Streamlined Assembly of a Benzo-fused Bridged Ketone Scaffold from 1,5,10-Enediynes via One-pot Ru-catalyzed Cyclization/Iodine-mediated Oxidative Ring Expansion

Yoshihiko Yamamoto*[a] Kei-ichiro Nishimura,[a] Shota Mori,[a] and Masatoshi Shibuya[a]

Dedication ((optional))

Abstract: In the presence of a cationic Ru catalyst, 1,6-diynes bearing a styryl terminal underwent [2 + 2 + 2] cyclization, producing dehydrobiphenylenes fused with a five-membered ring. Although the cycloadducts were unstable for purification, their one-pot iodine-mediated ring expansion successfully afforded unprecedented bridged ketone products bearing a benzo-fused bicyclo[3.2.1] framework.

Bicyclo[l.m.n] systems with carbonyl bridges are the core scaffolds of many important natural products such as hyperforin[1] and penostatin F[2] (Figure 1a). In particular, polyprenylated polycyclic acylphloroglucinol (PPAP) natural products including hyperforin have drawn considerable attention owing to their diverse variations and significant biological activities.[1] Enormous synthetic efforts have been devoted to efficiently access these promising drug leads. However, previous studies have mostly focused on target-oriented synthesis of natural products and/or efficient assembly of the relevant bicyclic core structures. Therefore, the development of new methods providing access to unprecedented bridged ketone scaffolds with diverse substituents is highly beneficial for drug discovery. However, lengthy synthetic manipulations are required to construct bridged ketone scaffolds. Thus, there is ample room for improving the access to such architecturally challenging scaffolds.[3] We developed a new one-pot assembly by combining Ru-catalyzed cyclization and iodine-mediated oxidative ring expansion; an unprecedented benzo-fused bridged ketone scaffold was generated.

Transition-metal-catalyzed [2 + 2 + 2] cyclization of enediynes is a powerful method to assemble tricyclic frameworks in a single operation.[4] Moreover, the resultant fused cyclohexadienes can be utilized in further synthetic operations.[5] Nevertheless, to the best of our knowledge, the combinations of an enediyne [2 + 2 + 2] cyclization and a subsequent skeletal rearrangement reaction have not been investigated, even though such combined processes have an exceptional synthetic potential to access unprecedented scaffolds with a significant topological complexity. Thus, we envisaged that the hitherto unknown [2 + 2 + 2] cyclization of 1,6-diynes with a styryl terminal would produced benzocyclobutene-fused cyclohexadienes, and their ring transformation utilizing strain relief would produce novel polycyclic scaffolds (Figure 1b). Herein we report the development of one-pot Ru-catalyzed [2 + 2 + 2] cyclization/iodine-mediated ring expansion of enediynes for the streamlined assembly of benzo-fused bridged ketones.

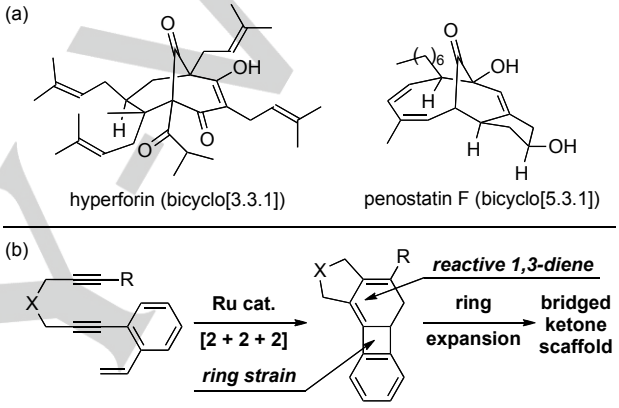

Figure 1. (a) Examples of natural products with a bridged ketone framework and (b) our strategy to assemble bridged ketone scaffold.

