

Enantioselective Preparation of 8-Oxabicyclo[3.2.1]octane Derivatives via Asymmetric [3+2]-Cycloaddition of Platinum-Containing Carbonyl Ylides with Vinyl Ethers

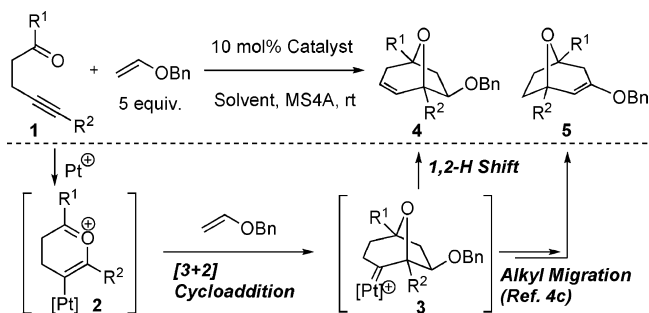
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Platinum(II)- or gold(I)-catalyzed electrophilic activation of alkynes has attracted much attention as an efficient method to facilitate atom-economical construction of complex molecules.¹ Asymmetric versions of these reactions would be highly attractive; however, there are only a few successful reports of asymmetric enyne cyclizations² and asymmetric reactions of carbene complexes generated by isomerization of propargyl esters.³ Herein, we report a platinum-catalyzed enantioselective preparation of synthetically useful 8-oxabicyclo[3.2.1]octane derivatives via an asymmetric [3+2]-cycloaddition reaction of a platinum-containing carbonyl ylide as a new type of asymmetric reaction based on the electrophilic activation of alkynes.

Scheme 1



Recently, we reported that treatment of acyclic γ,δ -ynones **1** with a catalytic amount of platinum(II) chloride in the presence of vinyl ethers gave 8-oxabicyclo[3.2.1]octane derivatives **5**^{4c} through the novel bifunctional reactive species, platinum-containing carbonyl ylides **2** (Scheme 1).^{4–6} The high utility of the product, **5**,⁷ prompted us to develop an asymmetric version of this reaction. For this purpose, we first examined the reactivity of platinum–phosphine complexes; however, the low electrophilicity of the model complex, *cis*-PtCl₂(PPh₃)₂, resulted in recovery of the starting materials. We then thought of using cationic platinum(II)–phosphine complexes^{2a–c,8} generated by treatment of platinum(II) chloride–phosphine complexes with a silver salt. As expected, the reaction proceeded smoothly at room temperature on treatment of acyclic γ,δ -ynone **1a** (R¹ = Ph, R² = Me) with 10 mol % of *cis*-PtCl₂(PPh₃)₂ associated with 10 mol % AgSbF₆ in the presence of excess benzyl vinyl ether (5 equiv) (Table 1, entry 2), and more importantly, the bicyclic alkene **4a**, the product formed through a 1,2-hydrogen shift of the carbene intermediate **3a**,⁹ was obtained in 45% yield as a single diastereomer, while the hydrolyzed ketone of the product **5a** formed by using PtCl₂ was obtained in only 10% yield as a minor product. Furthermore, the reaction with *cis*-PtCl₂[P(*m*-tol)₃]₂ afforded **4a** in higher yield and selectivity (entry 3).¹⁰ Use of 2 equiv (20 mol %) of AgSbF₆ resulted in polymerization of the vinyl ether (entry 4). It should also be noted that the reaction was significantly accelerated compared to the reaction of PtCl₂. To our knowledge, the electrophilic activation

Table 1. Reaction of **1a** (R¹ = Ph, R² = Me) with Benzyl Vinyl Ether in the Presence of Platinum(II)-Phosphine Complexes

entry	Catalyst	Solvent	Time	4a	5a
1	PtCl ₂	toluene	3 days	trace	74%
2	<i>cis</i> -PtCl ₂ (PPh ₃) ₂ AgSbF ₆ (1: 1)	CH ₂ Cl ₂	3.5 h	45%	10% ^a
3	<i>cis</i> -PtCl ₂ (<i>m</i> -tol ₃) ₂ AgSbF ₆ (1: 1)	CH ₂ Cl ₂	1.5 h	92%	8%
4	<i>cis</i> -PtCl ₂ (PPh ₃) ₂ AgSbF ₆ (1: 2)	CH ₂ Cl ₂	2 h	16%	—

^a Obtained as a hydrolyzed ketone.

