メタラクムレン類の特性を活かした炭素骨格形成法の開発

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６．研究の目的と成果

○　研究の目的

集積型二重結合であるアレン、すなわち1,2-プロパジエン部分を反応試剤として活用する反応が数多く報告されている。それらの中には、単純な二重あるいは三重結合では、達成し得ない集積型二重結合の特性を利用した反応が多くある。本研究では、アレンの金属類縁体として位置づけられるビニリデン錯体、さらにはアレニリデン錯体などのメタラクムレン類の炭素−炭素二重結合部位の反応性に着目し、その特性を活かした合成反応を探索する。配位子により制御される含金属集積型二重結合の反応性に関する知見を得るとともに、二炭素、さらには三炭素合成ユニットとしての利用を視野に入れ、炭素骨格形成反応における新たな試剤の開拓を目的とする。

カルベン錯体が、有機合成において欠くことのできない反応試剤となったが、その集積型類縁体と位置付けられるビニリデン、アレニリデン錯体などメタラクムレン類が有機合成において活用されているとは言い難い。そこで本研究は、有機金属錯体として構造、物性など多くの報告例があるが、合成的利用が限られているビスビニリデン錯体、さらにはアレニリデン錯体の反応性に着目し、合成的利用を検討する。

○　研究の過程

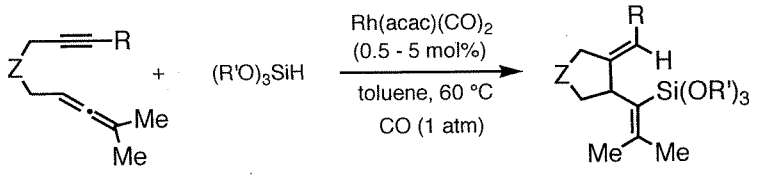
まず、1,2-プロパジエンよりさらに一炭素二重結合が集積された 1,2,3-ブタトリエンを反応試剤として用いる検討をした（研究成果3）。その結果、ブタトリエン類が、アレン類と比べ一般的に不安定であり、また、種々の官能基の導入が容易でないことがわかった。反応系中でブタトリエンエノラートを調製し、アルドール反応に用いることが出来たが、ブタトリエン類をエン部分として用いる遷移金属錯体による触媒反応への展開は困難であると判断した。

一方、これまでクロムやモリブデンなどの６Ａ族元素のカルボニル錯体より調製される電子不足なビニリデン錯体が主に用いられた。そこで本研究では、ロジウム、イリジウムなどの８族元素より比較的電子豊富なビニリデン錯体、さらにはアレニリデン錯体を調製し、その炭素－炭素二重結合の反応性を検討した。まず、末端アルキン錯体から異性化によりアレニリデン錯体を得る常法を用いた結果、異性化よりも付加環化反応が先行し、多彩の環状化合物を与えることがわかった（研究成果7）。そこで、研究の方針を変え、種々の遷移金属触媒を用いる環化反応の検討を総括的に行うこととした。

○ 研究成果

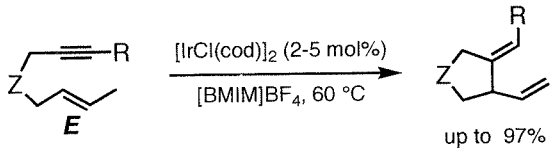
1)「アレンインのヒドロシリル化を伴う化学、かつ位置選択的な分子内環化反応」

ロジウム触媒存在下、アレンインとトリアルコキシシランを反応させると分子内環化反応が進行し、ビニルシラン部位をもつ1,4-ジエンが高収率で得られた。本反応は、アルキンに先行してアレン部分が、そして連続した二重結合のうち内側のみが反応する極めて化学かつ、位置選択的な反応である。



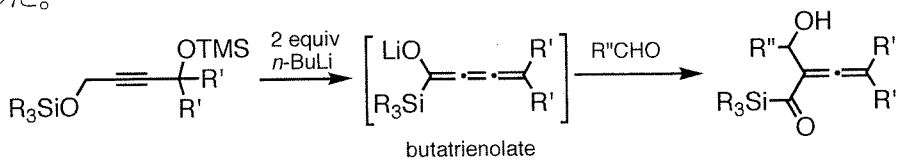
2) 「イオン性液体中で加速されるイリジウム触媒による分子内エン型反応」

イオン性液体とは、広い温度範囲において液体である不揮発性化合物であり、再利用可能で環境に優しい反応媒体である。本研究では、イリジウム触媒による1,6-エンインの環化異性化反応が、イオン性液体のひとつであるイミダゾリウム塩（[BMIM]BF_4）中で効率的に進行するだけでなく、有機溶媒中での反応より加速されることを見出した。



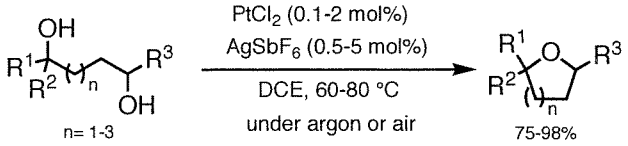
3)「ブタトリエノラートを求核試剤として用いるアルドール反応」

三つの二重結合が集積した「ブタトリエン」の合成的利用はこれまでほとんど報告例がない。そこで、2-ブチニルシリルエーテルから、1,4-脱離、レトロ Brook 転位により系中でブタトリエノラートを調製し、それを四炭素求核試剤として用い、アルデヒドとのアルドール反応を開発した。



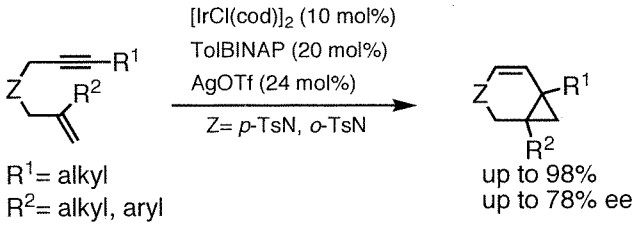
4)「白金触媒を用いたアルコールの分子内、ならびに分子間脱水反応によるエーテル合成」

カチオン性白金塩を用いると、ジオールより触媒的エーテル化反応が進行し、種々の環状エーテルが得られる。ベンジルアルコールを用いると分子間反応によりメチルエーテルを合成できる。これらの反応は、不活性雰囲気下のみならず、空気中でも速やかに進行する特徴がある。



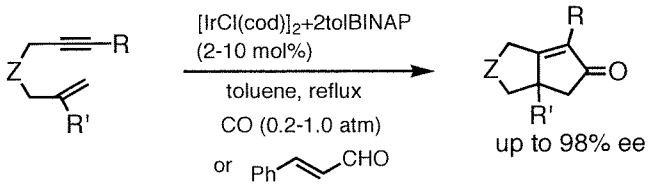
5)「イリジウム触媒による窒素架橋エンインの環化異性化反応による三員環合成」

カチオン性イリジウム触媒を用いると、窒素架橋 1,6-エンインの環化異性化反応が進行し、三員環と六員環が縮環した二環性生成物が得られる。また、キラルホスフィン配位子を添加すると、エナンチオ選択的な反応が進行する。



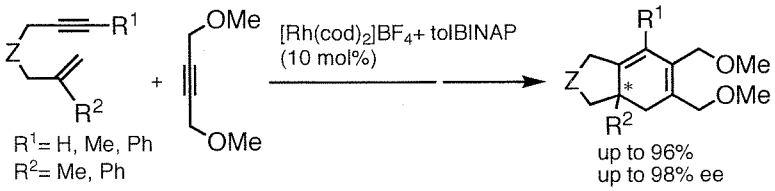
6)「イリジウム触媒を用いる 1,6-エンインのエナンチオ選択的 Pauson-Khand 型反応」

イリジウムーキラルホスフィン錯体は、エナンチオ選択的分子内 Pauson-Khand 型反応を進行させ、種々の 1,6-エンインより光学活性二環性シクロペテノンを与える。反応は、低一酸化炭素分圧下でより迅速、かつエナンチオ選択的に進行した。さらに、一酸化炭素ガスに替え、桂皮アルデヒドを CO 源として用いてもほぼ同程度の選択性を実現できる。



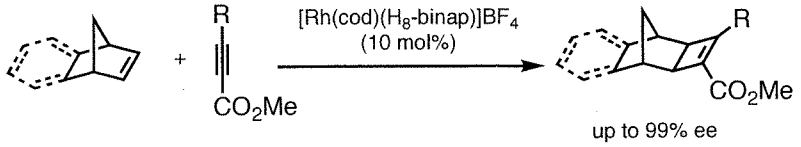
7)「触媒的不斉[2+2+2]付加環化反応による不斉 4 級炭素の構築」

不斉四級炭素中心を持つ化合物は、多くの天然物の構造に見られるため、その合成法の開発は有機合成化学において非常に有用である。本研究では、アルケン部位に置換基(R^2)を有する 1,6-エンインを用いて、アルキンとの分子間不斉[2+2+2]付加環化反応により、不斉四級炭素中心を持つ二環性シクロヘキサ-1,3-ジエンの合成を試みた。その結果、$[Rh(cod)_2]BF_4$ と不斉リン配位子 tolBINAP より調製されるカチオン性ロジウム錯体を不斉触媒として用いると、付加環化反応が高エナンチオ選択的(>90% ee)に進行することがわかった。



8) 「ノルボルネン類とアルキンの分子間不斉[2+2]付加環化反応による光学活性四員環合成」

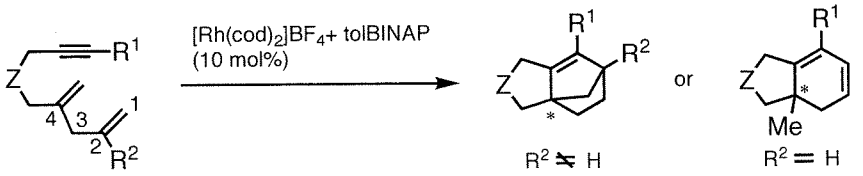
$[Rh(cod)_2]BF_4$ と光学活性二座ホスフィン配位子より系中で調製されるキラルロジウム触媒を用いると、ノルボルネン類とアルキンの[2+2]付加環化反応が進行し、シクロブテン骨格をもつ三、四環性の光学活性化合物が得られた。アルキン上のメトキシカルボニル基が高収率、高不斉収率実現のために重要である。



up to 99% ee

9) 「1, 4-ジエン-インの分子内[2+2+2]付加環化反応による不斉四級炭素の構築」

キラルロジウム触媒存在下、分子内に非共役なジエン部位とアルキン部位を有する 1, 4-ジエン-インの反応を検討した。その結果、2 位に置換基を有する基質の場合($R^2 \neq H$)、2 つの不斉四級炭素を有し、かつ歪みを持つ三環性化合物が生成した。一方、2 位に置換基を持たない基質の場合($R^2 = H$)、不斉四級炭素を一つもつ二環性化合物が得られた。いずれの場合も高エナンチオ選択的に反応が進行した。

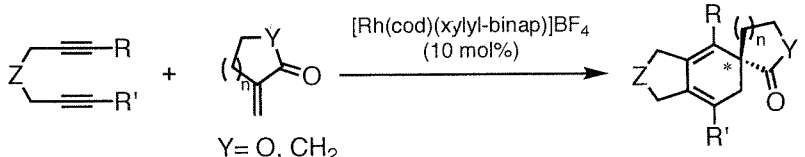


$R^2 \neq H$
up to >99% ee

$R^2 = H$
up to >99% ee

10) 「ジインと 1,1-二置換アルケンの分子間[2+2+2]付加環化反応よる不斉スピロ骨格の構築」

キラルロジウム触媒存在下、1,6-ジインと非対称な環状エキソメチレン化合物の分子間[2+2+2]付加環化反応が進行し、シクロ-1,3-ジエン部分をもつキラルスピロ化合物が高不斉収率で得られた。本反応は、非対称 1,1-二置換アルケンを用いても進行することから、汎用性の高い不斉四級炭素のエナンチオ選択的な構築法である。

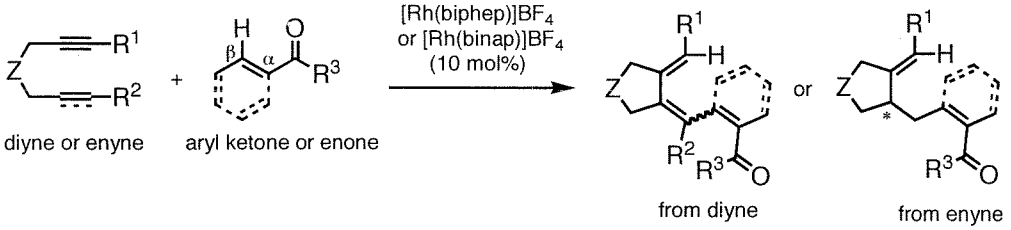


Y= O, CH_2

up to 99% ee

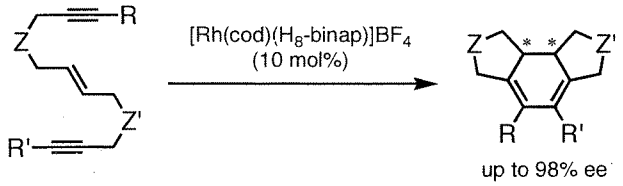
11) 「アリールケトンやエノンの C-H 結合切断を伴うジインやエンインとの反応」

ロジウム触媒存在下、ジインとアリールケトンやエノンとの反応を行うと、環化を伴ったヒドロアリール化、あるいはヒドロビニル化が進行し、単環性 1,3-ジエンが得られた。また、本反応はエンインを用いても進行し、キラルロジウム触媒を用いることにより、光学活性化合物が高不斉収率で得られた。



12) 「エンジインの分子内不斉[2+2+2]付加環化反応」

キラルロジウム触媒存在下、1,2-アルケンによって架橋されたジインを反応させると、分子内[2+2+2]付加環化反応が進行し、隣接した２つの不斉炭素を有する三環性シクロヘキサ-1,3-ジエンが高収率かつ高不斉収率で得られた。本反応は対称的な基質(R=R', Z=Z')のみならず、末端置換基や架橋部の構造の異なる非対称な基質においても進行する。



Organometallics **2004**, *23*, 4116−4120

Chemo- and Regioselective Intramolecular Hydrosilylative Carbocyclization of Allenynes

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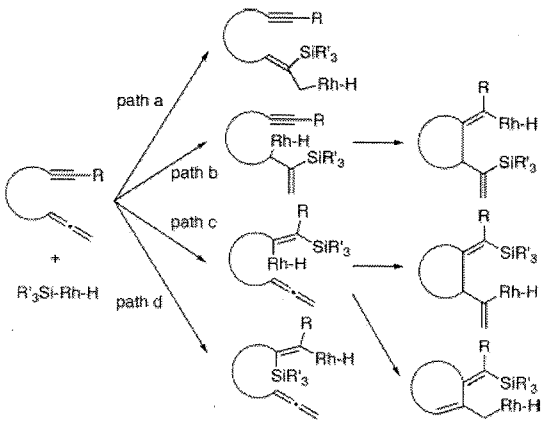
Rhodium complex catalyzed hydrosilylative carbocyclization of various allenynes and trialkoxysilanes proceeded smoothly under an atmosphere of carbon monoxide to give hydrosilylated cyclic products. The intramolecular coupling of allene and alkyne is chemo- and regioselective: silylrhodation to an internal olefinic moiety of the allene proceeded exclusively, and subsequent carbometalation to the alkyne provided cyclic 1,4-dienes. The use of alkoxysilane and the substituents on the allene terminus play pivotal roles in the selectivity.

Introduction

Transition-metal-catalyzed carbocyclization is a powerful and reliable synthetic method for the construction of various types of ring systems.[1] In particular, silylcarbocyclization, in which silicon-initiated carbometalation is a key step, is an established procedure. After Tamao and Ito reported the first example of nickel complex catalyzed silylcarbocyclization of 1,7-diynes,[2] Ojima comprehensively studied rhodium complex catalyzed silylcarbocyclization.[3] Enynes,[3a,e] diynes,[3b,4] triynes,[3c] and enediynes[3d] can all be used as substrates, and various types of functionalized cyclic systems have been obtained. Recently, cationic palladium[5] and platinum[6] complexes have been found to be efficient catalysts. However, to the best of our knowledge, the hydrosilylative carbocyclization of allenynes has not yet been reported.[7]

When an allenyne is subjected to hydrosilylation using a rhodium complex, there are several plausible pathways, depending upon the chemoselectivity between the alkyne and allene, the regioselectivity of the two olefinic moieties of the allene, and the direction of silylrhodation to an unsaturated bond. Scheme 1 shows four selected pathways, where silylation occurs at an sp carbon. On the basis of our study of transition-metal-catalyzed reactions using allenynes,[8] we considered that the regioselectivity could be controlled by the methyl substituents on the allene terminus.

Scheme 1



We report here the first example of hydrosilylative carbocyclization of allenynes catalyzed by a rhodium complex. The intramolecular coupling of allene and alkyne with various silanes was examined. A mechanistic study using a deuterated silane and the synthetic transformations of the obtained vinylsilanes are also described.

Results and Discussion

We chose allenyne **1a** as a model substrate and examined rhodium complex catalyzed silylcarbocyclization using dimethylphenylsilane under several reaction conditions (Table 1). The silylative coupling proceeded

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† Waseda University.
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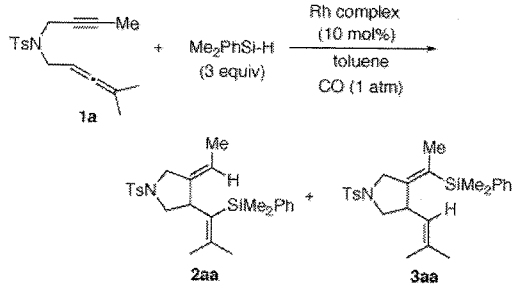
Table 1. Hydrosilylative Carbocyclization of Allenyne 1a under Various Conditions



entry	Rh complex	temp/°C	time/h	yield/%	2aa/3aa
1	$Rh(acac)(CO)_2$	120	0.5	85	2/1
2	$Rh(acac)(CO)_2$	60	0.5	90	7/1
3	$Rh(acac)(CO)_2$	room temp	1	47	9/1
4	$^1/_2[RhCl(cod)]_2$	40	1	67	12/1
5	$^1/_2[RhCl(cod)]_2 + 2PPh_3$	90	2	31	2/1
6	$^1/_2[RhCl(cod)]_2$ + DPPP[a]	90	6	64	3/1

[a] DPPP = 1,3-bis(diphenylphosphino)propane.

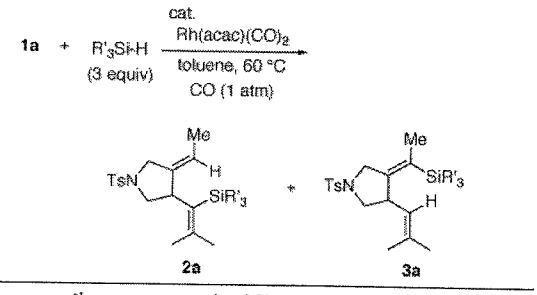
smoothly under an atmosphere of carbon monoxide using $Rh(acac)(CO)_2$ as a catalyst in toluene. At 120 °C, allenyne **1a** was consumed within 30 min and the hydrosilylated product was obtained in high yield; however, the chemoselectivity (**2aa** via path b vs **3aa** via path c) was low (entry 1). When the reaction temperature was lowered, the selectivity was improved and the vinylsilane **2aa** was the major product (entries 2 and 3). In the silylcarbocyclization of enynes, silylrhodation to the alkyne moiety, not the alkene, proceeded exclusively, following carbometalation to the alkene moiety. Interestingly, in the reaction of the allenyne, silylrhodation to the allene moiety, not the alkyne, is predominant. When $[RhCl(cod)]_2$ was used as a catalyst, the chemoselectivity was further improved; however, the yield was lower because of the formation of several unidentified side products (entry 4). The addition of phosphine ligands diminished the catalytic activity of the rhodium complex; moreover, the chemoselectivity was not sufficient (entries 5 and 6).

Using $Rh(acac)(CO)_2$ as a catalyst, several silanes were examined for the improvement of chemoselectivity (Table 2). With a more bulky triethylsilane, the formation of **3a** was suppressed, but the yield of **2a** was low (entry 1). When alkoxysilanes were used in place of trialkylsilanes, vinylsilane **2a** was the only silylative product identified and was obtained in high yield (entries 2–4). Trimethoxy- and triethoxysilane gave satisfying results, and 2 mol % of rhodium catalyst was sufficient to give a high yield in a short reaction time (entries 5 and 6). Moreover, the catalytic reaction proceeded even with as little as 0.5 mol % catalyst (entry 7). The reaction of allenyne proceeded even at room temperature under an atmosphere of CO (entry 8).[9]

The silylcarbocyclization of various allenynes and two trialkoxysilanes was examined using 5 mol % catalyst (Table 3). In the reported rhodium complex catalyzed silylcarbocyclization of enynes and diynes, the alkyne

(9) Under an atmosphere of argon or a high pressure of carbon monoxide (5 atm), silylcarbocyclization proceeded, yet in lower yield (48 and 55%, respectively), along with the formation of many unidentified products.

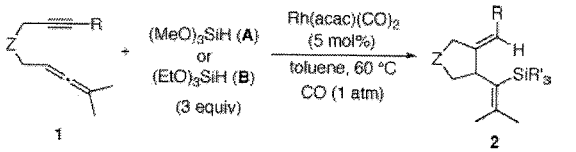
Table 2. Hydrosilylative Carbocyclization of Allenyne 1a with Various Silanes



entry	silane	cat./mol %	time/h	yield/%	2a/3a[a]
1	Et_3SiH	10	0.5	32	>20/1
2	$(MeO)_2MeSiH$	10	0.5	73	>20/1
3	$(MeO)_3SiH$	10	0.5	77	>20/1
4	$(EtO)_3SiH$	10	0.5	85	>20/1
5	$(MeO)_3SiH$	2	0.75	80	>20/1
6	$(EtO)_3SiH$	2	0.75	84	>20/1
7	$(EtO)_3SiH$	0.5	8	66	>20/1
8[b]	$(MeO)_3SiH$	10	6	53	>20/1

[a] The formation of **3a** could not detected by NMR spectra. [b] The reaction was examined at room temperature.

Table 3. Hydrosilylative Carbocyclization of Various Allenynes



entry	Z	R	allenyne	silane	time/h	yield/%
1[a]	TsN	Me	**1a**	A	0.75	80 (**2ab**)
2	TsN	Me	**1a**	B	0.5	82 (**2ac**)
3	TsN	*n*-Bu	**1b**	A	1	79 (**2bb**)
4	TsN	*n*-Bu	**1b**	B	1.5	72 (**2bc**)
5	TsN	Ph	**1c**	A	0.75	50 (**2cb**)
6	TsN	Ph	**1c**	B	1.5	52 (**2cc**)
7[a]	O	Me	**1d**	A	1	63 (**2db**)
8[a]	O	Me	**1d**	B	1	73 (**2dc**)
9	O	Ph	**1e**	A	0.75	54 (**2eb**)
10	O	Ph	**1e**	B	1	46 (**2ec**)
11	$(EtO_2C)_2C$	Ph	**1f**	A	1.5	49 (**2fb**)
12	$(EtO_2C)_2C$	Ph	**1f**	B	1.5	61 (**2fc**)

[a] These entries were examined using 2 mol % catalyst.

terminus is usually limited to hydrogen or alkyl groups. In the case of allene–alkyne coupling, both alkyls (entries 1–4) and an aryl group can be tolerated (entries 5 and 6). Oxygen-bridge allenynes **1d,e** are also good substrates, and the corresponding cyclic vinylsilanes **2db,dc** and **2eb,ec** were obtained in acceptable yields (entries 7–10). Allenylpropargylmalonate **1f** could also be transformed into the silylative product **2fb,fc** (entries 11 and 12). In each case, vinylsilanes **2a–f** were the only fully characterized products and the other silylative coupling products, including **3**, could not be isolated. Moreover, neither a cross-conjugated triene by an ene-type reaction[8a,10] nor bicyclic enones by a Pauson–Khand-type reaction[8b,11] could be detected.

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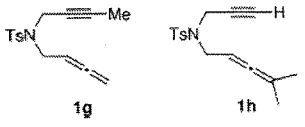
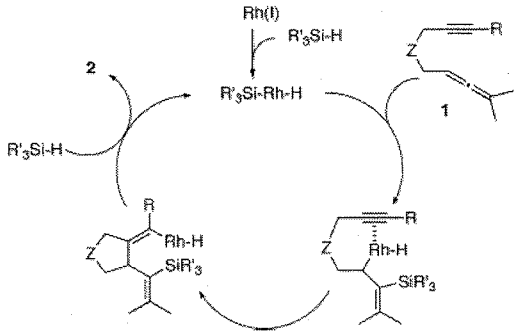
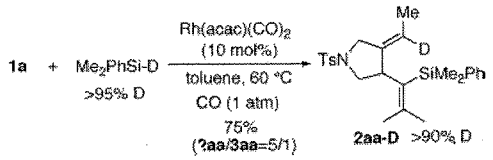


Figure 1. Other allenynes possessing no substituent on allene or alkyne terminus.

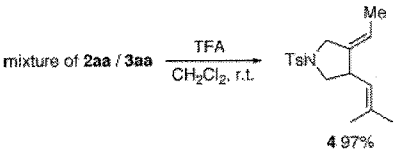
Scheme 2



Scheme 3



Scheme 4



When allenynes **1g,h** (Figure 1) were examined under the same reaction conditions, respectively, many silylated products were obtained, although none of them could be isolated or fully characterized. These results imply that the substituents on both the allene and alkyne termini play pivotal roles in the highly chemo- and regioselective silylcarbocyclization of allenynes.

The proposed mechanism is depicted in Scheme 2. Regioselective silylmetalation to the allene moiety could be achieved by the methyl groups on the allene terminus. Subsequent carbometalation gives the cyclic vinyl rhodium complex and reductive elimination provides the product **2** and regenerates the catalyst. The *Z* form of the obtained vinylsilane **2ab** was ascertained by NOE spectra. The results of a labeling experiment also support the above mechanism: when silylcarbocyclization was examined using the deuterated silane (>95% D),[12] the vinylic position derived from the alkyne moiety was labeled by deuterium at over 90% (Scheme 3).

The mixture of vinylsilanes **2aa/3aa** was desilylated by trifluoroacetic acid, and the cyclic 1,4-diene **4** was obtained as the sole product (Scheme 4). Alkoxyvinylsilane **2ad** (entry 2 in Table 1) was readily transformed into the isopropyl ketone **5** by Tamao oxidation (Scheme 5).[13]

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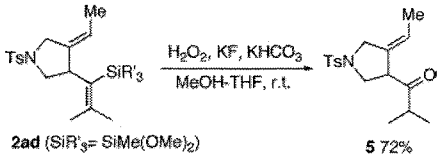
Scheme 5



Conclusions

In conclusion, this is the first report of the cyclization/hydrosilylation of allenynes. Rhodium complex catalyzed chemo- and regioselective reactions could be realized by using alkoxysilane and the methyl substituents on the allene terminus. The present coupling proceeds under an atmosphere of carbon monoxide, and nitrogen-, oxygen-, and carbon-bridged allenynes can be transformed into the cyclic vinylsilanes.

Experimental Section

General Considerations. IR spectra were recorded with a JASCO FT/IR-5000 spectrometer. NMR spectra were measured with a Varian VXR-300 spectrometer using tetramethylsilane as an internal standard, and $CDCl_3$ was used as solvent. High-resolution mass spectra were measured with a JEOL JMS-SX102A instrument. Elemental analyses were measured with Perkin-Elmer PE2400. Toluene was distilled from calcium hydride and dried over molecular sieves 4A (MS 4A). All reactions were examined using a CO balloon.

Typical Procedure for Hydrosilylative Carbocyclization of Allenynes (Table 2, Entry 6). (Acetylacetonato)dicarbonylrhodium(I) (2.2 mg, 8.46×10^{-3} mmol, 2 mol %) and triethoxysilane (209 mg, 1.27 mmol) in dry toluene (3.6 mL) were stirred under an atmosphere of carbon monoxide at room temperature. After the mixture was changed to a homogeneous solution, a solution of *N*-(but-2-ynyl)-*N*-(4-methylpenta-2,3-dienyl)tosylamine (**1a**; 128 mg, 0.423 mmol) in dry toluene (5.1 mL) was added to the mixture and stirred for 30 min at 60 °C. The solvent was removed under reduced pressure to give the crude product, which was further purified by thin-layer chromatography to give the pure product **2ac** (166.0 mg, 84%).

(*Z*)-4-(1-(Dimethylphenylsilyl)-3-ethylidene-2-methylprop-1-enyl)-1-tosylpyrrolidine (2aa). Yellow oil. IR (neat): 1601, 1350, 1164, 832, 816 cm^{-1}. ^1H NMR: δ −0.08 (s, 3H), 0.15 (s, 3H), 1.51−1.54 (m, 3H), 1.65 (s, 3H), 1.69 (s, 3H), 2.39 (s, 3H), 2.90 (dd, J = 9.6, 9.6 Hz, 1H), 3.51 (d, J = 14.4 Hz, 1H), 3.63 (dd, J = 9.6, 9.6 Hz, 1H), 3.85−3.88 (m, 1H), 4.06 (d, J = 14.4 Hz, 1H), 5.08−5.16 (m, 1H), 7.23−7.36 (m, 7H), 7.68 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 0.8, 1.3, 14.6, 21.6, 26.8, 46.2, 50.4, 52.6, 116.3, 127.5, 127.6, 128.0, 128.3, 129.5, 132.5, 133.4, 139.7, 140.6, 143.4, 149.1. HRMS (FAB): found, 440.2065; calcd for $C_{25}H_{34}NO_2SSi$ (MH^+), 440.2080.

(*Z*)-3-Ethylidene-4-(2-methyl-1-(trimethoxysilyl)prop-1-enyl)-1-tosylpyrrolidine (2ab). Colorless solid (hexane). Mp: 93−94 °C. IR (neat): 1601, 1346, 1164, 1089, 814 cm^{-1}. ^1H NMR: δ 1.50−1.55 (m, 3H), 1.75 (s, 3H), 1.92 (s, 3H), 2.42 (s, 3H), 2.96 (dd, J = 8.7, 10.4 Hz, 1H), 3.22 (s, 9H), 3.45−3.49 (m, 1H), 3.55 (dd, J = 8.7, 8.7 Hz, 1H), 3.74−3.80 (m, 1H), 4.10 (d, J = 14.1 Hz, 1H), 4.93−5.02 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 14.6, 21.5, 25.5, 44.9, 49.7, 50.4, 52.6, 115.3, 124.5, 128.0, 129.6, 132.3, 140.4, 143.2, 151.9; Anal. Calcd for $C_{20}H_{31}NO_5SSi$: C, 56.44; H, 7.34; N, 3.29. Found: C, 56.42; H, 7.47; N, 3.18.

The product was determined to be a *Z* isomer on the basis of the observation of NOEs in Figure 2.

(*Z*)-3-Ethylidene-4-(2-methyl-1-(triethoxysilyl)prop-1-enyl)-1-tosylpyrrolidine (2ac). White solid (hexane). Mp: 50−51 °C. IR (neat): 1601, 1348, 1164, 1079, 832, 814 cm^{-1}. ^1H NMR: δ 1.00 (t, J = 7.1 Hz, 9H), 1.48−1.52 (m, 3H), 1.74

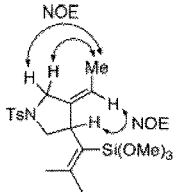


Figure 2. Determination of stereochemistry of **2ab** by NOEs.

(s, 3H), 1.94 (s, 3H), 2.42 (s, 3H), 3.04 (dd, J = 8.4, 10.5 Hz, 1H), 3.42–3.60 (m, 7H), 3.74 (d, J = 13.5 Hz, 1H), 3.72–3.77 (m, 1H), 4.10 (d, J = 13.5 Hz, 1H), 4.91–4.99 (m, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 14.5, 18.0, 21.5, 21.6, 25.7, 45.3, 50.4, 52.6, 57.7, 114.8, 124.9, 127.9, 129.3, 132.7, 140.4, 143.2, 151.7. HRMS (FAB): found, 468.2276; calcd for $C_{23}H_{38}NO_5SSi$ (MH^+), 468.2240.

(*Z*)- 4-(2-Methyl-1-(trimethoxysilyl)prop-1-enyl)-3-pentylidene-1-tosylpyrrolidine (2bb). White solid. Mp: 89–91 °C (hexane). IR (neat): 1601, 1348, 1164, 1087, 812 cm^{-1}. ^{1}H NMR: δ 0.84–0.88 (m, 3H), 1.23–1.28 (m, 4H), 1.75 (s, 3H), 1.82–1.92 (m, 2H), 1.93 (s, 3H), 2.42 (s, 3H), 2.94 (dd, J = 8.7, 10.2 Hz, 1H), 3.22 (s, 9H), 3.47 (d, J = 14.1 Hz, 1H), 3.57 (dd, J = 8.7, 8.7 Hz, 1H), 3.63–3.74 (m, 1H), 4.10 (d, J = 14.1 Hz, 1H), 4.88–4.94 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H). ^{13}C NMR: δ 14.0, 21.5, 22.3, 25.5, 29.3, 31.5, 44.9, 49.7, 50.4, 52.5, 121.2, 124.3, 127.9, 129.2, 132.3, 139.3, 143.1, 151.9. HRMS (FAB): found 468.2231; calcd for $C_{23}H_{38}NO_5SSi$ (MH^+), 468.2240.

(*Z*)-4-(2-Methyl-1-(triethoxysilyl)prop-1-enyl)-3-pentylidene-1-tosylpyrrolidine (2bc). Colorless oil. IR (neat): 1601, 1344, 1162, 1077, 955, 756 cm^{-1}. ^{1}H NMR: δ 0.84–0.89 (m, 3H), 1.00 (t, J = 7.1 Hz, 9H), 1.23–1.30 (m, 4H), 1.74 (s, 3H), 1.84–1.89 (m, 2H), 1.95 (s, 3H), 2.42 (s, 3H), 3.04 (dd, J = 8.6, 10.7 Hz, 1H), 3.43–3.59 (m, 7H), 3.68–3.82 (m, 2H), 4.11 (dd, J = 0.9, 13.2 Hz, 1H), 4.87–4.93 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 14.0, 18.0, 21.5, 21.6, 22.4, 25.7, 29.3, 31.5, 45.3, 50.4, 52.5, 57.7, 120.7, 124.8, 127.8, 129.3, 132.7, 139.2, 143.2, 151.8. HRMS (FAB): found, 510.2714; calcd for $C_{26}H_{44}NO_5SSi$ (MH^+), 510.2709.

(*Z*)-3-Benzylidene-4-(2-methyl-1-(trimethoxysilyl)prop-1-enyl)-1-tosylpyrrolidine (2cb). Pale yellow solid. Mp: 113–114 °C. IR (neat): 1301, 1348, 1168, 1091, 814 cm^{-1}. ^{1}H NMR: δ 1.82 (s, 3H), 1.98 (s, 3H), 2.42 (s, 3H), 2.99 (dd, J = 9.2, 10.4 Hz, 1H), 3.22 (s, 9H), 3.65 (dd, J = 9.2, 9.2 Hz, 1H), 3.84 (dt, J_d = 14.3, J_t = 2.4 Hz, 1H), 3.93–4.00 (m, 1H), 4.44 (dt, J_d = 14.3, J_t = 2.4 Hz, 1H), 5.82 (q, J = 2.5 Hz, 1H), 7.16–7.35 (m, 7H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 21.6, 21.7, 25.6, 46.7, 49.9, 51.7, 51.8, 121.4, 124.5, 126.4, 127.6, 128.0, 128.4, 129.4, 132.4, 137.1, 142.5, 143.4, 152.7. HRMS (FAB): found, 488.1920; calcd for $C_{25}H_{34}NO_5SSi$ (MH^+), 488.1972.

(*Z*)-3-Benzylidene-4-(2-methyl-1-(triethoxysilyl)prop-1-enyl)-1-tosylpyrrolidine (2cc). White solid. Mp: 82–84 °C (hexane). IR (neat): 1601, 1346, 1166, 1077, 957, 756 cm^{-1}. ^{1}H NMR: δ 0.97 (t, J = 6.9 Hz, 9H), 1.81 (s, 3H), 2.00 (s, 3H), 2.41 (s, 3H), 3.09 (dd, J = 8.4, 10.2 Hz, 1H), 3.43–3.58 (m, 6H), 3.63 (dd, J = 8.4, 8.4 Hz, 1H), 3.88 (dt, J_d = 14.4, J_t = 2.7 Hz, 1H), 3.93–3.99 (m, 1H), 4.44 (d, J = 14.4 Hz, 1H), 5.95 (d, J = 2.7 Hz, 1H), 7.07–7.34 (m, 7H), 7.75 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 18.0, 21.5, 21.7, 25.8, 47.0, 51.7, 51.8, 57.8, 121.1, 125.0, 126.3, 127.5, 127.9, 128.3, 129.4, 132.7, 137.2, 142.5, 143.4, 152.5. HRMS (FAB): found, 530.2368; calcd for $C_{28}H_{40}NO_5SSi$ (MH^+), 530.2396.

(*Z*)-3-Ethylidene-4-(2-methyl-1-(trimethoxysilyl)prop-1-enyl)-2,3,4,5-tetrahydrofuran (2db). Colorless oil. IR (neat) 1607, 1191, 1087, 801 cm^{-1}. ^{1}H NMR: δ 1.55–1.58 (m, 3H), 1.83 (s, 3H), 1.99 (s, 3H), 3.50 (s, 9H), 3.72 (dd, J = 6.8, 10.1 Hz, 1H), 3.76–3.85 (m, 1H), 4.00 (dd, J = 6.8, 6.8 Hz, 1H), 4.29 (dd, J = 1.8, 12.9 Hz, 1H), 4.48 (d, J = 12.9 Hz, 1H), 4.99–5.09 (m, 1H). ^{13}C NMR: δ 14.7, 21.7, 25.7, 46.6, 50.0, 67.0, 72.6, 112.4, 124.3, 144.1, 151.4. HRMS (FAB): found, 273.1543; calcd for $C_{13}H_{25}O_4Si$ (MH^+), 273.1522.