First, the optimal [2 + 2 + 2] cyclization conditions for enediyne **1a** were determined. In general, a neutral Ru complex, Cp*RuCl(cod) (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene), is an optimal catalyst for diverse [2 + 2 + 2] cycloadditions of diynes.[6] However, we recently found that Cp*RuCl(cod) catalyzed the cycloisomerization of **1a** rather than [2 + 2 + 2] cyclization, affording indenylidene cycloalkane (*Z*)-**3a**.[7] On the other hand, Saá group achieved a prototypical intermolecular cyclodimerization of *o*-alkynylstyrenes using a cationic Ru complex, $[Cp^*Ru(MeCN)_3]PF_6$, as the catalyst.[8] Following this report, we used the same Ru catalyst for the intramolecular reaction of **1a** (Scheme 1). The reaction of **1a** was performed in the presence of 10 mol % $[Cp^*Ru(MeCN)_3]PF_6$ in acetonitrile at room temperature for 2 h, affording an inseparable mixture of the desired product **2a** and (*Z*)-**3a** in 35% and 59% yields, respectively, as determined by ^{1}H NMR. Although **2a** was unstable and could not be separated from (*Z*)-**3a**, **2a** was identified as a dihydrobiphenylene derivative compared to previously reported cyclodimerization products.[8] Notably, a significant amount of (*Z*)-**3a** was still produced under the conditions using the cationic catalyst, indicating that the intramolecular setting is favorable for cycloisomerization. Nevertheless, when the reaction was performed in THF at room temperature, the reaction time was shortened to 0.5 h, and **2a** was predominantly produced in 96% NMR yield.

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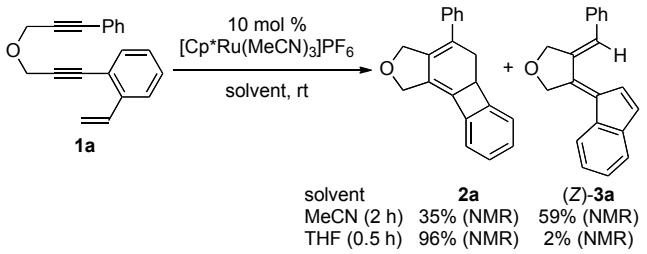
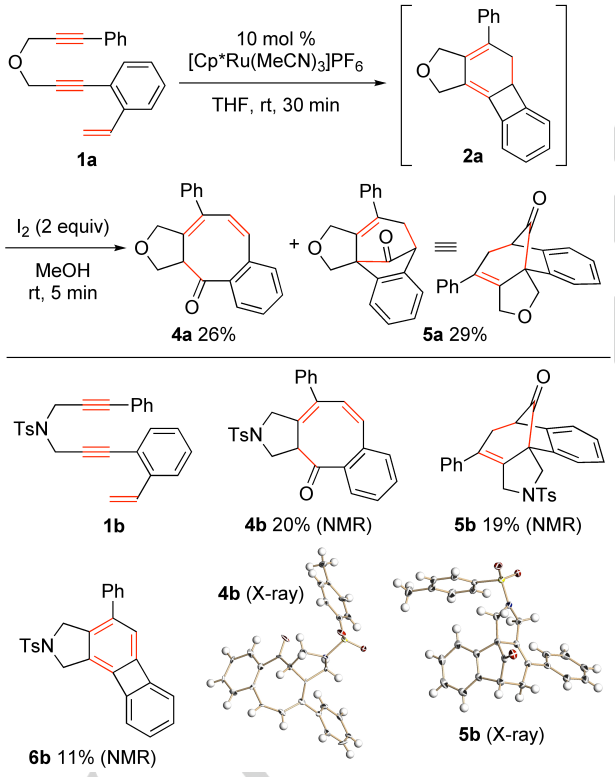


Scheme 1. Optimal conditions for [2 + 2 + 2] cycloaddition of enediyne **1a**.

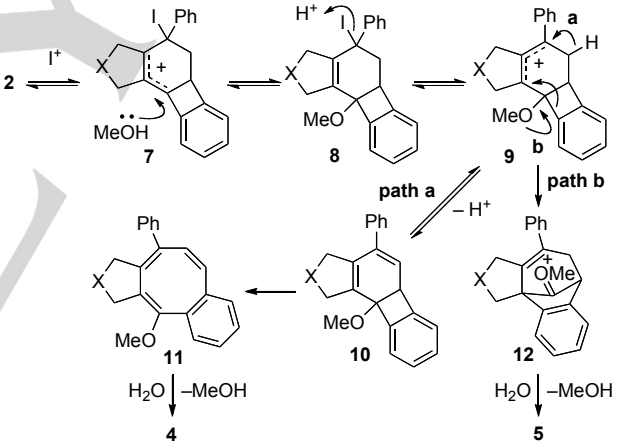
Although dihydrobiphenylene **2a** was predominantly produced, its isolation was difficult because of its instability. Therefore, we attempted to transform crude **2a** to stable and isolable product(s). However, dehydrogenative aromatization using DDQ or ceric ammonium nitrate resulted in decomposition of **2a**. Next, I_2 in MeOH was used.[9] Crude **2a** was treated with I_2 (2 equiv) in MeOH at room temperature for 5 min; after quenching the reaction, two major products **4a** and **5a** were obtained along with small amounts of unidentified minor products (Scheme 2). The IR spectra showed carbonyl stretching frequencies at 1670 and 1767 cm^{-1} for **4a** and **5a**, respectively. Moreover, NMR experiments including HMBC (Figure S1) and HRMS analyses showed that **4a** and **5a** have cyclooctatrienone and bicyclo[3.2.1]octadienone frameworks, respectively.



