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Iridium(I)-Catalyzed Cycloisomerization of Cyclohexadienyl Alkynes

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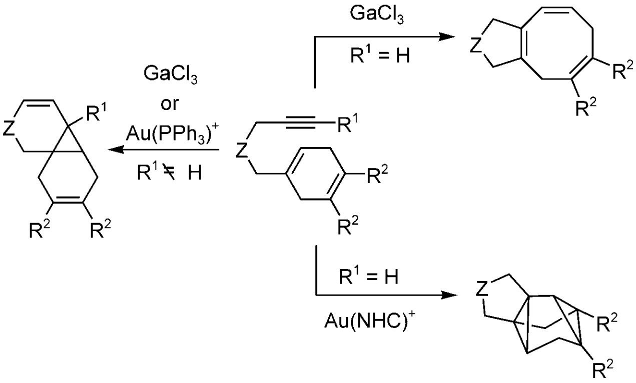
Abstract: From cyclohexadienyl alkynes with a terminal alkyne unit, double cyclopropanated products were obtained in reasonable to high yields. For cyclohexadienyl alkynes substituted at the alkyne unit, cyclopropanated products were obtained in high yields. When a keto carbonyl group was introduced to cyclohexadienyl alkynes with a substituted alkyne, Alder-ene-type products were obtained in reasonable to high yields.

Keywords: cyclohexadienyl alkynes; cycloisomerization; cyclopropanation; iridium

Recently, the cycloisomerization of enynes has attracted a lot of attention.[1] One of the reasons for this is that a variety of cycloisomerized products can be easily obtained depending upon the metal and the substrate.[2] The reaction patterns depend on the structure of the substrates and the nature of the catalyst systems. For this reason various transition metal complexes, such as those of Ti, Pt, Pd, Cu, Ru, Rh, Co, Ir, W, and Au have been used as catalysts.[3] In particular, the reaction patterns are highly influenced by a tether group.[4] However, in some cases, substantial structural variations are accommodated and different functional groups found to be compatible.[5] Progress in the catalytic cycloisomerization of enynes with iridium is far behind that with rhodium, palladium, platinum, or gold, although iridium catalysts have now been recognized as being particularly useful and many of these reactions have recently been reported.[6]

Many useful enynes have been used in the cycloisomerization. However, a new candidate to the list of available enyne substrates still needs to be added. We recently found that the introduction of an olefinic cycle to enynes enhanced the reactivity or influenced the reaction pathway (Scheme 1).[7] As Scheme 1 shows, the reaction patterns of cycloisomerization reactions depend on the structure of the substrates and the nature of the catalytic systems. We expected that new type of transformations could be explored through the interaction of alkynes and electrophilic transition metal complexes.



Scheme 1.

The feasibility of the use of iridium compounds as catalysts in the cycloisomerization of enynes was first mentioned by Murai's group in 1994.[8] The first use of an iridium catalyst in the cycloisomerization of enynes was reported by the same group in 2001.[6a] From enynes bearing a substituted alkyne moiety, 1,3-dienes were obtained as the products. Recently, Shibata's group reported[6b,c] the iridium-catalyzed cycloisomerization of 1,6-enynes to bicyclo[4.1.0]heptenes. Then Takeuchi's group reported[6d] the iridium-catalyzed cycloisomerization of carbon-tethered 1,6-enynes to (*Z*)-1-alkylidene-2-methylenecyclopentanes. Encouraged by the previous results, we studied the iridium-catalyzed cycloisomerization reaction of cy-

Table 1. Screening for optimum reaction conditions.[a]

Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	$[Ir(cod)Cl]_2$	toluene	20	24	45 (54)[c]
2	$[Ir(cod)Cl]_2$	toluene	70	3	77
3	$[Ir(cod)Cl]_2$	toluene	100	2.5	85[d]
4	$[Ir(cod)Cl]_2$	toluene	130	0.5	94
5	$[Ir(cod)Cl]_2$	THF	80	24	92
6	$[Ir(cod)Cl]_2$	CH_2Cl_2	20	24	71
7	$[Ir(cod)Cl]_2$	DCE	80	15	76
8	(IPr)Ir(cod)Cl[e]	toluene	130	24	0 (83)[c]
9	$IrCl_3$	toluene	130	24	0 (85)[c]
10	$[Rh(cod)Cl]_2$	toluene	100	3	50
11	$[Rh(OAc)_2]_2$	toluene	100	24	52
12	[Ru(*p*-cymene)$Cl_2]_2$	toluene	100	24	50

[a] 0.34 mmol of **1a** in 5 mL solvent was used.

[b] Isolated yield.

[c] The values in parenthesis represent the reactant recovered.

[d] Reaction carried out with 1 atm CO.

[e] IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene.

clohexadienyl alkynes. Herein we report our preliminary results.