(*Z*)-3-Ethylidene-4-(2-methyl-1-(triethoxysilyl)prop-1-enyl)-2,3,4,5-tetrahydrofuran (2dc). Colorless oil. IR (neat): 1605, 1296, 1079 cm^{-1}. ^{1}H NMR: δ 1.20 (t, J = 7.0 Hz, 9H), 1.53–1.56 (m, 3H), 1.82 (s, 3H), 2.00 (s, 3H), 3.67–3.87 (m, 8H), 3.98 (dd, J = 3.8, 4.7 Hz, 1H), 4.40 (dd, J = 1.2, 12.9 Hz, 1H), 4.47 (d, J = 12.9 Hz, 1H), 4.96–5.05 (m, 1H). ^{13}C NMR: δ 14.7, 18.2, 21.8, 25.8, 46.7, 57.9, 70.1, 72.8, 112.0, 124.9, 144.2, 151.0. HRMS (FAB): found, 315.1986; calcd for $C_{16}H_{31}O_4Si$ (MH^+), 315.1992.

(*Z*)-3-Benzylidene-4-(2-methyl-1-(trimethoxysilyl)prop-1-enyl)-2,3,4,5-tetrahydrofuran (2eb). Pale yellow oil. IR (neat): 1605, 1191, 1083, 801 cm^{-1}. ^{1}H NMR: δ 1.91 (s, 3H), 2.05 (s, 3H), 3.47 (s, 9H), 3.77 (dd, J = 12.2, 14.7 Hz, 1H), 4.00–4.09 (m, 2H), 4.64 (dt, J_d = 13.7, J_t = 2.2 Hz, 1H), 4.76 (dt, J_d = 13.7, J_t = 2.2 Hz, 1H), 6.05 (q, J = 2.2 Hz, 1H), 7.10–7.19 (m, 3H), 7.28–7.33 (m, 2H). ^{13}C NMR: δ 21.9, 25.7, 48.4, 50.2, 71.0, 71.8, 119.1, 124.2, 126.0, 127.5, 128.3, 137.9, 147.1, 152.3. HRMS (FAB): found, 335.1677; calcd for $C_{18}H_{27}O_4Si$ (MH^+), 335.1679.

(*Z*)-3-Benzylidene-4-(2-methyl-1-(triethoxysilyl)prop-1-enyl)-2,3,4,5-tetrahydrofuran (2ec). Yellow oil. IR (neat): 1603, 1218, 1079, 957, 756 cm^{-1}. ^{1}H NMR: δ 1.16 (t, J = 6.9 Hz, 9H), 1.90 (s, 3H), 2.06 (s, 3H), 3.64–3.80 (m, 6H), 3.87 (dd, J = 11.0, 14.0 Hz, 1H), 4.01–4.07 (m, 2H), 4.69 (dt, J_d = 13.5, J_t = 2.0 Hz, 1H), 4.75 (dt, J_d = 13.5, J_t = 2.0 Hz, 1H), 6.03 (q, J = 2.0 Hz, 1H), 7.08–7.33 (m, 5H). ^{13}C NMR: δ 18.2, 22.0, 25.9, 48.6, 58.0, 71.2, 71.9, 118.8, 124.9, 125.8, 127.4, 128.3, 138.0, 147.2, 152.0. HRMS (FAB): found, 375.2017; calcd for $C_{21}H_{31}O_4Si$ (M − 1), 375.1991.

Diethyl (*E*)-3-Benzylidene-4-(2-methyl-1-(trimethoxysilyl)prop-1-enyl)cyclopentane-1,1-dicarboxlate (2fb). Pale yellow oil. IR (neat): 1719, 1083, 756 cm^{-1}. ^{1}H NMR: δ 1.22 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 1.88 (s, 3H), 2.02 (s, 3H), 2.25 (dd, J = 12.1, 12.1, 1H), 2.49 (dd, J = 7.7, 12.1 Hz, 1H), 3.32–3.35 (m, 1H), 3.47 (s, 9H), 3.91–3.97 (m, 1H), 4.05–4.27 (m, 4H), 6.01 (d, J = 2.4 Hz, 1H), 7.12–7.17 (m, 1H), 7.32–7.52 (m, 4H). ^{13}C NMR: δ 14.1, 14.1, 21.6, 25.6, 38.8, 39.5, 47.4, 50.2, 59.9, 61.4, 61.4, 121.5, 125.6, 127.9, 128.1, 138.4, 147.0, 171.4, 171.7. HRMS (FAB): found, 476.2263; calcd for $C_{25}H_{36}O_7Si$, 476.2230.

Diethyl (*E*)-3-Benzylidene-4-(2-methyl-1-(triethoxysilyl)prop-1-enyl)cyclopentane-1,1-dicarboxylate (2fc). Yellow oil. IR (neat): 1731, 1077, 756 cm^{-1}. ^{1}H NMR: δ 1.13–1.29 (m, 15H), 1.87 (s, 3H), 2.03 (s, 3H), 2.38–2.45 (m, 2H), 3.29 (d, J = 16.8, 1H), 3.40 (dt, J_d = 16.8, J_t = 2.7, 1H), 3.66–3.79 (m, 6H), 3.90–3.98 (m, 1H), 4.07–4.25 (m, 4H), 5.98 (d, J = 2.1 Hz, 1H), 7.11–7.32 (m, 5H). ^{13}C NMR: δ 14.1, 14.1, 18.2, 21.7, 25.8, 38.8, 39.6, 47.5, 57.9, 60.0, 61.3, 61.4, 121.2, 125.5, 127.8, 128.9, 138.5, 147.0, 150.0, 171.4, 171.8. HRMS (FAB): found, 518.2704; calcd for $C_{28}H_{42}O_7Si$, 518.2700.

(*Z*)-4-(1-(Dimethoxymethylsilyl)-2-methylprop-1-enyl)-3-ethylidene-1-tosylpyrrolidine (2ad). Colorless solid (hexane). Mp: 119–120 °C. IR (neat): 1601, 1348, 1164, 1087, 832 cm^{-1}. ^{1}H NMR: δ 0.03 (s, 3H), 1.50–1.53 (m, 3H), 1.73 (s, 3H), 1.90 (s, 3H), 2.42 (s, 3H), 2.94 (s, 3H), 3.03 (dd, J = 8.7, 10.4 Hz, 1H), 3.17 (s, 3H), 3.47 (d, J = 13.5 Hz, 1H), 3.57 (dd, J = 8.7, 8.7 Hz, 1H), 3.76–3.82 (m, 1H), 4.09 (d, J = 13.5 Hz, 1H), 4.89–4.96 (m, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ −2.3, 14.5, 21.6, 24.9, 45.2, 49.0, 49.2, 50.5, 52.6, 114.9, 127.7, 128.0, 129.2,132.4, 140.7, 143.2, 149.6. Anal. Calcd for $C_{20}H_{32}NO_4SSi$; C, 58.64; H, 7.63; N, 3.42. Found: C, 58.77; H, 7.70; N, 3.35.

(*Z*)-3-Ethylidene-4-(2-methylprop-1-enyl)-1-tosylpyrrolidine (4). Yellow oil. IR (neat): 1618, 1350, 1166, 1093, 812 cm^{-1}. ^{1}H NMR: δ 1.50–1.54 (m, 3H), 1.60 (d, J = 1.2 Hz, 3H), 1.69 (d, J = 1.2 Hz, 3H), 2.44 (s, 3H), 2.56 (dd, J = 9.3, 9.3 Hz, 1H), 3.39–3.42 (m, 1H), 3.59–3.64 (m, 2H), 4.00 (dt, J_d = 14.4, J_t = 1.4 Hz, 1H), 4.74–4.76 (dt, J_d = 14.4, J_t = 1.4 Hz,

1H), 5.09–5.12 (m, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 14.5, 18.2, 21.6, 25.8, 42.3, 49.6, 53.6, 117.2, 122.3, 127.7, 129.5, 132.7, 135.4, 138.6, 143.4. HRMS (FAB): found, 306.1520; calcd for $C_{17}H_{24}NO_2S$ (MH^+), 306.1528.

(*Z*)-3-Ethylidene-4-(2-methyl-1-oxopropyl)-1-tosylpyrrolidine (5). Yellow oil. IR (neat): 1618, 1350, 1166, 1093, 812 cm^{-1}. ^{1}H NMR: δ 1.50–1.54 (m, 3H), 1.60 (d, J = 1.2 Hz, 3H), 1.69 (d, J = 1.2 Hz, 3H), 2.44 (s, 3H), 2.56 (dd, J = 9.3, 9.3 Hz, 1H), 3.39–3.42 (m, 1H), 3.59–3.64 (m, 2H), 4.00 (dt, J_d = 14.4, J_t = 1.4 Hz, 1H), 4.74–4.76 (dt, J_d = 14.4, J_t = 1.4 Hz, 1H), 5.09–5.12 (m, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 14.5, 18.2, 21.6, 25.8, 42.3, 49.6, 53.6, 117.2, 122.3, 127.7, 129.5, 132.7, 135.4, 138.6, 143.4. HRMS (FAB): found, 306.1520; calcd for $C_{17}H_{24}NO_2S$ (MH^+), 306.1528.

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Supporting Information Available: Listings of spectral data for allenyne **1a–f**, ^{1}H NMR charts of **2aa** and **2aa-D**, and copies of ^{1}H and ^{13}C NMR spectra for allenynes and products lacking analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Iridium Complex-Catalyzed Intramolecular Ene-Type Reaction of 1,6-Enynes Accelerated in Ionic Liquid

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Abstract: Iridium complex catalyzes an intramolecular ene-type reaction of 1,6-enynes to give cyclic 1,4-dienes. The reaction proceeds more efficiently in an imidazolium salt than in toluene and the ionic liquid can be reused.

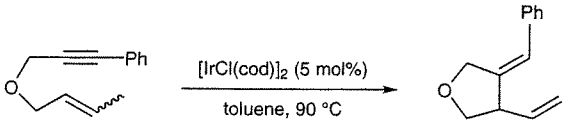
Key words: iridium, cycloisomerization, enynes, dienes, ionic liquid

Transition metal-catalyzed cycloisomerization is an atom-economical and powerful protocol for the synthesis of carbo- and heterocyclic systems.[1] Especially, an intramolecular ene-type reaction of enynes has been comprehensively studied and various transition metal complexes like Pd,[2] Pt,[3] Ti,[4] and Ru[5] ones are efficient catalysts. In these years, a series of Rh complex-catalyzed ene-type reaction of 1,6-enynes, possessing *Z*-olefinic moiety, has been reported.[6,7]

We here disclose an Ir complex-catalyzed intramolecular ene-type reaction, where 1,6-enynes, having *E*-olefinic moiety, are more reactive substrates than *Z*-olefinic moiety. Moreover, an imidazolium salt was found to be a superior reaction media to conventional organic solvents.

We chose allyl propargyl ether **1a**, where the *E*/*Z* ratio of the olefinic moiety is 2:1, as a model 1,6-enyne and examined a cycloisomerization using iridium complex $[IrCl(cod)]_2$ in toluene (Table 1, entry 1). As a result, the substrate was completely consumed in eight hours at 90 °C and an ene-type reaction proceeded to give cyclic 1,4-diene **2a** in good yield.[8] Unlike Ir complex-catalyzed carbonylative coupling[9] and [2+2+2] cycloaddition,[10] the addition of phosphine ligands deactivated the Ir-catalyst in the ene-type reaction. For an example, Ir–DPPP complex[9b] took longer reaction time to give product **2a** in lower yield (entry 2). When the reaction was quenched at 3 hours, 30% of enyne **1a** was recovered and the *Z*-isomer of **1a** was dominant (entry 3). These results imply that the *E*-isomer reacted more promptly than the *Z*-isomer. Actually, enyne **1a**, having *E*-olefinic moiety, was consumed only within three hours and the 1,4-diene **2a** was obtained in higher yield of 82% (entry 4).[11] On the contrary, enyne **1a**, having *Z*-olefinic moiety, gave much lower yield under the same reaction conditions (entry 5). Compound **1a-*Z*** was completely consumed by longer reaction time, however, the yield did not reach that by **1a-*E***. The higher reactivity of the *E*-isomer of enyne than the *Z*-isomer in ene-type reaction was opposite to the case in the Rh complex-catalyzed reaction.[6,12]

Table 1 Different Reactivity of Enyne, Having *E*- or *Z*-Olefinic Moiety in the Ir Complex-Catalyzed Ene-Type Reaction



1a **2a**

Entry	*E*/*Z*	Time (h)	Yield (%)
1	2:1	8	77
2[a]	2:1	22	42
3[b]	2:1	3	61
4	**>95:5**	**3**	**82**
5	< 5:95	3	31
6	< 5:95	10	50

[a] 1,3-Bis(diphenylphosphino)propane (10 mol%) was added as a ligand.
[b] Enyne (*E*/*Z* = 1:2) was recovered.

We got another interesting results by the choice of reaction media. When the present reaction was examined at 60 °C in toluene in 1 hour, the yield was low and most of enyne **1a-*E*** was recovered (Table 2, entry 1). However, when an imidazolium salt, which is one of typical ionic liquids and commonly used as a recyclable reaction media in place of organic solvents,[13] was used, the enyne was completely consumed under the same reaction conditions to give the ene product **2a** in good yield (entry 2). Tetrafluoroborate was a better choice as a counter anion of ionic liquid and the highest yield of 95% was achieved (entry 3).[14,15] When the amount of the catalyst was diminished from 5 mol% to 2 mol% in toluene at 120 °C, an apparent decrease in yield was observed (from 77% to 24%). In the case of $[BMIM]BF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) as solvent, a good yield was achieved by 2 mol% Ir-catalyst (entry 4). These results mean that the Ir complex could operate as a more active catalyst in

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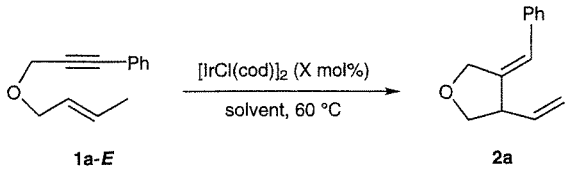
the imidazolium salt than in toluene.[16] Moreover, reuse of the ionic liquid could be possible and almost the same catalytic activity was ascertained by the second and third runs of reuse (entries 5, 6).[17]

Table 2 Ir Complex-Catalyzed Ene-Type Reaction in Toluene and Imidazolium Salts



Entry	Solvent	X (mol%)	Time (h)	Yield (%)
1	Toluene	5	1	28
2	[BMIM]PF_6	5	1	83
3	**[BMIM]BF_4**	**5**	**1**	**95**
4	[BMIM]BF_4	2	4	88
5[a]	[BMIM]BF_4	5	1	89
6[b]	[BMIM]BF_4	5	1	97

[a] [BMIM]BF_4, which was used at entry 3, was reused.
[b] [BMIM]BF_4, which was used at entry 5, was reused.

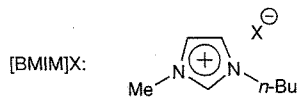
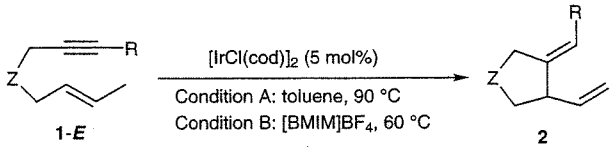


Table 3 shows the results of Ir complex-catalyzed reaction of several 1,6-enynes, having *E*-olefinic moiety, in toluene at 90 °C (Condition A) and in [BMIM]BF_4 at 60 °C (Condition B). Other than **1a-*E***, allyl propargyl ethers, having substituted aryl groups on their alkyne terminus, were also good substrates in the present reaction (entries 1–4). A nitrogen-bridged enyne was also transformed into the corresponding 1,4-diene under the same reaction conditions (entries 5, 6). An enyne, having an alkyl group on its alkyne terminus, could be also subjected to the ene-type reaction and acceptable yields were achieved by the higher reaction temperature both in toluene and [BMIM]BF_4 (entries 7, 8).[18]

Ionic liquids are one of promising alternatives to organic solvents as a reaction media.[13] Among them, imidazolium salts have been comprehensively studied and various types of transition metal-catalyzed reactions have been already reported.[19] Therefore, any advantages of the use of imidazolium salts, which cannot be realized by conventional molecular solvents, should be noted.[20] We found the first example of transition metal-catalyzed cycloisomerization in ionic liquid, as far as we know. Ir complex operated as a more efficient catalyst in imidazolium salts and the intramolecular ene-type reaction of 1,6-enynes, having *E*-olefinic moiety, smoothly proceeded to give cyclic 1,4-dienes in good to excellent yield.

Table 3 Ir Complex-Catalyzed Ene-Type Reaction of Several 1,6-Enynes



Entry	Z	R	Condition	Time (h)	Yield (%)
1	O	*p*-ClC_6H_4	A	3	86
2	O	*p*-ClC_6H_4	B	1	96
3	O	*p*-$MeOC_6H_4$	A	6	75
4	O	*p*-$MeOC_6H_4$	B	1	95
5	TsN	Ph	A	24	63
6	TsN	Ph	B	4	87
7	TsN	Me	A[a]	8	68
8	TsN	Me	B[b]	3	70

[a] The reaction was examined at 120 °C.
[b] The reaction was examined at 90 °C.

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(10) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382.
(11) Using **1a-*E*** as an enyne in toluene at 90 °C, no reaction proceeded by $[RhCl(cod)]_2$ and many unidentified products were obtained by $PtCl_2$.
(12) The higher reactivity of the *E*-isomer than the *Z* one is probably because the β-hydrogen is closer to the metal center in the metallacycle derived from the *E*-isomer.[4] However, the different selectivity of Ir- an Rh-catalyst could not yet be explained.
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(14) **Typical Experimental Procedure (Table 2, entry 3):** Under an atmosphere of argon, $[IrCl(cod)]_2$ (10.1 mg, 1.5×10^{-2} mmol, 5 mol%) and allyl propargyl ether **1a-*E*** (54.7 mg, 0.300 mmol) were placed in a flask. After the addition of $[BMIM]BF_4$ (0.5 mL), the mixture was stirred at 60 °C (bath temperature) for 1 h. The resulting mixture was extracted with Et_2O, then the combined ether phase was evaporated to dryness, and the obtained crude products were purified by thin layer chromatography to give pure **2a** (52.0 mg, 0.285 mmol, 95%).
(15) In $[BMIM]BF_4$ at 60 °C, it took 3 h to consume **1a-*Z*** and **2a** was obtained in 43% yield.
(16) No complexation from $[IrCl(cod)]_2$ and $[BMIM]BF_4$ could be observed by NMR measurement. However, the polarity of the solvent is not an answer because polar solvents like 1,2-dimethoxyethane and *N,N*-dimethlyformamide gave poorer results than toluene, therefore the role of imidazolium salts in the present catalytic reaction is unclear. See: Park, S.; Kazlauskas, R. J. *J. Org. Chem.* **2001**, *66*, 8395.
(17) $[BMIM]BF_4$ was washed with EtOAc and passed through an activated alumina column, then it could be reused.
(18) Under the same reaction conditions, crotylpropargylmalonate did not give an ene-type product.
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Bull. Chem. Soc. Jpn., 77, 1937–1938 (2004)

The Reaction of Butatrienolates with Aldehydes for the Syntheses of α-Vinylidene Acylsilanes

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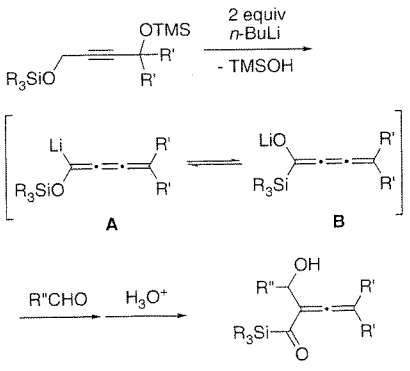
Lithium butatrienolates were prepared in situ by the 1,4-elimination from 2-butynyl trimethylsilyl ethers along with a retro-Brook rearrangement. The addition reaction of the enolates with the aldehydes afforded β-hydroxy-α-vinylidene acylsilanes.

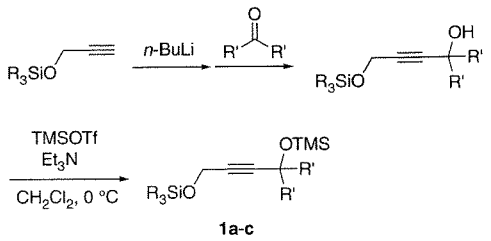
The aldol addition of enolates with aldehydes is one of the most important carbon–carbon forming reactions. In particular, the addition of α-silyl-substituted enolates gives acylsilanes,[1] which are useful synthetic intermediates for various transformations.[2] When α-silyl-substituted allenolates (propadienolates), which were prepared by the retro-Brook rearrangement of allenyllithiums, were used, the reaction with aldehydes gave α-methylene acylsilanes.[3,4] Here we disclose that the addition reaction of α-silyl-substituted butatrienolates with aldehydes affords α-vinylidene acylsilanes.

The 1,4-elimination of trimethylsilanol from 1,4-disiloxy-2-butyne using 2 equivalent amounts of base gives the lithiated butatriene **A**.[5] *C*-lithium **A** is known to exist in equilibrium with *O*-lithium **B** through a (retro-)Brook rearrangement.[6] We subjected the in situ prepared lithium butatrienolates to a reaction with aldehydes (Scheme 1).

1,4-Disiloxy-2-butynes **1a–c**, the precursors for butatrienolates, were readily available from the addition of the lithium salt of 1-siloxy-2-propyne to ketones along with the trimethylsilyl-protection of the obtained alcohols (Scheme 2).

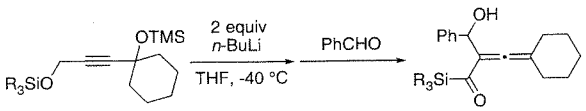


Scheme 1.



Scheme 2.

When the reaction of the *t*-butyldimethylsilyl-protected ether **1a** with benzaldehyde was examined, the corresponding β-hydroxy-α-vinylidene acylsilane **2a** was obtained in moderate yield along with the formation of several unidentified products derived from **1a**. The *t*-butyldiphenylsilyl ether **1b** gave the better result, a 72% yield. The more bulky silyl group probably stabilized the lithium salt. Actually, at the higher reaction temperature (−20 °C), the butatrienolate decomposed to give a complex mixture.



1a (SiR_3= Si*t*-BuMe_2)
1b (SiR_3= Si*t*-BuPh_2)

2a 46%
2b 72% (1)

The reaction of aldehydes with two butatrienolates was examined (Table 1). Alkyl and α,β-unsaturated aldehydes were also substrates and the corresponding β-hydroxy-α-vinylidene acylsilanes **2c, d** were obtained in good yields (Entries 1, 2). Only a trace amount of the 1,4-adduct was obtained in Entry 2. The dimethyl-substituted butatrienolate prepared from **1c** also reacted with aldehydes to give α-vinylidene acylsilanes **2e–g** in acceptable yields (Entries 3–5).

The unique reactivity of the cumulated carbon–carbon double bond is anticipated, which could not be realized in simple alkenes or conjugate systems. Recently, allenes (propadienes) were comprehensively studied as unique reagents for transition metal-catalyzed reactions, however, the synthetic use of the butatriene component is limited.[7] This paper discloses that the aldol reaction of lithium butatrienolate with aldehydes proceeded, and that β-hydroxy-α-vinylidene acylsilanes were obtained.

Experimental

General. ^{1}H NMR spectra were measured with a JNM AL-400 spectrometer and ^{13}C NMR spectra were measured with a JEOL Lambda 500 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. IR spectra were recorded with a Horiba FT730 spectrophotometer. High-resolution mass spectral analyses (FAB) were performed on a JEOL JMS-SX102A. All reactions were examined using an Ar balloon.

1-[3-(*t*-Butyldimethylsiloxy)prop-1-ynyl]-1-trimethylsiloxycyclohexane (1a). Pale yellow oil. ^{1}H NMR δ 0.09 (s, 6H), 0.15 (s, 9H), 0.88 (s, 9H), 1.19–1.22 (m, 1H), 1.40–1.64 (m, 7H), 1.78–1.81 (m, 2H), 4.33 (s, 2H); ^{13}C NMR δ −5.1, 2.1, 18.3, 23.1, 25.3, 25.8, 41.1, 51.8, 69.9, 83.6, 88.6; IR (neat) 1094 cm^{-1}; HRMS *m/z* calcd for $C_{18}H_{35}O_2Si_2$ (M^+ − 1): 339.2176. Found: 339.2151.

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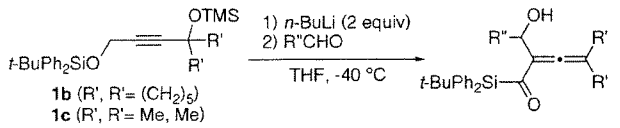
Table 1. The Reaction of in Situ Prepared Lithium Butatrienolates with Aldehydes



1b (R', R'= $(CH_2)_5$)
1c (R', R'= Me, Me)

Entry	1	R″	Yield/%
1	**1b**	*n*-Pr	71 (**2c**)
2	**1b**	CH_3CH=CH	85 (**2d**)
3	**1c**	Ph	72 (**2e**)
4	**1c**	*n*-Pr	65 (**2f**)
5	**1c**	CH_3CH=CH	60 (**2g**)

1-[3-(*t*-Butyldiphenylsiloxy)prop-1-ynyl]-1-trimethylsiloxycyclohexane (1b). Pale yellow oil. ^{1}H NMR δ 0.18 (s, 9H), 1.05 (s, 9H), 1.19–1.25 (m, 2H), 1.44–1.60 (m, 6H), 1.79–1.82 (m, 2H), 4.37 (s, 2H), 7.37–7.76 (m, 10H); ^{13}C NMR δ 2.2, 19.3, 23.2, 25.4, 26.7, 41.2, 52.8, 70.0, 83.4, 88.7, 127.6, 129.6, 133.0, 135.4; IR (neat) 1097 cm^{-1}; HRMS *m*/*z* calcd for $C_{28}H_{39}O_2Si_2$ (M^+ − 1): 463.2489. Found: 463.2446.

1-(*t*-Butyldiphenylsiloxy)-4-methyl-4-trimethylsiloxypent-2-yne (1c). Pale yellow oil. ^{1}H NMR δ 0.17 (s, 9H), 1.05 (s, 9H), 1.43 (s, 6H), 4.34 (s, 2H), 7.37–7.72 (m, 10H); ^{13}C NMR δ 1.9, 19.2, 26.7, 32.8, 52.7, 66.5, 81.1, 90.0, 127.7, 129.7, 133.2, 135.6; IR (neat) 1113 cm^{-1}; HRMS *m*/*z* calcd for $C_{25}H_{35}O_2Si_2$ (M^+ − 1): 423.2176. Found: 423.2199.

1-(*t*-Butyldimethylsilyl)-2-(cyclohexylidenemethylene)-3-hydroxy-3-phenylpropan-1-one (2a). Yellow oil. ^{1}H NMR δ 0.17 (s, 6H), 0.90 (s, 9H), 1.02–1.10 (m, 1H), 1.21–1.30 (m, 1H), 1.46–1.65 (m, 4H), 1.89–2.02 (m, 3H), 2.10–2.15 (m, 1H), 3.79 (d, J = 2.4 Hz, 1H), 5.66 (d, J = 2.4 Hz, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR δ −5.4, −5.3, 16.8, 25.4, 26.0, 26.1, 26.6, 30.4, 30.4, 72.0, 108.9, 117.5, 126.4, 127.1, 128.0, 141.9, 210.1, 235.9; IR (neat) 3487, 1946, 1575 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{31}O_2Si$ (M^+ − 1): 355.2094. Found: 355.2090.

1-(*t*-Butyldiphenylsilyl)-2-(cyclohexylidenemethylene)-3-hydroxy-3-phenylpropan-1-one (2b). To a THF solution (2 mL) of silyl ether **1b** (139.4 mg, 0.30 mmol) was added BuLi (0.72 mmol, 1.59 mol/L hexane solution) dropwise at −40 °C, and the mixture was stirred for 10 min. To the resulting mixture was added benzaldehyde (95.5 mg, 0.90 mmol) at −40 °C. After being stirred for 10 min, the reaction mixture was quenched with sat. NH_4Cl (aq), and the organic materials were then extracted with Et_2O. The extracts were then washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude products were purified by thin-layer chromatography (hexane/ethyl acetate = 10/1). Yellow oil. ^{1}H NMR δ 1.00 (s, 9H), 0.52–0.60 (m, 1H), 0.66–0.77 (m, 1H), 0.79–0.92 (m, 3H), 1.07–1.16 (m, 4H), 1.26–1.32 (m, 1H), 3.77 (d, J = 4.0 Hz, 1H), 5.71 (d, J = 4.0 Hz, 1H), 7.18–7.73 (m, 15H); ^{13}C NMR δ 18.6, 25.0, 25.6, 25.7, 26.8, 28.5, 28.6, 71.9, 110.7, 116.8, 126.3, 127.0, 127.6, 127.6, 127.9, 128.3, 129.3, 133.2, 133.2, 135.6, 135.7, 142.0, 210.1, 233.3; IR (neat) 3459, 1943, 1583 cm^{-1}; HRMS *m*/*z* calcd for $C_{32}H_{37}O_2Si$ (M^+ + 1): 481.2563. Found: 481.2565.

1-(*t*-Butyldiphenylsilyl)-2-(cyclohexylidenemethylene)-3-hydroxyhexan-1-one (2c). Yellow oil. ^{1}H NMR δ 0.86–0.93 (m, 3H), 1.00 (s, 9H), 1.03–1.13 (m, 6H), 1.23–1.43 (m, 5H), 1.47–1.55 (m, 3H), 3.18 (d, J = 5.5 Hz, 1H), 4.52 (dt, J = 5.5, 5.5 Hz, 1H), 7.34–7.73 (m, 10H); ^{13}C NMR δ 14.0, 18.6, 18.9, 25.2, 26.1, 26.1, 26.8, 28.8, 29.0, 37.2, 68.8, 110.4, 115.5, 127.6, 127.7, 128.3, 129.3, 129.4, 133.3, 133.4, 135.7, 209.0, 233.9; IR (neat) 3444, 1941, 1577 cm^{-1}; HRMS *m*/*z* calcd for $C_{29}H_{39}O_2Si$ (M^+ + 1): 447.2719. Found: 447.2711.

1-(*t*-Butyldiphenylsilyl)-2-(cyclohexylidenemethylene)-3-hydroxyhex-4-en-1-one (2d). Yellow oil. ^{1}H NMR δ 1.01 (s, 9H), 1.03–1.06 (m, 2H), 1.19–1.25 (m, 4H), 1.40–1.42 (m, 3H), 1.49–1.52 (m, 1H), 1.69 (d, J = 6.4 Hz, 3H), 3.38 (d, J = 5.5 Hz, 1H), 5.00 (dd, J = 5.5, 5.5 Hz, 1H), 5.49 (dd, J = 5.5, 15.2 Hz, 1H), 5.65–5.73 (m, 1H), 7.30–7.70 (m, 10H); ^{13}C NMR δ 17.7, 18.7, 25.3, 26.3, 26.3, 26.9, 29.0, 29.0, 70.2, 110.6, 115.3, 126.9, 127.7, 127.7, 129.4, 129.4, 131.2, 133.3, 133.3, 135.7, 135.8, 209.4, 233.4; IR (neat) 3451, 1942, 1577 cm^{-1}; HRMS *m*/*z* calcd for $C_{29}H_{36}O_2Si$ (M^+): 444.2485. Found: 444.2483.

1-(*t*-Butyldiphenylsilyl)-3-hydroxy-2-(isopropylidenemethylene)-3-phenylpropan-1-one (2e). Yellow oil. ^{1}H NMR δ 0.70 (s, 3H), 0.77 (s, 3H), 0.98 (s, 9H), 3.64 (d, J = 5.8 Hz, 1H), 5.61 (d, J = 5.8 Hz, 1H), 7.22–7.60 (m, 15H); ^{13}C NMR δ 17.8, 18.0, 18.6, 26.8, 71.9, 105.1, 116.4, 126.1, 127.2, 127.7, 127.7, 127.9, 128.4, 129.4, 133.0, 133.0, 135.6, 135.6, 142.3, 212.8, 233.4; IR (neat) 3515, 1954, 1593 cm^{-1}; HRMS *m*/*z* calcd for $C_{29}H_{33}O_2Si$ (M^+ + 1): 441.2250. Found: 441.2217.

1-(*t*-Butyldiphenylsilyl)-3-hydroxy-2-(isopropylidenemethylene)hexan-1-one (2f). Yellow oil. ^{1}H NMR δ 0.82 (s, 3H), 0.86 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H), 1.01 (s, 9H), 1.25–1.65 (m, 4H), 3.08 (d, J = 5.8 Hz, 1H), 4.49 (dt, J = 5.8, 5.8 Hz, 1H), 7.33–7.66 (m, 10H); ^{13}C NMR δ 14.0, 18.1, 18.2, 18.7, 18.9, 26.8, 37.4, 68.9, 104.5, 115.8, 127.7, 127.7, 129.4, 129.4, 133.1, 133.2, 135.6, 212.2, 234.0; IR (neat) 3451, 1947, 1585 cm^{-1}; HRMS *m*/*z* calcd for $C_{26}H_{35}O_2Si$ (M^+ + 1): 407.2406. Found: 407.2409.

1-(*t*-Butyldiphenylsilyl)-3-hydroxy-2-(isopropylidenemethylene)hex-4-en-1-one (2g). Yellow oil. ^{1}H NMR δ 0.83 (s, 3H), 0.87 (s, 3H), 1.01 (s, 9H), 1.69 (d, J = 6.0 Hz, 3H), 3.21 (d, J = 6.3 Hz, 1H), 4.93 (dd, J = 6.3, 6.3 Hz, 1H), 5.51 (dd, J = 6.3, 15.0 Hz, 1H), 5.66–5.74 (m, 1H), 7.33–7.67 (m, 10H); ^{13}C NMR δ 17.7, 18.1, 18.2, 18.7, 26.8, 70.2, 104.7, 115.4, 127.1, 127.7, 127.7, 129.4, 131.3, 133.1, 133.1, 135.6, 135.6, 135.7, 212.3, 233.4; IR (neat) 3451, 1947, 1587 cm^{-1}; HRMS *m*/*z* calcd for $C_{26}H_{31}O_2Si$ (M^+ − 1): 403.2094. Found: 403.2082.

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Cationic Platinum-Catalyzed Etherification by Intra- and Intermolecular Dehydration of Alcohols

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Abstract: Catalytic etherification of diols proceeds to give various cyclic ethers by use of cationic platinum salt, which is in situ prepared from $PtCl_2$ and $AgSbF_6$. Etherification of benzylic alcohols is also possible by intermolecular dehydration. Both of intra- and intermolecular etherifications smoothly proceed even under an atmosphere of air.

Key words: platinum, ethers, dehydration, diols, alcohols

Williamson ether synthesis is an established protocol for the synthesis of ethers from alcohols and halides, however, it is generally examined under the strongly basic conditions and a stoichiometric amount of salts is formed.[1] On the other hand, dehydration of alcohols is more direct synthesis of ethers, and protic acid catalysts[2] like amberlyst[3] and nafion-H[4] were reported for the etherification of diols. Lewis acid is another choice of a promoter for the dehydrative ether synthesis[2] and a stoichiometric amount of zinc chloride was used for the synthesis of cyclic ethers.[5] In these years, catalytic dehydrative etherifications of allylic and benzylic alcohols were also reported by use of various metal catalysts.[6,7]

We here disclose a catalytic ether synthesis using a cationic platinum salt. Intra- and intermolecular dehydrations of alcohols were examined under an atmosphere of argon and air.

We chose Pt(II) salt because of its high Lewis acidity.[8] Dehydration of 1,5-diphenylpentane-1,5-diol was examined by use of a catalytic amount of platinum dichloride in 1,2-dichloroethane (DCE) under an atmosphere of argon, however, no reaction proceeded at 60 °C (Table 1, entry 1). In order to increase Lewis acidity, silver salts were added for the generation of cationic platinum (entries 2–4). As a result, the choice of counter anion was important and 2,6-disubstituted tetrahydropyran was obtained in an excellent yield[9] by the combination of $PtCl_2$ and $AgSbF_6$ (entry 4). Argon atmosphere was not needed and no decrease of catalytic activity was observed even under an atmosphere of air (entry 5). Silver salt did not operate as a catalyst by itself (entry 6), therefore, the cationic platinum salt was an efficient catalyst for dehydrative etherification.

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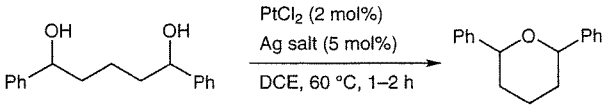
Table 1 Catalytic Etherification of 1,5-Diol Using Platinum Salts



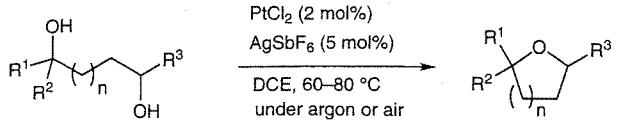
Entry	Ag salt	Yield (%)
1	None	NR[c]
2	$AgBF_4$	NR[c]
3	AgOTf	78
4	$AgSbF_6$	94
5[a]	$AgSbF_6$	94
6[b]	$AgSbF_6$	NR[c]

[a] Under an atmosphere of air.
[b] Without $PtCl_2$.
[c] NR = no reaction.

Table 2 shows the results of cationic platinum-catalyzed etherification of various diols under an atmosphere of argon or air.[9,10] A 1,4-diol gave 2,5-disubstituted tetrahydrofuran under the same reaction conditions (entry 1). At higher reaction temperature, even 0.1 mol% of platinum catalyst could work efficiently to give the cyclic ether in excellent yield (entry 3). Unsymmetrical diols also reacted and di- and mono-substituted tetrahydrofurans were obtained (entries 4–6). Other aryl groups could be also tolerated as substituents on 1,5-diols and the corresponding tetrahydropyran derivatives were provided (entries 7, 8). Under the dilute reaction conditions, a 1,6-diol also cyclized to a 7-membered cyclic ether (entry 9). Not only benzylic alcohols, but alkyl alcohols were also substrates (entries 10–14). From a diol, having tertiary and primary alcohols, a 2,2-dialkyl-substituted tetrahydrofuran was obtained (entries 10, 11).[11] 1,11-Diphenylundecane-4,8-diol gave a symmetrical 2,6-dialkyl-substituted tetrahydropyran in good yield (entry 12). 2-Alkyl- and 2-alkynyl-substituted tetrahydropyrans were also provided from the corresponding diols (entries 13–15). It is noteworthy that, even under an atmosphere of air, comparable yields were achieved (entries 5, 11, 14).