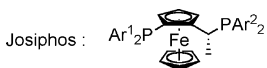
of alkynes by a monocationic platinum–bisphosphine complex depicted as [PtCl(phosphine)₂]⁺ is quite rare,¹¹ while some enyne cyclizations catalyzed by dicationic platinum–bisphosphine complexes were reported.^{2a,b,8a}

Then, we examined various chiral phosphines under the cationic conditions and found that the reaction with (*R*)-BINAP, (*R*)-SEGPHOS, (*S,S*)-DIOP, and Josiphos **6** gave the product **4a** with low enantioselectivity along with a small amount of the bicyclic enol ether **5a** (ee's were not determined) (Table 2).¹² On the other hand, when Walphos

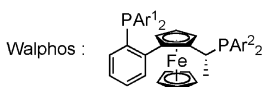
Table 2. Screening of Chiral Bisphosphine^a

entry	Bisphosphine	Time	4a		5a
			Yield (%) ^b	Ee (%) ^c	Yield (%) ^d
1 ^e	(<i>R</i>)-BINAP	7.5 h	21	4 (+)	17
2	(<i>R</i>)-SEGPHOS	25 h	33	18 (+)	detected
3 ^e	(<i>S,S</i>)-DIOP	3 h	67	4 (–)	31
4	Josiphos 6	22 h	50	10 (–)	16
5	Walphos 7a	rt-reflux	—	—	—
6	Walphos 7b	20.5 h	31	87 (–)	—
7	Walphos 7c	rt-reflux	trace	—	—
8	Walphos 7d	21.5 h	49	91 (–)	—
9 ^e	Walphos 7d	21.5 h	57	91 (–)	—
10 ^{e,f}	Walphos 7d	16.5 h	70	91 (–)	—
11	Walphos 7e	21.5 h	30	77 (–)	—

^a Reactions were performed by addition of AgSbF₆ (10 mol %) to a mixture of ynone **1a**, benzyl vinyl ether (5 equiv), PtCl₂(cod) (10 mol %), and bisphosphine (10 mol %) at RT. ^b Isolated yield. ^c Determined by chiral HPLC analysis (CHIRALPAK AD-H, 0.5 mL/min, 2-propanol/hexane = 1/99). ^d NMR yield. ^e Isolated PtCl₂(bisphosphine) complex was used instead of PtCl₂(cod) and bisphosphine. ^f 10 equiv of benzyl vinyl ether were used.



6 Ar¹ = Ph, Ar² = 3,5-xylyl



7a Ar¹ = Ph, Ar² = 3,5-di-trifluoromethylphenyl

7b Ar¹ = Ph, Ar² = Ph

7c Ar¹ = 3,5-dimethyl-4-methoxyphenyl
Ar² = 3,5-di-trifluoromethylphenyl

7d Ar¹ = Ph, Ar² = 3,5-xylyl

7e Ar¹ = 3,5-xylyl, Ar² = 3,5-xylyl

Table 3. Generality of the Reaction

entry	R ¹	R ²	R ³	Time	Yield(%) ^a /Ee(%) ^b
1	Ph	Me	Bn	16.5 h	70/91(–)
2	<i>p</i> -Me-C ₆ H ₄	Me	Bn	9 h	70/91(–)
3	<i>p</i> -CF ₃ -C ₆ H ₄	Me	Bn	21 h	79/89(–)
4	CH ₂ CH ₂ Ph	Me	Bn	11 h	80/91(–)
5 ^c	CH ₂ CH ₂ Ph	Me	TIPS	43 h	68/94(–)
6	<i>i</i> -Pr	Me	Bn	17 h	89/90(–)
7 ^d	<i>i</i> -Pr	Me	PMB	46 h	69/91(–)
8	(CH ₂) ₃ OTIPS	Me	Bn	8 h	83/93(–)
9 ^e	CH ₂ CH ₂ Ph	Bu	Bn	26 h	50/96(–)
10 ^f	Ph	CH ₂ OBn	Bn	9 h	51/97(–)
11 ^{c,g}	Ph	CH=CH ₂	TIPS	48 h	65/97(–)