Scheme 2. Transformations of cycloaddition products **2a** and **2b** using I_2 in MeOH.

Similarly, tosylamide analog **1b** underwent [2 + 2 + 2] cyclization. Although crude **2b** was less soluble in MeOH, subsequent treatment with I_2/MeOH afforded an inseparable mixture of products including **4b**, **5b**, and biphenylene **6b** in 20%, 19%, and 11% NMR yields, respectively. The ^1H and ^{13}C NMR data of **4b** and **5b** were very similar to those of **4a** and **5a**, respectively. Moreover, the structure of **5b** was successfully confirmed by the X-ray diffraction analysis of a single crystal obtained from a partially separated sample. The crystal structure of **4b** was also confirmed, albeit with a lower resolution owing to the disorder of solvent molecules. Biphenylene **6b** showed characteristic NMR spectra, similar to those of previously reported fused biphenylenes.[10]

Scheme 3 outlines a proposed mechanism for the formation of ring-expansion products **4** and **5**. Iodination of dihydrobiphenylene **2** generates allylic cation intermediate **7**, which is trapped by MeOH to form **8**. Under acidic conditions, **8** undergoes deiodination to produce allylic cation intermediate **9**. Subsequently, deprotonation of **9** generates **10**, which undergoes electrocyclic ring opening to afford benzocyclooctatetraene **11** (path a).[11] Alternatively, **9** undergoes pinacol-type rearrangement to afford bicyclic oxocarbenium intermediate **12** (path b).[12] Finally, **11** and **12** are hydrolyzed during the workup, affording **4** and **5**, respectively.



Scheme 3. Plausible mechanism for the oxidative ring expansion of **2**.

Although multiple products were produced by the I_2/MeOH-mediated transformation, gratifyingly, the one-pot transformation of dihydrobiphenylene **2a** using *N*-iodosuccinimide (NIS) instead of I_2 in MeOH selectively produced bicyclic product **5a** in 64% yield over 2 steps (Figure 2).[13,14] Selected enediynes **1** were also subjected to these one-pot conditions to determine the substrate scope. First, the effect of tether between the two alkynes was examined. Because dihydrobiphenylene **2b** was less soluble in THF/MeOH, the subsequent reaction was performed by adding CH_2Cl_2 as a co-solvent along with MeOH (THF/CH_2Cl_2/MeOH = 1:1:1 v/v/v). However, a rather complex reaction mixture was obtained, even though the desired **5b** (30% yield) was detected by ^1H NMR. Enediyne **1c** with a malonate

tether was selectively converted into **5c**, albeit in a moderate yield (48%).