Intermolecular dehydration of benzylic and allyl alcohols also proceeded by use of the cationic platinum catalyst (Table 3).[12] The reaction of 1-phenylethanol and allyl alcohol gave the corresponding ether in high yield (entry 1), moreover, the present etherification proceeded even under

Table 2 Etherification of Various Diols by Cationic Platinum Catalyst

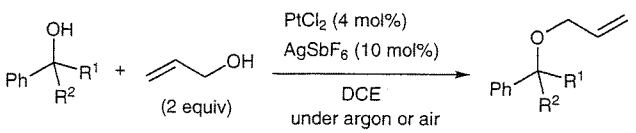


Entry	n	R^1	R^2	R^3	Temp (°C)	Time (h)	Yield (%)
1	1	Ph	H	Ph	60	0.5	97
2[a]	1	Ph	H	Ph	60	1	98
3[b]	1	Ph	H	Ph	80	0.5	95
4	1	Ph	H	Me	60	1	97
5[c]	1	Ph	H	Me	80	2	95
6	1	Ph	H	H	60	1	93
7	2	4-ClC_6H_4	H	4-ClC_6H_4	60	0.5	93
8	2	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	60	0.5	93
9[d]	3	Ph	H	Ph	60	1	75
10	1	3-Phenylpropyl	Me	H	60	2	91
11[c]	1	3-Phenylpropyl	Me	H	60	4	93
12[d]	2	3-Phenylpropyl	H	3-Phenylpropyl	70	8	77
13	2	Hexyl	H	H	80	5	78[f]
14[c]	2	Hexyl	H	H	80	4	76[f]
15[e]	2	1-Hexynyl	H	H	60	5	86

[a] $PtCl_2$ (0.5 mol%), $AgSbF_6$ (1.5 mol%).
[b] $PtCl_2$ (0.1 mol%), $AgSbF_6$ (0.5 mol%).
[c] Under an atmosphere of air. The other entries were examined under an atmosphere of argon.
[d] The concentration of diol in DCE is 0.020 M.
[e] The concentration of diol in DCE is 0.025 M.
[f] A five-membered cyclic ether (ca. 8%) was included as a side product.

an atmosphere of air without solvent (entry 2). Etherification of propargylic and tertiary alcohols occurred at room temperature (entries 3, 4). Generation of benzylic cation is probably important for the following nucleophilic addition of allyl alcohol.[13]

Table 3 Intermolecular Dehydration of Benzylic and Allyl Alcohols

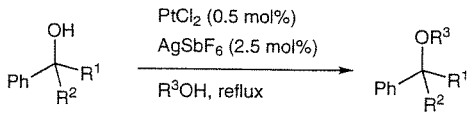


Entry	R^1	R^2	Temp (°C)	Time (h)	Yield (%)
1	Me	H	50	1.5	91
2[a]	Me	H	60	1	94
3	1-Propynyl	H	r.t.	1	75
4	Me	Me	r.t.	2	87

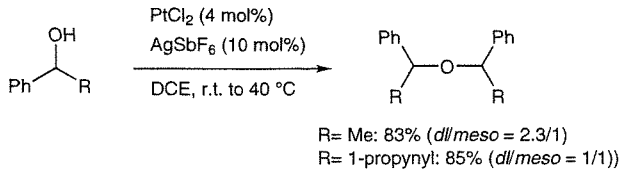
[a] Under an atmosphere of air without solvent.

In alcoholic solvents, methyl and ethyl ether syntheses from benzylic alcohols were possible using 0.5 mol% cationic platinum catalyst (Table 4). Symmetrical ethers were obtained by dimerization of alcohols, which are limited to benzylic ones (Equation 1).

Table 4 Intermolecular Etherification in Alcoholic Solvents



Entry	R^1	R^2	R^3	Time (h)	Yield (%)
1	1-Propynyl	H	Me	25	82
2	1-Propynyl	H	Et	4	67
3	Me	Me	Me	3	63



Equation 1

In summary, we developed a cationic platinum-catalyzed ether synthesis from alcohols. Catalytic intra- and intermolecular dehydration gave various cyclic and acyclic ethers. Moreover, the platinum catalyst is moisture-tolerant and the etherifications efficiently proceeded even under an atmosphere of air.

Acknowledgment

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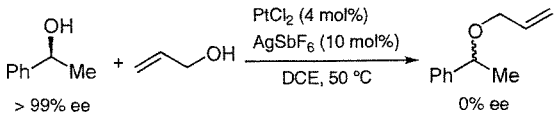
(9) All of the 2,n-disubstituted cyclic ethers were obtained as a mixture of *dl* and *meso* isomers (ca. 1:1).

(10) **Typical Experimental Procedure for Cyclic Ethers from Diols (Table 2):** $PtCl_2$ (1.1 mg, 0.004 mmol) was placed in a flask and a 1,2-dichloroethane solution (2.0 mL) of a diol (0.20 mmol, 0.10 M) was added. To the resulting mixture was added $AgSbF_6$ (3.6 mg, 0.010 mmol) and the mixture was stirred at the temperature cited in Table 2 for 0.5–8 h. After excluding the solvent to the volume of ca. 0.5 mL under reduced pressure, the obtained mixture was purified by column chromatography (hexane–EtOAc) using silica gel to give a pure cyclic ether.

(11) 2-Methyl-2-(3-phenylpropyl)tetrahydrofuran: IR (neat): 1496, 1454, 1057, 748, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.51–1.74 (m, 6 H), 1.82–1.95 (m, 2 H), 2.59–2.66 (m, 2 H), 3.74–3.85 (m, 2 H), 7.17–7.29 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 26.1, 26.7, 36.5, 36.7, 40.9, 67.1, 82.5, 125.6, 128.1, 128.3, 142.5. HRMS (FAB): *m/z* calcd for $C_{14}H_{20}O$ $[M^+]$: 204.1514. Found: 204.1508.

(12) **Typical Experimental Procedure for Acyclic Ethers (Table 3):** $PtCl_2$ (3.2 mg, 0.012 mmol) was placed in a flask and a 1,2-dichloroethane solution (4.5 mL) of an alcohol (0.30 mmol) and allyl alcohol (0.60 mmol) was added. To the resulting mixture was added $AgSbF_6$ (10.3 mg, 0.030 mmol) and the mixture was stirred at the temperature cited in Table 3 for 1–2 h. The following procedure is the same as in ref. 10.

(13) Complete racemization of a chiral alcohol indicates that the present etherification proceeded via S_N1 pathway (Scheme 1).



Scheme 1

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Tetrahedron 61 (2005) 9018–9024

Iridium-catalyzed enantioselective cycloisomerization of nitrogen-bridged 1,6-enynes to 3-azabicylo[4.1.0]heptenes

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Abstract—A cationic iridium complex catalyzes a cycloisomerization of nitrogen-bridged 1,6-enynes to give 3-azabicyclo[4.1.0]heptenes in good to high yield. When an iridium-chiral diphosphine complex is used, the reaction proceeds enantiomerically to give chiral cyclopropanes fused by a six-membered ring system.
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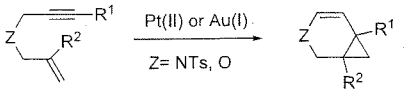
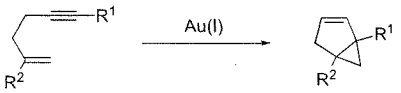
1. Introduction

Transition metal-catalyzed cycloisomerization of unsaturated systems provides an atom-economical protocol for the construction of cyclic compounds.[1] Especially, 1,*n*-enynes have been comprehensively investigated as the most common unsaturated motif,[2] and various types of cycloisomerizations have been reported according to the choice of enynes and transition metal catalysts including Pd,[3] Ru,[4] Rh,[5,6] Ti,[7] and Ir complexes.[8] Since Blum reported $PtCl_4$ catalyzed cycloisomerization of allyl propargyl ethers into 3-oxabicyclo[4.1.0]heptenes,[9] this type of transformation has been comprehensively studied from both a synthetic and mechanistic point of view:[10,11] $PtCl_2$ was found to be an efficient catalyst, and various 1,6-enynes bridged by nitrogen and oxygen were transformed into 3-aza- and 3-oxabicyclo[4.1.0]heptene skeletons, respectively (Eq. 1). Au(I) salt is another choice of catalyst,[12] and 1,5-enynes possessing no heteroatom on their tethers were also submitted to the present cycloisomerization (Eq. 2).[13]



(1)



(2)

This manuscript discloses a cationic iridium complex-catalyzed cycloisomerization of 1,6-enynes bridged by nitrogen, which gave 3-azabicyclo[4.1.0]heptenyl derivatives. Moreover, we achieved the first example of an enantioselective version of the present cycloisomerization by iridium-chiral diphosphine complexes and obtained optically active cyclopropanes fused by a six-membered ring system.

Iridium complex-catalyzed cycloisomerizations of 1,6-enynes, having carbon chains on their tethers, have already been reported, where cyclic 1,3-dienes[8a,c] or 1,4-dienes[8b] were obtained. The present results show a different pattern of transformation owing to the choice of enynes and iridium complexes.

2. Results and discussion

We have already reported iridium complex-catalyzed carbonylative couplings.[14] During our study, we examined Pauson–Khand-type reaction of enyne **1a** for the synthesis of a cyclopentenone having a quaternary carbon. No carbonylative product could be detected, however, bicyclic compound **2a** was obtained in good yield (Eq. 3). No iridium complex-catalyzed cycloisomerization along with cyclopropane ring formation has been reported; therefore, we have further investigated the reaction conditions.

Keywords: Iridium; Enynes; Cycloisomerization; Enantioselective; Cyclopropanes.
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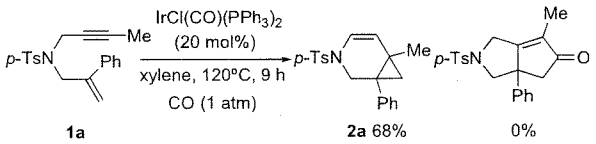
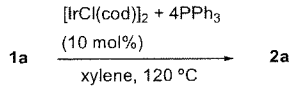


We used an in situ-prepared Ir–triphenylphosphine complex (Table 1). Under an atmosphere of argon, enyne **1a** was consumed but bicyclic product **2a** could not be detected (entry 1). Under an atmosphere of carbon monoxide, product **2a** was obtained in moderate yield, but enyne **1a** was not completely consumed within 24 h (entry 2). When the catalyst was prepared under CO, then the reaction was done under Ar, the reaction proceeded more smoothly to give cycloadduct **2a** in higher yield. These results imply that CO is important as a π-acceptor ligand of the catalyst.[15]

We next examined cationic iridium complexes, which were prepared from Vaska's complex and silver salts (Table 2).

Table 1. The effect of atmosphere on the cycloisomerization of **1a**

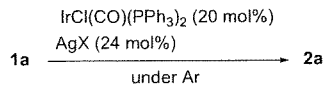


Entry	Atmosphere	Time (h)	Yield (%)
1	Ar	3	—
2	CO	24	41
3	CO then Ar	12	60

By addition of AgOTf to Vaska's complex in 1,2-dimethoxyethane (DME), the reaction proceeded at 60 °C to give product **2a** in very high yield (entry 1). Other ethereal solvents of higher boiling points (1,4-dioxane and dibutyl ether) accelerated the reaction but gave lower yields (entries 2, 3). Halogenated solvents (1,2-dichloroethane and chlorobenzene) also gave good results, but the yield did not exceed that of DME (entries 4, 5). As a result of the screening of the silver salts, the reaction proceeded more efficiently when SbF_6 was used as a counter anion of the catalyst (entries 1, 6, 7).

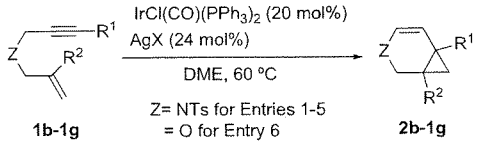
Various 1,6-enynes were submitted to the reaction using cationic iridium catalysts, which were in situ prepared from Vaska's complex and AgOTf or $AgSbF_6$ (Table 3). *n*-Butyl-substituted enyne **1b** was also transformed into the corresponding cycloadduct **2b** in refluxed DME (entry 1). Various aryl groups could be tolerable as a substituent on the alkene moiety of enynes (entries 2–4). Enyne **1f**, possessing methyl groups on its alkyne terminus and alkene, were a good substrate, and bicyclic product **2f** was obtained in almost quantitative yield by the addition of $AgSbF_6$ (entry 5). Oxygen-bridged enyne **1g** was also completely consumed under the same reaction conditions, but cyclopropane product **2g** could only be obtained in low yield from a complex mixture (entry 6). Nitrogen-bridged enyne **1h**, possessing a phenyl group on its alkyne terminus, and carbon-bridged enyne **1i** did not react even in refluxed DME.

Table 2. Effect of solvents and counter anions of cationic iridium complex on the cycloisomerization of **1a**



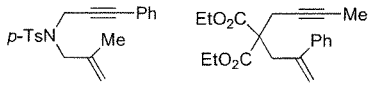
Entry	X	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	OTf	DME	60	24	94
2	OTf	Dioxane	100	3	74
3	OTf	Bu_2O	120	1	41
4	OTf	DCE	60	24	68
5	OTf	PhCl	100	3	89
6	SbF_6	DME	60	2	84
7	BF_4	DME	60	24	72

Table 3. Cationic iridium complex-catalyzed cycloisomerization of various enynes



Entry	R^1	R^2	1	AgOTf		$AgSbF_6$	
				Time (h)	Yield (%)	Time (h)	Yield (%)
1[a]	*n*-Bu	Ph	**1b**	20	55	1	84
2	Me	4-ClPh	**1c**	24	71	1.5	84
3	Me	4-MeOPh	**1d**	4	66	0.5	76
4	Me	2-Naphthyl	**1e**	8	60	0.5	72
5	Me	Me	**1f**	2	80	1	98
6	Me	Ph	**1g**	24	25	0.5	24

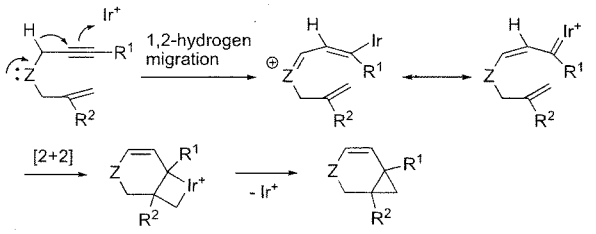
[a] In refluxed DME.



1h **1i**

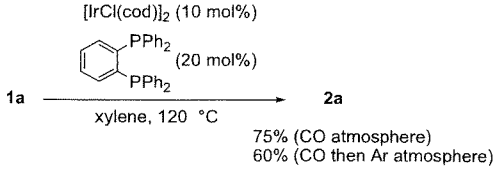
As in the Pt(II) salt-catalyzed reaction, the heteroatoms on the tether of the enynes are crucial in an iridium complex-catalyzed reaction. A mechanism via the carbene complex, which is stabilized by donor heteroatoms, could be possible (Scheme 1).[10c]

We further investigated an enantioselective version of the present cycloisomerization for the synthesis of chiral



Scheme 1. Proposed mechanism of cycloisomerization of heteroatom-bridged enynes.

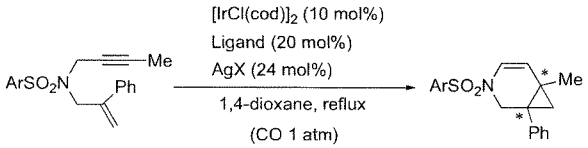
cyclopropanes. As a result of a preliminary experiment using an achiral bidentate ligand, 1,2-bis(diphenylphosphino)benzene was found to be best. Unlike the reaction using triphenylphosphine as a ligand, here a CO atmosphere throughout the reaction gave a better yield than an Ar atmosphere after complexation under a CO atmosphere (Eq. 4 and Table 1).[15]



(4)

Actually, enantioselective cycloisomerization was examined by cationic chiral iridium complexes, which were prepared from $[IrCl(cod)]_2$, a chiral diphosphine and a silver salt (Table 4). The reaction enantiomerically proceeded by BINAP ligand to give chiral cycloadduct **2a** in moderate ee of 52% (entry 1).[16] A substituent of nitrogen on the enyne apparently affects the enantioselectivity, and higher ee was achieved by *o*-TsN-bridged enyne **1j**, and TolBINAP was a better chiral ligand than BINAP in each case (entries 1–6). $AgBF_4$ gave almost the same results as AgOTf (entry 7). It took a longer reaction time, however,

Table 4. Optimization of enantioselective cycloisomerization of enynes by a chiral cationic iridium complex



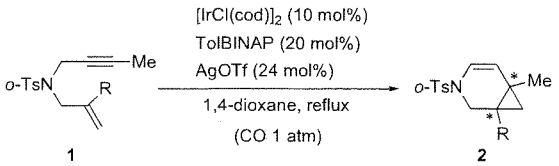
1a (Ar= *p*-tolyl)
1 j (Ar= *o*-tolyl)
1k (Ar= mesityl)

2a, j, k

Entry	Ar	X	Ligand	Time (h)	Yield (%)	ee (%)
1	*p*-Tolyl	OTf	BINAP	3	87	52
2	*p*-Tolyl	OTf	TolBINAP	2	92	66
3	*o*-Tolyl	OTf	BINAP	10	59	64
4	*o*-Tolyl	OTf	TolBINAP	2	79	75
5	Mesityl	OTf	BINAP	3	59	57
6	Mesityl	OTf	TolBINAP	2	70	64
7	*o*-Tolyl	BF_4	TolBINAP	6	82	74
8	*o*-Tolyl	SbF_6	TolBINAP	7	34	55
9[a]	*o*-Tolyl	OTf	TolBINAP	4	71	73
10[b]	*o*-Tolyl	OTf	TolBINAP	9	70	78

[a] $[IrCl(cod)]_2$ (5 mol%), TolBINAP (10 mol%), AgOTf (12 mol%).
[b] $[IrCl(cod)]_2$ (2 mol%), TolBINAP (4 mol%), AgOTf (5 mol%).

Table 5. Enantioselective cycloisomerization of nitrogen-bridged enynes by the chiral cationic iridium complex



1 **2**

Entry	R	1	Time (h)	Yield (%)	ee (%)
1	4-ClPh	**1l**	7	71	74
2	4-MeOPh	**1m**	5	69	44
3	2-Naphthyl	**1n**	9	71	35
4[a]	2-Naphthyl	**1e**	3	57	64

[a] *p*-TsN-bridged enynes **1e** was used.

decrease of the amounts of catalyst could be possible without loss of enantioselectivity (entries 9, 10).

Under the best reaction conditions (Table 4, entry 4), we examined an enantioselective cycloisomerization of several enynes (Table 5). Enyne **1l**, possessing 4-chlorophenyl on the alkene, gave the same enantioselectivity as the phenyl group, however, enyne **1m** gave moderate ee (entries 1,2). In the case of the naphthyl group, *p*-TsN-bridged enyne **1e** gave better ee than *o*-TsN-bridged enyne **1n** (entries 3, 4).

3. Conclusion

In summary, we have developed a cationic iridium complex-catalyzed cycloisomerization of nitrogen-bridged 1,6-enynes for the synthesis of a 3-azabicyclo[4.1.0] heptenyl skeleton. Enantioselective transformation was also realized by a cationic iridium–chiral phosphine complex. The enynes are limited to nitrogen-bridged ones, and the enantioselectivity is not sufficiently high, however, the present results open a new protocol for an iridium complex-catalyzed cycloisomerization and an enantioselective transformation.

4. Experimental

4.1. General

Optical rotation was measured using Jasco DIP-370 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. NMR spectra were measured with JASCO DIP-1000 or Varian VXR-300S spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. Mass spectra were measured with JEOL JMS-SX102A and elemental analyses with Perkin Elmer PE2400II. Dehydrated xylene, 1,2-dimethoxyethane, and 1,4-dioxane are commercially available and they were dried over molecular sieves 4 Å and degassed by argon or carbon monoxide bubbling before use. All reactions were examined using an argon or CO balloon.

4.2. Typical experimental procedure for cycloisomerization of enynes (Table 3)

Under an atmosphere of argon, $IrCl(CO)(PPh_3)_2$ (15.6 mg, 0.02 mmol) and AgOTf (6.2 mg, 0.024 mmol) or $AgSbF_6$ (8.2 mg, 0.024 mmol) was placed in a flask under an argon atmosphere. 1,2-Dimethoxyethane (1.5 mL) was added, then the resulting mixture was stirred at 60 °C for 0.5–24 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give cycloadduct **2**.

4.2.1. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*p*-tosyl)but-2-yn-1-amine (1a). White solid. Mp 120 °C; IR ($CHCl_3$) 2932, 2304, 2222, 903, 756 cm^{-1}; ^1H NMR δ=1.51 (t, J=2.4 Hz, 3H), 2.43 (s, 3H), 3.92 (d, J=2.4 Hz, 2H), 4.22 (s, 2H), 5.32 (s, 1H), 5.55 (s, 1H), 7.28–7.36 (m, 5H), 7.49–7.53 (m, 2H), 7.74 (d, J=8.4 Hz, 2H). ^{13}C NMR δ=3.3, 7.0, 21.6, 36.1, 50.5, 71.3, 81.9, 116.8, 126.3, 128.0, 128.3, 129.1, 135.6, 137.7, 141.4, 143.1. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.70; H, 6.34; N, 4.16.

4.2.2. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*p*-tosyl)hept-2-yn-1-amine (1b). Pale yellow oil; IR (neat) 2932, 2322, 901, 756 cm^{-1}; ^1H NMR δ=0.82–0.86 (m, 3H), 1.18–1.25 (m, 4H), 1.85–1.89 (m, 2H), 2.43 (s, 3H), 3.96 (s, 2H), 4.23 (s, 2H), 5.32 (s, 1H), 5.55 (s, 1H), 7.24–7.37 (m, 5H), 7.51–7.54 (m, 2H), 7.74 (d, J=7.5 Hz, 2H). ^{13}C NMR δ=13.6, 18.2, 21.6, 21.9, 30.5, 36.2, 49.9, 72.0, 86.6, 116.8, 126.3, 127.9, 128.0, 128.3, 129.2, 135.7, 137.7, 141.4, 143.1; HRMS for M+1 found *m/e* 382.1839, calcd for $C_{23}H_{28}NO_2S$: 382.1841.

4.2.3. *N*-[2-(4-Chlorophenyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1c). White solid. Mp 108–109 °C; IR ($CHCl_3$) 2922, 2302, 2224, 901, 762 cm^{-1}; ^1H NMR δ=1.50 (t, J=2.4 Hz, 3H), 2.44 (s, 3H), 3.89 (q, J=2.4 Hz, 2H), 4.18 (s, 2H), 5.32 (s, 1H), 5.54 (s, 1H), 7.28–7.31 (m, 4H), 7.43–7.48 (m, 2H), 7.71–7.76 (m, 2H). ^{13}C NMR δ=3.3, 21.6, 36.1, 50.0, 71.0, 82.0, 117.4, 127.6, 127.9, 128.4, 129.1, 133.8, 135.4, 136.0, 140.3, 143.3. Anal. Calcd for $C_{20}H_{20}ClNO_2S$; C, 64.25; H, 5.39; N, 3.75. Found: C, 64.29; H, 5.35; N, 3.66.

4.2.4. *N*-[2-(4-Methoxyphenyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1d). White solid. Mp 91–92 °C; IR ($CHCl_3$) 2922, 903, 758 cm^{-1}; ^1H NMR δ=1.49 (t, J=2.3 Hz, 3H), 2.43 (s, 3H), 3.80 (s, 3H), 3.90 (q, J=2.3 Hz, 2H), 4.18 (s, 2H), 5.21 (s, 1H), 5.47 (s, 1H), 6.85–6.88 (m, 2H), 7.28–7.31 (m, 2H), 7.47–7.50 (m, 2H), 7.73–7.76 (m, 2H). ^{13}C NMR δ=3.3, 21.6, 36.0, 50.1, 55.3, 71.2, 81.8, 113.6, 115.2, 127.5, 128.0, 129.0, 130.0, 135.6, 140.5, 143.1, 159.3. Anal. Calcd for $C_{21}H_{23}NO_3S$; C, 68.27; H, 6.27; N, 3.79. Found: C, 67.92; H, 6.24; N, 3.60; HRMS for M+1 found *m/e* 370.1489, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.2.5. *N*-[2-(2-Naphthyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1e). White solid. Mp 124–125 °C; IR ($CHCl_3$) 3024, 903, 756 cm^{-1}; ^1H NMR δ=1.53 (t, J=2.4 Hz, 3H), 2.43 (s, 3H), 3.95 (q, J=2.4 Hz, 2H), 4.33 (s, 2H), 5.42 (s, 1H), 5.69 (s, 1H), 7.26–7.99 (m, 11H). ^{13}C NMR δ=3.4, 21.6, 36.2, 50.1, 71.4, 81.9, 99.9, 117.3, 124.3, 125.5, 126.1, 127.4, 127.8, 128.0, 128.4, 129.1, 132.9, 133.2, 134.9, 135.7, 141.3, 143.1; HRMS for M+1 found *m/e* 390.1530, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.2.6. *N*-(2-Methylprop-2-en-1-yl)-*N*-(*p*-tosyl)but-2-yn-1-amine (1f). White solid. Mp 40–41 °C; IR ($CHCl_3$) 2932, 2308, 1342, 1334, 1160, 917 cm^{-1}; ^1H NMR δ=1.50 (t, J=2.4 Hz, 3H), 1.76 (s, 3H), 2.42 (s, 3H), 3.69 (s, 2H), 3.97 (q, J=2.4 Hz, 2H), 4.94 (s, 1H), 4.95 (s, 1H), 7.28 (dd, J=0.6, 8.7 Hz, 2H), 7.72–7.75 (m, 2H). ^{13}C NMR δ=3.3, 19.8, 21.6, 36.1, 52.4, 71.5, 81.5, 115.0, 127.8, 129.0, 136.1, 139.4, 143.0. Anal. Calcd for $C_{15}H_{19}NO_2S$; C, 64.95; H, 6.90; N, 5.05. Found: C, 65.18; H, 7.09; N, 5.07.

4.2.7. But-2-yn-1-yl 2-phenylprop-2-en-1-yl ether (1g). Colorless oil; IR (neat) 3022, 2402, 1216, 756 cm^{-1}; ^1H NMR δ=1.87 (t, J=2.4 Hz, 3H), 4.15 (q, J=2.4 Hz, 2H), 4.45 (s, 2H), 5.36 (s, 1H), 5.55 (s, 1H), 7.24–7.49 (m, 5H). ^{13}C NMR δ=3.8, 57.6, 71.2, 75.0, 82.6, 114.9, 125.9, 127.7,

128.2, 138.5, 143.5; HRMS for M+1 found *m/e* 187.1121, calcd for $C_{13}H_{15}O$: 187.1123.

4.2.8. 6-Methyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2a). White solid. Mp 120–121 °C; IR ($CHCl_3$) 3026, 1647, 1166, 762 cm^{-1}; ^1H NMR δ=0.85 (s, 3H), 0.96 (dd, J=1.2, 4.7 Hz, 1H), 1.20 (d, J=4.7 Hz, 1H), 2.43 (s, 3H), 2.97 (d, J=11.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 5.35 (d, J=8.1 Hz, 1H), 6.36 (dd, J=1.2, 8.1 Hz, 1H), 7.18–7.31 (m, 7H), 7.63 (d, J=8.1 Hz, 2H). ^{13}C NMR δ=19.2, 21.2, 22.0, 24.5, 40.0, 48.4, 118.2, 121.1, 127.3, 127.4, 128.7, 130.0, 135.1, 139.1, 143.9. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.57; H, 6.41; N, 4.01.

4.2.9. 6-Butyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2b). Pale yellow oil; IR (neat) 2932, 1216, 977, 756 cm^{-1}; ^1H NMR δ=0.60–0.67 (m, 1H), 0.75 (t, J=7.2 Hz, 3H), 0.99–1.37 (m, 7H), 2.43 (s, 3H), 3.02 (d, J=11.3 Hz, 1H), 3.92 (d, J=11.3 Hz, 1H), 5.45 (d, J=8.1 Hz, 1H), 6.39 (d, J=8.1 Hz, 1H), 7.19–7.26 (m, 5H), 7.30 (d, J=8.7 Hz, 2H), 7.63 (d, J=8.4 Hz, 2H). ^{13}C NMR δ=14.1, 21.7, 22.6, 22.8, 23.7, 29.1, 33.7, 40.4, 48.3, 116.0, 121.1, 127.0, 127.1, 128.3, 129.6, 129.7, 134.9, 138.8, 143.6; HRMS for M found *m/e* 381.1753, calcd for $C_{23}H_{27}NO_2S$: 381.1762.

4.2.10. 1-(4-Chlorophenyl)-6-methyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2c). White solid. Mp 42–43 °C; IR ($CHCl_3$) 3030, 2930, 1644, 1164, 752 cm^{-1}; ^1H NMR δ=0.77 (s, 3H), 0.86 (dd, J=1.1, 4.5 Hz, 1H), 1.14 (d, J=4.5 Hz, 1H), 2.36 (s, 3H), 2.85 (d, J=11.3 Hz, 1H), 3.85 (d, J=11.3 Hz, 1H), 5.26 (d, J=7.8 Hz, 1H), 6.29 (dd, J=1.1, 7.8 Hz, 1H), 7.05–7.25 (m, 6H), 7.55 (d, J=8.4 Hz, 2H). ^{13}C NMR δ=19.0, 20.9, 21.7, 24.2, 39.0, 48.0, 117.6, 121.0, 126.9, 128.6, 129.7, 131.0, 132.9, 134.7, 137.4, 143.7; HRMS for M found *m/e* 373.0928, calcd for $C_{20}H_{20}ClNO_2S$: 373.0903.

4.2.11. 1-(4-Methoxyphenyl)-6-methyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2d). White solid. Mp 39–40 °C; IR ($CHCl_3$) 3030, 2956, 1164, 756 cm^{-1}; ^1H NMR δ=0.85 (s, 3H), 0.91 (d, J=4.5 Hz, 1H), 1.18 (d, J=4.5 Hz, 1H), 2.42 (s, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.78 (s, 3H), 3.93 (d, J=11.7 Hz, 1H), 5.33 (d, J=8.1 Hz, 1H), 6.34 (d, J=8.1 Hz, 1H), 6.80–6.83 (m, 2H), 7.10–7.13 (m, 2H), 7.30 (d, J=7.8 Hz, 2H), 7.63 (d, J=8.1 Hz, 2H). ^{13}C NMR δ=18.9, 20.9, 21.6, 24.3, 39.0, 48.1, 55.3, 113.8, 118.0, 120.6, 126.9, 129.7, 130.7, 130.9, 134.8, 143.5, 158.5; HRMS for M+1 found *m/e* 370.1465, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.2.12. 6-Methyl-1-(2-naphthyl)-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2e). Colorless oil; IR (neat) 3022, 1216, 756 cm^{-1}; ^1H NMR δ=0.89 (s, 3H), 1.11 (dd, J=1.1, 4.7 Hz, 1H), 1.30 (d, J=4.7 Hz, 1H), 2.43 (s, 3H), 3.08 (d, J=11.4 Hz, 1H), 4.00 (d, J=11.4 Hz, 1H), 5.39 (d, J=8.1 Hz, 1H), 6.41 (dd, J=1.1, 8.1 Hz, 1H), 7.29–7.78 (m, 11H). ^{13}C NMR δ=19.1, 20.9, 21.7, 24.4, 39.8, 48.0, 117.8, 120.8, 125.8, 126.1, 127.0, 127.5, 127.6, 128.0, 128.5, 129.7, 132.4, 133.3, 134.7, 136.4, 143.6; HRMS for M+1 found *m/e* 390.1533, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.2.13. 1,6-Dimethyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2f). Spectral data were accorded with those in literature.[10b]

4.2.14. 6-Methyl-1-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (2g). Colorless oil; IR (neat) 3012, 1647, 936, 756 cm^{-1}; ^1H NMR δ=0.90 (s, 3H), 1.10 (d, J=4.5 Hz, 1H), 1.48 (d, J=4.5 Hz, 1H), 3.79 (d, J=10.2 Hz, 1H), 4.07 (d, J=10.2 Hz, 1H), 5.21 (d, J=5.7 Hz, 1H), 6.20 (d, J=5.7 Hz, 1H), 7.22–7.32 (m, 5H). ^{13}C NMR δ=18.0, 20.8, 24.0, 38.2, 68.6, 112.5, 126.8, 128.3, 129.8, 138.5, 141.0; HRMS for M+1 found *m/e* 187.1159, calcd for $C_{13}H_{15}O$: 187.1123.

4.3. Typical experimental procedure for enantioselective cycloisomerization of enynes (Table 5)

Under an atmosphere of carbon monoxide, TolBINAP (13.6 mg, 0.02 mmol) and $[Ir(cod)Cl]_2$ (6.7 mg, 0.01mmol) were stirred in 1,4-dioxane (0.5 mL) at room temperature. After the addition of a 1,4-dioxane solution (1.0 mL) of enyne **1** (0.10 mmol) and AgOTf (6.2 mg, 0.024 mmol), the reaction mixture was stirred under reflux for 2–7 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give chiral cycloadduct **2**. Enantiomeric excess was determined by HPLC analysis using a chiral column.

4.3.1. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*o*-tosyl)but-2-yn-1-amine (1j). White solid. Mp 101–102 °C; IR ($CHCl_3$) 3202, 756 cm^{-1}; ^1H NMR δ=1.72 (t, J=2.4 Hz, 3H), 2.37 (s, 3H), 3.94 (q, J=2.4 Hz, 2H), 4.28 (s, 2H), 5.36 (d, J=0.9 Hz, 1H), 5.47 (d, J=0.9 Hz, 1H), 7.14–7.25 (m, 6H), 7.29–7.34 (m, 1H), 7.45 (dt, J_d=1.2 Hz, J_t=7.5 Hz, 1H), 7.98 (dd, J=1.4, 8.0 Hz, 1H). ^{13}C NMR δ=3.6, 20.4, 35.4, 50.0, 72.2, 81.5, 117.3, 125.8, 126.1, 127.8, 128.2, 130.1, 132.5, 132.6, 137.0, 138.0, 138.4, 142.0. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.74; H, 6.25; N, 4.07.

4.3.2. *N*-Mesityl-*N*-(2-phenylprop-2-en-1-yl)but-2-yn-1-amine (1k). White solid. Mp 118–119 °C; IR ($CHCl_3$) 2922, 2302, 2222, 754, 665 cm^{-1}; ^1H NMR δ=1.82 (t, J=2.4 Hz, 3H), 2.32 (s, 3H), 2.42 (s, 6H), 3.89 (q, J=2.4 Hz, 2H), 4.19 (s, 2H), 5.38 (s, 1H), 5.43 (s, 1H), 6.88–6.96 (m, 4H), 7.06–7.13 (m, 2H), 7.17–7.23 (m, 1H). ^{13}C NMR δ=3.7, 21.1, 22.8, 34.7, 49.7, 72.8, 81.1, 117.8, 126.0, 127.6, 128.0, 131.8, 132.1, 138.1, 140.6, 142.2, 142.4. Anal. Calcd for $C_{22}H_{25}NO_2S$; C, 71.90; H, 6.86; N, 3.81. Found: C, 71.94; H, 6.80; N, 3.74.

4.3.3. *N*-[2-(4-Chlorophenyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1l). White solid. Mp 67–69 °C; IR ($CHCl_3$) 2924, 2304, 2226, 1328, 903, 748 cm^{-1}; ^1H NMR δ=1.69 (t, J=2.4 Hz, 3H), 2.41 (s, 3H), 3.92 (q, J=2.4 Hz, 2H), 4.25 (s, 2H), 5.37 (s, 1H), 5.46 (s, 1H), 7.10–7.24 (m, 5H), 7.31 (m, 1H), 7.45 (dt, J_d=1.5 Hz, J_t=7.5 Hz, 1H), 7.96 (dd, J=1.5, 8.0 Hz, 1H). ^{13}C NMR δ=3.9, 20.9, 35.8, 50.3, 72.2, 82.0, 118.3, 126.2, 127.8, 128.6, 130.4, 132.8, 133.0, 134.0, 136.7, 137.2, 138.5, 141.2. Anal. Calcd for $C_{20}H_{20}ClNO_2S$; C, 64.25; H, 5.39; N, 3.75. Found: C, 64.12; H, 5.55; N, 3.76.

4.3.4. *N*-[2-(4-Methoxyphenyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1m). Colorless oil; IR (neat) 2922, 2260, 2226, 1325, 909, 758 cm^{-1}; ^1H NMR δ= 1.69 (t, J=2.4 Hz, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 3.93 (q, J=2.4 Hz, 2H), 4.25 (s, 2H), 5.26 (d, J=0.9 Hz, 1H), 5.40 (d, J=0.9 Hz, 1H), 6.71–7.17 (m, 4H), 7.22–7.34 (m, 2H), 7.44 (dt, J_d=1.5 Hz, J_t=7.5 Hz, 1H), 7.97 (dd, J=1.5, 8.0 Hz, 1H). ^{13}C NMR δ=3.5, 20.6, 35.3, 50.1, 55.3, 72.1, 80.5, 81.4, 113.5, 115.8, 125.8, 127.3, 130.1, 130.3, 132.4, 132.6, 138.3, 141.1, 159.2; HRMS for M+1 found *m/e* 370.1482, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.3.5. *N*-[2-(2-Naphthyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1n). Colorless oil; IR (neat) 2922, 2300, 2226, 1328, 897, 756 cm^{-1}; ^1H NMR δ=1.72 (t, J= 2.4 Hz, 3H), 2.32 (s, 3H), 3.97 (q, J=2.4 Hz, 2H), 4.39 (s, 2H), 5.46 (s, 1H), 5.61 (s, 1H), 7.09–7.79 (m, 10H), 8.00 (dd, J=1.5, 8.1 Hz, 1H). ^{13}C NMR δ=3.6, 20.4, 35.4, 50.1, 72.2, 81.5, 117.9, 124.2, 125.1, 125.8, 126.0, 127.3, 127.8, 128.2, 130.1, 132.5, 132.6, 132.8, 132.9, 135.3, 136.9, 138.2, 141.8; HRMS for M+1 found *m/e* 390.1539, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.3.6. 6-Methyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2a). $[\alpha]_D^{24}$ −72.54 (*c* 0.85, $CHCl_3$, 52% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 19 min for major isomer and 22 min for minor isomer).