In the experience of our group, no reaction or decomposition had been observed for an enyne having no substituents on the alkyne and alkene termini. Therefore, the use of an enyne with a terminal alkyne (**1a**) as a model substrate was from the outset somewhat unusual. However, cycloisomerization was studied using **1a** as a model substrate and $[Ir(cod)Cl]_2$ as a catalyst in toluene.

We screened various reaction conditions including the reaction temperature, the reaction time, and the effect of carbon monoxide on the cycloisomerization of **1a**. The results are summarized in Table 1. When the reaction was conducted at 20 °C for 1 day, a tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane derivative, **1b**, was obtained in 45% with a recovery of the reactant (54%). Compound **1b** was previously reported by us in the gold N-heterocyclic carbene-catalyzed cycloisomerization of **1a**.[7c] As the reaction temperature increased, the yield of **1b** increased and the reaction time was shortened. At 130 °C, the reaction time was shortened to 30 min with 94% yield. Examination of the reaction medium led to the selection of toluene. In many transition metal-catalyzed reactions, the presence of carbon monoxide is helpful to the reaction.[6a,9] Thus, a cycloisomerization reaction under 1 atm of carbon monoxide was also studied. However, there was no noticeable effect on the yield (85%). Thus, the optimized reaction conditions were established to be as follows: 2.5 mol% $[Ir(cod)Cl]_2$, 0.34 mmol enyne, 5 mL of toluene, 130 °C, and 0.5 h. A brief survey of different metal complexes (entries 10–12) such as $[Rh(cod)Cl]_2$ (50%), $[Rh(OAc)_2]_2$ (52%), and [Ru(*p*-cymene)$Cl_2]_2$ (50%) indicated that $[Ir(cod)Cl]_2$ is the best catalyst of those examined.

We next investigated the cycloisomerization of cyclohexadienyl alkynes with a terminal alkyne under these optimized reaction conditions (Table 2).[10] The reaction was highly dependent upon the tether group. When the tether atom was carbon (entries 1–6), the expected cage compound **b** was obtained in 56–95%

Table 2. Ir(I)-catalyzed cycloisomerization of cyclohexadienyl alkynes.[a]

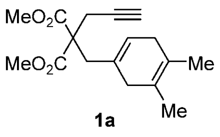
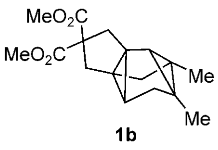
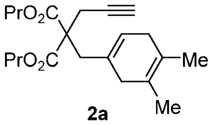
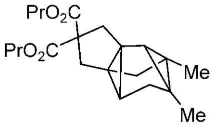
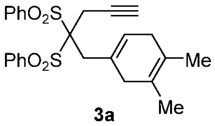
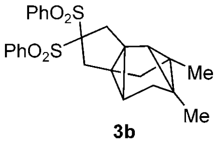
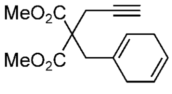
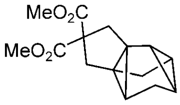
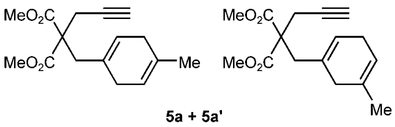
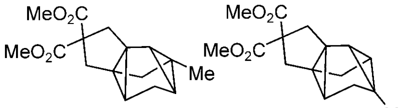
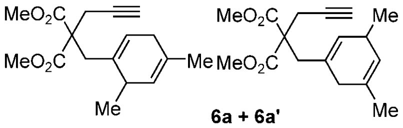
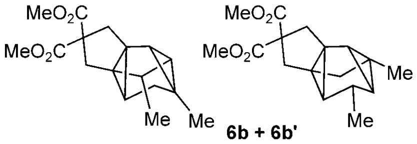
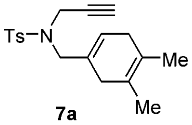
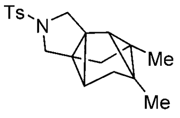
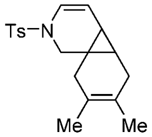
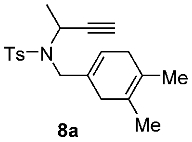
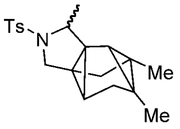
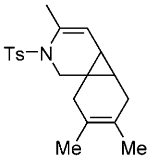
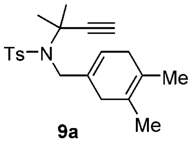
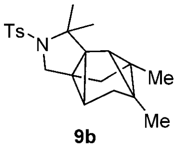
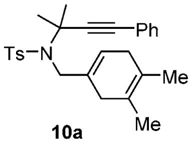
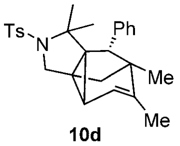
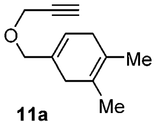
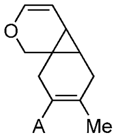
Entry	Reactant	Product	Time [h]	Yield [%][b]
1			0.5	94

