 100 °C was attempted with **2a−c, 2f**, and **2h**. Although 80−85% conversion of the starting materials to the corresponding trienes was observed, the trienes could not be separated from the unreacted starting materials by using chromatography or distillation techniques. In order to find reaction conditions enabling 100% conversion of the bromodienes, a catalytic system composed of $PdCl_2$ (5 mol %) and dppf (5 mol %) was examined for **2a−c, 2f**, and **2h**. In this instance, conversions in the range of 90−95% were observed. Finally, cross-coupling of vinylboronic acid pinacol ester with various bromodienes in the presence of a catalytic amount of PEPPSI-*i*-Pr (5 mol %) was undertaken (Scheme 3). Gratifyingly, the reactions with bromodienes **2a−c, 2f**, and **2h** proceeded with full conversion of the starting materials already at 50 °C, giving the corresponding products **3a−c, 3f**, and **3h** in nice isolated yields. It should be mentioned that during the cross-coupling reactions of phenyl-substituted substrates isomerization to the *trans* isomer (with respect to the relative positions of the vinyl and allyl groups) of up to 5% was noticed.

Then conversion of the prepared dienes to the corresponding cyclopentadienes was undertaken. In general, ring-closing metathesis of trienes **3** with Grubbs I catalyst (2.5 mol %) in dichloromethane (~0.05 M) proceeded, according to ^1H NMR, within ~30 min to provide the corresponding cyclopentadienes **4** (Scheme 4).[20] The use of Grubbs II catalyst (5 mol %) in dichloromethane (~0.05 M) provided the same results; however, usually 6−12 h of reaction time was required to achieve full conversion. Although the metathesis reactions

Scheme 4. Ring-Closing Metathesis of 3 To Form Cyclopentadienes 4



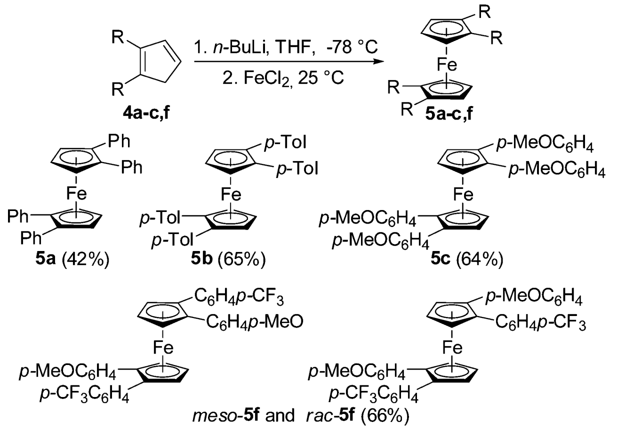
[a]Full conversion of the starting material was observed, but **4j** could not be detected in the reaction mixture. [b]Full conversion of the starting material to afford **4k** was observed, and its structure was confirmed by spectroscopic data.

proceeded quantitatively, the stumbling block became isolation of the formed cyclopentadienes as analytically pure substances. In general, column chromatography of the crude reaction mixtures on silica gel resulted in the formation of intractable products. Only **4a** was isolated as an analytically pure compound in 68% yield. In all other cases, column chromatography on Brockmann 4 alumina had to be performed to harvest pure products in the 58–83% yield range. Although full conversion of the starting material **3j** was observed under metathesis conditions, the isolated substance did not have structural features required for **4j**. Since the low stability of **4j** was noticed previously,[21] we assume that after its formation it rapidly undergoes further reactions. In a similar manner, cyclopentadiene **4k** was also unstable upon standing and underwent decomposition upon isolation. Nonetheless, NMR measurements and other analytical techniques applied to the crude product provided data that unequivocally confirmed its structure (see comments in the Supporting Information).

Finally, metalation of the isolated cyclopentadienes **4a**, **4b**, and **4c** with *n*-BuLi followed by reaction with anhydrous $FeCl_2$ provided the corresponding new ferrocenes **5a**, **5b**, and **5c** in 42%, 65%, and 64% isolated yield, respectively, as orange-colored solids (Scheme 5). X-ray structure analysis of **5b** unambiguously confirmed its structure (Figure 1). Analogously, the transformation of cyclopentadiene **4f** was carried out, giving rise an inseparable mixture of *meso*- and *rac*-**5f** in 66% isolated yield.

In conclusion, we have described a hitherto-unexplored approach to the class of 1,2-substituted cyclopentadienes based on transition-metal-catalyzed methodologies composed of haloallylation of internal alkynes, cross-coupling, and ring-closing metathesis. The reaction proceeded under mild conditions with a rather broad tolerance to pendant functional groups and was high-yielding. The formed cyclopentadienes were in general stable enough to be converted into the corresponding metallocenes, as demonstrated by the syntheses of several ferrocenes. There is no doubt that this new protocol could also be used to prepare other 1,2-disubstituted cyclopentadienes and their corresponding metallocenes.

Scheme 5. Formation of Ferrocenes 5a–c and *meso*- and *rac*-5f



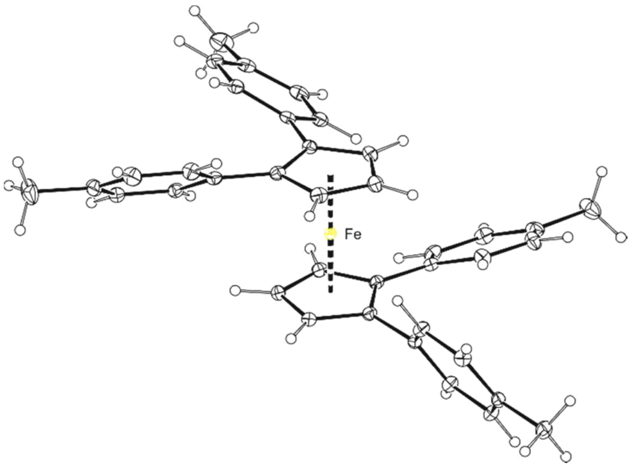


Figure 1. X-ray structure of ferrocene **5b**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01682.

Experimental procedures, analytical data for all new compounds, and crystallographic data for **5b** (PDF)

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Notes

The authors declare no competing financial interest.

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