4.3.7. 6-Methyl-1-phenyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2j). White solid. Mp 156–157 °C; IR ($CHCl_3$) 3028, 1649, 1162, 762 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 1.02 (d, J=4.5 Hz, 1H), 1.19 (d, J=4.5 Hz, 1H), 2.60 (s, 3H), 3.18 (d, J=12.2 Hz, 1H), 3.80 (d, J=12.2 Hz, 1H), 5.39 (d, J=7.8 Hz, 1H), 6.46 (d, J=7.8 Hz, 1H), 7.19–7.47 (m, 8H), 7.87 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.1, 20.9, 21.0, 24.5, 40.0, 47.8, 117.4, 120.7, 126.2, 127.1, 128.4, 129.6, 129.9, 132.7, 132.9, 136.5, 137.4, 138.7; HRMS for M+1 found *m/e* 340.1347, calcd for $C_{20}H_{22}NO_2S$: 340.1371. $[\alpha]_D^{19}$ −206.16 (*c* 1.42, $CHCl_3$, 75% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 7 min for major isomer and 9 min for minor isomer).

4.3.8. 3-Mesityl-6-methyl-1-phenyl-3-azabicyclo[4.1.0]hept-4-ene (2k). Pale yellow oil; IR (neat) 2928, 1160, 758 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 1.05 (d, J=4.6 Hz, 1H), 1.27 (d, J=4.6 Hz, 1H), 2.30 (s, 3H), 2.57 (s, 6H), 3.19 (d, J=11.7 Hz, 1H), 3.62 (d, J=11.7 Hz, 1H), 5.36 (d, J= 7.8 Hz, 1H), 6.44 (d, J=7.8 Hz, 1H), 6.94 (s, 2H), 7.21–7.32 (m, 5H). ^{13}C NMR δ=19.3, 21.0, 23.1, 24.6, 39.8, 47.3, 116.5, 120.5, 127.0, 128.1, 128.4, 129.6, 131.9, 132.0, 138.9, 139.9, 142.6; HRMS for M+1 found *m/e* 368.1661, calcd for $C_{22}H_{26}NO_2S$: 368.1684. $[\alpha]_D^{27}$ −64.73 (*c* 0.23, $CHCl_3$, 57% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 5 min for major isomer and 6 min for minor isomer).

4.3.9. 1-(4-Chlorophenyl)-6-methyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2l). Colorless oil; IR (neat) 3030, 2930, 1352, 1166, 750 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 0.98 (d, J=4.8 Hz, 1H), 1.20 (d, J=4.8 Hz, 1H), 2.60 (s, 3H), 3.13 (d, J=11.7 Hz, 1H), 3.78 (d, J=11.7 Hz, 1H), 5.37 (d, J=7.8 Hz, 1H), 6.46 (d, J=7.8 Hz, 1H), 7.13–7.49 (m, 7H), 7.88 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.0, 20.7, 20.8, 24.5, 39.2, 47.6, 117.1, 120.9, 126.3, 128.7, 129.9, 131.1, 131.3, 132.8, 133.1, 136.5, 137.3, 137.5; HRMS for M found *m/e* 373.0913, calcd for $C_{20}H_{20}ClNO_2S$: 373.0903. $[\alpha]_D^{20}$ −103.89 (*c* 0.36, $CHCl_3$, 74% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8 min for major isomer and 14 min for minor isomer).

4.3.10. 1-(4-Methoxyphenyl)-6-methyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2m). White solid. Mp 41–42 °C; IR (neat) 2924, 1518, 1164, 756 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 0.96 (dd, J=1.1, 4.5 Hz, 1H), 1.16 (d, J=4.5 Hz, 1H), 2.60 (s, 3H), 3.12 (d, J=11.7 Hz, 1H), 3.77 (d, J=11.7 Hz, 1H), 3.77 (s, 3H), 5.37 (d, J=8.1 Hz, 1H), 6.43 (dd, J=1.1, 8.1 Hz, 1H), 6.80–7.47 (m, 7H), 7.87 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.1, 20.8, 20.9, 24.6, 39.4, 47.8, 55.3, 113.8, 117.5, 120.5, 126.2, 129.9, 130.7, 130.8, 132.7, 132.8, 136.5, 137.4, 158.5; HRMS for M found *m/e* 369.1406, calcd for $C_{21}H_{23}NO_3S$: 369.1399. $[\alpha]_D^{19}$ −85.59 (*c* 0.21, $CHCl_3$, 44% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AD: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 9 min for major isomer and 8 min for minor isomer).

4.3.11. 6-Methyl-1-(2-naphthyl)-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2n). White solid. Mp 45–46 °C; IR ($CHCl_3$) 3024, 2930, 1642, 1342, 1164, 754 cm^{-1}; ^1H NMR δ=0.91 (s, 3H), 1.16 (dd, J=1.2, 4.8 Hz, 1H), 1.28 (d, J=4.8 Hz, 1H), 2.62 (s, 3H), 3.28 (d, J=12.0 Hz, 1H), 3.84 (d, J=12.0 Hz, 1H), 5.42 (d, J=7.8 Hz, 1H) 6.50 (dd, J=1.2, 8.1 Hz, 1H), 7.26–7.80 (m, 10H), 7.88 (d, J= 7.8 Hz, 1H). ^{13}C NMR δ=19.3, 20.9, 20.9, 24.7, 40.0, 47.7, 50.7, 117.2, 120.7, 125.8, 126.1, 126.2, 127.5, 127.6, 128.0, 128.5, 129.9, 132.4, 132.7, 132.9, 133.3, 136.3, 137.4; HRMS for M found *m/e* 389.1462, calcd for $C_{24}H_{23}NO_2S$: 389.1449. $[\alpha]_D^{20}$ −147.54 (*c* 1.04, $CHCl_3$, 35% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 11 min for major isomer and 14 min for minor isomer).

4.3.12. 6-Methyl-1-(2-naphthyl)-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2e). $[\alpha]_D^{26}$ −94.65 (*c* 0.53, $CHCl_3$, 64% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AD-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 23 min for major isomer and 15 min for minor isomer).

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16. Almost no asymmetric induction was observed by MeDUPHOS and CHIRAPHOS (<2% ee).

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Iridium-catalyzed enantioselective Pauson–Khand-type reaction of 1,6-enynes

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Abstract—Iridium–chiral diphosphine complex catalyzes an enantioselective intramolecular Pauson–Khand-type reaction to give various chiral bicyclic cyclopentenones. The enantioselective reaction proceeds more smoothly and enantioselectively under a lower partial pressure of carbon monoxide. Moreover, aldehyde can be used as a CO source in the enantioselective carbonylative coupling.
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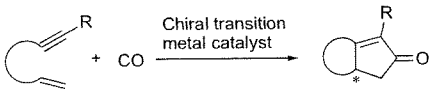
1. Introduction

The Pauson–Khand reaction is a carbonylative coupling of alkyne and alkene, which was originally reported using a stoichiometric amount of a cobalt carbonyl complex in 1973.[1] The reaction gives synthetically useful cyclopentenones; in fact, it has been used as a key reaction in natural product syntheses.[2] In the 1990s, efforts were extended toward developing a catalytic reaction, and Jeong reported a practical intramolecular reaction of enynes using a cobalt–phosphite complex;[3] many publications on catalytic reaction conditions followed.[4] Further progress was made by reactions using other transition metal complexes as catalysts, known as a Pauson–Khand-type reaction.[5] Since Buchwald reported Ti-catalyzed intramolecular reaction of enynes,[6] Ru[7] and Rh complexes[8] were found to be efficient catalysts. The first catalytic and enantioselective Pauson–Khand-type reaction was also realized by Buchwald using a chiral titanium complex, where various enynes were transformed into the corresponding chiral bicyclic cyclopentenones in high ee.[9] Further achievements include enantioselective reactions using a cobalt complex by Hiroi,[10] a rhodium one by Jeong[11] and an iridium one by us[12] in 2000 (Eq. 1), and the development of an enantioselective Pauson–Khand-type reaction is still an intriguing topic these days.[13]



(1)

This manuscript discloses further investigation of an iridium-catalyzed enantioselective Pauson–Khand-type reaction. Various types of enynes were submitted to the reaction under an atmospheric pressure or a lower partial pressure of carbon monoxide.[14] Moreover, an iridium-catalyzed Pauson–Khand-type reaction using an aldehyde as a CO source is also presented.

2. Results and discussion

2.1. Iridium complex-catalyzed enantioselective coupling with carbon monoxide

In order to investigate the catalytic activity of an iridium complex, we first examined an intramolecular Pauson–Khand-type reaction of enyne **1a** (Eq. 2). The iridium complex, possessing triphenylphosphine as an achiral ligand, operated as a more efficient catalyst than that without phosphine ligands. The results were opposite to those of a rhodium complex-catalyzed reaction, where the addition of triphenylphosphine deactivated the catalytic activity,[8c] and they prompted us to examine chiral ligands for iridium-catalyzed enantioselective intramolecular Pauson–Khand-type reaction.

Keywords: Iridium; Enynes; Carbonylation; Pauson–Khand reaction; Enantioselective.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
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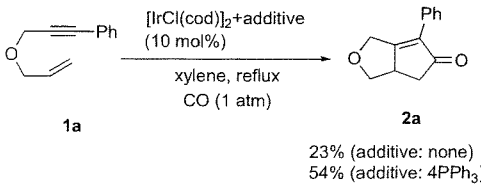


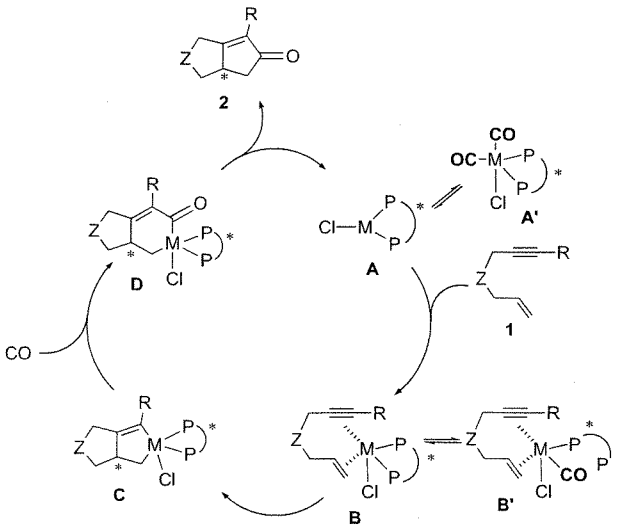
(2)

Next we investigated chiral diphosphines as chiral ligands (Table 1); with the increase of yield, enantioselectivity was improved and tolBINAP was found to be best among them. A good yield of 83% and high ee of 93% were achieved[15] (entries 1–5). Decreasing the amounts of catalyst to 5 mol% gave slightly poorer yield and enantioselectivity; however, drastic decrease of ee was observed, and a considerable amount of enyne **1** was recovered by 2 mol% catalyst (entries 6, 7). In order to increase the catalytic efficiency, the concentration of the chiral catalyst was found to be important: the higher yield and the same ee were achieved using 2 mol% catalyst when the reaction was examined for longer reaction time under the same concentration as that of entry 5 (entries 8, 9).

Various 1,6-enynes were submitted to the reaction using the chiral iridium catalyst,[16] which was prepared in situ from $[IrCl(cod)]_2$ and tolBINAP (Table 2). Electron-donating and -withdrawing substituents on the phenyl ring produced almost no effect, and the corresponding bicyclic enones **2b,c** were obtained in good yield with high ee (entries 1, 2). In place of aryl groups on the alkyne terminus of enyne, an isopropenyl group could be possible, yet with moderate yield (entry 3). Enynes, having alkyl groups on their alkyne termini, were also good substrates, and methyl-substituted enyne **1e** gave enone **2e** in the highest ee of 98% (entries 4–6). Not only oxygen-bridged enynes but also nitrogen-bridged enyne **1g** was enantiomerically transformed into bicyclic compound **2g** (entry 7); however, carbon-bridged enyne **1h** gave carbonylative product **2h** in moderate yield even over longer reaction time, and a considerable amount of enyne **1h** was recovered (entry 8). Decreasing a partial pressure of carbon monoxide accelerated the carbonylative coupling also in an iridium-catalyzed system,[8c] and higher yield was achieved under a 0.2 partial pressure of carbon monoxide without any lowering of ee.[17] Longer reaction time realized further better yield of ca. 90% (entries 9, 10).

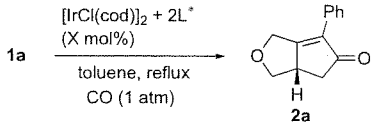
Also in the case of enyne **1i**, possessing a functionalized substituent on its alkyne terminus, decrease of a partial pressure of carbon monoxide worked well; moreover, ee was also significantly improved (entries 11, 12). Enyne, having 1,1-disubstituted olefin as an alkene moiety, is known to be rather inactive, and considerable amounts of enynes **1j,k** were recovered, respectively, under an atmospheric pressure of carbon monoxide (entries 13, 15). Due to the decrease of the partial pressure of CO, bicyclic cyclopentenones **2j,k**, having a chiral quaternary carbon, were obtained in acceptable yield and ee (entries 14, 16).

Scheme 1 depicts a possible mechanism: π-complexation of enyne **1** to chiral catalyst **A** induces an oxidative coupling to give metallacyclopentene **C**, where a chiral carbon is generated. Carbonyl insertion to **C** gives acyl complex **D**,[18] and the following reductive elimination provides enone **2** with regeneration of the active iridium species. In the reaction mixture, the mole amount of CO is much larger than that of the catalyst, which means that complex **A′** and **B′** could also exist by CO coordination. Complex **A′** is less reactive than **A**, and an oxidative coupling of **B′** lowers enantioselectivity. When the coupling is done under a lower



Scheme 1. A possible explanation for the effect of a partial pressure of CO.

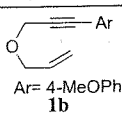
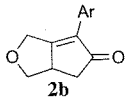
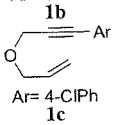
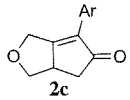
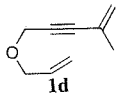
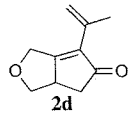
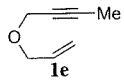
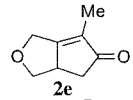
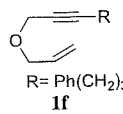
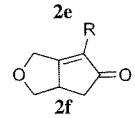
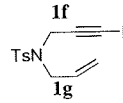
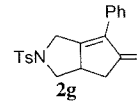
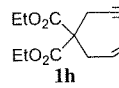
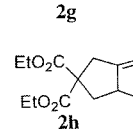
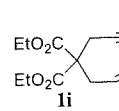
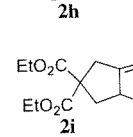
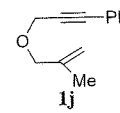
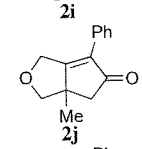
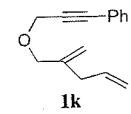
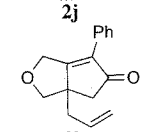
Table 1. Investigation of chiral ligands and amounts of catalyst in iridium-catalyzed enantioselective Pauson–Khand-type reaction



Entry	X	Chiral ligand[a]	[M]/mM[b]	Time/h	Yield/%	ee/%
1	10	CHIRAPHOS	15	12	13	<1
2	10	BDPP	15	12	23	22
3	10	DIOP	15	12	53	17
4	10	BINAP	15	12	64	86
5	10	tolBINAP	15	12	83	93
6	5	tolBINAP	7.5	24	75	91
7	2	tolBINAP	3	48	33	74
8	2	tolBINAP	15	48	59	93
9	2	tolBINAP	15	72	88	92

[a] (*S,S*)-isomers were used for entries 1–3. (*S*)-isomers were used for entries 4–10.
[b] Concentration of catalyst.

Table 2. Enantioselective Pauson–Khand-type reaction of various enynes under a CO atmosphere

Entry[a]	Enyne	Cyclopentenone	CO/atm	Time/h	Yield/%	ee/%
1	 Ar= 4-MeOPh **1b**	 **2b**	1.0	20	80	96
2	 Ar= 4-ClPh **1c**	 **2c**	1.0	20	78	95
3	 **1d**	 **2d**	1.0	20	54	97
4	 **1e**	 **2e**	1.0	20	60	98
5			1.0	48	75	97
6	 R= $Ph(CH_2)_3$ **1f**	 **2f**	1.0	20	54	90
7	 **1g**	 **2g**	1.0	12	85	95
8	 **1h**	 **2h**	1.0	36	51	88
9			0.2^b	36	71	85
10			0.2^b	72	89	86
11	 **1i**	 **2i**	1.0	72	15	84
12			0.2^b	72	50	88
13	 **1j**	 **2j**	1.0	24	30	88
14			0.2^b	72	86	93
15	 **1k**	 **2k**	1.0	96	22	86
16			0.2^b	96	62	94

[a] $[IrCl(cod)]_2$ + 2(*S*)-tolBINAP (10 mol%), toluene, reflux.
[b] CO (0.2 atm) + Ar (0.8 atm).

partial pressure of CO, the content of **A** and **B** increases as compared with that of **A′** and **B′**, which probably brings about the acceleration of the coupling and the increase of ee.[19]

Table 2 shows wide generality of the present iridium-catalyzed enantioselective Pauson–Khand-type reaction; however, there is a limitation of enynes (Fig. 1): under the same reaction conditions as Table 2, enynes, containing 1,2-disubstituted olefin as an alkene moiety, a 1,7-enyne, and enynes with no substituent on the alkyne terminus met with failure, and only a trace amount of or no carbonylated product was detected.

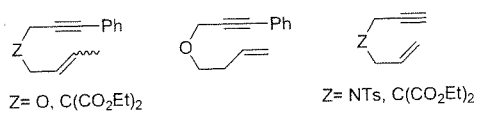
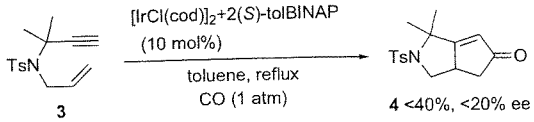


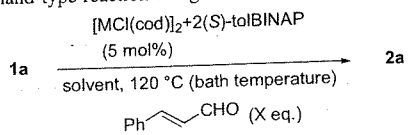
Figure 1. Enynes, which did not give carbonylated products.

We further examined enyne **3**, having no substituent on the alkyne terminus and having two methyls at the propargylic position, which deter isomerization of alkyne moiety to vinylidene complex.[20] Enone **4** was obtained yet only with low ee (Eq. 3). This result implies that the substituent on the alkyne terminus plays a pivotal role for high enantioselectivity.



(3)

Table 3. Examination of enantioselective Pauson–Khand-type reaction using cinnamaldehyde as a CO source



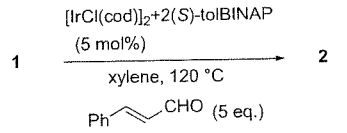
Entry	M	Solvent	*X*/equiv	Time/h	Yield/%	ee/%
1	Rh	None	20	5	89	82
2	Rh	Xylene	20	36	54	8
3	Ir	None	20	6	27	88
4	Ir	Xylene	20	12	52	86
5	Ir	Xylene	5	9	66	92
6	Ir	Toluene	5	24	25	95

2.2. Iridium complex-catalyzed enantioselective coupling using an aldehyde as a CO source

Recently, Morimoto and Kakiuchi[21] and we[22] independently reported a Rh-catalyzed Pauson–Khand-type reaction using aldehydes as a CO source in place of CO gas. Enantioselective reaction was also realized, where solvent-free condition is essential for high yield and ee (Table 3, entry 1).[22b] When the coupling was examined in xylene, it took much longer reaction time to consume enyne **1a** and enantioselectivity was extremely low (entry 2). We next examined an iridium-catalyzed coupling using an aldehyde as a CO source[23] and found that ee was high both with and without solvent; however, solvent was needed for high yield (entries 3, 4). Higher yield and ee were achieved by decreasing the amounts of cinnamaldehyde (entry 5). These results imply that the chiral rhodium complex would be stable and less reactive, and it works as a catalyst in harsh reaction conditions; on the contrary, the chiral iridium complex would be unstable, and solvent is needed for operating as an efficient catalyst.

Under the best reaction conditions (Table 3, entry 5), we examined an enantioselective coupling of several enynes (Table 4). In each entry, yield was moderate; however, ee was very high and exceeded that of rhodium-catalyzed coupling.[22b]

Table 4. Enantioselective Pauson–Khand-type reaction of various enynes using cinnamaldehyde as a CO source



Entry	Enyne	Time/h	Yield/%	ee/%
1	**1b**	5	57	91
2	**1c**	9	56	91
3	**1e**	24	30	85
4	**1g**	5	55	94
5	**1h**	24	51	87
6	**1j**	24	40	90

3. Conclusion

In summary, we have developed a catalytic and enantioselective Pauson–Khand-type reaction using a chiral iridium complex, which is readily prepared in situ from a commercially available and stable iridium complex and chiral diphosphine. Various enynes could be transformed into chiral bicyclic cyclopentenones in high ee. Especially, a low partial pressure of carbon monoxide facilitated the carbonylative coupling and improved the enantioselectivity. Furthermore, an enantioselective Pauson–Khand-type reaction using cinnamaldehyde as a CO source could be also achieved by chiral iridium complex and higher enantioselectivity was realized than that by the rhodium complex.

4. Experimental

4.1. General

Optical rotation was measured using Jasco DIP-370 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. NMR spectra were measured with JEOL AL-400 or Varian VXR-300S spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. Mass spectra were measured with JEOL JMS-SX102A and elemental analyses with Perkin Elmer PE2400II. Dehydrated toluene is commercially available and it was dried over molecular sieves 4 Å and degassed by carbon monoxide bubbling before use. All reactions were examined using a CO balloon or a balloon of CO and Ar (2:8). Spectral data of **2a–2c**, **2e–2h**, and **2j** were already published by others[4b,h,8b,c,9b,11,24,25] and us.[12,22]

4.2. Typical experimental procedure for enantioselective coupling with carbon monoxide (Table 2)

Preparation of a balloon with mixed gas of carbon monoxide and argon (2:8): CO (2 atm) was introduced into an autoclave (30 mL) then Ar (8 atm) was introduced into the autoclave; then the pressurized mixed gas (10 atm) was released into a balloon at an atmospheric pressure.

Under an atmosphere of carbon monoxide, tolBINAP (34.0 mg, 0.050 mmol) and $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol) were stirred in toluene (2.0 mL) at room temperature. After the addition of a toluene solution (2.0 mL) of enyne **1** (0.25 mmol), the reaction mixture was stirred under reflux for an appropriate time (cited in the table). The solvent was removed under reduced pressure, and the crude products were purified by thin-layer

chromatography to give chiral cycloadduct **2**. Enantiomeric excess was determined by HPLC analysis using a chiral column.

4.2.1. 2-Isopropenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (2d). Pale yellow oil. IR (neat) 2852, 1712, 1651, 1456, 1028, 903 cm^{-1}; ^1H NMR δ=1.80 (s, 3H), 2.22 (dd, J=3.0, 17.4 Hz, 1H), 2.72 (dd, J=3.0, 17.4 Hz, 1H), 3.21–3.25 (m, 2H), 4.33 (dd, J=5.8, 5.8 Hz, 1H), 4.63 (d, J=16.6 Hz, 1H), 4.77 (d, J=16.6 Hz, 1H), 5.21 (s, 1H), 5.61 (s, 1H); ^{13}C NMR δ=22.2, 40.2, 43.3, 66.4, 71.4, 118.0, 134.6, 135.1, 176.5, 206.6; HRMS (EI^+) for M found *m/e* 164.0824, calcd for $C_{10}H_{12}O_2$: 164.0837. $[\alpha]_D^{31}$ −178.3 (*c* 1.17, $CHCl_3$, 97% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 15 min for major isomer and 16 min for minor isomer).

4.2.2. Diethyl 2-(benzyloxy)methyl-3-oxobicyclo[3.3.0]oct-1-en-7,7-dicarboxylate (2i). Pale yellow oil. IR (neat) 2982, 1730, 1672, 1267 cm^{-1}; ^1H NMR δ=1.21–1.30 (m, 6H), 1.69 (dd, J=12.7, 12.7 Hz, 1H), 2.11 (dd, J=3.3, 17.9 Hz, 1H), 2.64 (dd, J=6.2, 17.9 Hz, 1H), 2.78 (dd, J=7.7, 12.7 Hz, 1H), 2.98–3.06 (m, 1H), 3.34 (d, J=20.6 Hz, 1H), 3.42 (d, J=20.6 Hz, 1H), 4.19–4.24 (m, 6H), 4.53 (s, 2H), 7.25–7.34 (m, 5H); ^{13}C NMR δ=14.1, 34.7, 38.8, 41.6, 43.5, 61.1, 61.9, 62.0, 63.1, 73.1, 127.5, 128.2 133.6, 137.8, 170.6, 171.3, 181.2, 207.4; HRMS (FAB) for M+1 found *m/e* 387.1811, calcd for $C_{22}H_{27}O_6$: 387.1808. $[\alpha]_D^{31}$ −48.2 (*c* 1.11, $CHCl_3$, 88% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AS-H: 4×250 mm, 254 nm UV detector, room temperature, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for minor isomer and 17 min for major isomer).

4.2.3. 2-Phenyl-5-(2-propenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one (2k). IR (neat) 1711, 1021, 919, 764 cm^{-1}; ^1H NMR δ=2.25 (dd, J=6.6, 13.5 Hz, 1H), 2.39 (d, J=17.4 Hz, 1H), 2.48 (dd, J=8.1, 13.5 Hz, 1H), 2.69 (d, J=17.4 Hz, 1H), 3.40 (d, J=8.1 Hz, 1H), 4.14 (d, J=8.1 Hz, 1H), 4.58 (d, J=16.4 Hz, 1H), 4.93 (d, J=16.4 Hz, 1H), 5.12 (d, J=0.9 Hz, 1H), 5.16 (d, J=4.5 Hz, 1H), 5.59–5.77 (m, 1H), 7.32–7.51 (m, 5H); HRMS (EI^+) for M found *m/e* 240.1160, calcd for $C_{16}H_{16}O_2$: 240.1150. $[\alpha]_D^{23}$ +5.28 (c 0.56, $CHCl_3$, 94% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 nm, 254 nm UV detecter, room temperature, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8 min for minor isomer and 10 min for major isomer).

4.3. Typical experimental procedure for enantioselective coupling using cinnamaldehyde as a CO source (Table 4)

Under an atmosphere of argon, tolBINAP (20.4 mg, 0.030 mmol) and $[Ir(cod)Cl]_2$ (10.1 mg, 0.015 mmol) were stirred in xylene (1.5 mL) at room temperature. After the addition of a xylene solution (0.5 mL) of enyne **1** (0.30 mmol) and cinnamaldehyde (198.0 mg, 1.5 mmol), the reaction mixture was stirred at 120 °C for an appropriate time (cited in the table). After the exclusion of excess cinnamaldehyde and xylene, the crude products were purified by thin-layer chromatography, and pure bicyclic enone **2** was obtained. Enantiomeric excess was determined by HPLC analysis using a chiral column.

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Enantioselective Construction of Quaternary Carbon Centers by Catalytic [2 + 2 + 2] Cycloaddition of 1,6-Enynes and Alkynes

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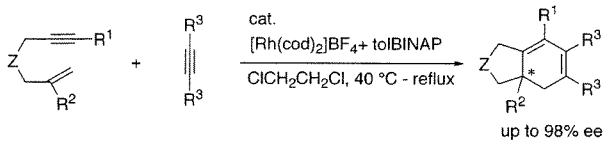
ABSTRACT



up to 98% ee

The enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes using chiral rhodium catalysts gave cycloadducts containing quaternary carbon stereocenters. Both symmetrical and unsymmetrical alkynes and acetylene could be used as coupling partners, and the corresponding bicyclic cyclohexa-1,3-dienes were obtained in good to excellent ee.

The catalytic and enantioselective construction of various stereocenters is of great importance in organic synthesis.[1] The synthesis of compounds that contain asymmetric quaternary carbon centers is particularly valuable because they are found in many naturally occurring compounds. Indeed, various approaches have been reported as efficient protocols,[2] including the enantioselective aldol, alkylation, Diels–Alder, and Heck reactions. Nonetheless, the development of a new strategy for the synthesis of asymmetric quaternary carbon centers is still an intriguing topic.[3]

We report here an enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes as a new approach for the synthesis of chiral compounds possessing a quaternary carbon stereocenter. Transition-metal-catalyzed [2 + 2 + 2] cycloaddition of unsaturated motifs is a reliable and atom-economical protocol for the construction of six-membered ring systems.[4] The synthesis of cyclohexa-1,3-dienes by the [2 + 2 + 2] cycloaddition of two alkynes and an alkene is also a well-known procedure.[5] However, to the best of our knowledge there is no reported example in which it has been

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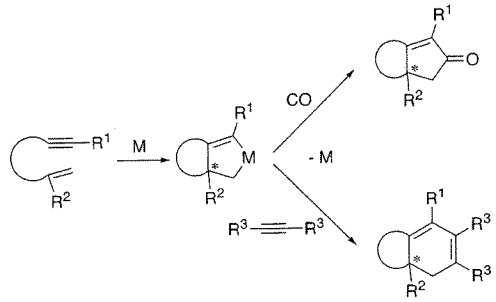
used for the enantioselective synthesis of an asymmetric quaternary carbon.[6,7]

We have studied the enantioselective carbonylative coupling of an alkyne and alkene, i.e., a Pauson–Khand-type reaction, using chiral Ir or Rh complexes.[8] The asymmetric carbon center would be generated by the oxidative coupling of enynes, and this is followed by carbonyl insertion and reductive elimination of the metal catalyst (Scheme 1). We

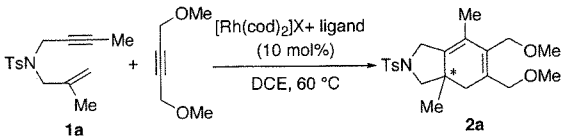
Scheme 1



considered that the enantioselective coupling of an enyne with 1,1-disubstituted olefin as an alkene moiety along with alkyne insertion could provide a chiral bicyclic 1,3-diene with a quaternary carbon stereocenter.

We chose nitrogen-bridged enyne **1a** and 1,4-dimethoxybut-2-yne as a model enyne and alkyne, respectively, and examined the enantioselective [2 + 2 + 2] cycloaddition under various reaction conditions using chiral rhodium and iridium complexes with BINAP as a chiral ligand. The coupling proceeded smoothly and enantioselectively with a cationic rhodium complex in hot 1,2-dichloroethane (DCE) (Table 1, entry 1).[9] The counteranion of the metal catalyst slightly affected both the yield and ee, and BF_4 gave the best results (entries 1–3). Chiral diphosphines possessing a binaphthyl scaffold generally gave good results,[10,11] and we further examined this reaction using tolBINAP, which resulted in the best yield and ee (entries 4–7). While it took a longer reaction time, 1.5 equiv of alkyne also gave a good yield and high ee (entry 8).

Table 1. Screening of Various Reaction Conditions

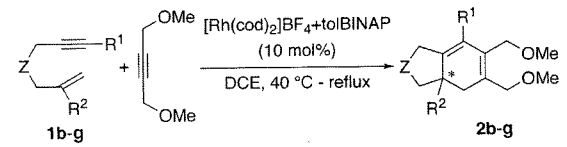


entry[a]	X	ligand[b]	time/h	yield/%	ee/%
1	BF_4	BINAP	9	77	93
2	SbF_6	BINAP	12	71	87
3	OTf	BINAP	12	62	89
4	BF_4	tolBINAP	12	81	97
5	BF_4	xylylBINAP	24	36	91
6	BF_4	H_8-BINAP	6	83	95
7	BF_4	SEGPHOS[c]	6	72	94
8[d]	BF_4	tolBINAP	24	80	96

[a] Enyne **1a**/alkyne is 1/2 if otherwise noted. [b] *S*-Isomers were used as a chiral ligand. [c] (4,4′-Bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine). [d] Enyne **1a**/alkyne is 1/1.5.

Various enynes were subjected to the enantioselective [2 + 2 + 2] cycloaddition (Table 2).[12] The reaction of enyne

Table 2. Cycloaddition of Various Enynes and an Alkyne



entry[a]	Z	R^1	R^2	T/°C	time/h	yield/%	ee/%
1[b]	NTs	Ph	Me	reflux	4	96 (**2b**)	88
2[b]	NTs	Me	Ph	reflux	24	61 (**2c**)	89
3	NTs	H	Me	40	13	41 (**2d**)	97
4	NTs	H	Me	40	15	72 (**2d**)	98
5	NTs	H	Ph	40	30	44 (**2e**)	95
6	NTs	H	Ph	80	2	52 (**2e**)	92
7	$C(CO_2Me)_2$	H	Me	40	12	60 (**2f**)	92
8	O	H	Me	40	5	38 (**2g**)	92
9[c]	O	H	Me	80	1	65 (**2g**)	97

[a] Enyne/alkyne is 1/2 for entries 1–3. Enyne/alkyne is 1/10 for entries 4–9. [b] The volume of solvent is half as much as that in other entries (ref 12). [c] Enyne was added dropwise over 1 h.

1b, which has a phenyl group on its alkyne terminus, proceeded sluggishly, and a higher reaction temperature and concentration were needed to consume enyne **1b** completely; a high yield and ee were achieved (entry 1). A phenyl group on the alkene moiety could also be tolerated and enyne **1c** was transformed into bicyclic diene **2c** in high ee (entry 2). Enyne **1d**, which has no substituent on its alkyne terminus, was a good substrate, and a higher ee of 97% was achieved. However, it was too reactive and the yield of the cross-

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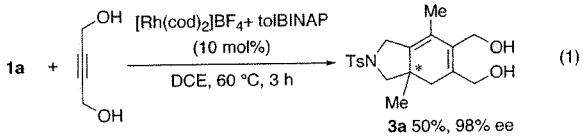
(11) Only a trace amount of cycloadduct **2a** was obtained using 1,2-bis(2,5-dimethylphospholano)benzene (MeDUPHOS) as a chiral ligand under the same reaction conditions.

(12) Typical experimental procedure: Under an atmosphere of argon, tolBINAP (6.8 mg, 0.010 mmol) and $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol) were stirred in 1,2-dichloroethane (0.25 mL) at room temperature to give a yellow solution. Then, 1,4-dimethoxybut-2-yne (22.8 mg, 0.20 mmol or 114.1 mg, 1.00 mmol) and an enyne (0.10 mmol) in 1,2-dichloroethane (0.75 mL) were added to the solution and the mixture was stirred at the appropriate temperature (cited in Table 2). After completion of the reaction, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give a chiral cycloadduct. The ee was determined by HPLC analysis using a chiral column.

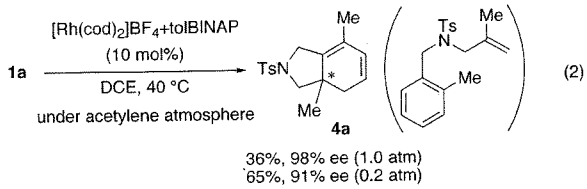
coupling product **2d** was moderate due to the formation of a self-coupling product of enyne **1d** (entry 3). The use of excess amounts of 1,4-dimethoxybut-2-yne suppressed the formation of a self-coupling product, and the yield of **2d** was increased (entry 4). With enyne **1e**, the reaction proceeded with high enantioselectivity (entries 5 and 6). Not only nitrogen-bridged enynes but also carbon- and oxygen-bridged enynes **1f** and **1g** reacted with 1,4-dimethoxybut-2-yne, and the corresponding cycloadducts **2f** and **2g** were obtained in high ee (entries 7 and 8). However, the self-coupling of enyne **1g** dominantly proceeded even with the use of excess amounts of the monoalkyne, and cycloadduct **2g** was obtained in only moderate yield (entry 8). Dropwise addition of enyne **1g** to a solution of the chiral catalyst and the monoalkyne at a higher reaction temperature improved the yield without any loss of ee (entry 9).

We also found that protection of the diol was unnecessary: but-2-yne-1,4-diol acted as a coupling partner and the corresponding chiral diol **3a** was obtained in moderate yield with excellent ee (eq 1).



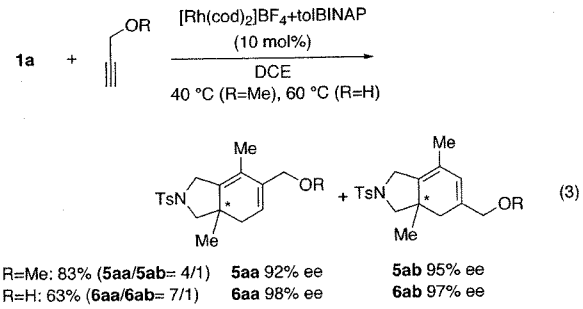
(1)

Next, we examined the reaction of enyne **1a** under an atmospheric pressure of acetylene. While the desired cycloadduct **4a** was obtained in high ee, the intermolecular trimerization of two acetylenes and an alkyne moiety of enyne **1a** was a major pathway. A decrease of the partial pressure of acetylene gas to 0.2 atm improved the yield with a slight decrease in ee (eq 2).



(2)

Methyl propargyl ether, an unsymmetrical alkyne, also reacted with enyne **1a** under the same reaction conditions. While the regioselectivity of the alkyne was not very high, both regioisomers were obtained in high ee (eq 3). In the case of propargyl alcohol, while a higher reaction temperature was needed, better regioselectivity and excellent enantioselectivities were realized.



