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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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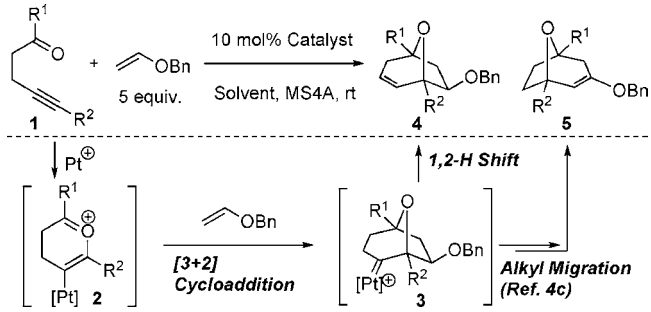
Platinum(II)- or gold(I)-catalyzed electrophilic activation of alkynes has attracted much attention as an efficient method to facilitate atom-economical construction of complex molecules.[1] Asymmetric versions of these reactions would be highly attractive; however, there are only a few successful reports of asymmetric enyne cyclizations[2] 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*-$PtCl_2(PPh_3)_2$, resulted in recovery of the starting materials. We then thought of using cationic platinum(II)−phosphine complexes[2a−e,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** (R^1 = Ph, R^2 = Me) with 10 mol % of *cis*-$PtCl_2(PPh_3)_2$ associated with 10 mol % $AgSbF_6$ 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 $PtCl_2$ was obtained in only 10% yield as a minor product. Furthermore, the reaction with *cis*-$PtCl_2[P(m\text{-tol})_3]_2$ afforded **4a** in higher yield and selectivity (entry 3).[10] Use of 2 equiv (20 mol %) of $AgSbF_6$ 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 $PtCl_2$. To our knowledge, the electrophilic activation 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]

Table 1. Reaction of **1a** (R^1 = Ph, R^2 = 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	*cis*-$PtCl_2(PPh_3)_2$ $AgSbF_6$ (1: 1)	CH_2Cl_2	3.5 h	45%	10%[a]
3	*cis*-$PtCl_2(m\text{-tol}_3)_2$ $AgSbF_6$ (1: 1)	CH_2Cl_2	1.5 h	92%	8%
4	*cis*-$PtCl_2(PPh_3)_2$ $AgSbF_6$ (1: 2)	CH_2Cl_2	2 h	16%	−

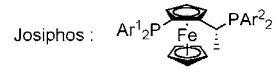
[a] Obtained as a hydrolyzed ketone.

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

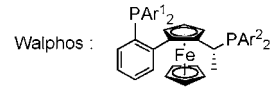
Table 2. Screening of Chiral Bisphosphine[a]

			4a		5a
entry	Bisphosphine	Time	Yield (%)[b]	Ee (%)[c]	Yield (%)[d]
1[e]	(*R*)-BINAP	7.5 h	21	4 (+)	17
2	(*R*)-SEGPHOS	25 h	33	18 (+)	detected
3[e]	(*S*, *S*)-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 $AgSbF_6$ (10 mol %) to a mixture of ynone **1a**, benzyl vinyl ether (5 equiv), $PtCl_2$(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 $PtCl_2$(bisphosphine) complex was used instead of $PtCl_2$(cod) and bisphosphine. [f] 10 equiv of benzyl vinyl ether were used.



6 Ar^1 = Ph, Ar^2 = 3,5-xylyl



7a Ar^1 = Ph, Ar^2 = 3,5-di-trifluoromethylphenyl
7b Ar^1 = Ph, Ar^2 = Ph
7c Ar^1 = 3,5-dimethyl-4-methoxyphenyl
Ar^2 = 3,5-di-trifluoromethylphenyl
7d Ar^1 = Ph, Ar^2 = 3,5-xylyl
7e Ar^1 = 3,5-xylyl, Ar^2 = 3,5-xylyl

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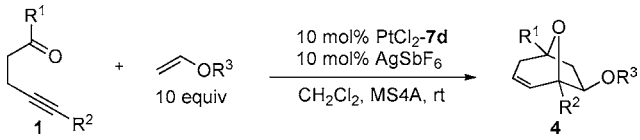
Table 3. Generality of the Reaction



entry	R^1	R^2	R^3	Time	Yield(%)[a]/Ee(%)[b]
1	Ph	Me	Bn	16.5 h	70/91(−)
2	*p*-Me-C_6H_4	Me	Bn	9 h	70/91(−)
3	*p*-CF_3−C_6H_4	Me	Bn	21 h	79/89(−)
4	CH_2CH_2Ph	Me	Bn	11 h	80/91(−)
5[c]	CH_2CH_2Ph	Me	TIPS	43 h	68/94(−)
6	*i*-Pr	Me	Bn	17 h	89/90(−)
7[d]	*i*-Pr	Me	PMB	46 h	69/91(−)
8	$(CH_2)_3$OTIPS	Me	Bn	8 h	83/93(−)
9[e]	CH_2CH_2Ph	Bu	Bn	26 h	50/96(−)
10[f]	Ph	CH_2OBn	Bn	9 h	51/97(−)
11[c,g]	Ph	CH═CH_2	TIPS	48 h	65/97(−)

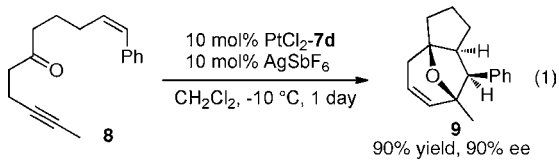
[a] Isolated yield. [b] Determined by chiral HPLC analysis (see Supporting Information). [c] 5 equiv of triisopropylsilyl vinyl ether were used. [d] 1.5 equiv of 4-methoxybenzyl vinyl ether and 5 mol % of catalysts were used. [e] **5** was obtained as a hydrolyzed ketone in 27% yield. [f] Hydrolyzed 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 $PtCl_2$−**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 R^1 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 R^2 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 A[14] 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 enynone **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 $[PtCl(\mathbf{7d})]^+$. 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.

(13) The absolute configuration of **4a** was determined by X-ray crystal structure analysis of the corresponding dibromide. (see Supporting Information).

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