Asymmetric Baeyer–Villiger Oxidation of Prochiral Cyclobutanones Using a Chiral Cationic Palladium(II) 2-(Phosphinophenyl)pyridine Complex as Catalyst

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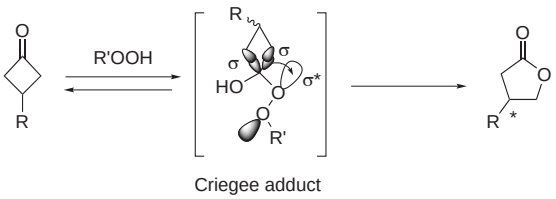
Abstract: Chiral cationic palladium(II) 2-(phosphinophenyl)pyridine (**1a**) complex was found to be an effective catalyst for asymmetric Baeyer–Villiger oxidation of prochiral cyclobutanones. For example, good and excellent enantioselectivities (80% and >99% ees) were achieved in the reactions of 3-phenylcyclobutanone and a tricyclic cyclobutanone, respectively.

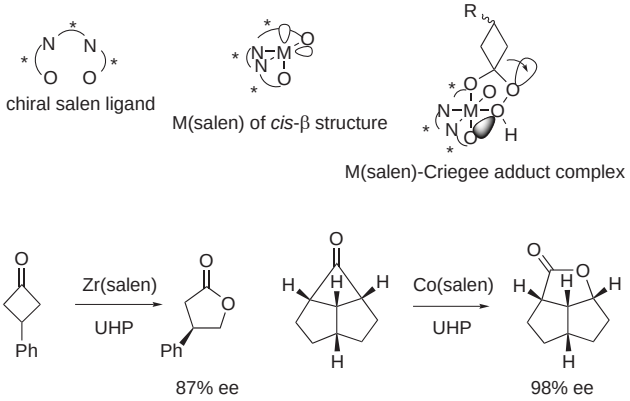
Key words: asymmetric Baeyer–Villiger oxidation, asymmetric catalysis, palladium, chiral P-N ligand

Baeyer–Villiger (B–V) oxidation is a potent tool for transforming carbonyl compounds to lactones or esters, and it is widely used in organic synthesis.[1] Naturally, its asymmetric version is expected to be a useful method for the synthesis of chiral lactones that are efficient chiral building blocks. In the last decade, much effort has been directed toward study of asymmetric B–V oxidation. In 1994, Bolm et al. and Strukul et al. independently reported metal-mediated asymmetric B–V oxidation.[2] Since then, several catalytic asymmetric B–V oxidations have been developed,[3–5] but satisfactory enantioselectivity has not been achieved except for a few examples.[4d–4f] In contrast, bio-catalyzed B–V oxidation is well known to proceed with excellent enantioselectivity.[6] B–V oxidation is a two-step reaction: i) nucleophilic addition of peroxide compound to carbonyl group giving a Criegee adduct and ii) the rearrangement of the adduct to ester (or lactone) by migration of the C-C bond to proximal oxygen atom of the peroxide unit (Scheme 1). The migration that is irreversible and rate-determining step proceeds smoothly when the σ-orbital of the C-C bond interacts with the σ*-orbital of the O-O bond. Thus, it was expected that highly enantioselective B–V oxidation would be achieved, if one of the two σ-bonds interacts with the σ*-bond enantiotopos-selectively.[5e] In bio-catalyzed B–V oxidations, the conformation of Criegee adduct has been considered to be controlled by weak bond interactions such as hydrogen bond between the adduct and enzyme and the migration to occur enantiotopos-selectively.[6]



Scheme 1

Criegee adduct is a kind of η^2 ligand and the adduct is considered to make a chelate with a metal ion possessing two vacant *cis*-coordination sites. Thus, it was expected that the conformation of the Criegee adduct could be regulated to allow the enantiotopos-selective σ–σ* interaction, if the adduct makes a chelate with a metal ion bearing an appropriate chiral ligand. Indeed, chiral cationic Co(salen) complex of *cis*-β structure and Zr(salen) complex that can adopt a *cis*-β structure dynamically have recently be found to be efficient catalysts for asymmetric B–V reaction using urea–hydrogen peroxide adduct (UHP) as the oxidant (Scheme 2).[7] In these reactions, M(salen)-Criegee adduct complexes (M = Co, Zr) have been considered to take octahedral coordination. However, the concept of stereoelectronic control of B–V oxidation is not confined to the reaction via an octahedral adduct complex. Thus, we explored B–V oxidation via metal-Criegee adduct complex of square planar coordination.