(3)

In conclusion, we developed a highly enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes and alkynes. This catalytic reaction provides a new and facile protocol for the construction of quaternary carbon stereocenters. Recently, we[13] and other groups[14] independently reported catalytic enantioselective [2 + 2 + 2] cycloadditions of diynes and monoalkynes for the synthesis of axially chiral biaryl compounds. The present report proposes another use of transition-metal-catalyzed [2 + 2 + 2] cycloaddition in asymmetric synthesis.

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Supporting Information Available: Spectral data for cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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Rh-Catalyzed Enantioselective [2 + 2] Cycloaddition of Alkynyl Esters and Norbornene Derivatives

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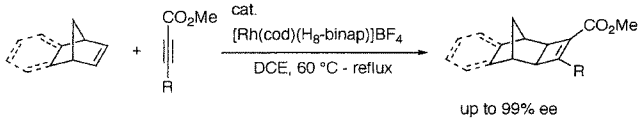
ABSTRACT



up to 99% ee

The enantioselective [2 + 2] cycloaddition of alkynes possessing an ester functionality and norbornene derivatives proceeded efficiently using a chiral rhodium catalyst. The chiral tri- and tetracyclic cyclobutenes were obtained in moderate to high ee.

Transition-metal-catalyzed cycloaddition of unsaturated motifs, such as alkynes, alkenes, etc., which is represented by $[m + n]$ or $[l + m + n]$ cycloaddition, is an atom-economical and reliable protocol for the synthesis of carbo- and heterocyclic skeletons.[1] Various types of cycloadditions have been reported for the construction of complex multicyclic compounds.[2] The advantage of transition-metal-catalyzed cycloaddition is that it can be readily applied as an asymmetric version because direct coordination of the reaction site to the chiral transition-metal complex gives high enantioselectivity. Our group has also described highly enantioselective [2 + 2 + 1] and [2 + 2 + 2] cycloadditions using chiral Ir and Rh complexes as catalysts.[3]

We report here the Rh-catalyzed enantioselective [2 + 2] cycloaddition of alkynyl esters and norbornene derivatives for the synthesis of chiral cyclobutenes.[4] There are a few examples of the transition-metal-catalyzed [2 + 2] cycloaddition of alkynes and alkenes, compared with other types of cycloadditions: ever since a pioneering work on the Ru-catalyzed [2 + 2] cycloaddition of alkynes with ester functionalities and norbornene derivatives,[5] only Pd-,[6] Ni-,[7] and Co-catalyzed[8] reactions have been described.[9] Recently, Ru-catalyzed [2 + 2] cycloaddition of various alkynes has been studied comprehensively,[10] including a diastereoselec-

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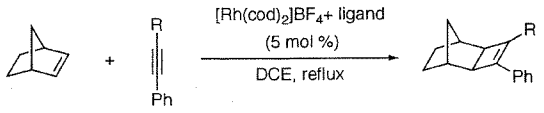
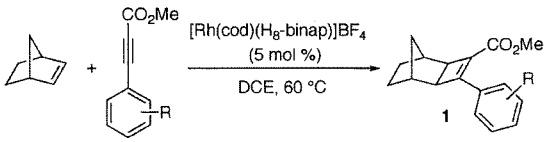
Table 1. Screening of Various Reaction Conditions



entry[a]	R	ligand[b]	time/h	yield/%	ee/%
1	CO_2Me	BINAP	9	93	66
2	CO_2Me	tolBINAP	9	87[c]	65
3	CO_2Me	xylylBINAP	6	quant	51
4	CO_2Me	H_8-BINAP	9	quant	73
5	CO_2Me	SEGPHOS	9	ca. 30[c]	67
6	CO_2Bn	H_8-BINAP	4	82	48
7	CO_2-*t*-Bu	H_8-BINAP	9	61[c]	32
8	C(O)Me	H_8-BINAP	12	94	14
9	CH_2OMe	H_8-BINAP	60	59[c]	26

[a] Alkyne/norbornene is 1/5. [b] *S*-Isomers were used as chiral ligands. [c] Alkynes were not completely consumed.

Table 2. [2 + 2] Cycloaddition of Various Arylpropiolates



entry[a]	R	time/h	yield/%	ee/%
1	H	24	85 (**1a**)	80
2[b]	4-OMe	6	98 (**1b**)	90
3	3-OMe	18	96 (**1c**)	78
4	2-OMe	72	quant (**1d**)	55
5	4-Me	24	97 (**1e**)	86
6[b]	3-Me	4	92 (**1f**)	82
7[b]	4-Br	24	91 (**1g**)	74
8	4-CO_2Et	24	83 (**1h**)	58
9	2,3-benzo	96	54 (**1i**)	63

[a] Alkyne/norbornene is 1/5. [b] The amount of catalyst is 10 mol %.

tive [2 + 2] cycloaddition using chiral alkynes.[11] However, to the best of our knowledge, there has been no example of a catalytic and enantioselective [2 + 2] cycloaddition for the synthesis of chiral cyclobutenes, except for only two examples of the chiral Lewis acid catalyzed [2 + 2] cycloadditions of alkynyl sulfides and electron-deficient alkenes.[12]

During our study of enantioselective transition-metal-catalyzed cycloadditions using alkynes as unsaturated motifs, we considered that active Rh complexes could be used to realize [2 + 2] cycloaddition: for comparison with previous examples, we chose the reaction of an alkynyl ester and norbornene and examined various rhodium complexes. As a result, cationic Rh complexes with phosphine ligands were found to be efficient catalysts[13] (Table 1): in the presence of chiral Rh catalyst, which was prepared in situ from [Rh(cod)$_2$]BF_4 and BINAP, the [2 + 2] coupling of methyl 3-phenylpropiolate with norbornene proceeded in refluxed 1,2-dichloroethane (DCE), and a chiral cyclobutene **1a** was obtained in high yield with moderate ee[14] (entry 1). Among the chiral diphosphine ligands of BINAP derivatives that we examined, H_8-BINAP was the best choice (entries 1−5).[15] In the case of benzyl and *tert*-butyl esters, the enantioselectivity apparently decreased (entries 6 and 7). Moreover, the reaction of alkynyl ketone proceeded to give a cycloadduct in high yield, but the ee was very poor. (entry 8). On the contrary, the reaction of propargyl ether sluggishly proceeded; however, the ee was slightly improved (entry 9). These results suggest that the electron-deficient moiety on an alkyne terminus is important to promote the [2 + 2] cycloaddition and that etheric oxygen atom plays a pivotal role in asymmetric induction in the present Rh-catalyzed enantioselective [2 + 2] cycloaddition.

Next, the chiral catalyst [Rh(cod)(H_8-binap)]BF_4 was isolated and subjected to the enantioselective [2 + 2] cycloaddition of methyl 3-phenylpropiolate and norbornene: cyclobutene **1a** was obtained at 60 °C with a higher ee of 80% (Table 2, entry 1).[16] Under the present reaction conditions, various methyl 3-arylpropiolates were examined as a coupling partner for norbornene. A 4-methoxyphenyl substituent on an alkyne terminus realized further higher enantioselectivity, and the corresponding cyclobutene **1b** was obtained almost quantitatively with 90% ee using 10 mol % catalyst (entry 2). The reactions of 3-methoxyphenyl- and 2-methoxyphenyl-substituted alkynes also proceeded to give cycloadducts in excellent yield; however, the ee was not sufficiently high (entries 3 and 4). An electron-donating group at the para position apparently induced better enantioselectivity, and the coupling of methyl 3-(4-methylphenyl)-propiolate gave cycloadduct **1e** in higher ee (entry 5). Methyl 3-(3-methylphenyl)propiolate also gave cycloadduct **1f** in good ee (entry 6). Electron-withdrawing groups, such as bromo and ethoxycarbonyl groups, could be tolerated as a substituent on the benzene ring, and chiral cyclobutenes **1g**, **h** were obtained in good to high yield with moderate ee (entries 7, 8). The reaction of alkynyl naphthalene was very

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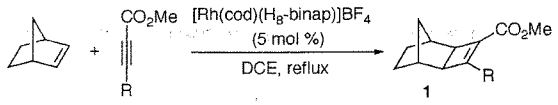
(14) The obtained ester **1a** was reduced to the corresponding alcohol, whose absolute configuration was determined by the comparison of the sign of the optical rotation (ref 11b), because it was derived from a chiral amide with a chiral auxiliary, whose absolute configuration was determined by the X-ray analysis; see: Lough, A. J.; Villeneuve, K.; Tam, W. *Acta Crystallogr.* **2004**, *E60*, o1566.

(15) BDPP (ca. 10%, 13% ee) and MeDUPHOS (ca. 5%, 4% ee) were inappropriate chiral ligands for the present reaction.

(16) **Typical Experimental Procedure.** Under an atmosphere of argon, [Rh(cod)((*S*)-H_8-binap)]BF_4 (9.3 mg, 0.010 mmol) was stirred in degassed 1,2-dichloroethane (0.4 mL) at room temperature to give a yellow solution. Then methyl 3-phenylpropiolate (32.0 mg, 0.20 mmol) and norbornene (94.2 mg, 1.00 mmol) in 1,2-dichloroethane (1.6 mL) were added to the solution, and the reaction mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography (EtOAc/hexane = 1:20) to give pure cycloadduct **1a** (43.1 mg, 85%). The ee was determined to be 80% by HPLC analysis using a chiral column.

Table 3. [2 + 2] Cycloaddition of Alkyl-Substituted Propiolates



1

entry[a]	R	time/h	yield/%	ee/%
1	Me	1	55 (**1j**)	99
2[b]	Me	1	64 (**1j**)	93
3[b]	Bu	2	87 (**1k**)	73

[a] Alkyne/norbornene is 1/2. [b] The quadruple volume of solvent (8 mL) was used (see ref 16).

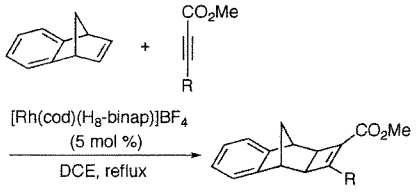
slow, but the corresponding cycloadduct **1i** was obtained in moderate ee (entry 9).

We further examined alkyl-substituted propiolates as a coupling partner for norbornene (Table 3). The [2 + 2] cycloaddition of methyl but-2-ynoate proceeded under reflux conditions using Rh−H_8-BINAP catalyst to give cyclobutene **1j** with almost perfect enantioselectivity (entry 1). The [2 + 2 + 2] cycloadducts of two but-2-ynoates and norbornene, including three regioisomers, were obtained as byproducts. The diluted conditions improved the yield; however, a slight decrease in ee was observed (entry 2). Methyl hept-2-ynoate was also a substrate, and cycloadduct **1k** was obtained in higher yield with acceptable ee (entry 3).

The reaction of benzonorbornadiene required a higher temperature (Table 4). As in the case of norbornene, 3-(4-methoxyphenyl)propiolate achieved higher enantioselectivity than 3-phenylpropiolate (entries 1 and 2). In the reaction of but-2-ynoate, the enantioselectivity exceeded 90% (entry 3).

In conclusion, we developed the Rh-catalyzed [2 + 2] cycloaddition of alkynyl esters and norbornene derivatives,

Table 4. [2 + 2] Cycloaddition of Benzonorbornadiene



2

entry[a]	R	time/h	yield/%	ee/%
1	C_6H_5	10	92 (**2a**)	79
2[b]	4-$MeOC_6H_4$	5	95 (**2b**)	87
3	Me	2	68 (**2j**)	94

[a] Alkyne/benzonorbornadiene is 1/2. [b] The amount of catalyst is 10 mol %.

and various tri- and tetracyclic cyclobutenes were obtained in good to excellent yield. The chiral Rh−H_8-BINAP catalyst realized moderate to high enantioselectivity. This present reaction provides a new and facile protocol for the construction of chiral cyclobutenes.

Acknowledgment. We thank Prof. H. Ishida (Faculty of Science, Okayama University) for helpful discussions. We also thank Takasago International Corp. for the gift of H_8-BINAP and SEGPHOS. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Spectral data for cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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Enantioselective Intramolecular [2 + 2 + 2] Cycloaddition of 1,4-Diene-ynes: A New Approach to the Construction of Quaternary Carbon Stereocenters

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Transition-metal-catalyzed cycloaddition is an atom-economical and powerful tool for the synthesis of cyclic carbon skeletons.[1] Various cycloadditions, including more than two alkyne and/or alkene moieties as reaction components, have been reported using transition metal catalysts.[2] In particular, [2 + 2 + 2] cycloaddition is a general protocol for the synthesis of six-membered ring systems,[3] and intramolecular [2 + 2 + 2] cycloaddition gives a tricyclic compound in one pot. The starting material can be classified into three types (Scheme 1): (1) the two reaction components (i.e., alkyne(s) and/or alkene(s)) are connected by a 1,2-disubstituted alkyne and triynes are most commonly used;[4-6] (2) the two reaction components are connected by a 1,2-disubstituted alkene;[7] (3) the two synthetic units are connected by a 1,1-disubstituted alkene. Cycloaddition of the last substrate, a dienyne,[8] is very attractive because it can give strained bridged compounds, which possess two asymmetric carbon centers, including a quaternary carbon stereocenter, at the bridgehead position. Tricyclic compound **A** or **B** would be obtained depending on the direction of olefin insertion. However, to the best of our knowledge, this type of [2 + 2 + 2] cycloaddition has never been reported.

We report here an intramolecular [2 + 2 + 2] cycloaddition of 1,4-diene-ynes for the synthesis of strained bridged compounds. Tricyclic compounds, including a bicyclo[2.2.1]heptene skeleton with two quaternary carbon stereocenters, are enantiomerically obtained by a chiral Rh catalyst. Depending on the substituent on the 1,4-diene moiety, chiral bicyclic cyclohexa-1,3-dienes with a quaternary carbon stereocenter are products.

We chose nitrogen-bridged 1,4-diene-yne **1a** as a model substrate and subjected it to cationic Rh-catalyzed cycloaddition (Table 1).[9] After we screened ligands, BINAP derivatives were found to efficiently activate the Rh complex for the present reaction:[10] 1,4-diene-yne **1a** was completely consumed and tricyclic compound **2a** with two quaternary carbon stereocenters (type **A** in Scheme 1) was the sole detectable product with a very high enantiomeric excess (entry 1). Among BINAP derivatives, tolBINAP was the best chiral ligand, and the minor enantiomer could not be detected by HPLC analysis using a chiral column (entry 2).[11]

Several 1,4-diene-ynes were examined using a Rh–tolBINAP catalyst (Table 2). Butyl-substituted 1,4-diene-yne **1b** required higher reaction temperature, but gave high enantioselectivity (entry 1). A functional group on the alkyne terminus was tolerable (entry 2). 1,4-Diene-ynes with no substituent on the alkyne terminus were also good substrates (entries 3 and 4). In particular, with 1,4-diene-yne **1e**, which has a phenyl group at the 2-position of the 1,4-diene moiety (R^2 = Ph), cycloadduct **2e** with a phenyl group at the quaternary carbon stereocenter was obtained (entry 4), and its structure and absolute configuration were determined by X-ray measurements (Figure 1). Carbon- and oxygen-bridged 1,4-diene-ynes **1f,g** were also transformed into the corresponding chiral tricyclic compounds **2f,g** with two quaternary carbon stereocenters (entries 5 and 6).

Scheme 1. Types of Substrates for the Intramolecular [2 + 2 + 2] Cycloaddition

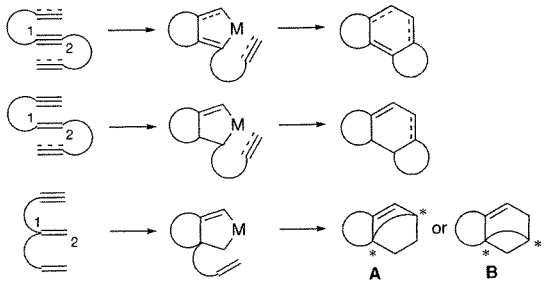
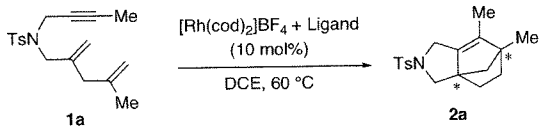


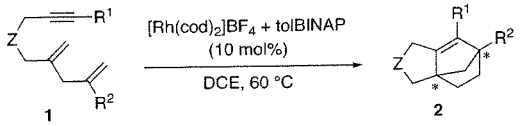
Table 1. Screening of Chiral Ligands



1a 2a

entry	ligand	time/h	yield/%	ee/%
1	(*S*)-BINAP	48	69	97
2	(*S*)-tolBINAP	48	81	>99
3	(*S*)-xylylBINAP	48	82	99
4	(*S*)-H_8-BINAP	36	71	95
5	(*S*)-SEGPHOS	36	69	97

Table 2. Enantioselective [2 + 2 + 2] Cycloaddition for the Construction of Bicyclo[2.2.1]heptene Skeleton



1 2

entry	R^1	R^2	Z	dienyne	time/h	yield/%	ee/%
1[a]	Bu	Me	NTs	**1b**	48	46 (**2b**)	>99
2	$BnOCH_2$	Me	NTs	**1c**	48	83 (**2c**)	88
3	H	Me	NTs	**1d**	6	83 (**2d**)	93
4	H	Ph	NTs	**1e**	6	72 (**2e**)	91
5	H	Me	$C(CO_2Bn)_2$	**1f**	48	76 (**2f**)	93
6	Ph	Me	O	**1g**	24	40 (**2g**)	92

[a] The reaction was examined at 80 °C.

We further examined the cycloaddition of 1,4-diene-yne **1h**, which does not have a substituent at the 2-position of the 1,4-diene moiety, under the same reaction conditions. Unexpectedly, bicyclic cyclohexa-1,3-diene **3h** was exclusively obtained with almost perfect enantioselectivity (Table 3, entry 1). When 1,4-diene-yne **1i**, which does not have a substituent on the alkyne terminus, was used, the enantioselectivity exceeded 99% (entry 2). Carbon- and oxygen-bridged 1,4-diene-ynes **1j–l** were also suitable substrates (entries 3–5). In all cases, the corresponding bicyclic cyclohexa-

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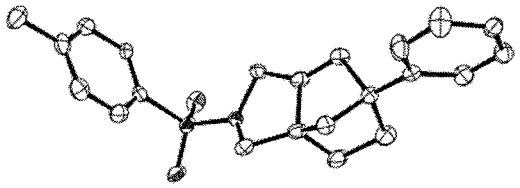
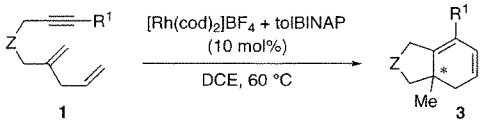


Figure 1. ORTEP diagram of cycloadduct **2e**.

Table 3. Enantioselective [2 + 2 + 2] Cycloaddition for the Synthesis of Bicyclic Cyclohexa-1,3-dienes



1 3

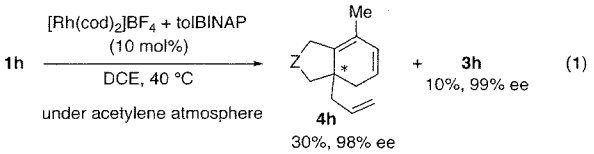
entry	R^1	Z	dienyne	time/h	yield/%	ee/%
1	Me	NTs	**1h**	12	91 (**3h**)	99
2[a]	H	NTs	**1i**	12	79 (**3i**)	>99
3	H	$C(CO_2Bn)_2$	**1j**	6	80 (**3j**)	90
4	Ph	O	**1k**	48	55 (**3k**)	92
5	$Ph(CH_2)_3$	O	**1l**	6	64 (**3l**)	94

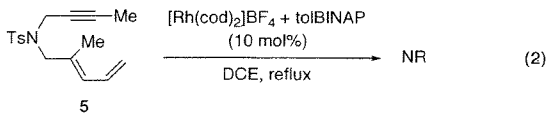
[a] The reaction was examined at 40 °C.

1,3-dienes were obtained with high enantiomeric excess, and tricyclic compounds **2** could not be detected.

The proposed mechanism for the present cycloaddition is shown in Scheme 2. Oxidative coupling of the metal complex to alkyne and alkene moieties of 1,4-diene-yne **1** gives metallacyclopentene **C**, and the intramolecular olefin insertion follows. When R^2 is not hydrogen, tricyclic compound **2** is obtained by reductive elimination from **D**. In contrast, when R^2 is hydrogen, a 1,3-hydrogen shift accompanied by ring cleavage would proceed to provide metallacycloheptadiene **E**, and subsequent reductive elimination gives bicyclic cyclohexa-1,3-diene **3**.[12]

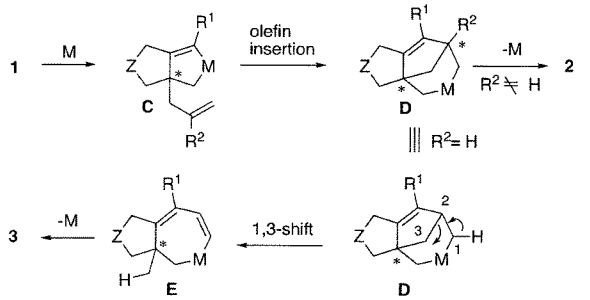
When the reaction of **1h** was examined under acetylene atmosphere, intermolecular [2 + 2 + 2] cycloaddition of enyne and acetylene proceeded to give cyclohexa-1,3-diene **4h** with high enantiomeric excess along with the formation of **3h** (eq 1).[13] The reaction of 1,3-diene-yne **5** did not proceed even under reflux conditions (eq 2). These results suggest that bicyclic cyclohexa-1,3-diene **3** would be formed via metallacyclopentene **C** and is not an intramolecular [4 + 2] cycloadduct of the conjugated 1,3-diene-yne, which could be obtained by double bond isomerization of 1,4-diene-yne **1**.





In conclusion, we have developed an enantioselective intramolecular [2 + 2 + 2] cycloaddition of 1,4-diene-ynes, which provides a new approach to the construction of strained multicyclic compounds with quaternary carbon stereocenters.[14] Therefore, the present protocol is a new synthetic use of [2 + 2 + 2] cycloaddition in asymmetric synthesis, and further applications are under investigation.

Scheme 2. Proposed Mechanism of Formation of **2** and **3**



Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details and spectral data for 1,4-diene-ynes and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) On the basis of Bredt's rule, [2 + 2 + 2] cycloaddition of yne-ene-yne would be impossible.
(9) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reaction*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 12, p 241.
(10) When triphenylphosphine, 1,3-bis(diphenylphosphino)propane, or (*S,S*)-CHIRAPHOS was used as a ligand, almost no reaction proceeded, and cycloadduct **2a** could not be detected under the same reaction conditions.
(11) An opposite enantiomer of cycloadduct **2a** was surely obtained with almost the same yield and enantioselectivity using (*R*)-tolBINAP.
(12) In the course of the reaction of **1h**, the ee was not changed (2 h: 29%, 99% ee; 4 h: 43%, 99% ee; 8h: 79%, 99% ee), and the double bond isomerization of cycloadduct **3h** could not be observed under the same reaction conditions. These results imply that high ee of **3h** is derived from the cycloaddition of **1h**, not from the double bond isomerization of **3h** as a secondary reaction.
(13) (a) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (b) Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4955.
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Highly Enantioselective Construction of a Chiral Spirocyclic Structure by the [2 + 2 + 2] Cycloaddition of Diynes and *exo*-Methylene Cyclic Compounds

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Enantioselective cycloaddition using a chiral transition metal catalyst is a well-established strategy for the synthesis of chiral compounds possessing various cyclic structures. In particular, the cycloaddition of enynes has been comprehensively studied: an oxidative coupling gives a bicyclic metallacyclopentene, in which an asymmetric carbon atom is generated. The following insertion and reductive elimination provides a cyclic compound with a chiral center at the ring-fused carbon. Pauson-Khand-type reaction ([2 + 2 + 1] cycloaddition),[1] [2 + 2 + 2] cycloaddition of an enyne and alkyne,[2] and intramolecular [4 + 2] cycloaddition of a dienyne[3] are the selected examples (Scheme 1).[4,5]

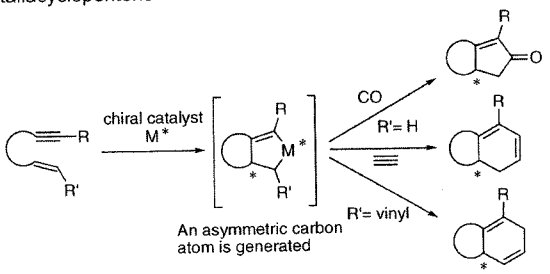
We here propose a new approach for asymmetric induction using a [2 + 2 + 2] cycloaddition of a diyne and an alkene (Scheme 2): an oxidative coupling gives a bicyclic metallacyclopentadiene, in which no asymmetric carbon atom is generated.[6] The following insertion of a 1,1-disubstituted alkene along with reductive elimination induces a chiral quaternary carbon atom on the ring. The [2 + 2 + 2] cycloaddition of diynes and monosubstituted or 1,2-disubstituted alkenes is already reported.[7] However, neither the reaction using 1,1-disubstituted alkenes nor the enantioselective reaction was reported.

We chose an *exo*-methylene cyclic compound as an alkene component because the [2 + 2 + 2] cycloaddition gives a chiral spirocyclic compound, which could never have been obtained by the conventional enantioselective cycloadditions (Scheme 1). We examined a Rh-catalyzed reaction of carbon-tethered symmetric diyne **1a** and α-methylene-γ-butyrolactone (**2a**) under the various reaction conditions (Table 1); when the Rh-BINAP catalyst was used at 60 °C in 1,2-dichloroethane (DCE), diyne **1a** was completely consumed within 3 h, and the desired bicyclic cyclohexa-1,3-diene **3aa**, possessing a spirocyclic system, was obtained in very high enantiomeric excess. However, the yield was moderate because of the formation of a self-coupling cycloadduct of diyne **1a** (entry 1). Dropwise addition of diyne **1a** to a mixture of the chiral catalyst and lactone **2a** at 80 °C over 30 min significantly improved the yield (entry 2). Under the present reaction conditions, several BINAP derivatives were examined as chiral ligands (entries 3−6). As a result, xylylBINAP was the best choice, and almost perfect enantioselectivity was achieved (entry 4). It is also noteworthy that only 3 equiv of alkene **2a** was sufficient to achieve a high yield in the present diyne−alkene coupling.[8]

We further examined a preliminarily isolated chiral rhodium complex, [Rh(cod){(*S*)-xylyl-binap}]BF_4, and the yield exceeded 90% (Table 2, entry 1). Under the optimal reaction conditions, various symmetric diynes and *exo*-methylene cyclic compounds were subjected to the present enantioselective [2 + 2 + 2] cycloaddition. Lactones **2b,c** with six- and seven-membered ring systems also underwent cycloaddition, and the corresponding spirocyclic compounds **3ab** and **3ac** were obtained in excellent enantiomeric excesses (entries 2 and 3). *exo*-Methylene cyclic ketones **2d,e** were more reactive, and the reaction proceeded at lower temperature; however, the enantioselectivity decreased (entries 4 and 5). Unsubstituted diyne **1b** was also an appropriate substrate; high yield and enantiomeric excess were achieved without double bond isomerization of the 1,3-diene moiety (entry 6). The reaction of nitrogen- and oxygen-tethered diynes **1c,d** and lactones **2a,b** also gave spirocyclic compounds with high to excellent enantiomeric excess, but excess amounts of alkenes were needed because heteroatom-tethered diynes are more reactive than carbon-tethered diynes and susceptible to self-coupling (entries 7−9). Cycloadduct **3cb** was determined to be an (*R*)-isomer by X-ray measurements (Figure 1).

Next, we examined the [2 + 2 + 2] cycloaddition of unsymmetric diyne **1e**, which possesses methyl and phenyl groups on its alkyne

Scheme 1. Conventional Enantioselective Cycloadditions via a Metallacyclopentene with a Chiral Carbon Stereocenter



Scheme 2. A New Enantioselective Cycloaddition via a Metallacyclopentadiene without a Chiral Carbon Stereocenter

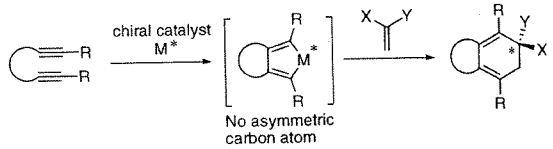
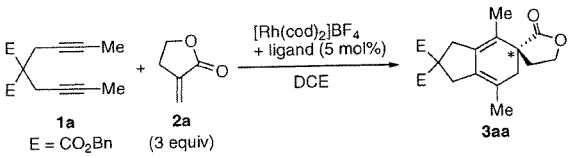


Table 1. Screening of Various Reaction Conditions



entry	ligand	temp (°C)	time (min)	yield (%)	ee (%)
1	(*S*)-BINAP	60	180	42	97
2	(*S*)-BINAP	80	30[a]	55	96
3	(*S*)-tolBINAP	80	30[a]	62	96
4	(*S*)-xylylBINAP	80	30[a]	84	99
5	(*S*)-H_8-BINAP	80	30[a]	64	97
6	(*S*)-SEGPHOS	80	30[a]	49	92

[a] Diyne **1a** was added dropwise over 30 min.

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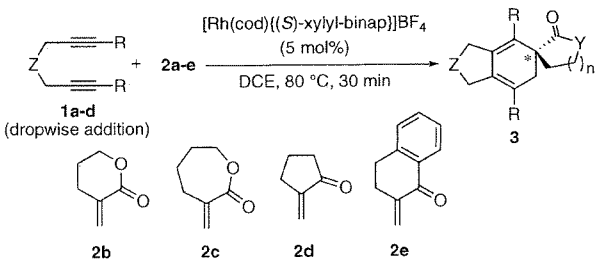
Table 2. Cycloaddition of Various Diynes and *exo*-Methylene Cyclic Compounds



entry	Z	R	diyne	alkene[a]	yield (%)	ee (%)
1	$C(CO_2Bn)_2$	Me	**1a**	**2a**	94 (**3aa**)	99
2	$C(CO_2Bn)_2$	Me	**1a**	**2b**	93 (**3ab**)	98
3	$C(CO_2Bn)_2$	Me	**1a**	**2c**	88 (**3ac**)	97
4[b,c]	$C(CO_2Bn)_2$	Me	**1a**	**2d**	62 (**3ad**)	81
5[b,c]	$C(CO_2Bn)_2$	Me	**1a**	**2e**	72 (**3ae**)	80
6[d]	$C(CO_2Bn)_2$	H	**1b**	**2a**	81 (**3ba**)	95
7	NTs	Me	**1c**	**2a**[e]	92 (**3ca**)	97
8	NTs	Me	**1c**	**2b**[e]	89 (**3cb**)	99
9[b]	O	Et	**1d**	**2a**[f]	50 (**3da**)	92

[a] 3 equiv. [b] At 60 °C. [c] The reaction mixture was stirred for further 2.5 h. [d] At 40 °C. [e] 10 equiv. [f] 20 equiv.

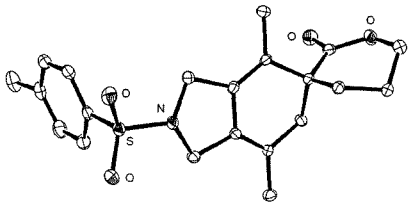
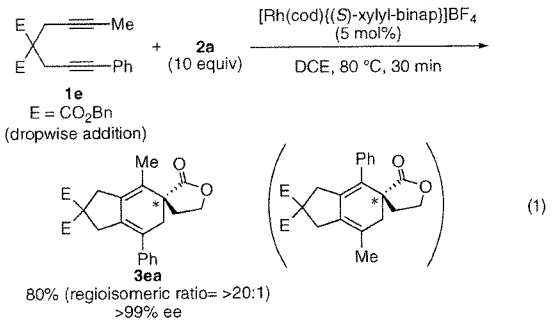


Figure 1. Crystal structure of (*R*)-**3cb**.

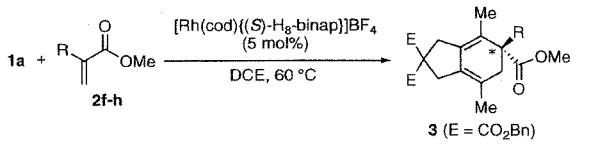
termini, with lactone **2a** (eq 1). The regioselectivity of the alkene and enantioselectivity were almost perfect, and cycloadduct **3ea** was the sole isolated spirocyclic compound.



(1)

In addition to *exo*-methylene cyclic compounds, *exo*-methylene acyclic compounds were also good coupling partners, and H_8-BINAP was found to be a better chiral ligand (Table 3); the cycloaddition of diyne **1a** with methyl methacrylate (**2f**) gave cycloadduct **3af** in almost perfect enantioselectivity (entry 1). The reaction of methyl 2-phenylacrylate (**2g**) required excess amounts and higher temperature, but a quaternary carbon stereocenter with a phenyl group was generated (entry 2). It is noteworthy that methyl acrylate (**2h**) also gave cycloadduct **3ah**, which is a highly enolizable ester, with high enantiomeric excess.

Table 3. Cycloaddition of Acrylates as Alkenes



entry	R	alkene	equiv	yield (%)	ee (%)
1	Me	**2f**	3	92 (**3af**)	>99
2[a]	Ph	**2g**	10	54 (**3ag**)	93
3	H	**2h**	3	87 (**3ah**)	91

[a] Diyne was added dropwise at 80 °C.

In conclusion, we have developed a Rh-catalyzed highly enantioselective [2 + 2 + 2] cycloaddition of diynes and alkenes. The use of *exo*-methylene cyclic compounds as alkenes realized a new protocol for the catalytic synthesis of a chiral spirocyclic structure.[9] The present enantioselective [2 + 2 + 2] cycloaddition provides access to a new chiral library possessing a quaternary carbon stereocenter, including a spirocyclic system.

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Supporting Information Available: Experimental details, spectral data for products, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) We recently reported an enantioselective intramolecular [2 + 2 + 2] cycloaddition of 1,4-diene-yne, in which a chirality at the fused carbon atom was generated also in the metallacyclopentene intermediate: Shibata, T.; Tahara, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11766.

(6) Three groups, including us, independently reported an enantioselective [2 + 2 + 2] cycloaddition of a diyne and alkyne for the generation of axial chirality; however, the chirality would be generated in the metallacyclopentadiene intermediate due to the ortho-substituted aryl groups on the diyne termini: (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795. (b) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. (c) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510.

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Rh-Catalyzed Cyclization of Diynes and Enynes Initiated by Carbonyl-Directed Activation of Aromatic and Vinylic C–H Bonds

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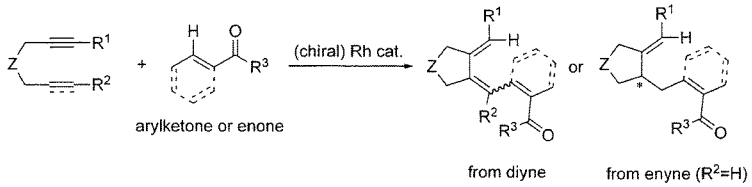
ABSTRACT



The Rh-catalyzed hydroarylative and hydrovinylative cyclization of diynes with aryl ketones or enones gave monocyclic 1,3-dienes. Enynes also underwent the same reaction and chiral products were obtained with high ee using a chiral Rh catalyst. Carbonyl-directed activation of aromatic and vinylic C–H bonds is likely the initial step in the present transformation.

Direct functionalization of unreactive C–H bonds is a valuable and challenging topic in organic synthesis. In particular, many researchers have focused on transition metal-catalyzed C–H activation along with C–C bond formation.[1] Jordan reported a catalytic direct addition of a C–H bond in α-picoline to olefins using a Zr complex.[2] Subsequently, Moore reported a Ru-catalyzed C–H activation in pyridine, which was accompanied by coupling of carbon monoxide and olefin.[3] Murai's report of the Ru-catalyzed addition of a C–H bond in aromatic ketones to vinylsilane is recognized as a monumental work in catalytic C–H activation and has led to a new area of C–C bond formation initiated by heteroatom-directed C–H activation.[4] Various types of catalytic Csp^2–H activation, such as enones,[5] aldimines,[6] and phenols,[7] have been reported since then.[8]

We report here a Rh-catalyzed hydroarylative and hydrovinylative cyclization of diynes and enynes with aryl ketones and enones, including an enantioselective variant.[9,10] We consider that carbonyl-directed Csp^2–H bond activation of aryl ketones and enones is likely to be the initial step in the present reaction.

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(10) During the preparation of this manuscript, Tanaka, and coworkers reported the Rh-catalyzed, hydroarylative cyclization of diynes with aryl ketones, and they proposed a metallacyclopentadiene as an intermediate without direct proof, see: Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 2203.

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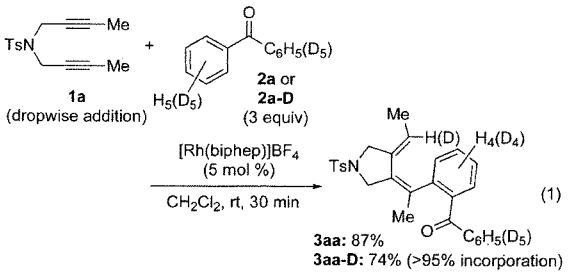
After the enantioselective [2 + 2 + 2] cycloaddition of diynes with alkenes,[11a] we recently reported a Rh-catalyzed hetero-[2 + 2 + 2] cycloaddition of diynes with carbonyl compounds.[11b] During the course of our study, we examined the reaction of diyne **1a** with benzophenone: hetero-[2 + 2 + 2] cycloaddition did not proceed but hydroarylative cyclization proceeded to give cyclic 1,3-diene **3aa**, whose structure was determined by X-ray measurements (eq 1, Figure 1). Diyne **1a** was promptly consumed at room



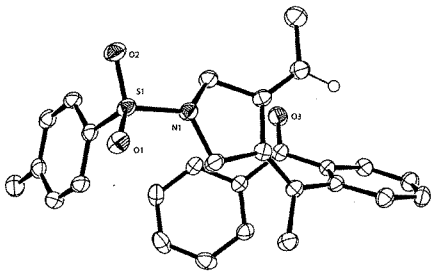
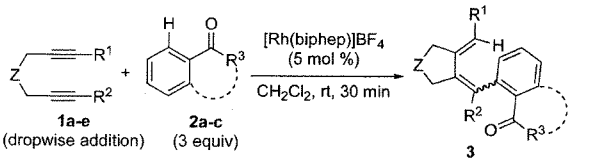


Figure 1. ORTEP diagram of **3aa**

temperature using [Rh(cod)(biphep)]BF_4 (BIPHEP: 2,2′-bis-(diphenylphosphino)-1,1′-biphenyl), which was treated in situ with hydrogen gas to exclude 1,5-cyclooctadiene (COD) before use.[12] We ascertained cleavage of the aromatic C−H bond adjacent to the carbonyl group and the almost perfect transfer of hydrogen by a labeling experiment using benzophenone-d_{10} (**2a-D**).