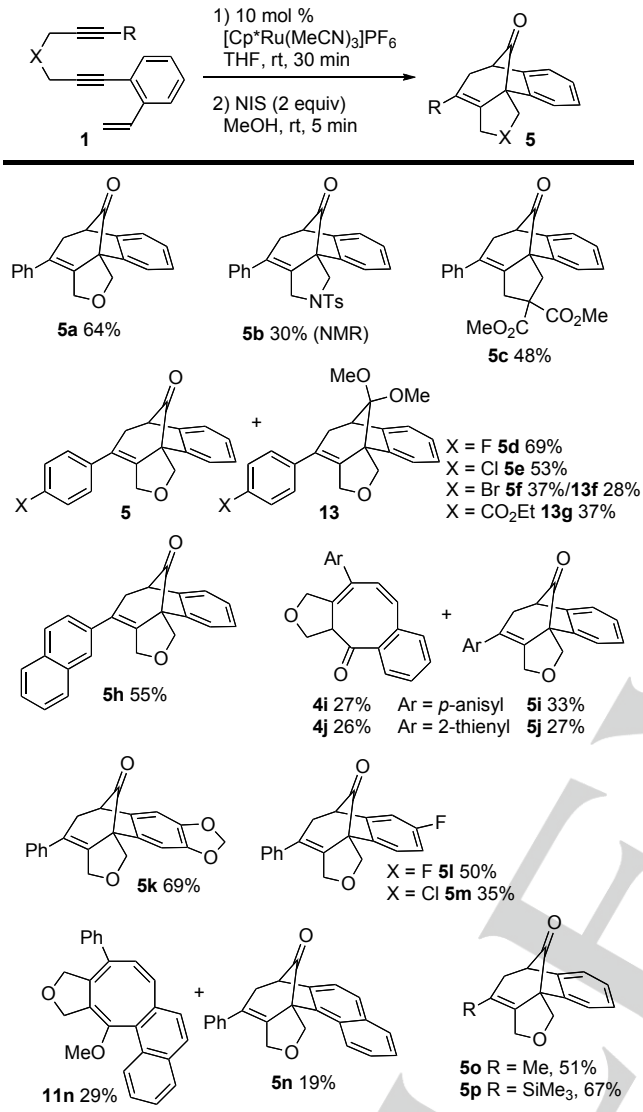


Figure 2. One-pot sequential transformations of **1** using NIS in MeOH.

Subsequently, the effects of the aryl terminal and phenylene tether were evaluated. The reaction of enediynes **1d**, **1e**, and **1h** with a *p*-halophenyl or 2-naphthyl terminal afforded **5d**, **5e**, and **5h** as the predominant products in 53–69% yields. Interestingly, enediynes **1f** with a *p*-bromophenyl terminal afforded **5f** along with its ketal **13f** in 65% combined yield.[14] Ketal **13g** was also obtained from **1g** bearing a *p*-ethoxycarbonylphenyl terminal. In contrast, the reaction of enediynes **1i** and **1j** with a *p*-anisyl and 2-thienyl terminal, respectively, produced benzocyclooctatrienones **4i**,**j** and bridged ketones **5i,j** in an almost 1:1 ratio. This loss of selectivity can be ascribed to the electron-donating aryl terminals that stabilized a cationic intermediate **9**, retarding the path b. Similarly, bridged ketones **5k–m** were obtained in 35–69% yields from the corresponding enediynes with selectivity irrespective of the electronic bias of the phenylene tethers. When using substrate **1n** bearing a 2-vinyl-1-naphthyl terminal, benzocyclooctatetraene **11n** was obtained as a major product along with bridged ketone **5n**. The alkenyl ether moiety of **11n** was preserved probably owing to the steric shielding by the fused naphthalene. Moreover, enediyne **1o** with a methyl terminal and enediyne **1p** with a trimethylsilyl terminal produced bridged ketones **5o** and **5p** in 51% and 67% yields, respectively. As a general trend, electron-withdrawing groups on the phenyl terminal and phenylene tether lowered the yields of the ring expansion products due to the destabilization of cationic intermediates,[15] although the [2 + 2 + 2] step were not affected. The remaining C–Br and ester substituents on the phenyl terminal can be used as synthetic handles for further manipulations. The observations of ketals **13f,g** and ether **11n** underpin the proposed mechanism shown in Scheme 3.

In contrast, **1q** and **1r** bearing a α- or β-methylstyryl terminal afforded no [2 + 2 + 2] cycloadduct, probably due to the unfavorable insertion of the sterically demanding disubstituted alkenes (Figure 3). The former exclusively produced cycloisomerization products (*Z*)/(*E*)-**3q** under similar reaction conditions. No reaction occurred with enediyne **1s** bearing a internal 3-vinyl-2-pyridyl terminal under the same conditions. This is probably because the strong coordination of the pyridyl moiety to the cationic Ru center inhibited the catalyst turnover. Terminal alkyne was also found detrimental for [2 + 2 + 2] cyclization as no reaction occurred with enediyne **1t**. This intramolecular [2 + 2 + 2] cyclization is confined to enediyne substrates with 1,6-diyne moiety as 1,5,11-enediyne **1u** was found to be inefficient under the standard cyclization conditions.