Scheme 2

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In 1994, Strukul et al. reported an enantiomer-differentiating B–V oxidation of racemic 2-substituted cycloalkanones with hydrogen peroxide in the presence of chiral cationic platinum(II)BINAP complex as the chiral catalyst. This reaction has been proposed to proceed through a platinum-Criegee adduct complex possessing a square planar coordination, and the mechanism of asymmetric induction has been explained by steric factor.[4e] Several other catalytic[4c,d,f] and stoichiometric[5] B–V reactions using chiral bidentate ligand have been reported, but the detailed mechanism of their asymmetric induction has not been given.

In order to realize highly enantioselective B–V oxidation via square planar metal-Criegee adduct complex, it was considered that two factors, geometry of the complex (**A** or **B**) and the conformation of the chelate of the adduct (**A** or **B**, the conformers of **B** are not given here), had to be regulated strictly (Figure 1).[8]

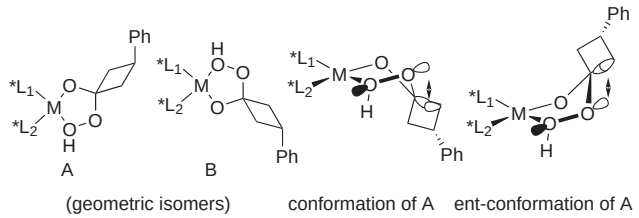


Figure 1 Schematic draws of M-Adduct complexes

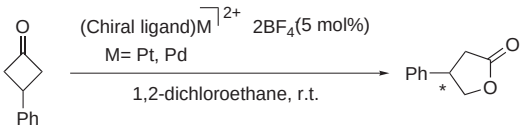
We have reported that the chiral bipyridines, in which the substituent at the chiral center protrudes in the vicinity of the metal center, are efficient chiral auxiliaries for copper-catalyzed asymmetric cyclopropanation and ring-enlargement reactions.[9a–d] We have also revealed that chiral 2-(phosphinophenyl)pyridine ligand bearing 7-substituted dihydropyrindine unit are efficient chiral auxiliaries for palladium-catalyzed allylic substitution of both acyclic and cyclic alkenyl substrates, which proceeds through a square planar π-allyl palladium complex.[9e,f] Thus, we expected that the chiral auxiliary bearing 7-substituted dihydropyrindine unit would be an efficient auxiliary for controlling the geometry and the conformation of metal-Criegee adduct complex of square planar coordination.

B–V oxidation of 3-phenylcyclobutanone using urea–hydrogen peroxide adduct (UHP) as a terminal oxidant[7] in the presence of a cationic platinum(II) complex of 2-(phosphinophenyl)pyridine ligand **1a** was first examined (Table 1). The platinum complex was prepared by mixing $(COD)PtCl_2$ and **1a** in situ in 1,2-dichloroethane and subsequent treatment with silver tetrafluoroborate. The B–V oxidation proceeded smoothly at room temperature but was low enantioselective (7% ee, entry 1). Use of aqueous hydrogen peroxide as a terminal oxidant vitiated the enantioselectivity (entry 2). However, we were pleased to find that the cationic palladium(II) complex of **1a** showed moderate enantioselectivity of 41% ee (entry 3). Replacing tetrafluoroborate with hexafluoroantimonate somewhat improved the enantioselectivity and catalytic activity (entry 4). Use of aqueous hydrogen peroxide as a terminal oxidant again diminished enantioselectivity (entry 5). Compound **1b** bearing bulky 1-(*t*-butyldimethylsiloxy)-1-methylethyl group was a less efficient auxiliary in terms of reactivity and enantioselectivity (entry 6). We also examined the reaction using chiral 2-(phosphinophenyl)oxazolines **2a**,**b**, which are efficient chiral auxiliaries for palladium-catalyzed allylic alkylation[10a–c] and Heck reaction,[10d] but only moderate enantioselectivities were observed (entries 7 and 8). Reactions using C_2-symmetric ligands such as bipyridines **3a**,**b**, bis(oxazoline)s **4a**,**b** and BINAP **5** (Figure 2) were also studied but their enantioselectivities were low (entries 9–14).