We further examined hydroarylative cyclization using several aryl ketones and diynes (Table 1). Aromatic C−H bonds of acetophenone (**2b**) and tetralone (**2c**) were also activated and reacted with diyne **1a**; however, partial double-bond isomerization was observed in product **3ac** (entries 1, 2). Even phenyl-substituted diyne **1b** could be used in this

Table 1. Cyclization of Various Diynes and Aryl Ketones

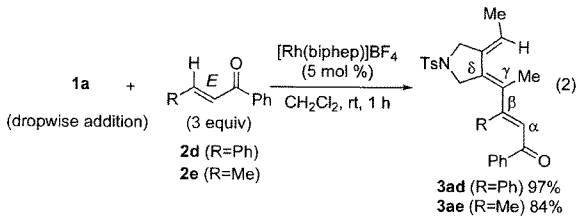


entry	Z	R^1, R^2	diyne	R^3	ketone	yield (%)	*E*/*Z*[a]
1	NTs	Me, Me	**1a**	Me	**2b**	55 (**3ab**)	>20/1
2	NTs	Me, Me	**1a**	$(CH_2)_3$	**2c**	87 (**3ac**)	4/1
3	NTs	Ph, Ph	**1b**	Ph	**2a**[b]	73 (**3ba**)	1/2
4	NTs	Me, Ph	**1c**	Ph	**2a**	86 (**3ca**)	1/1
5[c]	NTs	Me, Ph	**1c**	Ph	**2a**	63 (**3ca**)	>20/1
6	$C(CO_2Bn)_2$	Me, Me	**1d**	Ph	**2a**	78 (**3da**)	1/>20[d]
7	$\{C(CO_2Et)_2\}_2$	Me, Me	**1e**	Ph	**2a**	>99 (**3ea**)	1/16[d]

[a] See Supporting Information. [b] Reaction run using 10 equiv. [c] *rac*-BINAP was used as a ligand. [d] From the nomenclature rule, *E*/*Z* ratio is opposite but the major geometry is the same as entries 1, 2, and 5.

reaction, but double-bond isomerization proceeded further and the *Z* isomer of **3ba** was a major product (entry 3). When unsymmetrical diyne **1c** was used, a regioselective reaction proceeded to give diene **3ca**, and the *E*/*Z* ratio was low (entry 4). Intriguingly, Rh-BINAP catalyst suppressed isomerization completely (entry 5).[13] Carbon-tethered 1,6-diyne **1d** and 1,7-diyne **1e** also underwent C−H bond-cleaved hydroarylative cyclization to give 1,3-diene **3da** and **3ea** in high to quantitative yield (entries 6, 7).

We next examined the reaction using *trans*-chalcone as a carbonyl compound (eq 2). Vinylic C−H activation preceded aromatic C−H activation, and monocyclic trienone **3ad** was obtained exclusively in excellent yield. Moreover, two alkene moieties (α,β- and γ,δ-positions), which were derived from the C−C double-bond of *trans*-chalcone and an alkyne moiety of the diyne, respectively, were completely isomerized into the (*Z*,*Z*)-isomer. Also, in the case of phenyl 1-propenyl ketone (**2e**), the vinylic C−H activation proceeded predominantly along with the complete isomerization of two C−C double bonds.



The present hydroarylative and hydrovinylative cyclization also proceeded with enynes and α,β-unsaturated ketones: the reaction of nitrogen-tethered enyne **4a** with benzophenone gave monocyclic product **5aa**, where hydrogen added to the alkyne moiety and the aryl group added to the alkene moiety of the enyne, and another pattern of hydroarylative product **6aa** could not be detected. These results indicate the reaction

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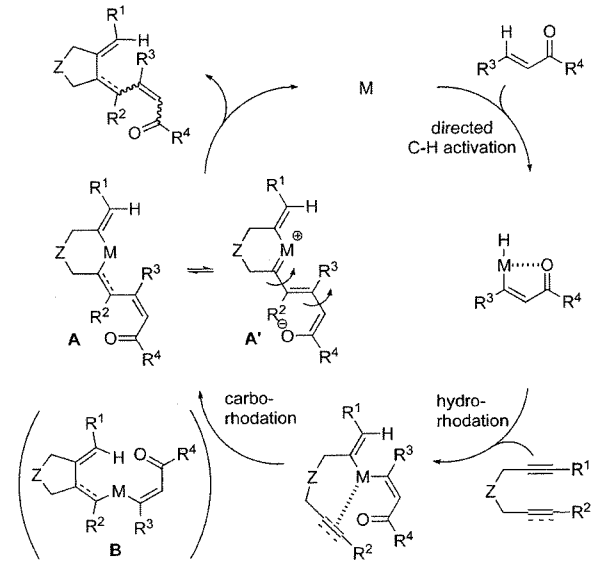
(12) A typical experimental procedure (eq 1): CH_2Cl_2 (1 mL) was added to [Rh(cod)(biphep)]BF_4 (3.8 mg, 0.005 mmol) in the Ar-filled flask, and the solution was stirred at ambient temperature for 5 min. After the flask was purged with hydrogen gas, the solution was stirred for 30 min. Both the solvent and hydrogen gas were removed under reduced pressure. Then argon gas was introdued to the flask, and the CH_2Cl_2 solution (0.3 mL) of benzophenone (**2a**) (54.0 mg, 0.30 mmol) was added. Diyne **1a** (27.6 mg, 0.10 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise over 30 min at room temperature, and the mixture was stirred for 5 min. After completion of the reaction, the solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography (hexane/AcOEt = 4/1) to give pure **3aa** (40.0 mg, 87%).

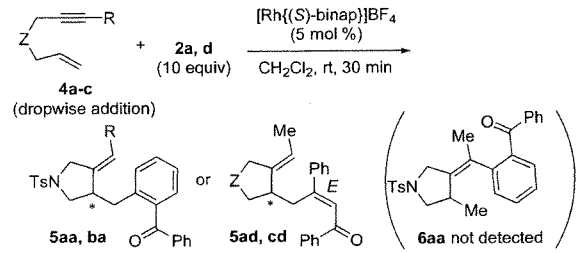
(13) These compounds were primary products because the *E*/*Z* ratios were not changed if they were heated in 1,2-dichloroethane at 40 °C for 24 h.

Scheme 1. A Possible Mechanism of the Present Cyclization



mechanism described later (Scheme 1). When a chiral catalyst (Rh-(*S*)-BINAP complex) was used, highly enantioselective induction was observed (Table 2, entry 1). Phenyl-

Table 2. Enantioselective Cyclization of Enynes



entry	Z	R	enyne	ketone	yield (%)	ee (%)
1	NTs	Me	**4a**	**2a**	69 (**5aa**)	92
2[a]	NTs	Ph	**4b**	**2a**	45 (**5ba**)	91
3	NTs	Me	**4a**	**2d**	37 (**5ad**)	97
4	$C(CO_2Bn)_2$	Me	**4c**	**2d**	76 (**5cd**)	96

[a] The reaction was carried out for 2.5 h.

substituted enyne **4b** was sluggish to react with **2a** and the yield was moderate, but the ee of the product **5ba** remained high (entry 2). The vinylic C−H activation of chalcone along with enantioselective cyclization was also possible, and dienone **5ad** was obtained (entry 3).[14] Carbon-tethered enyne **4c** was a good substrate and the corresponding product **5cd** was obtained in excellent ee (entry 4).[15]

On the basis of the above results, we can now speculate a reaction mechanism (Scheme 1), where an enone is depicted as a representative reactant. The oxidative addition of Rh(I) to vinylic C−H bond is initiated by the directing effect of a carbonyl group,[16] and this is followed by hydrorhodation to the alkyne moiety of the diyne or enyne.[17] A carborhodation pathway can be ruled out because the reaction of enyne, where an alkyne moiety is more reactive than an alkene moiety, did not give a benzylidene product such as **6aa**. Subsequent intramolecular carborhodation would give metallacyclohexane **A**. In the case of diynes, an equilibrium would exist between metallacycle **A** and zwitterionic carbene complex **A′**, and the most thermodynamically favored geometry is obtained by double-bond isomerizations.[18] This is a good explanation for complete isomerization in the case of diyne **1a** and enones. Another pattern of carborhodation, which gives **B**, would be less likely because double-bond isomerization would also occur in the hydroarylative product **3ab**, which was derived from benzophenone, as with product **3ad** from chalcone (entry 1 in Table 1 and eq 2).[19]

In summary, we have developed the hydroarylative and hydrovinylative cyclizations, which would be initiated by carbonyl-directed C−H activation. The reaction of diynes with aryl ketones or enones gave 1,3-dienes, and the enantioselective reaction of enynes gave chiral compounds with high ee. Although we provide a possible mechanism, further study is in progress.

Acknowledgment. We thank Prof. Nobuharu Iwasawa (Tokyo Institute of Technology, Japan) for his helpful discussion and Ai Kawachi (Waseda University, Japan) for her experimental assistance. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Spectral data for products and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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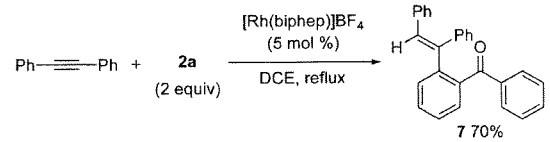
(14) Even using Rh-BIPHEP catalyst, no isomerization of C−C double bond, derived from C−C double bond of chalcone, was observed in product **5ad**.

(15) Under the same reaction conditions, the [2 + 2 + 2] cycloaddition of carbon-tethered enyne **4c** with methyl acrylate or methyl pyruvate did not proceed, where metallacyclopentene would be an intermediate. These results indicate that the metallacyclopentene would not be an intermediate for the formation of present hydroarylative cycloadduct **5cd**.

(16) In place of diynes, tolan as a monoyne also reacted with benzophenone using the same catalyst at higher temperature to give the hydroarylated product **7** in good yield. This result shows that C−H bond cleavage surely occurred without the formation of metallacyclopentadiene intermediate.



(17) An example of hydrorhodation of arylrhodium hydride complex to an alkyne: Jones, W. D.; Chandler, V. L.; Feher, F. J. *Organometallics* **1990**, *9*, 164.

(18) This isomerization mechanism via carbene complex was already reported, see: (a) Tanke, R. S.; Crabtree, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 7984. (b) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P. *Organometallics* **1990**, *9*, 3127.

(19) The reaction mechanism involving the oxidative coupling of diynes or enynes could not be wholly ruled out but it cannot give reasonable explanations for the C−C double bond isomerization, which depends on the substrates.

JOC Article

Enantioselective Intramolecular [2 + 2 + 2] Cycloaddition of Enediynes for the Synthesis of Chiral Cyclohexa-1,3-dienes

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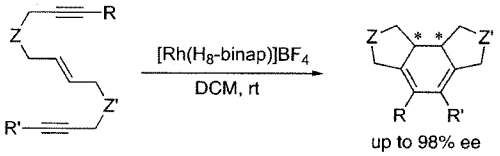
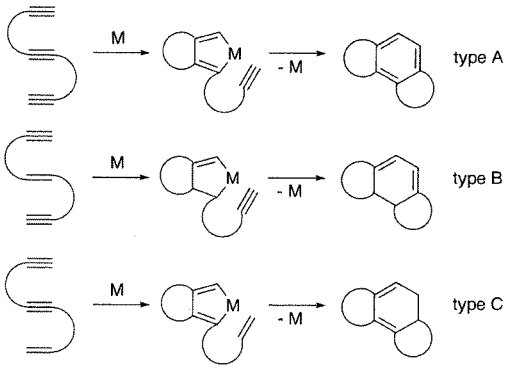


The enantioselective intramolecular [2 + 2 + 2] cycloaddition of various enediynes, where two acetylenic moieties are connected by a trans-olefinic moiety, gave chiral tricyclic cyclohexa-1,3-dienes using Rh-H_8-BINAP catalyst. In the case of carbon-atom-tethered enediynes, enantioselectivity was generally good-to-high regardless of the substituents on their alkyne termini. In contrast, with heteroatom-tethered enediynes, appropriate substituents were required to induce the oxidative coupling of alkyne and alkene moieties before that of two alkyne moieties, which would be important for highly enantioselective intramolecular cycloaddition.

Introduction

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of C2-unsaturated motifs, such as alkynes and alkenes, is a powerful and reliable method for the synthesis of a six-membered carbon skeleton.[1] There are several types of cycloadditions, including intermolecular and intramolecular reactions. Among the latter reactions (Scheme 1), the cycloaddition of triynes is a well-known protocol for the synthesis of substituted benzene derivatives (type A), and various transition-metal complexes including those of Rh,[2] Ni,[3] Pd,[4] Ru,[5] Co,[6] Mo,[7] and Fe[8] have been shown to be efficient catalysts. Three examples

SCHEME 1. Types of Intramolecular [2 + 2 + 2] Cycloadditions



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of an enantioselective reaction have also been reported: a helically chiral compound was obtained using a chiral Ni catalyst,[9] *ortho*-diarylbenzenes with two axial chiralities were provided using a chiral Ir catalyst,[10] and planar chiral metacyclophanes were obtained using a chiral Rh catalyst.[11] Compared with the abundant information regarding triynes, there are few examples of enediynes, including yne-ene-ynes (type B) and yne-yne-enes (type C).[12] Yamamoto and co-workers reported the Pd-catalyzed reaction of an oxygen-tethered yne-ene-yne, which gave a mixture of cyclohexa-1,3- and 1,4-dienes.[13] Pd catalyst could also be used in the cycloaddition of yne-yne-enes.[13] While the cobalt-mediated reaction of yne-yne-enes,[14] including a diastereoselective version,[15] has been reported, to the best of our knowledge the catalytic and enantioselective cycloaddition of enediynes remains unexplored.[16,17]

Recently, Roglans and co-workers reported a Rh-catalyzed intramolecular [2 + 2 + 2] cycloaddition, where macrocyclic enediynes with an *E*-olefinic moiety gave *dl* cycloadducts and those with a *Z*-olefinic moiety gave meso cycloadducts.[18] Therefore, the enantioselective cycloaddition of an acyclic enediyne with an *E*-olefinic moiety using a chiral catalyst would give a tricyclic cyclohexa-1,3-diene with two chiral carbon centers via a bicyclic metallacyclopentene (Scheme 2). If a symmetrical substrate (R = R′) were used, a C_2 symmetrical compound would be obtained.

We report here that the cationic Rh-H_8-BINAP complex catalyzes an enantioselective [2 + 2 + 2] cycloaddition of symmetrical and unsymmetrical (*E*)-enediynes. The different enantioselectivities of this cycloaddition between a reaction pathway via alkyne−alkene coupling and that via alkyne−alkyne coupling are also discussed.

SCHEME 2. Enantioselective [2 + 2 + 2] Cycloaddition of (*E*)-Enediynes

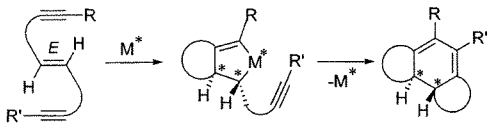
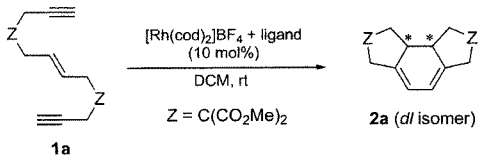


TABLE 1. Screening of Various Chiral Ligands



entry	ligand	time/h	yield/%	ee/%
1	(*S*)-BINAP	24	59	19
2	(*S*)-tolBINAP	24	15	1
3	(*S*)-H_8-BINAP	1/4	75	76
4[a]	(*S,S*)-BDPP	3	NR	
5[a]	(*S,S*)-MeDUPHOS	3	NR	

[a] DCE was used as solvent, and the reaction temperature was gradually raised to reflux.

Results and Discussion

We chose carbon-atom-tethered symmetrical enediyne **1a** as a model substrate and used it in the reaction using cationic rhodium complexes with various chiral diphosphine ligands in dichloromethane (DCM) at room temperature (Table 1).[19] When BINAP was used, [2 + 2 + 2] cycloadduct **2a** was obtained as a *dl* isomer, as expected; however, its enantiomeric excess was low (entry 1). In the case of tolBINAP, which was an efficient chiral ligand for the enantioselective intermolecular [2 + 2 + 2] cycloaddition of enynes with alkynes,[20] the reaction proceeded sluggishly, and almost no enantioselectivity was observed (entry 2). In contrast, H_8-BINAP was found to be an appropriate ligand for the present reaction: enediyne **1a** was consumed within 15 min and cycloadduct **2a** was obtained in good yield and ee (entry 3). Rh-MeDUPHOS and -BDPP complexes showed almost no catalytic activity (entries 4 and 5).

When a preliminarily isolated chiral rhodium complex, [Rh(cod){(*S*)-H_8-binap}]BF_4, was used, slight increases in yield and ee were observed (Table 2, entry 1). Under these reaction conditions, carbon-atom-tethered symmetrical (*E*)-enediynes with various substituents on their termini were examined.[21] In the case of methoxycarbonyl- and benzyloxymethyl-substituted

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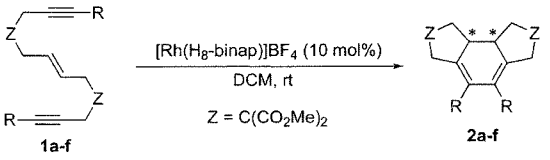
(21) When (*Z*)-enediyne **1a** was examined under the same reaction conditions, an ene-type product derived from the enyne moiety was a major product and [2 + 2 + 2] cycloadduct could not be detected. For enantioselective ene-type reaction of 1,6-enynes with (*Z*)-olefinic moiety using chiral Rh catalysts, see: (a) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104−4106. (b) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198−8199. (c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526−4529.
(22) Only a trace amount of cycloadduct **2d** was detected at room temperature for 24 h.

TABLE 2. [2 + 2 + 2] Cycloaddition of Carbon-Tethered Symmetrical Enediynes

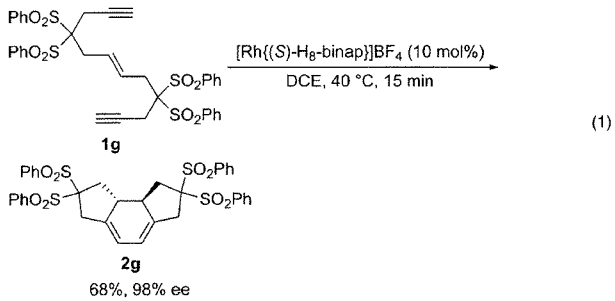


entry	R		time/h	yield/%	ee/%
1	H	**1a**	1/4	81 (**2a**)	78
2	CO_2Me	**1b**	1	72 (**2b**)	98
3	CH_2OBn	**1c**	6	63 (**2c**)	98
4[a]	Me	**1d**	24	81 (**2d**)	97
5[a]	Br	**1e**	24	48 (**2e**)	91
6[a,b]	Ph	**1f**	24	41 (**2f**)	95

[a] DCE was used as solvent at 60 °C. [b] The amount of the catalyst was 20 mol %.

enediynes **1b** and **1c**, the reaction proceeded at room temperature and the enantioselectivity was extremely high (entries 2 and 3). Me-substituted enediyne **1d** was less reactive than enediynes **1b** and **1c**, and a higher reaction temperature was required;[22] however, the ee of cycloadduct **2d** was still extremely high (entry 4). On the basis of the reaction temperature and time, the reactivity of enediynes depending on the substituents of their alkyne termini was in the order methoxycarbonyl > benzyloxymethyl > methyl. Bromo-substituted enediyne **1e** also underwent the cycloaddition, and 2,3-dibromocylcohexa-1,3-diene **2e** was obtained (entry 5). A phenyl substituent retarded the cycloaddition and harsher conditions were required, but cycloadduct **2f** was obtained in high ee (entry 6).

Next, we examined enediyne **1g** which has geminal phenylsulfonyl groups on its tethers (eq 1): in contrast to enediyne **1a** (Table 2, entry 1), extremely high ee was achieved despite the lack of a substituent on its alkyne termini. Moreover, cycloadduct **2g** was determined to be an (*R*,*R*)-isomer by X-ray crystallographic measurements (Supporting Information).

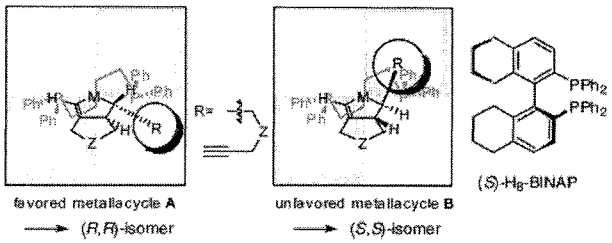


(1)

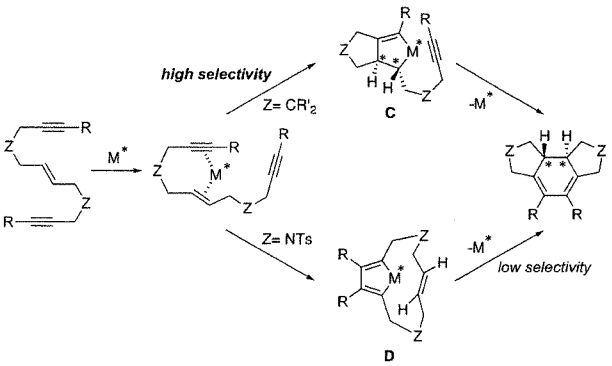
Scheme 3 shows a possible explanation for the asymmetric induction of the (*R*,*R*)-isomer by the Rh-(*S*)-H_8-BINAP catalyst. Two asymmetric carbon atoms would be induced at the formation of metallacyclopentene derived from an enyne moiety of enediyne. Because of the equatorial phenyls on phosphorus atoms of H_8-BINAP, the first and third quadrants are congested. As a result, metallacyclopentene **A**, where the R substituent is located at the fourth quadrant, is more favorable than metallacyclopentene **B**, where steric repulsion between R and phenyl groups exists.

Unsymmetrical enediyne **1h**, which has methoxycarbonyl and methyl groups on its termini, was also a good substrate, and

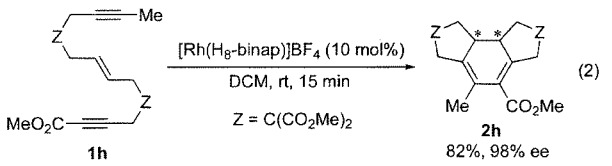
SCHEME 3. Possible Explanation of Asymmetric Induction and the Structure of H_8-BINAP



SCHEME 4. Possible Explanation for the Different Enantioselectivity

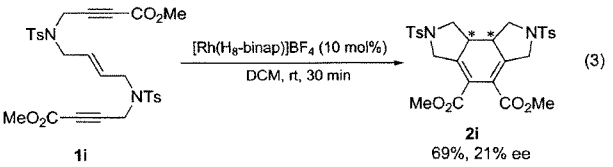


the corresponding cycloadduct **2h** was obtained in good yield and extremely high ee (eq 2).



(2)

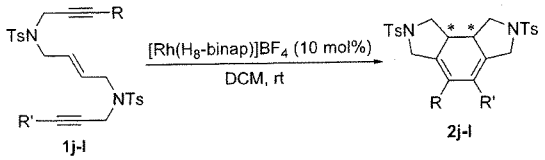
Next, we examined nitrogen-tethered enediyne **1i** with methoxycarbonyl groups on its termini, which gave the best enantioselectivity in the case of carbon-tethered enediynes (Table 2, entry 2): the substrate was completely consumed within 30 min and the corresponding cycloadduct **2i** was obtained, but its enantiomeric excess was very low (eq 3).



(3)

We assumed that the different enantioselectivity depending on the structure of tethers derives from the reaction pathway (Scheme 4): π-complexation of the metal catalyst to the enyne moiety of enediyne would be the beginning of the present cycloaddition. In the case of carbon-tethered enediyne, the oxidative coupling would proceed with high enantioselectivity to give bicyclic metallacyclopentene **C**, where two chiral carbon centers are generated. The subsequent intramolecular alkyne insertion along with reductive elimination gives a tricyclic cyclohexa-1,3-diene. In contrast, in the case of nitrogen-tethered enediyne, the oxidative coupling of two distant alkyne moieties would proceed before that of the enyne moiety to give a bicyclic

TABLE 3. [2 + 2 + 2] Cycloaddition of Nitrogen-Tethered Enediynes

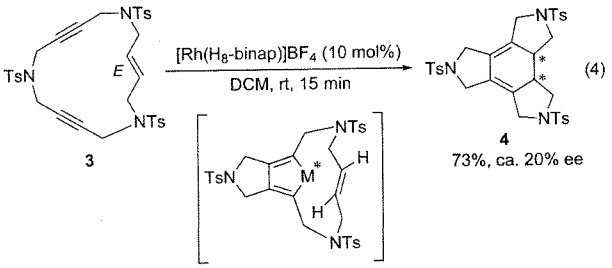


1j-l 2j-l

entry	R	R′		time/h	yield/%	ee/%
1	CH_2OBn	CH_2OBn	**1j**	2	75 (**2j**)	51
2	Me	CH_2OBn	**1k**	2	71 (**2k**)	71
3	Bu	Bu	**1l**	4	90 (**2l**)	89

metallacyclopentadiene **D** because nitrogen tether activates the alkynes more than carbon tether. The enantioselectivity of the subsequent intramolecular alkene insertion is expected to be very low, and the corresponding cycloadduct would be obtained in poor ee.

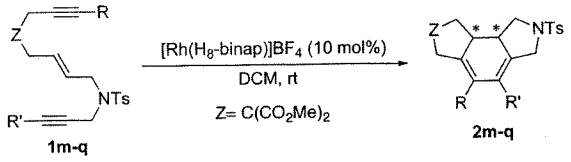
To ascertain the validity of the above speculation, we subjected cyclic enediyne **3** with an *E*-olefinic moiety[18] to enantioselective [2 + 2 + 2] cycloaddition, where oxidative coupling of a diyne moiety would proceed predominantly before that of an enyne moiety. Under the same reaction conditions as those of acyclic enediynes, tetracyclic cyclohexa-1,3-diene **4** was obtained in good yield, but its enantiomeric excess was very low, as expected (eq 4).



These results imply that the selective formation of metallacyclopentene from an enyne moiety of an enediyne would induce high enantioselectivity. To suppress the oxidative coupling of two alkyne moieties, we introduced appropriate substituents to the alkyne termini of enediyne, which would decrease the reactivity of alkyne moieties (Table 3). When enediyne **1j** with benzyloxymethyl groups was used, enantiomeric excess of cycloadduct **2j** was drastically increased (entry 1). The introduction of alkyl group(s) further improved the enantioselectivity (entries 2 and 3): in the case of enediyne **1l** with two butyls on its alkyne termini, the enantiomeric excess reached almost 90%.[23]

We further examined unsymmetrical enediynes possessing carbon and nitrogen tethers (Table 4). In the case of enediyne **1m** with unsubstituted alkyne termini, enantioselectivity was low, probably because terminal alkynes are very reactive and the oxidative coupling of two alkyne moieties would proceed predominantly before that of the enyne moiety (entry 1). In fact, the introduction of a methyl group decreased the reactivity of the alkyne of the nitrogen-tethered enyne moiety and enantioselectivity was improved (entry 2). When a methoxycarbonyl group was introduced to the alkyne terminus of the carbon tether, the oxidative coupling of two alkyne moieties could be further impaired and the ee of cycloadduct **2o** exceeded 90% (entries 3 and 4). Nitrogen-tethered enynes are generally more reactive than carbon-tethered enynes, but the introduction of an ester functionality increased the reactivity of alkyne and oxidative coupling would mainly occur at the carbon-tethered enyne moieties in enediynes **1o** and **1p**. Methyl groups at alkyne termini sufficiently interfered with alkyne−alkyne oxidative coupling, and extremely high enantioselectivity was achieved (entry 5).

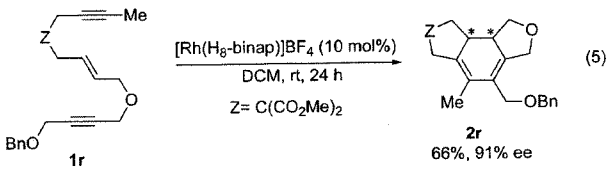
TABLE 4. [2 + 2 + 2] Cycloaddition of Unsymmetrical Enediynes with Carbon and Nitrogen Tethers



1m-q 2m-q

entry	R	R′		time/h	yield/%	ee/%
1	H	H	**1m**	1/4	41 (**2m**)	15
2	H	Me	**1n**	1	55 (**2n**)	64
3	CO_2Me	Me	**1o**	1/4	66 (**2o**)	91
4	CO_2Me	Ph	**1p**	1/4	68 (**2p**)	91
5	Me	Me	**1q**	1/2	>99 (**2q**)	97

Enediyne **1r** with carbon and oxygen tethers could also be transformed into the corresponding chiral tricyclic product **2r** in high ee (eq 5).



Conclusions

We here developed an enantioselective intramolecular [2 + 2 + 2] cycloaddition of various enediynes using Rh-H_8-BINAP catalyst. The reaction of carbon-tethered enediynes proceeded with high enantioselectivity to give tricyclic cyclohexa-1,3-dienes. In the case of nitrogen-tethered enediynes, the choice of substituents on the alkyne termini is very important for high enantioselectivity to prevent alkyne−alkyne oxidative coupling of enediynes prior to alkyne−alkene coupling. Unsymmetrical enediynes with carbon and heteroatom tethers were also transformed into [2 + 2 + 2] cycloadducts in high ee.

Experimental Section

General. Anhydrous DCM and 1,2-dichloroethane (DCE) are commercially available, and they were dried over molecular sieves 4 Å (MS 4 Å) and degassed by argon bubbling before use. All reactions were examined under an argon atmosphere. NMR spectra were measured using TMS as an internal standard, and $CDCl_3$ was used as a solvent.

Typical Experimental Procedure for the Enantioselective Intramolecular [2 + 2 + 2] Cycloaddition of Enediyne 1a (Table 2, Entry 1). Under an atmosphere of argon, [Rh(cod)(H_8-binap)]-BF_4 (10.0 mg, 0.010 mmol) was stirred in DCM (1.0 mL) at room temperature. The flask was purged with hydrogen gas, and the solution was stirred for a further 30 min. After the solvent and

(23) We examined enediyene **1l** with two butyls because an enediyene with two methyls on its alkyne termini gave insoluble products and their structures could not be determined.

hydrogen were excluded under reduced pressure, argon gas was introduced. To the flask was added DCM (0.2 mL), and the solution was stirred; then enediyne **1a** (39.2 mg, 0.10 mmol) in DCM (0.8 mL) was added, and the mixture was stirred at ambient temperature for 15 min. The solvent was removed under reduced pressure, and the resulting crude products were purified by thin-layer chromatography to give pure cycloadduct **2a** (31.8 mg, 0.081 mmol, 81%).

(*E*)-Tetramethyldodec-6-ene-1,11-diyne-4,4,9,9-tetracarboxylate (1a): White solid. mp 102 °C (hexane/Et_2O); IR (CH_2Cl_2) 3286, 2956, 1737, 1201, 690 cm^{-1}; ^1H NMR δ = 2.02 (t, J = 2.7 Hz, 2H), 2.76−2.78 (m, 8H), 3.74 (s, 12H), 5.40−5.44 (m, 2H); ^{13}C NMR δ = 22.6, 35.3, 52.8, 56.8, 71.5, 78.8, 128.6, 170.1; Anal. Calcd for $C_{20}H_{24}O_8$: C, 61.22; H, 6.16. Found: C, 61.31; H, 6.27.

***trans*-Tetramethyl-1,3,6,8,8a,8b-hexahydro-*as*-indacene-2,2,7,7-tetracarboxylate (2a):** White solid. mp 81 °C (hexane/Et_2O); IR (CH_2Cl_2) 2954, 1731, 1280, 1218, 764 cm^{-1}; ^1H NMR δ = 1.92 (dd, J = 11.0, 13.1 Hz, 2H), 2.38−2.44 (m, 2H), 2.67 (dd, J = 5.5, 13.1 Hz, 2H), 2.91 (d, J = 17.7 Hz, 2H), 3.16 (d, J = 17.7 Hz, 2H), 3.72 (s, 6H), 3.74 (s, 6H), 5.79 (s, 2H); ^{13}C NMR δ = 37.9, 40.0, 44.5, 52.8, 52.8, 59.6, 117.3, 140.6, 172.0, 172.0; Anal. Calcd for $C_{20}H_{24}O_8$: C, 61.22; H, 6.16. Found: C, 61.23; H, 6.16. $[\alpha]^{25}_D$ 42.0° (*c* 1.36, $CHCl_3$, 78% ee). The ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel Doubly Arrayed OD-H: 4 × 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 21 min for minor isomer and 23 min for major isomer).

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Supporting Information Available: Spectral data for all new compounds and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070762D

総合論文

イリジウム，ロジウム錯体を用いる触媒的付加環化反応の開発

柴田　高範*

Iridium and Rhodium Complex-Catalyzed Cycloadditions

Takanori Shibata*

Transition metal-catalyzed cycloaddition is an atom-economical and powerful synthetic tool for the construction of cyclic carbon skeletons. Various types of cycloadditions, including [2+2+1], [2+2+2], [4+2] cycloaddition, etc., have been reported. Their asymmetric versions using chiral transition metal catalysts have also been reported to give enantiomerically-enriched multi-cyclic compounds.

First, an iridium-catalyzed enantioselective Pauson-Khand-type reaction is summarized. Pauson-Khand(-type) reaction is a [2+2+1] cycloaddition of an alkyne, alkene and carbon monoxide, and gives synthetically useful cyclopentenones. Rhodium- and iridium-catalyzed Pauson-Khand-type reactions using an aldehyde as a CO source were also mentioned. Second, two types of enantioselective [2+2+2] cycloadditions are described: One is an iridium-catalyzed [2+2+2] cycloaddition of diynes and monoalkynes for the synthesis of chiral teraryls with two axial chiralities. Another is a rhodium-catalyzed [2+2+2] cycloaddition of enynes and monoalkynes for the synthesis of bicyclic cyclohexa-1,3-dienes with a chiral quaternary carbon center. Third, a rhodium-catalyzed enantioselective [2+2] cycloaddition of alkynes and alkenes for the synthesis of chiral cyclobutenes is mentioned.

Key words: cycloaddition, catalysis, iridium, rhodium, chirality, enynes, diynes

はじめに

付加環化反応とは一般に，複数の反応ユニット間で，複数の結合生成を伴うことにより環状化合物を与える反応であり，原料の構成成分がすべて生成物に含まれるため，原子効率が高い反応である。反応ユニットとしては，アルキン，アルケン，ジエン，アレンなど炭素-炭素多重結合が多用される。特に，遷移金属錯体を用いる触媒的付加環化反応は，中心金属，配位子の適切な選択により，比較的穏やかな反応条件下，高い化学選択性，位置選択性，立体選択性を実現できることから，多環状化合物合成の強力な合成ツールである[1]。反応機構は，低原子価遷移金属錯体の2つの反応ユニットへの酸化的カップリングによるメタラサイクルの生成に始まり，別の反応ユニットの挿入などを経て，遷移金属錯体の還元的脱離により環状化合物が得られるとともに触媒が再生される。反応部位である不飽和結合のπ電子が，遷移金属錯体へ配位することが起点であるため，ルイス酸触媒による付加環化反応と異なり，ヘテロ元素を含んだ官能基が不要であり，また不斉反応において，高いエナンチオ選択性を実現できる場合が多い。

本総合論文では，筆者の研究グループが開発したイリジウム，ロジウム触媒を用いる[2+2+1]，[2+2+2]，[2+2]付加環化反応について，不斉反応を中心に概説する。

2004年度有機合成化学奨励賞受賞

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1. [2+2+1]付加環化反応

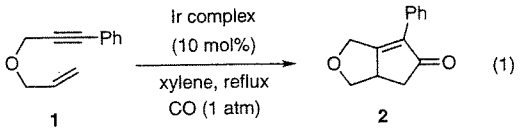
1.1 触媒的不斉 Pauson-Khand 型反応[2]

アルキン，アルケン，一酸化炭素の[2+2+1]付加環化反応が，化学量論量の$Co_2(CO)_8$を用いることにより進行し，シクロペンテノンを与える。この反応が，1973年にKhandとPausonにより発表され(Pauson-Khand反応)[3]，その後，エンインを用いる分子内反応に展開されたことにより，合成的有用性が飛躍的に高まり，天然物の全合成における鍵反応として利用された。想定反応機構からは，触媒量の$Co_2(CO)_8$により反応が進行し得ると考えられたが，実際には1994年にJeongが$P(OPh)_3$を配位子とするCo錯体により，エンインの触媒的分子内反応を報告した[4]。その後，コバルト錯体以

外のチタン，ルテニウム，ロジウム錯体を用いることにより次々と触媒的 Pauson-Khand 型反応〔本稿では，コバルト錯体以外を触媒として用いる反応を Pauson-Khand 型反応(PKR)として区別する〕が達成された[5]。

一方，不斉 Pauson-Khand 型反応としては，エンインのアルキン，アルケン上，あるいはアルキンとアルケンの架橋部にキラル部分をもつ光学活性エンインを用いるジアステレオ選択的反応の報告例があった。さらに，光学活性なコバルト二核錯体を用いるエナンチオ選択的反応も報告された。しかしながら，筆者が本研究に着手した頃，触媒的かつエナンチオ選択的反応としては，1996 年に Buchwald により発表された，光学活性シクロペンタジエニル配位子をもつキラルチタン錯体を用いる分子内反応が唯一の例であった[6]。本反応は，種々のエンインより対応する光学活性二環性シクロペンテノンを高不斉収率で与える。

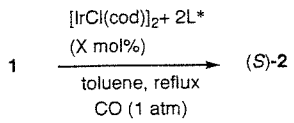
そこで筆者は，これまで Pauson-Khand 型反応の触媒として報告例のないイリジウム錯体を用いて，触媒的かつエナンチオ選択的反応を試みた。まず予備実験として，酸素架橋型エンイン 1 を用い，Pauson-Khand 型反応におけるイリジウム錯体の触媒活性を検討した。その結果，一酸化炭素雰囲気下，$[IrCl(cod)]_2$ のみを触媒として用いた場合より，配位子として PPh_3 を添加した触媒を用いた場合の方が，反応がより効率的に進行した(式 1)。



$[IrCl(cod)]_2$: 23%
$[IrCl(cod)]_2$+ $4PPh_3$: 54%

光学活性ホスフィン配位子を用いて，触媒的不斉 Pauson-Khand 型反応を検討した結果(表 1)，本反応においては BINAP が有効であり(entry 1)，特に TolBINAP(以降，本稿ではすべて *S* 体を使用)を用いた場合に，対応する光学活性二環性シクロペンテノンが高不斉収率で得られた(entry 2)。さらに，2 mol%まで$[IrCl(cod)]_2$を減らしても，長い反応時間を要するが，高収率かつ高不斉収率を達成できた(entry 3)。

Table 1 Ir-catalyzed enantioselective PKR.