Table 2. (Continued)

Entry	Reactant	Product	Time [h]	Yield [%][b]
2	 **2a**	 **2b**	0.5	95
3	 **3a**	 **3b**	0.5	67
4	 **4a**	 **4b**	0.5	56
5	 **5a + 5a'**	 **5b + 5b'**	1	69
6	 **6a + 6a'**	 **6b + 6b'**	2	91
7	 **7a**	 **7b**  **7c**	0.5	72 (12/60)
8	 **8a**	 **8b**  **8c**	7	68 (32/36)
9	 **9a**	 **9b**	0.5	83
10	 **10a**	 **10d**	48	30
11	 **11a**	 **11c**	2	52

[a] 0.34 mmol of cyclohexadienyl alkyne and 2.5 mol% $[Ir(cod)Cl]_2$ were reacted in 5 mL toluene at 130 °C.

[b] Isolated yield.

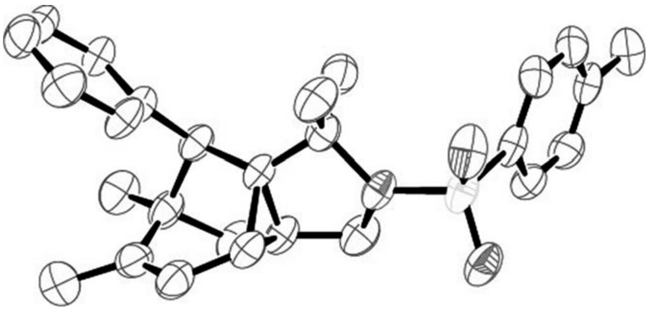


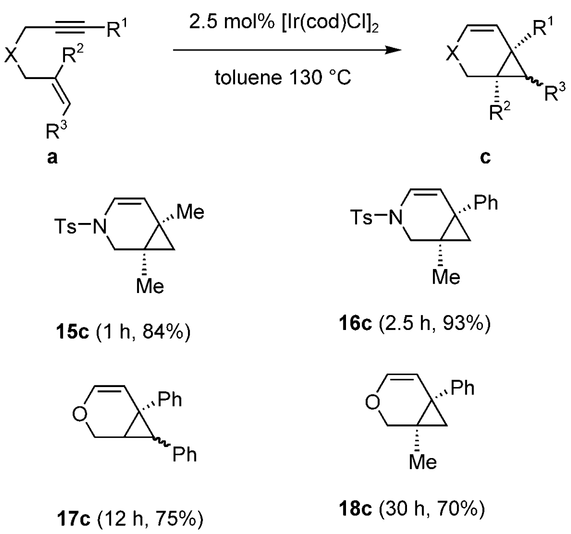
Figure 1. X-ray crystal structure of **10d**.

yield. However, when the tether group was changed to N-Ts (entry 7), a cyclopropanated product (**7c**) was obtained in 60% with the concomitant formation of a tetracyclooctane derivative (**7b**) in 12% yield. When a methyl group was introduced to the propargylic carbon of enynes to bring any steric effect (entry 8), a slight increase of the yield (32%) of **b** was observed.

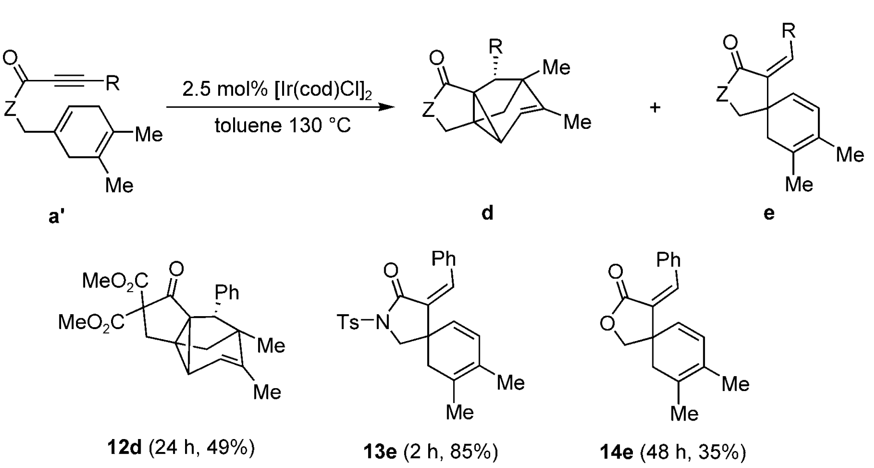
To our surprise, when an enyne substrate with a disubstituted propargyl carbon was used as a substrate (entry 9), only **9b** was obtained in 83% yield as the sole product. It seemed that disubstitution at the propargyl carbon might protect a reaction pathway to **c** and enhance the formation of **b**. When an enyne with a phenyl-substituted alkyne and disubstitution at the propargyl carbon was used as a substrate (entry 10), a new cycloisomerized product (**10d**) derived from an incomplete double cyclopropanation was formed in 30% yield. The formation of **10d** was confirmed by ^{1}H and ^{13}C NMR and by X-ray diffraction analysis (Figure 1).[10] However, a terminal cyclohexadienyl alkyne (**11a**) with an oxygen tether atom provided only **11c** in 52% yield as the sole product (entry 11).