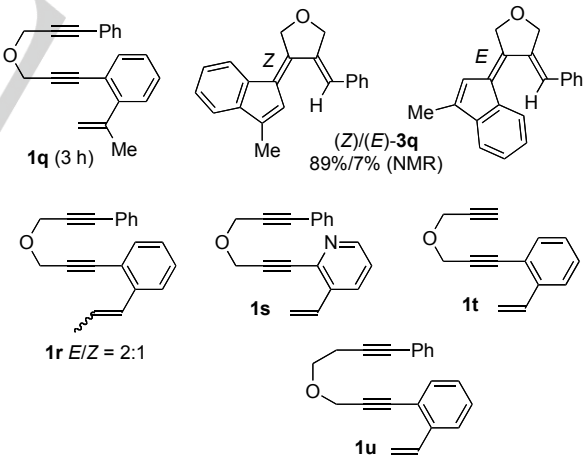
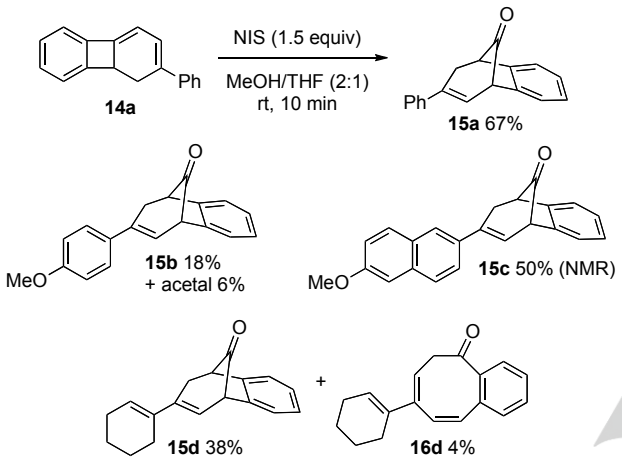


Figure 3. Enediyne substrates that failed to undergo [2 + 2 + 2] cyclization.

Finally, we investigated the ring expansion of nonfused dihydrobiphenylenes, which were prepared via intermolecular [2 + 2 + 2] cycloaddition of *o*-ethynylstyrene following the Saá's procedure.[8] In a similar manner to the one-pot reaction, **14a** was treated with NIS (1.5 equiv) in a mixed solvent system (MeOH/THF, 2:1 v/v) at room temperature for 10 min, producing the expected ring-expansion product **15a** in 67% yield (Scheme

4). Therefore, the fused five-membered ring is not essential for the ring-expansion. In contrast, the reaction of **14b** bearing a *p*-anisyl substituent generated a complex product mixture; the corresponding bridged ketone **15b** and its ketal were obtained as an inseparable mixture (18% and 6% yields, respectively). The reaction of **14c** bearing a 6-methoxynaphthalen-2-yl substituent afforded bridged ketone **15c** in 50% yield (NMR). Because of its low solubility, **15c** was isolated by recrystallization (35%). Moreover, cyclohexene derivative **15d** was also obtained as an inseparable mixture with benzocyclooctatrienone **16d**, showing that a trisubstituted alkene was tolerated.



Scheme 4. Ring-expansion reaction of dihydrobiphenylenes **14a**–**d**.

In conclusion, we developed a one-pot sequential transformation of 1,6-diynes with a styryl terminal to unprecedented benzo-fused bicyclo[3.2.1]octadienones. In this novel process, the enediyne substrates were first converted into fused dehydrobiphenylenes via Ru-catalyzed [2 + 2 + 2] cyclization; subsequent treatment of the cycloadducts with NIS in THF/MeOH in one pot produced the desired bridged ketone products. In some cases, benzocyclooctatrienones were also obtained.

Acknowledgements

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Keywords: Ruthenium • Enediyne • Bridged ketone • Ring expansion • Cyclization

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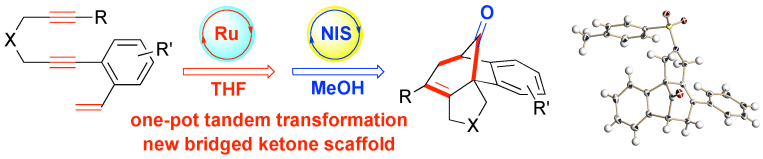

An unprecedented bridged ketone scaffold was straightforwardly assembled by one-pot tandem Ru-catalyzed [2 + 2 + 2] cyclization/Iodine-mediated oxidative ring expansion. The [2 + 2 + 2] cyclization proceeded in the presence of a cationic Ru catalyst in THF at room temperature and subsequent ring expansion was performed by adding NIS and MeOH to the crude reaction mixture at room temperature.

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