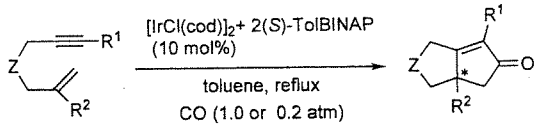


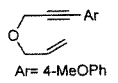
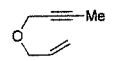
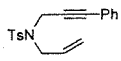
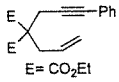
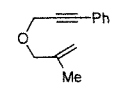
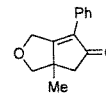
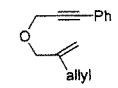
entry	X/mol%	L*	time/h	yield/%	ee/%
1	10	(*S*)-BINAP	12	64	86
2	10	(*S*)-TolBINAP	18	83	93
3	2	(*S*)-TolBINAP	72	88	92

先に述べたキラルチタン触媒を用いる Pauson-Khand 型反応では，光学活性シクロペンタジエニル配位子を合成するために数段階を要する。さらに不斉触媒が金属-炭素 σ 結合を持ち，しかも低原子価チタン錯体であることから極めて不安定であり，厳密な嫌気，嫌水条件下で反応を行う必要がある。一方本反応は，市販かつ空気中でも秤量可能な$[IrCl(cod)]_2$と TolBINAP より反応系中で調製した不斉触媒を用いることにより，高エナンチオ選択的 Pauson-Khand 型反応を実現できる。

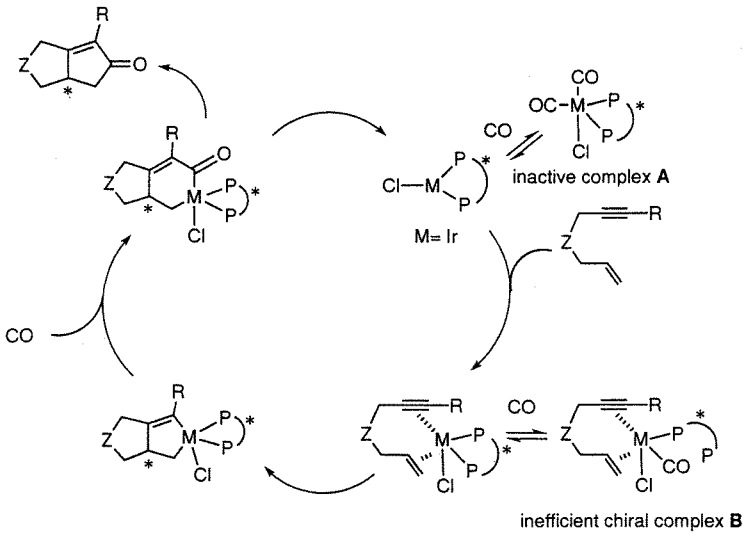
そこで，一酸化炭素常圧下，キラルイリジウム触媒により基質一般性を検討したところ(表 2)，エンインのアルキン上の置換基としてアリール基(entry 1)，アルキル基(entry 2)，アルキンとアルケンの架橋部に，酸素原子以外の窒素原子(entry 3)や炭素原子(entry 4)をもつエンインの場合も，対応する二環性シクロペンテノンが高不斉収率で得られた。

Table 2 Ir-catalyzed enantioselective PKR of various enynes.



entry	enyne	cyclopentenone	CO/atm	time/h	yield/%	ee/%
1	 Ar= 4-MeOPh		1.0	20	80	96
2			1.0	20	60	98
3			1.0	24	85	95
4	 E= CO_2Et		1.0 0.2	72 72	74 89	84 86
5			1.0 0.2	24 72	30 86	88 93
6			1.0 0.2	96 96	22 62	86 94

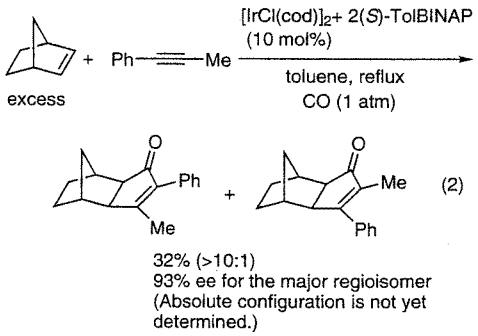
ただし，炭素架橋のエンイン(entry 4)やアルケン上に置換基をもつエンインの場合(entries 5, 6)，反応の進行が遅く，未反応のエンインが回収された。そこで，一酸化炭素低分圧下(CO: 0.2 atm, Ar: 0.8 atm)で反応を行ったところ[7]，エンインの消費が促進され，収率が向上するだけでなく，不斉収率も上昇した。この結果は，推定反応機構(スキーム 1)より，次のように説明できる。すなわち，配位不飽和なキラルイリジウム錯体に対



Scheme 1 Explanation for the effect of low partial pressure of CO gas.

し，エンインがπ配位する。その際に，一酸化炭素分圧が下がると，不活性な配位飽和錯体Aが減少することにより触媒効率が上昇する。また過剰の一酸化炭素により，わずかではあるが平衡的に生じると考えられる錯体Bが減少し，エナンチオ選択性が向上すると考えられる。

活性なアルケンであるノルボルネンを用いれば，高エナンチオ選択的分子間反応も可能だが，収率を改善するために，さらなる触媒検討が必要である(式2)。

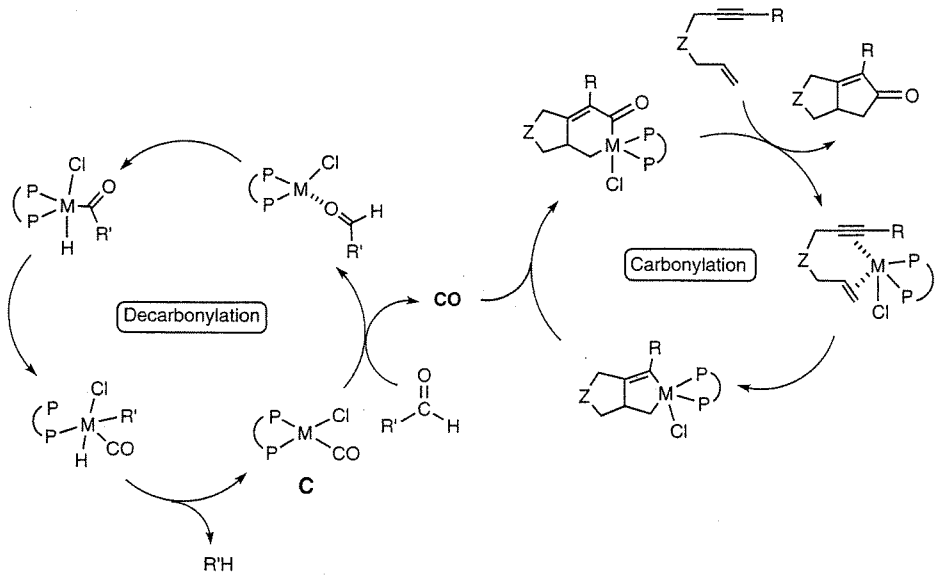


1.2 アルデヒドをCO源として用いる触媒的Pauson-Khand型反応[8)]

一酸化炭素分圧を下げることにより，触媒効率は上昇する(表2)が，一酸化炭素雰囲気下で反応を行っている限り，配位不飽和なイリジウム錯体へのCOの配位により，触媒の不活性化を防ぐことはできない。そこで，非一酸化炭素雰囲気下で反応を行い，カルボニル化の過程で，必要量のみCOを供給できれば，Pauson-Khand型反応の効率が飛躍的に向上すると期待できる。

そこで筆者は，アルデヒドの脱カルボニル化反応をCOの供給法として考えた。すなわち，ロジウム，イリジウム錯体によるアルデヒド類の触媒的脱カルボニル化反応が報告されているので[9)]，アルデヒド存在下，ロジウム，あるいはイリジウム触媒を用いるエンインのPauson-Khand型反応を行えば，メタルカルボニル錯体CがCOの供給源となり，結果として，アルデヒドのカルボニル部分をCO源とするPauson-Khand型反応が可能であると考えた(スキーム2)[10)]。

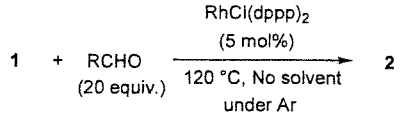
触媒として$RhCl(dppp)_2$〔dppp: 1,3-ビス(ジフェニルホスフィノ)プロパン〕を用い，無溶媒条件下，種々のアルデヒドを用いた結果を表3に示す。シンナムアルデヒドが極めて有効なCO源であり，反応は2時間で終了し，ほぼ定量的に生成物を与えた(entry 1)。アルデヒドを過剰量(20 equiv.)からほぼ当量(1.2 equiv.)に減らしても，高収率を達成できる(entry 1)。また，α,β-不飽和アルデヒドが，飽和アルデヒドより優れたCO源であった(entries 3, 4)。実際にエンインを添加せずに，

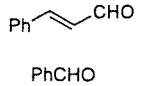
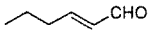
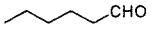


Scheme 2 Proposed scheme of PKR using an aldehyde as a CO source.

$RhCl(dppp)_2$存在下，触媒的脱カルボニル化反応を行ったところ，表中の4つのアルデヒドの中でシンナムアルデヒドが，最も速く消費された。

Table 3 Rh-catalyzed PKR using aldehydes as a CO source.

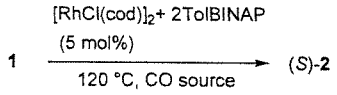


entry	aldehyde	time/h	yield/%
1		2	98(83)[a]
2	PhCHO	3	87
3		2	68
4		2	30

[a] Aldehyde (1.2 equiv.) was used.

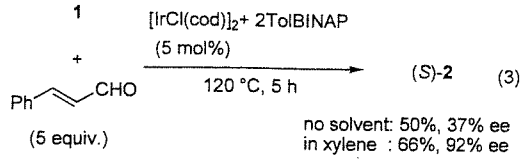
さらに無溶媒条件下，シンナムアルデヒドをCO源とする不斉Pauson-Khand型反応を試みたところ，$[RhCl(cod)]_2$とTolBINAPより系中で調製する不斉触媒を用いることにより，高エナンチオ選択的反応を実現した(表4, entry 1)。本反応をキシレン溶媒中で行うと，エンインの消費に長時間を要し，しかも不斉収率は極めて低かった(entry 2)。また，通常のPauson-Khand型反応と同様に一酸化炭素ガスをCO源として用いると，ある程度不斉収率は改善されるが，収率が低く，エンインが回収された(entry 3)。従って，$[RhCl(cod)]_2$とTolBINAPより調製される中性ロジウム錯体が不斉触媒として機能するためには，無溶媒条件で，かつアルデヒドをCO源として用いることが重要である。なお本反応は，表2に示した種々のエンインより，高収率，高不斉収率で対応する環化生成物を与えた。

Table 4 Enantioselective PKR using an aldehyde as a CO source.



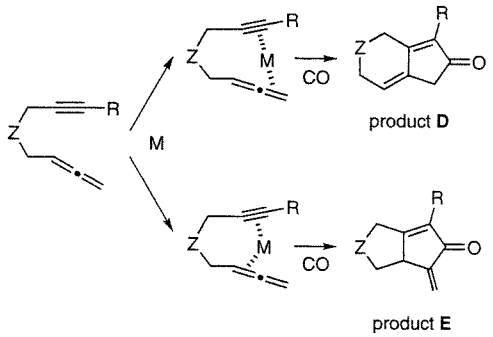
entry	CO source	solvent	time/h	yield/%	ee/%
1	cinnamaldehyde	none	4	89	82
2	cinnamaldehyde	xylene	36	54	8
3	CO gas	toluene	36	19	70

また，シンナムアルデヒドをCO源とする不斉Pauson-Khand型反応は，イリジウム錯体でも進行し，ロジウム錯体の場合より高い不斉収率を実現できる。ただし，ロジウム錯体の場合と異なり，溶媒中で反応を行うことが必要である(式3)。この結果は，ロジウム錯体は触媒活性が低いが安定であるため，より過酷な無溶媒条件で不斉触媒として機能するのに対し，イリジウム錯体は触媒活性は高いが不安定であるため，溶媒の存在が必要であると考えると理解できる[11]。



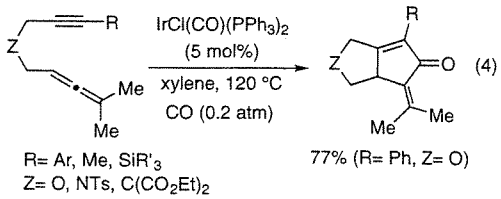
1.3 アレンインの触媒的Pauson-Khand型反応[12]

エンインのアルケン部位をアレンに替えたアレンインによる分子内Pauson-Khand(型)反応では，二重結合の反応部位により，2つの生成物D, Eが考えられる(スキーム3)。これまでに，筆者が報告した鉄カルボニル錯体を用いる当量反応[13]，奈良坂，向，Brummondらがそれぞれ報告したロジウム錯体による触媒反応[7,14]は，いずれも生成物Dを与えた。生成物Eを選択的に与える反応としては，モリブデン錯体を用いる反応[15]が知られているが，当量反応であるため，生成物Eを与える触媒反応の検討を行った。

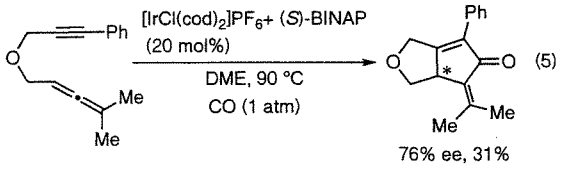


Scheme 3 Two reaction pathways of PKR of allenyne.

その結果，アレン末端にジメチル基を有するアレンインを基質とし，イリジウム触媒(Vaska錯体)を用い，一酸化炭素低分圧下(CO: 0.2 atm, Ar: 0.8 atm)で反応を行うことにより，選択的にアルキリデン基をもつシクロペンテノンを与えた(式4)。なお，イリジウム錯体に替え，対応するロジウム錯体$[RhCl(CO)(PPh_3)_2]$を用いると，アレンの外側で反応した後，β-水素脱離が進行した交差共役型トリエンが生成する[16]。

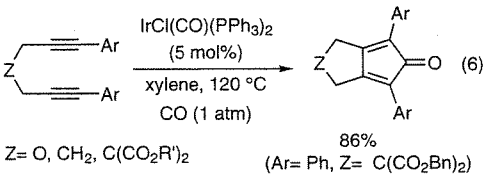


生成物Eを与える反応は，不斉反応への展開も可能である。収率は低いが，カチオン性イリジウム錯体を用いることにより，初めてのアレンインのエナンチオ選択的Pauson-Khand型反応を達成した(式5)[17]。

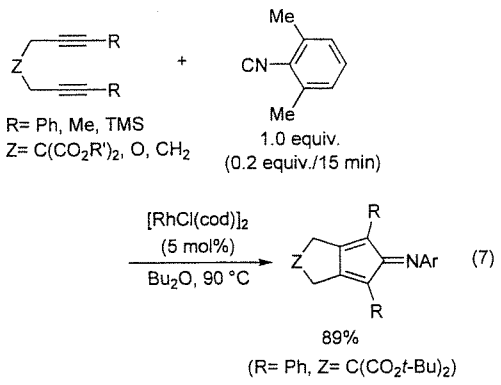


1.4 ジインを用いるシクロペンタジエノン合成[18)]

エンインに替え，ジインを用い，一酸化炭素雰囲気下[2+2+1]付加環化反応を行うと，活性なジエンとして合成化学上有用なシクロペンタジエノンが得られる。しかしながら，シクロペンタジエノンは反芳香族性4π系の極限構造を持つため不安定であり，その汎用な触媒的合成法はほとんど報告されていなかった。一方筆者は，かさ高いトリアルキルシリル基を有するアルキンを用いることにより，当量のコバルトカルボニル錯体を用いる2分子のアルキン，またはジインと一酸化炭素の[2+2+1]付加環化反応を報告した[19)]。そこで触媒反応への展開を検討したところ，イリジウム錯体が高い触媒活性をもつことを見出した。本反応は，対称ジインより種々の対称二環性シクロペンタジエノンを与える(式6)。



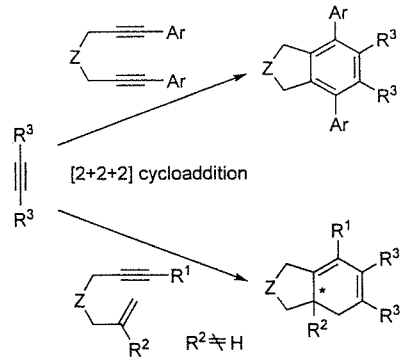
さらに，イソシアニドとジインとの[2+2+1]付加環化反応によるイミノシクロペンタジエンの触媒的合成を検討した。イソシアニドは一酸化炭素と等電子構造を持つが，金属への配位能が高いため，イソシアニドの挿入を伴う触媒的付加環化反応の報告例がほとんどなかった。実際に，上記の一酸化炭素挿入反応で有効だったVaska錯体を用いても，[2+2+1]付加環化反応は全く進行しなかった。金属触媒，反応条件を精査した結果，$[RhCl(cod)]_2$を用い，イソシアニド0.2当量を5回に分けて15分おきに添加することにより，筆者が知る限り初めてのイソシアニドの挿入を伴う触媒的[2+2+1]付加環化反応を達成した(式7)。



2. 不斉[2+2+2]付加環化反応

[2+2+2]付加環化反応，特にアルキンの三量化によるベンゼン誘導体の合成反応は，有機合成上有用な反応である。1948年にReppeが，ニッケル錯体存在下，アセチレンの反応においてベンゼンの生成を確認し[20)]，1967年に山崎が報告したコバルト錯体によるジフェニルアセチレンの三量化反応により，有機合成への利用の道が開かれた[21)]。その後，Vollhardtにより$CpCo(CO)_2$を用いる反応が包括的に研究され，特にジインとアルキンとの半分子内(semi-intramolecular)[2+2+2]付加環化反応が天然物合成へ利用されたことにより，その合成的有用性は飛躍的に増大した[22)]。そして，ロジウム，ニッケル，パラジウム錯体など種々の遷移金属錯体が触媒として機能することが報告された[1d,e)]。さらに最近では，アルキンだけでなく，アルケンを含んだ三量化反応も報告されている。

筆者は，末端にアリール基を有するジインと二置換アルキンとの[2+2+2]付加環化反応により，軸不斉を有するビアリール骨格の合成を行った。また，アルケン上に置換基をもつエンインと，アルキンとの[2+2+2]付加環化反応により，縮環部に不斉四級炭素をもつ二環性化合物の合成を行った(スキーム4)。



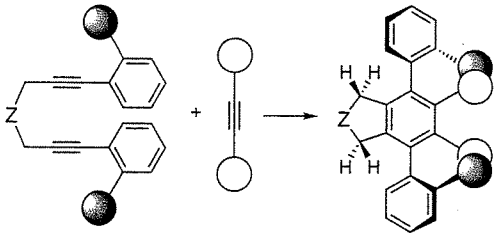
Scheme 4 [2+2+2] Cycloaddition for the generation of chirality.

2.1 軸不斉ビアリール骨格の構築[23)]

これまで，アルキンの触媒的[2+2+2]付加環化反応は数多く報告されているが，不斉[2+2+2]付加環化反応は，筆者が知る限り2例のみであった。森は，キラルなニッケル触媒を用いたトリインとアセチレンとのエナンチオトピックなグループ区別反応により，ベンジル位に不斉炭素原子をもつベンゼン誘導体を合成している[24)]。一方Staráは，キラルなニッケル触媒を用いたトリインの分子内反応により，らせん不斉を有するヘリセン誘導体を得ているが，中程度の不斉収率である上，反応例も少ない[25)]。

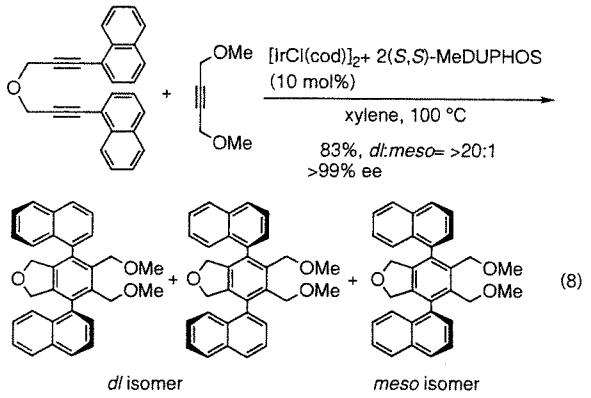
そこで筆者は，新規な不斉[2+2+2]付加環化反応として，オルト置換アリール基を末端にもつジインと，二

置換モノアルキンとの反応を着想した。環化生成物であるテルアリール化合物におけるアリール間の2つの単結合は，オルト位の置換基，ジインの架橋部に由来する環構造により，自由回転が阻害され，2つの軸不斉が生ずると考えられる(スキーム5)[26,27]。



Scheme 5 [2+2+2] Cycloaddition for the generation of two axial chiralities.

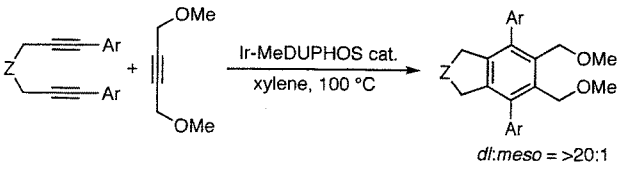
まず，両末端にナフチル基をもつジプロパルギルエーテルと1,4-ジメトキシ-2-ブチンをそれぞれジイン，モノアルキンとして用い，$[IrCl(cod)]_2$と種々の光学活性二座リン配位子より系中で調製した不斉触媒によるエナンチオ選択的[2+2+2]付加環化反応を検討した。その結果，本反応においてMeDUPHOS〔1,2-(ビス-2,5-ジメチルホスホラノ)ベンゼン，以降すべて(*S*,*S*)体を使用〕が極めて有効な不斉配位子であり，*meso*体の生成が400 MHz ^{1}H NMRで確認できず，*dl*体の鏡像体過剰率は99%以上であった(式8)。



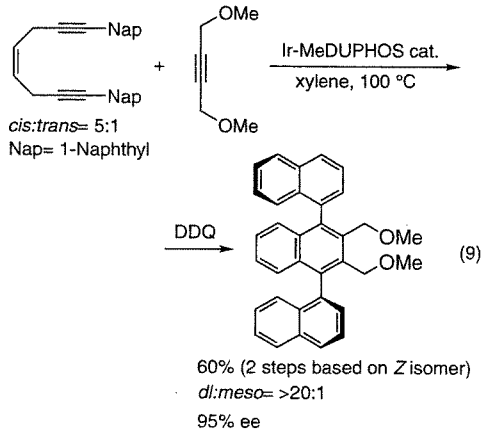
$[IrCl(cod)]_2$とMeDUPHOSより反応系中で調製する不斉触媒(以後Ir-MeDUPHOS cat.と表記)を用いることで，[2+2+2]付加環化反応が高ジアステレオ，かつ高エナンチオ選択的に進行し，種々のオルト置換アリール基を両末端に有するジイン(entries 1−3)，窒素原子や炭素原子を架橋部にもつジイン(entries 4−6)より，対応するC_2対称をもつ軸不斉テルアリール化合物が得られる(表5)。

さらに，*cis*-オレフィン部分により架橋されたジインも同条件下で反応し，DDQ酸化による芳香化を経て，高不斉収率でテルナフタレン化合物を与える(式9)。

Table 5 Enantioselective [2+2+2] cycloaddition of various diynes.



entry	Z	Ar	yield/%	ee/%
1	O	4-MeO-1-Naphthyl	72	99
2	O	2-MePh	85	99
3	O	2-ClPh	85	98
4	NTs	1-Naphthyl	92	99
5	$C(CO_2Et)_2$	1-Naphthyl	77	>99
6	CH_2	1-Naphthyl	96	>99



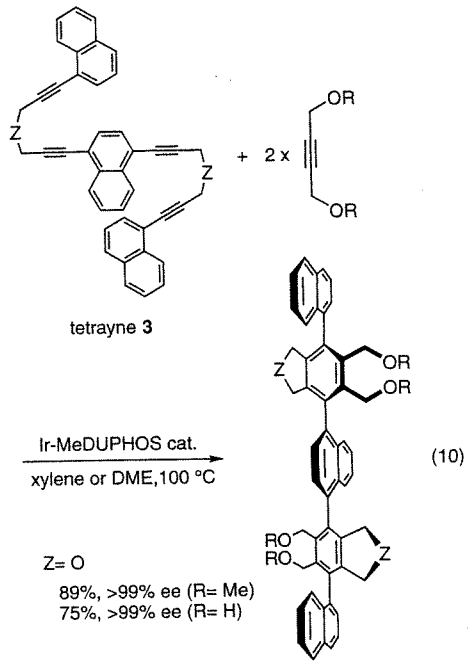
2.2 連続する軸不斉によるらせん化合物の合成[28]

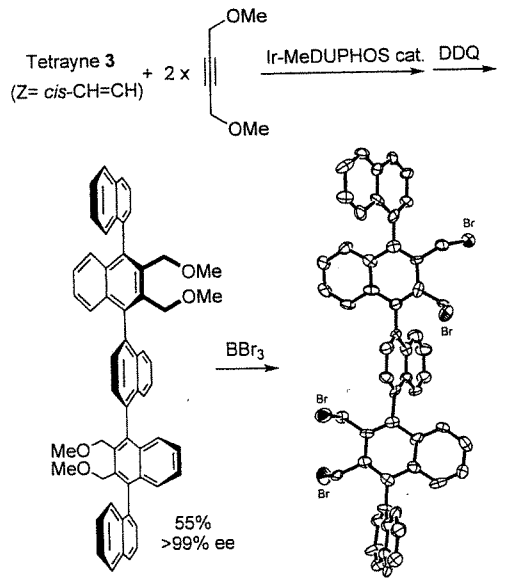
次に本反応の展開として，ジイン部位を複数もつポリインを原料とする連続的不斉[2+2+2]付加環化反応を検討した。その結果，これまでと同じキラルイリジウム触媒を用いると，ナフタレン環をスペーサーとするテトライン3と，モノアルキンとの反応がほぼ完全にエナンチオ選択的に進行し，4つの軸不斉をもつ光学活性キンクアリール化合物が収率よく得られた(式10)。モノアルキンとしてジオールを用いても，溶解性の高いDME(1,2-ジメトキシエタン)を溶媒に用いることにより，高いエナンチオ選択性を実現できる。

ジインの場合と同様に，*cis*-オレフィンにより架橋されたテトラインも反応し，引き続く芳香化により，光学活性キンクナフタレン化合物を与える(スキーム6)。メトキシ基をブロモ基に変換することにより，単結晶構造解析が可能となり，軸不斉に由来し，5つのナフタレン環がらせん状に配置していることを確認できた。

さらに4つのジイン部位をもつオクタインを用いて，不斉[2+2+2]付加環化反応を行ったところ，8つの連続する軸不斉が完全に制御され，ほぼ一方の鏡像異性体のみが，高収率で得られた(式11)。

また，1,3,5-トリエチニルベンゼンを中心骨格にもつ



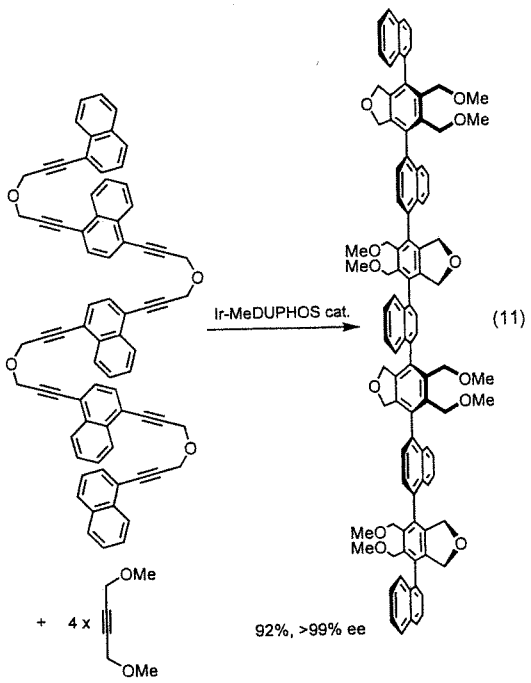


Scheme 6 Helical chirality based on consecutive axial chiralities.

ヘキサインも同様に反応し，軸不斉を6つもつデンドリマー型キラル化合物が，ほぼ一方の鏡像異性体のみ得られた(式12)[29]。

2.3 軸不斉オルトジアリールベンゼン誘導体の合成[30]

次に，トリインの分子内反応において，不斉[2+2+2]付加環化反応を試みたところ，この場合もIr-MeDUPHOS錯体が有効な不斉触媒として機能した。例えば，トリインの両末端にナフチル基をもち，酸素原子により架橋されたトリインの場合(Ar＝1-Naphthyl, Z＝O)，高不斉収率で対応する環化体を与えた(スキーム7)。両末端の置換基を種々のアリール基に替えることにより，オルト位に連続した軸不斉をもつオルトジアリールベンゼン誘導体が高エナンチオ選択的に得られる。



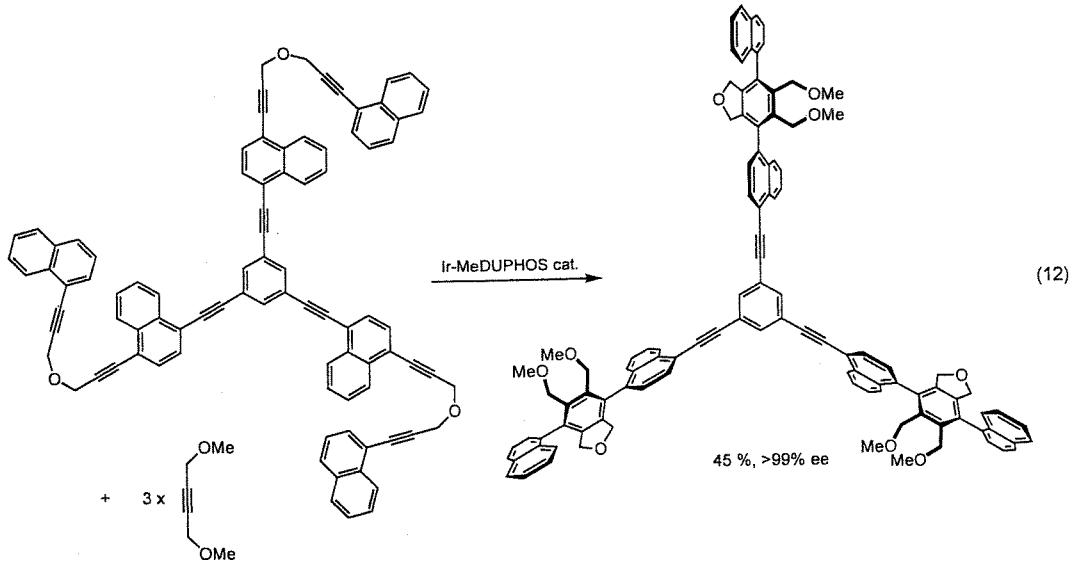
2.4 [2＋2＋2]付加環化反応による不斉四級炭素の構築[31]

次に筆者は，1,6-ジインに替え，1,6-エンインとの反応を行った。アルケン部位に置換基を有するエンインとアルキンとの間で，不斉[2+2+2]付加環化反応が進行することにより，縮環部に不斉四級炭素をもつ二環性シクロヘキサ-1,3-ジエンが得られる。反応条件を検討した結果，本反応においては，カチオン性ロジウム錯体が極めて活性であった。TolBINAPを不斉配位子としてもつ触媒を用いることにより，付加環化反応は高エナンチオ選択的に進行した(スキーム8)。本反応は，エンインのアルキン末端の置換基(R^1)，アルケン上の置換基(R^2)，架橋部(Z)について広い一般性を有し，対応する二環性シクロヘキサ-1,3-ジエンが，高鏡像体過剰率で得られた[32]。

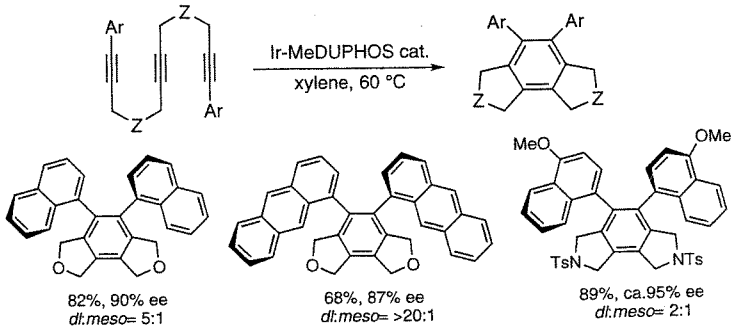
さらにアルキンとして，アセチレンガスを利用することも可能である(式13)。アセチレン分圧を下げることにより，アセチレンとエンインのアルキン部分の2：1環化体であるベンゼン誘導体の副生をある程度抑えられ，収率が向上する。

また，非対称なアルキンとのカップリング反応も進行する。アルキンの位置選択性は極めて高いとは言えないが，いずれの環化体も，高不斉収率で得られた(式14)。

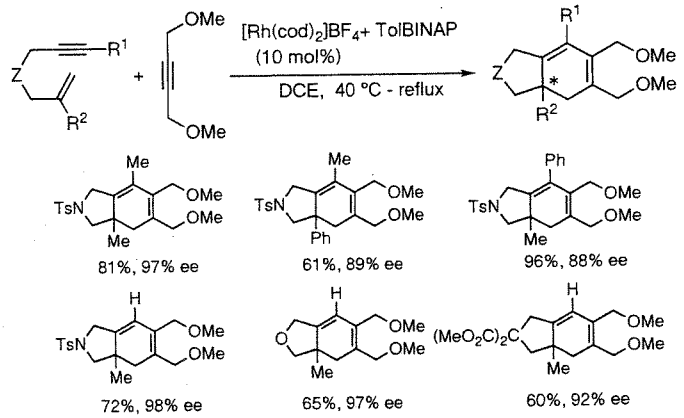
不斉四級炭素の効率的合成法の開発は，有機合成化学において重要なテーマの1つであり，これまでに，Diels-Alder反応，溝呂木-Heck反応，アルキル化反応など種々の触媒的かつ高エナンチオ選択的な手法が報告されている。上記したエンインとアルキンの不斉[2+2+2]付加環化反応は，不斉四級炭素構築の新規な



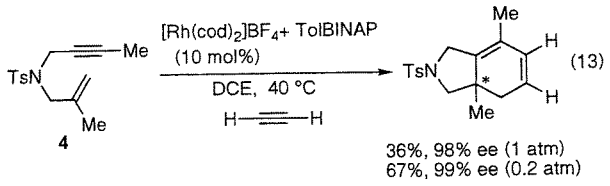
(12)



Scheme 7 Intramolecular [2+2+2] cycloaddition of triynes.



Scheme 8 [2+2+2] cycloaddition for the generation of a quaternary carbon center.



(13)

アプローチと言える。

3. 不斉[2＋2]付加環化反応[33)]

[2+2]付加環化反応は，4員環骨格を構築する最も直接的な合成手法である。しかしながら，[2+2+1]，[2+2+2]，[4+2]付加環化反応の報告例と比較すると，遷移金属錯体を用いる触媒的[2+2]付加環化反応の例は少ない。アルキンとアルケンとのカップリングによるシクロブテン骨格形成反応としては，ニッケル，ルテニウム触媒を用いる例が報告されているが，光学活性シクロブテンを与える不斉[2+2]付加環化反応は，キラルなアルキンを用いるジアステレオ選択的反応のみである[34)]。そこで筆者は，活性なアルケンであるノルボルネンを用いてアルキンとの分子間[2+2]付加環化反応を検討した結果，キラルなカチオン性ロジウム触媒を用いることにより，高エナンチオ選択的[2+2]付加環化反応を達成した。

アルキン上にエステル基を持つフェニル置換プロピオン酸メチルエステルとノルボルネンとの反応では，Rh-H_8-BINAP触媒を用いることにより，シクロブテンが高不斉収率で得られた(表6, entry 1)。ベンゼン環上に電子供与性基を導入すると，エナンチオ選択性が向上する(entries 2, 3)。なお，アルキニルケトンの場合，収率は高いが，不斉収率が極めて低い(entry 4)。一方，カルボニル基を持たないエーテルの場合，収率は低いが，アルキニルケトンの場合より不斉収率は若干向上する(entry 5)。以上の結果は，本反応において，高収率，高エナンチオ選択性を実現するためには，アルキンの一方に電子供与性基が，もう一方に電子吸引性基としてエステル基を有することが重要であると言える。

実際に，電子供与能が大きいメチル基を持つ2-ブチ

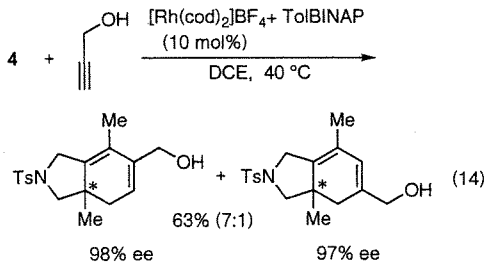
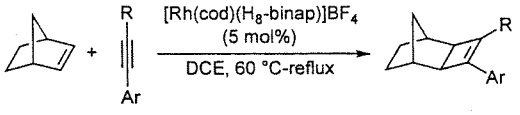
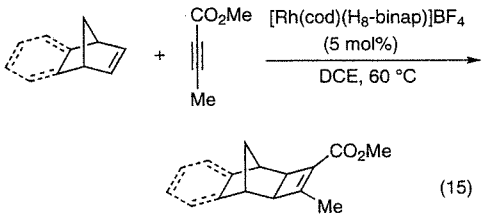


Table 6 Enantioselective [2+2] cycloaddition of norbornene and alkynes.



entry	R	Ar	yield/%	ee/%
1	CO_2Me	Ph	85	80
2	CO_2Me	4-MeOPh	98	90
3	CO_2Me	4-MePh	97	86
4	C(O)Me[a]	Ph	94	14
5	CH_2OMe[a]	Ph	59	26

[a] The chiral catalyst was *in situ* prepared from $[Rh(cod)_2]BF_4$ and H_8-BINAP.