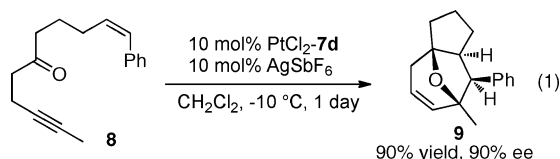
^a Isolated yield. ^b Determined by chiral HPLC analysis (see Supporting Information). ^c 5 equiv of triisopropylsilyl vinyl ether were used. ^d 1.5 equiv of 4-methoxybenzyl vinyl ether and 5 mol % of catalysts were used. ^e **5** was obtained as a hydrolyzed ketone in 27% yield. ^f Hydrolyzed ketone of **5** and an isomer of **4** were obtained in 17% and 13% yield, respectively. ^g Product was isolated as an alcohol by deprotection of the silyl group.

was employed, the product **4a** was obtained with good enantioselectivity as a single diastereomer. Further screening of Walphos ligands revealed that the use of Walphos **7d** gave the product **4a** in 49% yield and 91% ee.¹³ Furthermore, the use of the isolated PtCl₂–**7d** complex and 10 equiv of vinyl ether increased the yield of **4a** to 70% without lowering the enantioselectivity.

The generality of this asymmetric reaction is summarized in Table 3. Ynones bearing various aryl or alkyl groups as R¹ gave the corresponding products **4** in good yields and mostly in over 90% ee's. 4-Methoxybenzyl vinyl ether could be used as dipolarophiles to give the desired product **4** bearing a PMBO group which can easily be deprotected selectively in the presence of an olefin moiety. Furthermore, triisopropylsilyl vinyl ether could be used as a dipolarophile to give the product **4** with higher enantioselectivity. The reactions of ynones bearing butyl, benzyloxymethyl, and vinyl group as the alkyne substituent R² afforded the desired bicyclic alkenes **4** in lower yield but with higher enantioselectivity. In most cases, **4** were obtained as a single diastereomer bearing the alkoxy group in the *exo* orientation.

It should be noted that the products, 8-oxabicyclo[3.2.1]octane derivatives equipped with several functional groups, are useful intermediates not only for the synthesis of related natural products containing this basic skeleton, such as (–)-englerin A¹⁴ and cortistatin,¹⁵ but also for the preparation of a variety of valuable functionalized cyclic compounds through manipulation of the functional groups.

Finally, the reaction was successfully applied to the intramolecular cycloaddition. Thus, treatment of an enyne **8** with 10 mol % of the catalyst gave the desired tricyclic oxacycle **9** in 90% ee in high yield (eq 1).



In summary, we have developed the enantioselective synthesis of potentially useful 8-oxabicyclo[3.2.1]octane derivatives **4** by a simple treatment of acyclic γ,δ -ynones **1** and vinyl ethers with a

cationic platinum–phosphine complex [PtCl(**7d**)]⁺. To our knowledge, this is the first report of the catalytic enantioselective cycloaddition of metal-containing zwitterionic intermediates generated from alk-4-yn-1-ones.

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Supporting Information Available: Preparative methods and spectral and analytical data of all new materials (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) We reported that a 1,2-hydrogen shift of the carbene intermediate **3** occurred in the reaction of ynones bearing an alkyl or an alkoxy group at the propargylic position with platinum(II) chloride. See ref 4c.
- (10) We believe both electronic and steric parameters of the ligand influence the reaction pathway. Examination of other ligands suggests that bulkier ligands favor a 1,2-hydrogen shift product. Details will be reported in due course.
- (11) For example of the electrophilic activation of alkenes by monocationic platinum-bisphosphine complex, see ref 8c.
- (12) The [3+2]-cycloaddition reaction was thought to proceed in a stepwise manner beginning with the nucleophilic addition of the vinyl ether to the oxonium carbon, which was apart from the chiral ligand on platinum.
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