Table 1 Asymmetric B–V Oxidation of 3-Phenylcyclobutanone[a]

Entry	Metal	Ligand	Time (h)	Yield (%)	% ee[b]	Config.[c]
1	Pt	**1a**	24	79	7	*R*
2[d]	Pt	**1a**	24	84	3	*R*
3	Pd	**1a**	20	87	41	*R*
4[e]	Pd	**1a**	2	100	47	*R*
5[d]	Pd	**1a**	20	88	26	*R*
6	Pd	**1b**	45	52	8	*R*
7	Pd	**2a**	17	94	10	*R*
8	Pd	**2b**	18	100	38	*R*
9	Pd	**3a**	–	–	–	–
10	Pd	**3b**	89	35	9	*S*
11	Pd	**4a**	12	88	14	*S*
12	Pd	**4b**	70	44	15	*R*
13	Pd	**5**	3	100	18	*R*
14[d]	Pd	**5**	3	100	10	*R*

[a] Reactions were carried out at room temperature in 1,2-dichloroethane using UHP as a terminal oxidant, unless otherwise mentioned.
[b] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH, 95:5).
[c] Configuration was determined by comparison of the elution order with the authentic samples (ref.[7c]).
[d] Aqueous hydrogen peroxide (30%) was used as a terminal oxidant, instead of UHP.
[e] Silver hexafluoroantimonate was used in the preparation of the catalyst, instead of silver tetrafluoroborate.



Scheme 3

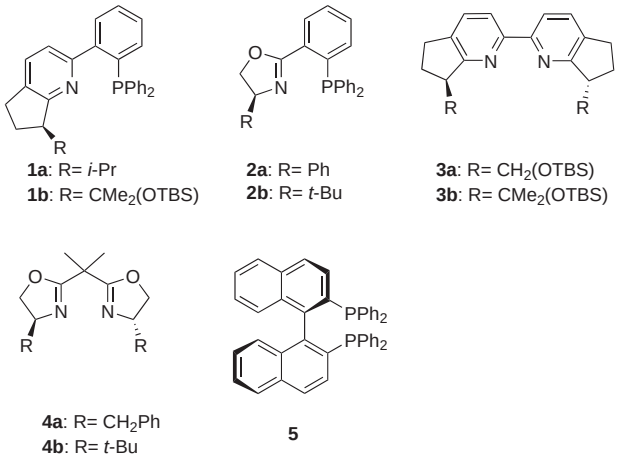


Figure 2

Table 2 Optimization of the Reaction Conditions for Asymmetric B–V Oxidation of 3-Phenylcyclobutanone Using Palladium(II)-**1a** Hexafluoroantimonate Complex as the Catalyst

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)	% ee[a]
1	CH_2Cl_2	r.t.	10	100	50
2	1,4-Dioxane	r.t.	19	95	47
3	Et_2O	r.t.	18	94	44
4	AcOEt	r.t.	1.5	100	53
5	EtOH	r.t.	0.5	100	51
6	Acetone	r.t.	19	100	51
7	DMF	r.t.	23	98	48
8	DME	r.t.	0.5	100	57
9	DME	–40	46	93	73
10	THF	rt	23	92	59
11	THF	–20	18	100	73
12	THF	–40	24	100	78
13	THF	–60	214	91	80
14	THF	–80	186	98	60

[a] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH, 95:5).