55%, 99% ee (norbornene)
68%, 94% ee (benzonorbornadiene)

ン酸メチルエステルを用いた場合，エナンチオ選択性はさらに向上し，ノルボルネンあるいはベンゾノルボルナジエンとの反応で，対応する多環性シクロブテンが高不斉収率で得られた(式15)。

これまで，アルキンとアルケンとのエナンチオ選択的[2+2]付加環化反応としては，キラルルイス酸触媒を用いる反応が報告されている[35]。本反応は，筆者が知る限り初めての遷移金属触媒を用いるエナンチオ選択的反応と位置付けられる。

おわりに

イリジウム，あるいはロジウム錯体を用いることにより，種々の形式の不斉付加環化反応が進行し，多彩な多環状化合物を与えることを見出した。エンイン，一酸化炭素による不斉[2+2+1]付加環化反応では，キラルイリジウム錯体を不斉触媒として用いることにより，高エナンチオ選択性を実現し，合成上有用な光学活性二環性シクロペンテノンを得た。反応性に乏しいエンインの場合，一酸化炭素分圧を低下させることにより，収率ならびに不斉収率の改善を行った。さらに，CO源としてアルデヒドを用いることにより，有毒性の一酸化炭素ガスの使用が避けられるだけでなく，より効率的なCOの挿入を伴う触媒系を構築できた。また，ジインとアルキンとの[2+2+2]付加環化反応では，ベンゼン環の構築を伴って，極めて高エナンチオ選択的な軸不斉誘起を達成できた。一方エンインとアルキンとの[2+2+2]付加環化反応では，効率的な不斉四級炭素の構築が可能であり，不斉反応における新たな合成ツールとしての[2+2+2]付加環化反応を提案できた。誌面の都合上割愛したが，イリジウム触媒を用いた不斉[4+2]付加環化反応[36]，エン型反応[37]，環化異性化反応による光学活性三員環合成法[38]も開発した。

反応条件を検討する中で，イリジウム，ロジウム錯体のいずれか一方のみで進行する反応，あるいは(不斉)配位子は異なるが，いずれでも進行する反応がある。今後，それぞれの触媒の特性を活かし，新反応，あるいはこれまで合成に多段階を要したり，高エナンチオ選択的供給法が報告されていない炭素骨格のより簡便な構築法の開発を目指す。

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Recent Advances in the Catalytic Pauson–Khand-Type Reaction

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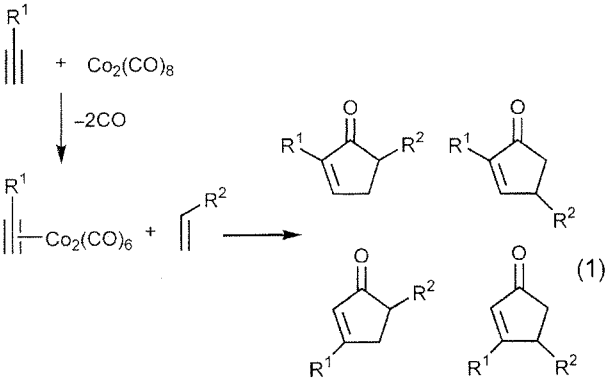
Abstract: The Pauson–Khand-type reaction is formally a [2+2+1] cycloaddition involving an alkyne, an alkene and carbon monoxide catalyzed or mediated by transition metal complexes. This review focuses on the catalytic reaction and describes the recent research on the Pauson–Khand-type reaction.

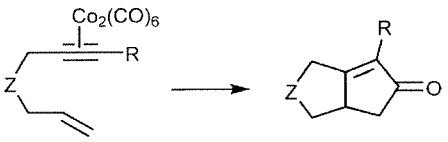
Keywords: asymmetric catalysis; carbonylation; cycloaddition; enones; enynes; transition metals

1 Introduction

In 1973, I. U. Khand and P. L. Pauson reported a [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide. An alkyne-$Co_2(CO)_6$ complex, which was prepared from $Co_2(CO)_8$ and an alkyne along with the generation of carbon monoxide, reacted with an alkene to give a synthetically useful cyclopentenone.[1] In the initial study of an intermolecular reaction, symmetrical and active alkenes, such as ethylene and norbornene, were used because four regioisomers, which are often difficult to separate, could be obtained when an unsymmetrical alkyne and alkene were used [Eq. (1)].

Use of the intramolecular reaction avoids the formation of the regioisomers. Carbonylative coupling of an enyne gives a bicyclic cyclopentenone [Eq. (2)]. In the 1980s, the Pauson–Khand reaction was recognized as a useful synthetic protocol and was used as a key reaction for the construction of carbocyclic skeletons in natural product syntheses.[2]





In this short review, I briefly summarize the early research on the catalytic Pauson–Khand reaction prior to 2000, and then summarize the recent reports, most of which were published after 2000.[3]

2 The Road to the Catalytic Pauson–Khand(-Type) Reaction

The proposed mechanism of the Pauson–Khand reaction is shown in Scheme 1.[4] It suggests that a catalytic reaction could be possible under an atmosphere of carbon monoxide; however, there have been only a few limited examples, in which large excess amounts of active alkenes were needed under a high pressure of carbon monoxide. This would be probably because $[Co_2(CO)_6]$ is readily transformed into more stable

InterScience
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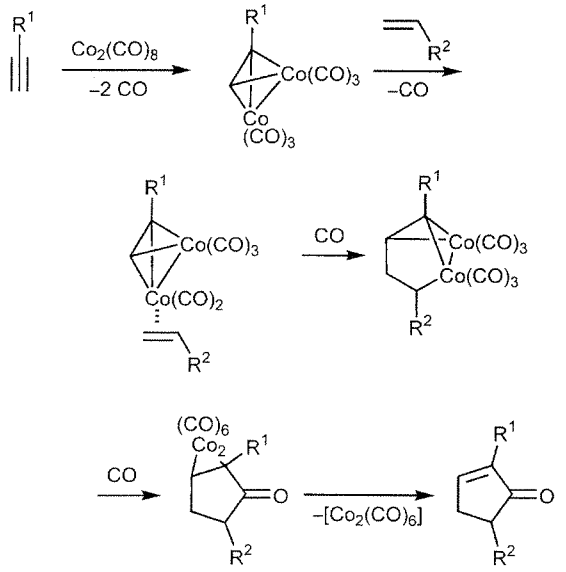
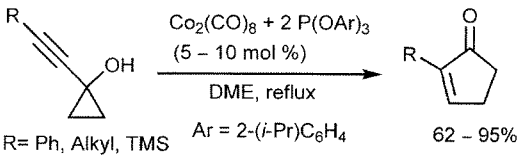
Takanori Shibata was born in 1966 in Tokyo, Japan. He studied chemistry at the University of Tokyo and earned his Ph.D in 1994 under the supervision of Prof. Koichi Narasaka. As a Research Associate, he moved to the Faculty of Science, Kitasato University (1994–1995), then to the Faculty of Science, Tokyo University of Science in the group of Prof. Kenso Soai (1995–1999). He was promoted to Associate Professor in 1999 at the Faculty of Science, Okayama University, then moved to Waseda University in 2003. He has been Professor of the School of Science and Engineering at Waseda University since 2006. He worked with Prof. E. J. Corey (Harvard University) as a postdoctoral fellow in 2001. He received the Daicel Award in 1997 and the Incentive Award in Synthetic Organic Chemistry, Japan in 2005. His current research interests concentrate on transition metal-catalyzed cycloadditions, especially asymmetric reactions.



Scheme 1. Proposed mechanism of the Pauson–Khand reaction.

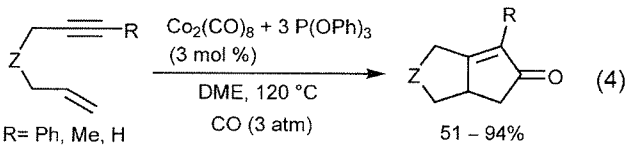
oligomeric cobalt complexes prior to the complexation with the alkyne.

In 1993, Iwasawa reported a Co-catalyzed rearrangement of alkynylcyclopropanols to cyclopentenones. Use of a triaryl phosphite as a ligand of the cobalt carbonyl complex realized a catalytic reaction [Eq. (3)].[5]



R= Ph, Alkyl, TMS; Ar = 2-(*i*-Pr)C_6H_4; 62 – 95% (3)

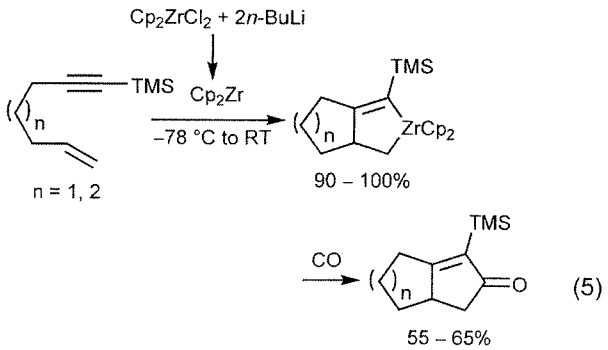
In 1994, Jeong disclosed a catalytic carbonylative coupling of enynes using $Co_2(CO)_8$ with triphenyl phosphite under the condition of pressurized carbon monoxide [Eq. (4)].[6] This report represented the



R= Ph, Me, H; Z= $C(CO_2Et)_2$, CMe_2, O, NTs; 51 – 94% (4)

starting point for catalytic and practical Pauson–Khand reactions, and various reaction conditions using a catalytic amount of cobalt carbonyl complexes were published.[3]

In another approach to the synthesis of bicyclic cyclopentenones from enynes, Negishi reported a Zr-mediated reaction. The reaction of two-valent zirconium, which was prepared in situ from Cp_2ZrCl_2 and *n*-BuLi, with an enyne gave the metallacyclopentene, and this was readily transformed into a bicyclic cyclopentenone under an atmospheric pressure of CO [Eq. (5)].[7]



n = 1, 2; 90 – 100%; 55 – 65% (5)

In 1996, Buchwald reported a Ti-catalyzed intramolecular coupling of various enynes under an atmosphere of carbon monoxide, and bicyclic cyclopentenones were directly obtained in good to excellent yields [Eq. (6)].[8] The present reaction is recognized

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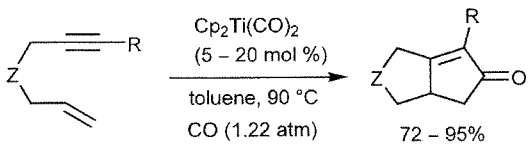
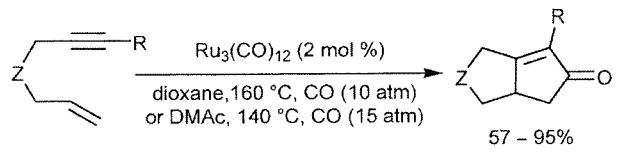


(6)

R= Ar, Me, H
Z= $C(CO_2Et)_2$, CH_2, O, NPh

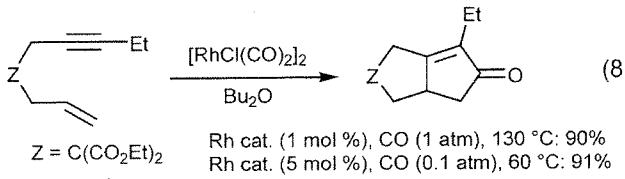
as the first catalytic Pauson–Khand-type reaction, which means a carbonylative coupling of an alkyne and an alkene catalyzed by transition metal complexes except for cobalt ones.

$Ru_3(CO)_{12}$ operated as an efficient catalyst under a high pressure of carbon monoxide at high temperatures [Eq. (7)].[9] In the case of $[RhCl(CO)_2]_2$, the carbonylative coupling proceeded more smoothly under a lower partial pressure of carbon monoxide, probably because excess amounts of carbon monoxide deactivate the Rh catalyst by coordination to the metal center [Eq. (8)].[10,11]



(7)

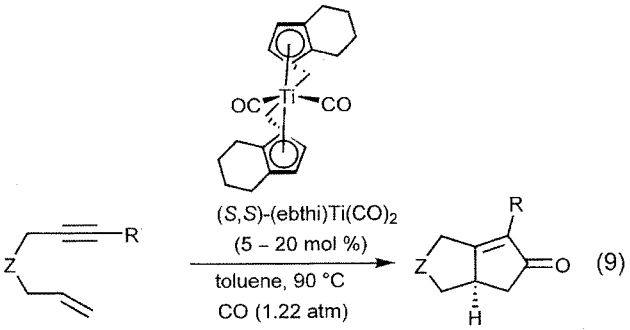
R= Ar, Alkyl, TMS
Z= $C(CO_2Et)_2$, O, NTs



(8)

3 Enantioselective Pauson–Khand(-Type) Reaction

Diastereoselective Pauson–Khand reactions using enynes with chiral auxiliaries on the alkyne or alkene terminus or tethers have been reported as have also enantioselective reactions using a stoichiometric amount of chiral cobalt complexes.[3a,d] However, a catalytic and enantioselective reaction had to wait till Buchwald's report in 1996.[12] A highly enantioselective reaction under a CO atmosphere using a transition metal catalyst with a chiral ligand is rather difficult because the chiral ligand is dissociated from the metal center by excess amounts of CO and part of the reaction proceeds by an achiral metal catalyst.[13] Buchwald overcame the difficulty by using a chiral Ti complex in which the metal center and chiral moiety were connected by a σ-bond [Eq. (9)]. Various enynes

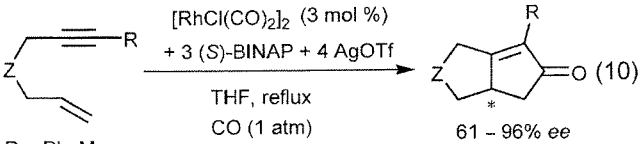


(9)

R = Ar, Alkyl, H
Z = $C(CO_2Et)_2$, CH_2, O, NBoc

were transformed into chiral bicyclic cyclopentenones by the chiral Ti-catalyzed highly enantioselective intramolecular Pauson–Khand-type reaction. However, several steps were needed for the preparation of the chiral ligand, and the Pauson–Khand-type reaction must be conducted in a glovebox because the low-valent Ti complex with a Ti–C σ-bonds is very sensitive to air and moisture.

In 2000, Jeong reported a cationic Rh-catalyzed, enantioselective Pauson–Khand-type reaction. The chiral catalyst was prepared *in situ* from $[RhCl(CO)_2]_2$ and BINAP by the addition of AgOTf [Eq. (10)].[14] Recently, a spiro-monophosphoramidite was reported to be a chiral ligand for the Rh catalyst but the enantioselectivity did not exceed that achieved by BINAP.[15]



(10)

R = Ph, Me
Z = $C(CO_2Et)_2$, O, NTs

Quite independently, Shibata reported the catalysis by Ir-tolBINAP. The chiral Ir catalyst was readily prepared *in situ* from $[IrCl(cod)]_2$ and tolBINAP, both of which are commercially available and air-stable [Eq. (11)].[16] The condition of low partial pressure of CO (0.2 atm) worked well also in the Ir-catalyzed enantioselective reaction: higher yield and enantioselectivity were achieved than under an atmospheric pressure of CO [Eq. (12)].

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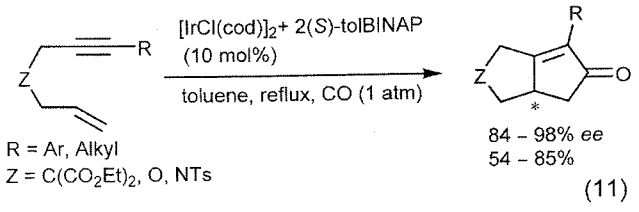

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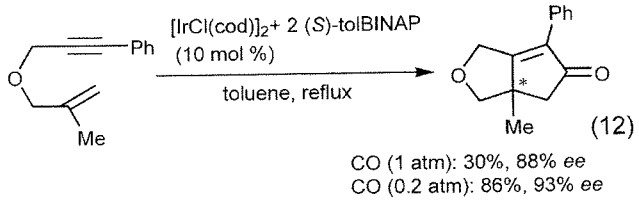
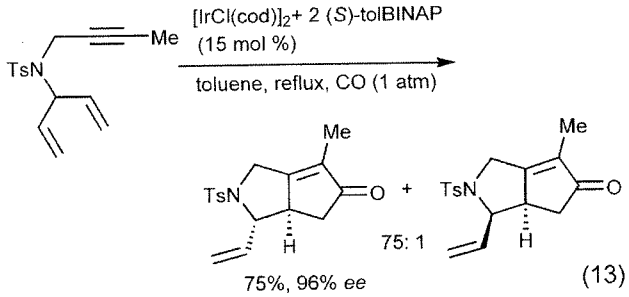


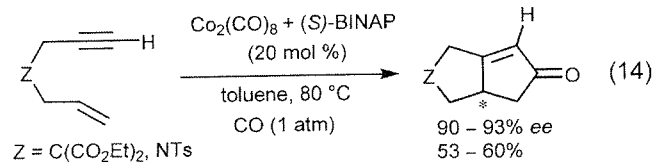
(12)

The chiral Ir catalyst was also used in the desymmetrization of *meso*-dienynes.[17] A highly enantio- and diastereoselective Pauson–Khand-type reaction proceeded to give vinyl-substituted bicyclic cyclopentenones with two chiral centers [Eq. (13)].



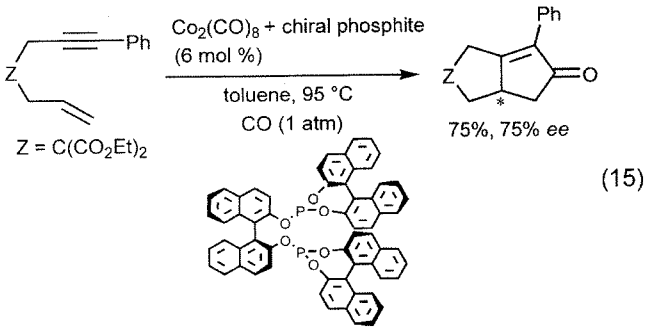
(13)

Prior to the Rh- and Ir-catalyzed reactions, Hiroi reported a $Co_2(CO)_8$-BINAP complex-catalyzed reaction.[18] High enantioselectivity was achieved; however, substrates were limited to enynes with no substitu-



(14)

ent on the alkyne terminus [Eq. (14)]. A $Co_2(CO)_8$-chiral phosphite catalyst was also reported but the enantioselectivity and generality of enynes were inferior to those with chiral Ti, Rh and Ir catalysts as mentioned above [Eq. (15)].[19]

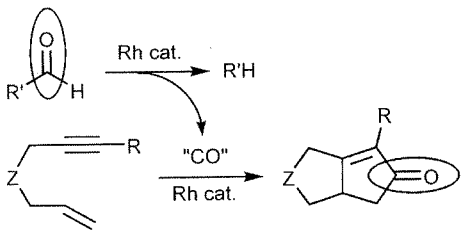


(15)

4 Pauson–Khand-Type Reactions Using Aldehydes as a CO Source

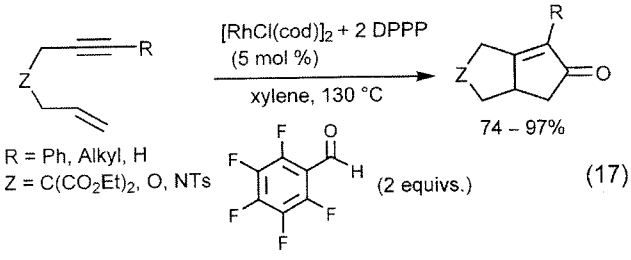
The transition metal-catalyzed decarbonylation of carbonyl compounds, such as aldehydes, ketones and acid chlorides, was already reported in the 1960s, and it was a key step in transition metal-catalyzed unique transformations.[20] However, the use of generated carbon monoxide by a decarbonylation step was largely neglected.

Rh complexes catalyze both the decarbonylation of aldehydes and the Pauson–Khand-type reaction, namely carbonylative coupling of enynes; therefore, a Pauson–Khand-type reaction using aldehydes as a CO source would be possible [Eq. (16)].



(16)

Morimoto realized the reaction using pentafluorobenzaldehyde as a CO source. Enynes were transformed into the corresponding bicyclic cyclopentenones under an atmosphere of nitrogen [Eq. (17)].[21] Shibata independently disclosed the same type of reaction using cinnamaldehyde as a CO source [Eq.



(17)

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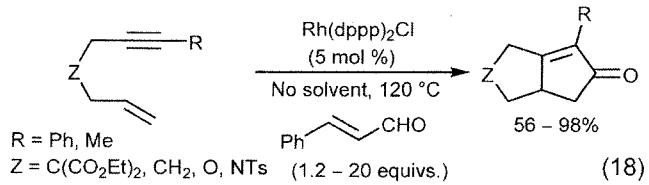
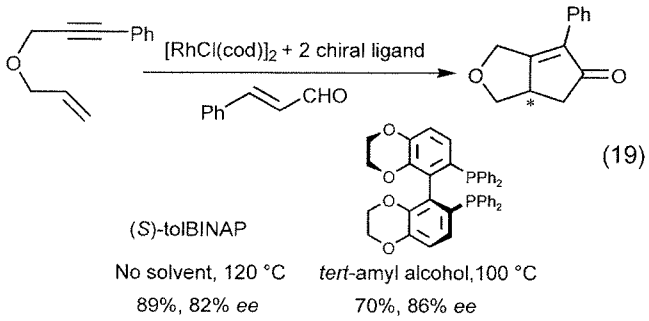
(18)].[22] The reaction efficiently proceeded without solvent under an atmosphere of argon.



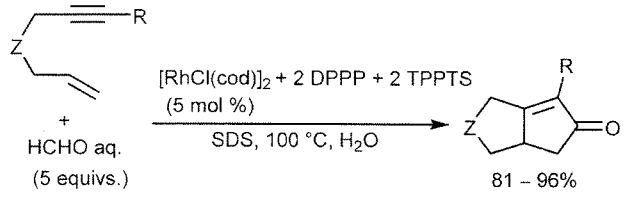
(18)

The reaction using cinnamaldehyde as a CO source could be applied for the enantioselective reaction using Rh-tolBINAP catalyst under no solvent conditions[22b] and Rh-Bisbenzodioxan Phos catalyst in *tert*-amyl alcohol[23] [Eq. (19)].



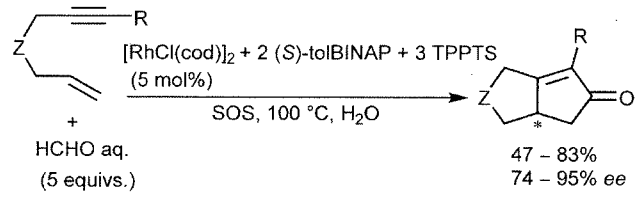
(19)

The present reaction provided a new protocol for carbonylation without the use of toxic carbon monoxide gas.[24] However, from the viewpoint of atom-economy, pentafluorobenzene and styrene were wasted. Morimoto further developed the Pauson–Khand-type reaction using formaldehyde as a CO source under the aqueous conditions.[25] The combined use of hydrophobic [DPPP = 1,3-bis(diphenylphosphino)propane] and hydrophilic (TPPTS = triphenylphospholane-3,3′,3″-trisulfonic acid trisodium salt) phosphines with a surfactant (SDS = sodium dodecyl sulfate) was essential for high yield. Morimoto proposed that decarbonylation and carbonylation take place independently, and that the former proceed in an aqueous phase and the latter in a micellar phase [Eq. (20)]. In place of DPPP, tolBINAP was used as a chiral and hydrophobic phosphine, and a highly enantioselective Pauson–Khand-type reaction using formalin (37% aqueous solution of formaldehyde) and sodium octadecyl sulfate (SOS) was achieved under the aqueous conditions [Eq. (21)].[26]



R = Ph, Alkyl
Z = C(CO2Et)2, O, NTs

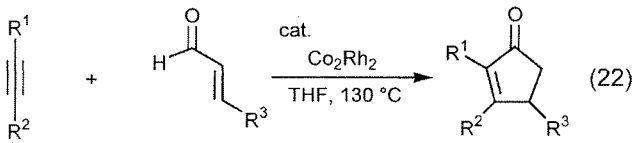
(20)



R = Ph, Alkyl
Z = C(CO2Et)2, O, NTs

(21)

The most atom-economical reaction is when an α,β-unsaturated aldehyde is used as both CO source and alkene moiety. Co/Rh heterobimetallic nanoparticles, derived from $Co_2Rh_2(CO)_{12}$, catalyzed the reaction of α,β-unsaturated aldehydes with alkynes to give cyclopentenones [Eq. (22)].[27] Chung ascertained that the reaction is a carbonylative coupling of an alkyne and alkene, and that it is not a hydroacylation along with a cyclization.



R1, R2 = Ph, Me, H
R3 = Ph, Alkyl, TMS

(22)

5 Pauson–Khand-Type Reactions of Allenes

The Pauson–Khand-type reaction of an allene moiety as the ene component has been an intriguing topic.[28] In the case of an intramolecular reaction of allenynes, there are two possible reaction pathways (Scheme 2). The reaction of an external π-bond of the allene moiety gives a bicyclic dienone (product **A**). On the other hand, the reaction of an internal π-bond gives a bicyclic cyclopentenone with an alkylidene substituent (product **B**).

Narasaka and Shibata reported the first intramolecular Pauson–Khand-type reaction of allenyne using an iron carbonyl complex under irradiation conditions. Independent of the length of the tether between

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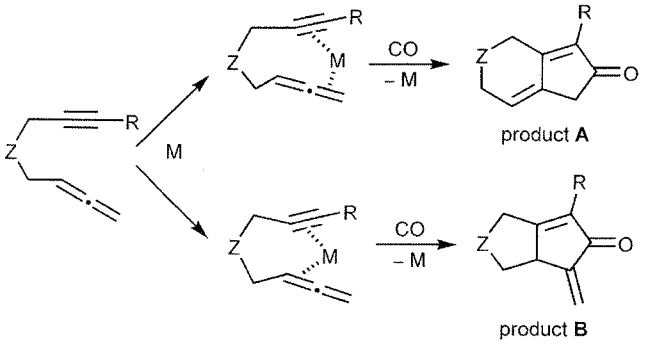
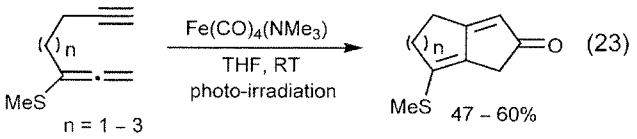
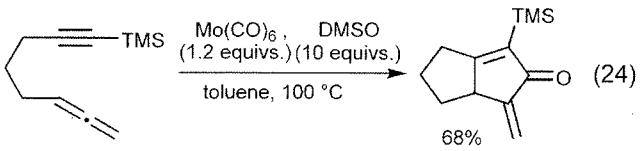


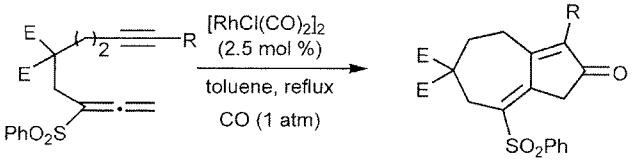
Scheme 2. Two reaction pathways of allenynes.

the allene and alkyne, bicyclic dienones (product **A**) were obtained [Eq. (23)].[29] Brummond reported an Mo-mediated reaction in which α-methylene cyclopentenone (product **B**) was obtained [Eq. (24)].[30] But these are both stoichiometric reactions.



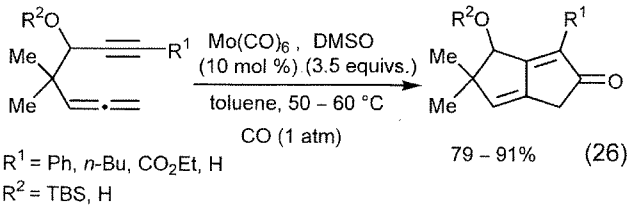


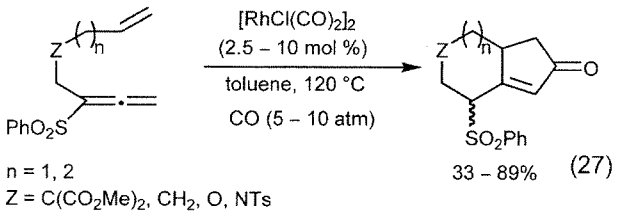
In the catalytic reaction using a Ti[8b] or Rh[10b] complex, product **A** was obtained. In the case of an Rh-catalyzed reaction, the construction of seven-membered ring systems was also possible [Eq. (25)].[31]



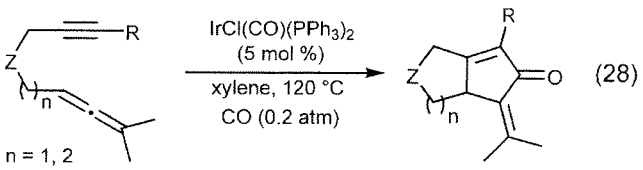
When allenynes with two-atom tethers were used under an atmospheric pressure of CO, the $Mo(CO)_6$-catalyzed reaction also gave product **A** because product **B** has a strained [3.2.0]heptenone skeleton [Eq. (26)].[32]

Recently, Mukai reported an Rh-catalyzed reaction of allenenes.[33] An intramolecular carbonylative coupling of an allene-alkene, which is tethered by three or four atoms, gave a bicyclic cylopentenone with a 6–5 or 7–5 fused ring system along with the double bond isomerization [Eq. (27)].

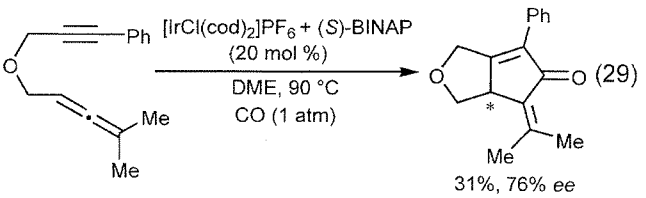




An Ir-catalyzed Pauson–Khand-type reaction resulted in a different regioselectivity. When allenynes with two substituents on the allene terminus were used under a low partial pressure of CO, the internal π-bond of allene moiety was the major reaction site and bicyclic cyclopentenones with an alkylidene substituent were obtained [Eq. (28)].[34] When, in place



of $IrCl(CO)(PPh_3)_2$, $RhCl(CO)(PPh_3)_2$ was used as a catalyst under the same reaction conditions, reaction of the external π-bond of the allene moiety was the major pathway. The present transformation realized the first example of an enantioselective Pauson–Khand-type reaction of an allenyne, although the reaction conditions have not been optimized yet [Eq. (29)].[35]



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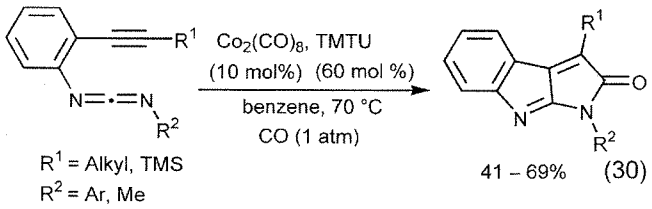
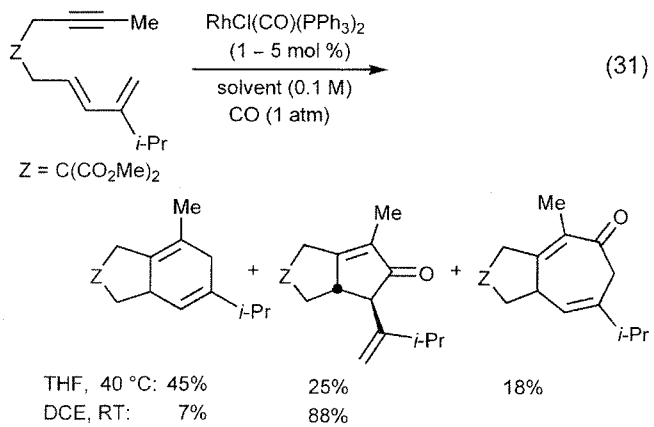
As a nitrogen analogue of an allene, a carbodiimide could also operate as an ene moiety in a Pauson–Khand reaction. After Saito's report of an Mo-mediated reaction,[36] Mukai disclosed a $Co_2(CO)_8$-catalyzed hetero-Pauson–Khand reaction of an alkyne-carbodiimide in the presence of TMTU (tetramethylthiourea) [Eq. (30)].[37]

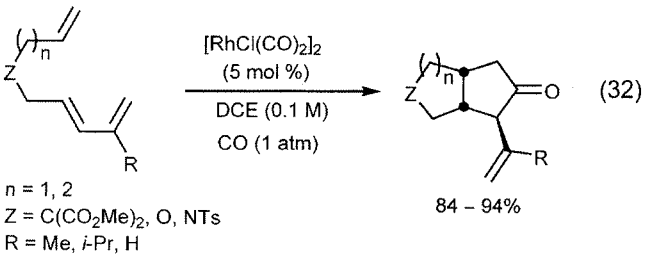


6 Pauson–Khand-Type Reactions of Dienes

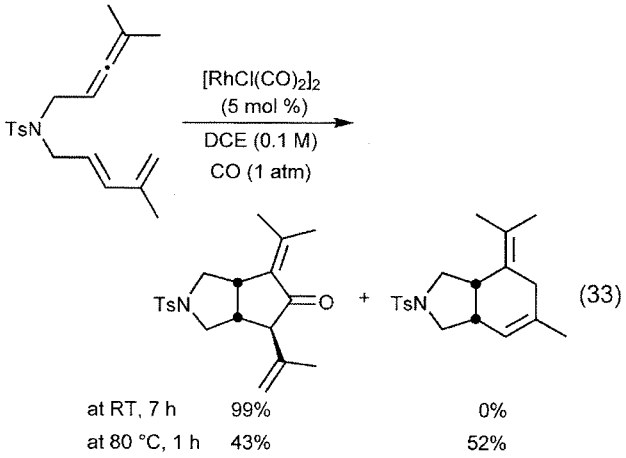
Wender studied Pauson–Khand-type reactions using dienes as the ene moiety. When the Rh-catalyzed reaction of 1,3-diene-yne was examined under an atmospheric pressure of CO at 40 °C in THF, a [4+2] cycloaddition proceeded as the major pathway, and [2+2+1] and [4+2+1] cycloadducts were minor products. On the other hand, when the reaction was examined at room temperature in 1,2-dichloroethane (DCE), a [2+2+1] cycloaddition predominantly and diastereoselectively proceeded to give a bicyclic cyclopentenone with an isopropenyl group [Eq. (31)].[38] In



place of 1,3-diene-ynes, 1,3-diene-enes also underwent the [2+2+1] cycloaddition to give bicyclic cyclopentanones as a single diastereomer [Eq. (32)].[39] The diene component plays a pivotal role in the cycloaddition, and no cycloadduct was obtained from bis-enes.

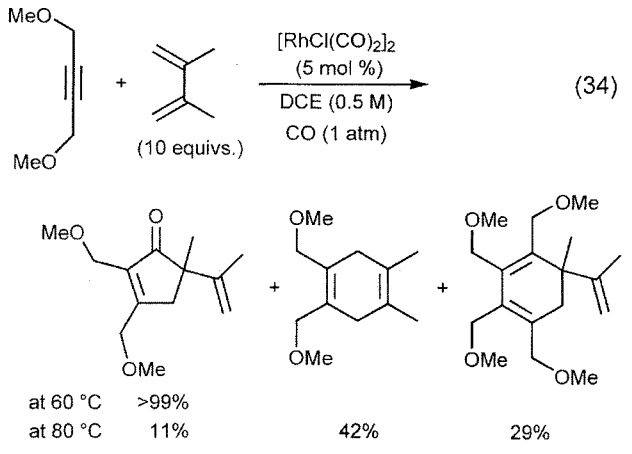


A [2+2+1] cycloaddition of a 1,3-diene-allene was also possible, and a bicyclic cyclopentanone with an alkylidene and a vinyl substituent was obtained at room temperature [Eq. (33)]. The reaction tempera-



ture determined the cycloaddition pathways, and a [4+2] cycloadduct was the major product at 80 °C.[40]

The use of a diene moiety enabled the realization of an intermolecular Pauson–Khand-type reaction. The Rh-catalyzed reaction of 2,3-dimethylbuta-1,3-diene and an alkyne efficiently proceeded at 60 °C to give a cyclopentenone with an isopropenyl group [Eq. (34)]. The choice of the reaction temperature was cru-



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cial also in this reaction, and two [4+2] cycloadducts were major products at 80 °C.[41]

7 Conclusion

This manuscript offers a brief summary of the catalytic Pauson–Khand(-type) reaction and the recent advances in this reaction type. In the 1990s, the Pauson–Khand reaction was dramatically developed into the Pauson–Khand-type reaction, and various transition metal catalysts including chiral species have been reported. Recently, modified (chiral) catalysts and reaction conditions, and new types of substrates, such as allenes and dienes, are major topics of interest. However, the limitation of alkynes and alkenes still exists, especially in enantioselective and/or intermolecular reactions. Therefore, further optimization of the catalysts and reaction conditions for the Pauson–Khand-type reaction is desired.

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