In cycloisomerization reactions, a subtle change in the substrate may lead to a different reaction path, resulting in a different reaction product; therefore, an exception to the general reaction product can be easily seen. Thus, in the hope of finding a new reaction pathway, we introduced a keto carbonyl to the enyne substrates and studied their reaction in the presence of the iridium catalyst (Scheme 2). When a keto carbonyl was introduced to a carbon-tethered enyne substrate with a phenyl substrate on the alkyne terminus, an incomplete double cyclopropanation occurred to give **12d** in 49% yield. However, other keto cyclohexedienyl alkynes with a heteroatom tether provided the Alder-ene-type product (**13e** and **14e**) in 85% and 35% yields, respectively, depending upon the tether group, N-Ts and oxygen. According to the NOE study of **13e** and **14e**, only the *Z*-isomer was observed (see Supporting Information). A similar Alder-ene-type reaction was observed in the palladium-catalyzed reaction of cyclopentenyl.[11]

We also investigated the iridium-catalyzed cycloisomerization of various enynes with an internal alkyne. Our preliminary study (Scheme 3) showed that the cy-



Scheme 3. Ir(I)-catalyzed cyclopropanation of enynes.



Scheme 2. Ir(I)-catalyzed cycloisomerization of keto cyclohexadienyl alkynes.

cloisomerization reaction of various enynes with a disubstituted triple bond provided bicyclo[4.1.0]heptanes. The reaction times and yields were highly dependent upon the substrate. As already mentioned, Shibata et al.[6b] also reported the formation of bicyclo[4.1.0]heptenes from 1,6-enynes using a cationic iridium species [20 mol% $IrCl(CO)(PPh_3)_2$/24 mol% AgX (X = OTf or SbF_6)] as a catalyst. Compared to their system, our catalytic system used 2.5 mol% $[Ir(cod)Cl]_2$ in the absence of any additive. Moreover, our catalytic system is also effective for an allyl propargyl ether (**18a**) although the reaction time is lengthened to 30 h. Thus, for the scope of available enyne substrates our catalytic system seemed to have a wide applicability.

Based on our experimental observations and the previous study,[7c] a plausible reaction mechanism for the formation of **b**, **c**, **d** and **e** is presented in the Supporting Information.

In conclusion, we have demonstrated that our catalytic system is effective for both cyclopropanation and double cyclopropanation. The reaction pathways are highly sensitive to the substrate, particularly to the tether atom and (a) substituent(s) at the alkyne moiety. For enynes with a terminal alkyne and a carbon- or nitrogen-tether, double-cyclopropanated compounds were obtained in reasonable to high yields. For enynes substituted at the alkyne, cyclopropanated compounds were obtained in high yields. However, a disubstituion at the propargyl carbon of an enyne with a disubstituted alkyne and an N-Ts tether can alter the reaction pathway to give an incomplete double cyclopropanation product. When a keto carbonyl was introduced to enynes having a phenyl at the alkyne, Alder-ene-type products were obtained in reasonable to high yields for hetero-atom-tethered substrates. Our catalytic system is also effective for the cycloisomerization of various enynes with an internal alkyne to give bicyclo[4.1.0]heptenes. Further synthetic applications of these reactions are under investigation.

Experimental Section

General Procedure for Iridium(I)-Catalyzed Cycloisomerization of Cyclohexadienyl Alkynes

To a flame-dried 10-mL Schlenk flask capped with a rubber septum, toluene (5 mL) and $[Ir(cod)Cl]_2$ (5.3 mg, 2.5 mol%) were added under a flow of N_2. To the resulting mixture, **1a** (0.11 g, 0.34 mmol) was added under N_2. The reaction mixture was stirred at 130 °C and was monitored by TLC. After the reaction mixture had been cooled to room temperature, the reaction mixture was filtered and all the solvent was evaporated under reduced pressure. A flash column chromatography on a silica gel eluting with hexane and ethyl acetate (v/v, 10:2) gave the **2b**; yield: 94%.

Acknowledgements

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[10] The synthetic procedures and spectroscopic data of the new compounds are summarized in the Supporting Information. CCDC 744770 contains the supplementary crystallographic data for compound **10d** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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