With these results at hand, we next attempted the optimization of the reaction conditions for the B–V oxidation using palladium(II)-**1a** hexafluoroantimonate complex as the chiral catalyst (Table 2). Although strong solvent effect on enantioselectivity was not observed (entries 1–10), use of 1,2-dimethoxyethane (DME) or tetrahydrofuran (THF) enhanced enantioselectivity up to 57% and 59% ees, respectively (entries 8 and 10). Lowering reaction temperature further improved enantioselectivity (entries 9 and 11–13) and high enantioselectivity of 80% ee was obtained when the reaction was conducted in THF at –60 °C.[11] However, lowering the reaction temperature to –80 °C decreased enantioselectivity to considerable extent (entry 14).

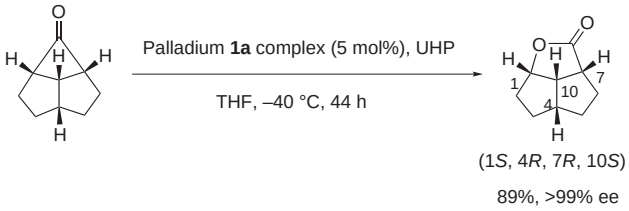
Under the optimized reaction conditions, we next examined B–V oxidation of several other 3-substituted cyclobutanones (Table 3). The reactions of 3-aryl-substituted cyclobutanones showed good to high enantioselectivities (entries 1–3), while that of 3-octylcyclobutanone exhibited moderate selectivity (entry 4).

Table 3 Asymmetric B–V Oxidation of Several 3-Substituted Cyclobutanones Using **1a** as the Chiral Source[a]

Entry	3-Substituent (*R*)	Time (h)	Yield	% ee	Confign.
1	*p*-Chlorophenyl	208	76	73[b]	*R*[c]
2	*p*-Methoxyphenyl	208	52	73[b]	–[d]
3	2-Naphthyl	211	94	83[b]	–[d]
4	*n*-Octyl	211	65	60[e]	–[d]

[a] Reactions were carried out in THF at –60 °C using UHP as a terminal oxidant.
[b] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH, 95:5).
[c] Configuration was determined by comparison of the elution order with the authentic samples (ref.[7c]).
[d] Configuration has not been determined.
[e] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OD-H; hexane–*i*-PrOH, 90:10) after converted into the corresponding γ-hydroxy benzylamide according to the reported procedure (ref.[7c]).

The B–V oxidation of tricyclic cyclobutanone was also examined and excellent enantioselectivity of >99% ee was achieved.



Scheme 4

In conclusion, we were able to demonstrate that 2-(phosphinophenyl)pyridine **1a** was an effective chiral controller for palladium(II)-catalyzed B–V oxidation, which possibly proceeds through a square planar palladium(II)-Criegee adduct complex. To the best of our knowledge, this is the first success example of the B–V oxidation using chiral palladium(II) complex as catalyst. Further studies on metal-mediated B–V oxidation are underway in our laboratory.

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(11) **Typical experimental procedure**
To a solution of bis(benzonitrile)palladium(II) chloride (1.9 mg, 5.0 mol) in THF (0.4 mL) was added ligand **1a** (2.3 mg, 5.5 mol) under nitrogen and stirred at room temperature for 1 h. Silver hexafluoroantimonate (3.4 mg, 10 mol) was placed another flask under nitrogen and to this flask was added the above palladium(II)-**1a** dichloride solution. After being stirred for 1 h at room temperature, the mixture was filtered through a pad of Celite under nitrogen. To the filtrate was added 3-phenylcyclobutanone (15.2 mg, 0.1 mmol) and then cooled to –60 °C. To the cooled solution was added UHP (12.2 mg, 0.13 mmol) and the mixture was further stirred at the temperature for 214 h. The mixture was concentrated and the residue was chromatographed on silica gel (hexane–EtOAc, 9:1) to give dihydro-4-phenylfuran-2(3*H*)-one (14.8 mg, 91%). The enantiomeric excess of the product was determined to be 80% ee by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH, 95:5).