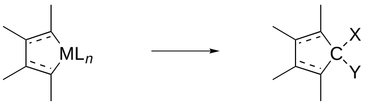
A Titanacycle-to-Carbocycle Relay Leading to an Expedient Synthesis of Cyclopentadienols**

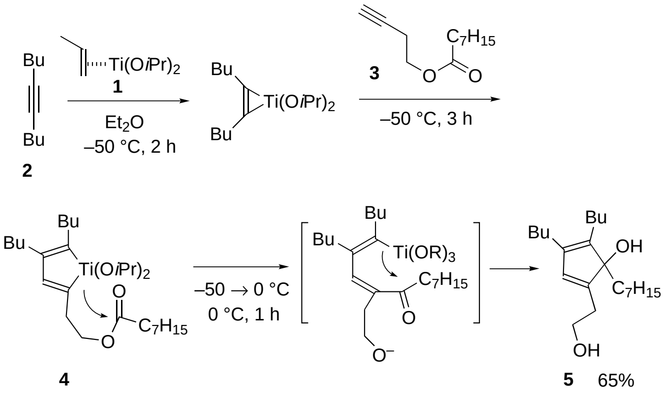
Hirokazu Urabe, Miho Narita, and Fumie Sato*

Five-membered metallacycles of a Group 4 element such as the one shown in Equation (1) (M = Ti, Zr) are well-known and readily accessible.[1] Conversion of these metallacycles into carbocycles, where the metal is eventually replaced with a carbon atom, is an attractive method for the construction of five-membered carbocycles. Formation of the corresponding carbonyl compound by treatment of the metallacycles with carbon monoxide or isocyanides[1–3] and the equivalent reaction with triphosgene ($O{=}C(OCCl_3)_2$)[4] should be the most representative and useful entry to this reaction [Eq. (1); $ML_n = ZrCp_2, TiCp_2, Ti(OiPr)_2$; CXY = CO]. However, other variations of the reaction are notably limited.[5] We report here a new entry to this transformation starting with a titanacyclopentadiene.



(1)

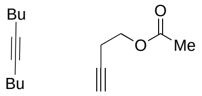
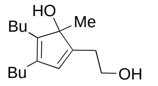
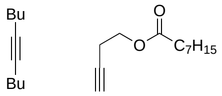
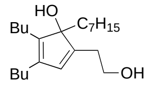
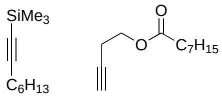
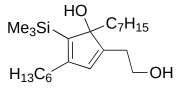
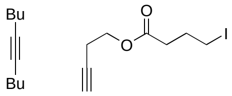
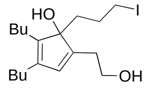
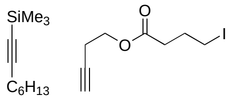
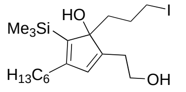
The coupling of acetylenes **2** and **3** with [(η^2-propene)Ti(O*i*Pr)$_2$] (**1**),[6, 7] which is readily prepared from [Ti(O*i*Pr)$_4$] and *i*PrMgCl in situ,[8] generates the titanacyclopentadiene **4** at low temperature (Scheme 1).[7] When the reaction mixture was simply allowed to warm up to 0 °C, tandem addition of the two carbon–titanium bonds of **4** to the ester group of the same molecule[9, 10] took place to furnish the cyclopentadienol **5** in good yield. Thus, this simple operation has achieved the aforementioned metallacycle-to-carbocycle process [Eq. (1)] without any further manipulation.



Scheme 1.

The scope of this transformation can be seen in Table 1. For a 1-silyl-1-alkyne, the product was obtained as a single regioisomer and arises from the highly regioselective cross-coupling reaction of the two different acetylenes (entries 3 and 5). Even though the reaction is conducted in the presence of a low-valent titanium reagent and/or a Grignard reagent, the iodoalkyl moiety of the starting materials was not affected; the desired (iodoalkyl)cyclopentadienols, which are useful precursors for the subsequent ring closure (see below), are obtained without decrease in yields (entries 4 and 5). In addition to the synthesis of monocyclic compounds, five- and six-membered ring-fused cyclopentadienols could be readily prepared as well from diynol esters (Table 2).

Table 1. Preparation of cyclopentadienols.

Entry	Substrates	Product	Yield [%]
1			49
2			65
3			49
4			57
5			54

Cyclopentadienols[11] should be interesting intermediates for further synthetic elaboration, because up to five carbon atoms can be fully functionalized. Some reactions are exemplified in the following. A silylcyclopentadienol was iodinated with I_2 in the presence of aqueous $NaHCO_3$ to give the corresponding iododiene (Scheme 2). Scheme 3 illustrates hydrogenation followed by ring closure, directly giving a bicyclic tetrahydrofuran.

Intramolecular carbometalation[12] to the dienol moiety proved to be quite useful for obtaining fused ring systems, as shown in Schemes 4 and 5. Thus, the lithiation of the substrate having an iodoalkyl side chain first with *n*BuLi (OH → OLi) and then with *t*BuLi ($CH_2I \rightarrow CH_2Li$) induced the regioselective carbolithiation of the diene together with the elimination of the hydroxy group to give the bicyclic product (Scheme 4). In the case of a bicyclic starting material, the above carbolithiation was unsatisfactory, but the addition of a catalytic amount of a copper salt permitted the reaction to proceed smoothly, again in a highly regioselective manner to give the single tricyclic compound in good yield (Scheme 5).

Besides the method shown in Scheme 5 for preparing tricyclic compounds, the aforementioned titanium-mediated

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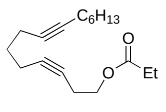
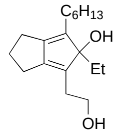
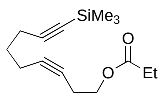
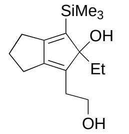
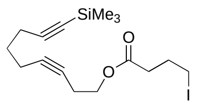
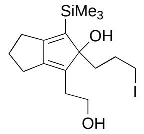
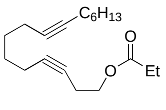
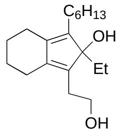
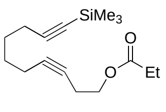
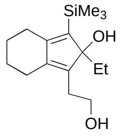
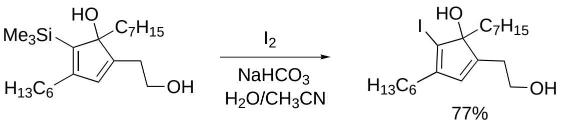
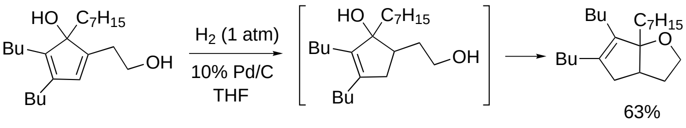
[**] We thank the Ministry of Education, Science, Sports and Culture (Japan) for financial support.

Table 2. Preparation of fused-ring cyclopentadienols.

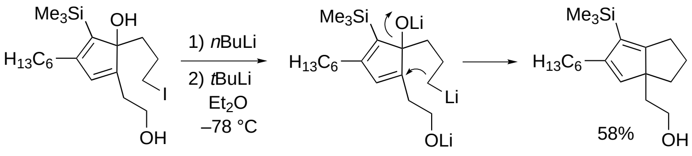
Entry	Diynol esters	Product	Yield [%]
1			70
2			56
3			51
4			76
5			85



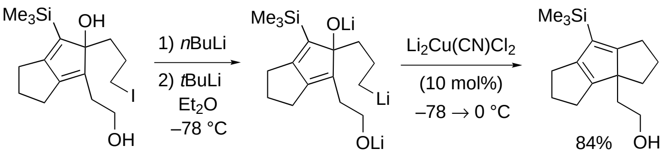
Scheme 2.



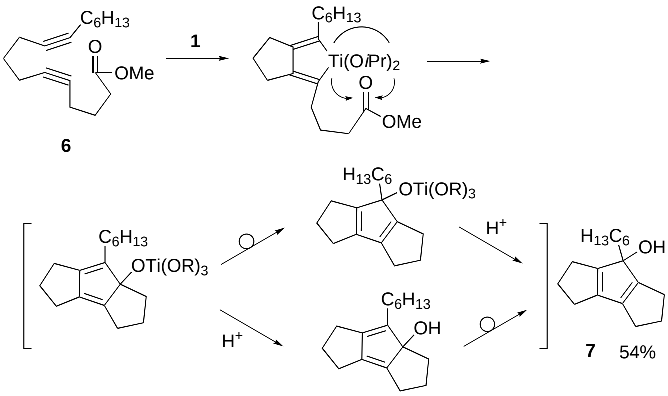
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

cyclization itself serves this purpose in a more straightforward manner. Thus, **1**-mediated cyclization of an open-chain precursor, diynoate **6**, afforded a tricyclic compound **7** in one step (Scheme 6). It should be noted that the positions of the hydroxy group and the carbon–carbon double bonds in the resultant cyclopentadienol **7** are different from that expected from the results in Tables 1 and 2, most likely due to the isomerization before or during the workup.

In summary, the reaction shown here represents an example of the facile conversion of titanacyclopentadienes into cyclopentadienols, the preparation of which otherwise entails a tedious procedure. The construction of condensed bi- or tricyclic systems has been achieved by the tandem cyclization[9] of the bis-acetylenic substrates, and it is also based on the resultant cyclopentadienols. The very low cost of the titanium reagent and the simple laboratory operation will encourage further applications of the present method in organic synthesis.[13]

Experimental Section

Typical procedure (entry 1 in Table 2): To a stirred solution of pentadeca-3,8-diynyl propionate (30 mg, 0.109 mmol) and $[Ti(O\textit{i}Pr)_4]$ (0.039 mL, 0.131 mmol) in Et_2O (1.5 mL) was added *i*PrMgCl (1.54 M in Et_2O, 0.170 mL, 0.262 mmol) at −78 °C under argon. After stirring for 30 min, the solution was allowed to warm to −50 °C over 30 min and kept at this temperature for 3 h. After the solution was allowed to reach 0 °C and then stirred at 0 °C for an additional 10 min, the reaction was terminated by the addition of aqueous 1N HCl at 0 °C. The organic layer was separated, washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to an oil. The crude product was purified by chromatography on silica gel (pretreated with 5% NEt_3 in hexane and then eluted with diethyl ether/hexane containing a trace amount of NEt_3) to afford 3-ethyl-2-hexyl-4-(2-hydroxyethyl)-1,4-bicyclo[3.3.0]octadien-3-ol (22 mg, 70%) as a colorless oil, which was fully characterized by IR and ^1H and ^{13}C NMR spectroscopy and elemental analysis.

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Development of New Chiral P,N Ligands and Their Application in the Cu-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Enones**

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The conjugate addition of various organometallic reagents to enones is one of the most widely used synthetic methods for carbon–carbon bond formation.[1] Many chiral auxiliaries or stoichiometric reagents have been reported for highly stereoselective 1,4-additions. Great attention has been devoted recently to developing enantioselective catalytic 1,4-addition reactions.[2] Chiral copper, nickel, and other metal complexes have been investigated as catalysts for enantioselective additions of organolithium, Grignard, and diorganozinc reagents to enones.[3] Most notable among these reagents are the chiral phosphorus–Cu^I complexes, for example, Feringa's chiral phosphoramidite,[4] which have proven effective for enantioselective conjugate additions to cyclic enones. In addition, several other efficient enantioselective Michael addition reactions with cyclic enones have been described.[5] In contrast to the cyclic enones, highly enantioselective Cu-catalyzed conjugate addition ($>95\%$ *ee*) to acyclic enones has not been realized (*ee* values around 90% have been reported in several promising systems[3d, 4a]). Because strong substrate dependence is quite common for asymmetric carbon–carbon bond forming reactions catalyzed by transition metals, the development of new chiral ligands plays a pivotal role for overcoming this substrate limitation. Herein we report the synthesis of novel chiral P,N ligands for highly enantioselective Cu-catalyzed conjugate addition of diethylzinc to acyclic enones. In addition, these P,N ligands are also very efficient for the Cu-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one.

A number of chiral P,N ligands have been developed for transition metal-catalyzed asymmetric reactions.[6] Pfaltz et al.[4c] and Stangeland and Sammakia[7] have applied chiral oxazoline–phosphite and oxazoline–phosphane ligands to Cu-catalyzed conjugate addition of organometallics to enones. We are particularly interested in exploring new chiral motifs to build effective P,N ligands for broad applications in asymmetric catalysis. Chiral 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **1**; see scheme 1) developed by Kocovsky et al. has proven to be an excellent framework for construct-

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