DOI: 10.1002/adsc.200900304

Kinetic Resolution of P-Chirogenic Compounds by Palladium-Catalyzed Alcoholysis of Vinyl Ethers

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Received: April 29, 2009; Published online: July 16, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900304.

Abstract: The palladium-catalyzed asymmetric alcoholysis of vinyl ethers of P-chirogenic compounds has been achieved. The kinetic resolution of aryl *tert*-butyl(2-vinyloxyaryl)phosphinates was catalyzed by palladium/chiral diamine complexes with high selectivities (k_{rel}: 12–196).

Keywords: alcoholysis; chirality; kinetic resolution; phosphorus

Introducing chirality at a phosphorus atom is of particular importance because chirogenic phosphorus centers are common partial structures of a variety of functional molecules, including chiral ligands for asymmetric catalysis[1] and bioactive compounds such as herbicides,[2a] pesticides,[2b] neurotoxins,[2c] antitumor agents[2d] and modified oligonucleotides.[2e] In spite of the significance of the P-chirogenic compounds, only limited numbers of methodologies to approach them have been developed. The most classical method is fractional crystallization of diastereomeric salts.[3] Later, enzymatic resolution by hydrolysis[4a] or esterification,[4b] stereoselective synthesis[5a–d] and catalytic asymmetric synthesis including desymmetrization with Li-sparteine catalysts,[5e] organocatalysts,[5f] Rh-catalyzed [2+2+2]cyclization,[5g] and cross-coupling of R_2PH with ArI[5h,i] have been developed. Recently, an interesting method based on the Appel reaction was reported.[5j] This process realized a dynamic kinetic resolution,[6] but the observed selectivities were moderate (max. 80% *ee*) and a stoichiometric chiral reagent is required.

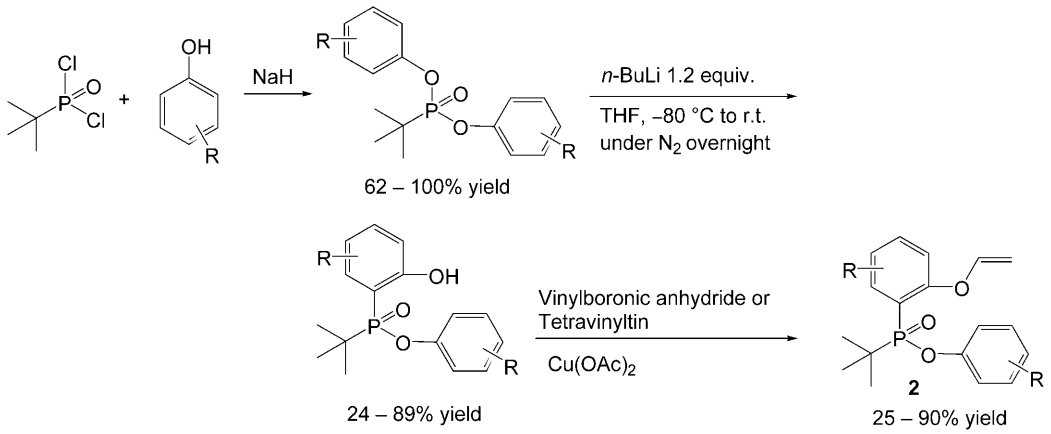
Catalytic hydrolysis and alcoholysis are environmentally benign, practical tools for asymmetric synthesis.[7] However, in the field of homogeneous catalysis, little progress has been made compared to biocatalysis. We have developed the first example of an asymmetric alcoholysis of vinyl ethers catalyzed by Pd-chiral diamine (**1a**) complexes.[7d] The kinetic resolution of axially chiral compounds has been achieved. In our recent study, the phosphoryl (PO) group was found to be an efficient directing group and monophosphoryl, monovinyl derivatives of axially chiral diols underwent kinetic resolution in high selectivity.[7g]

In the present study, we have extended this strategy to P-chiral compounds which have been considered as difficult targets in the asymmetric synthesis. We directed our attention to phosphinate derivatives having an *o*-vinyloxyphenyl group as a P-chirogenic substrate.[8] This class of compounds has been used as chelate ligands,[8d] parts of crown ethers,[8e,g,i] precursors of phosphachromones[8g] and biocides.[8c]

The substrates **2** were synthesized from *tert*-butylphosphonic dichloride by diphenyl ester formation, isomerization of one ester group to form the phosphinate by *ortho*-mono-lithiation,[8a,b,f,i] and then vinylation[9] (Scheme 1). A P-chirogenic compound **2a** (R = H) was chosen for the test of the reaction.

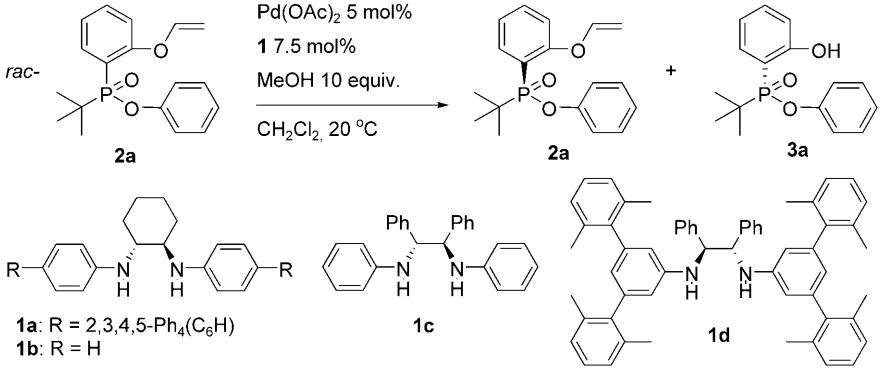
Asymmetric alcoholysis of **2a** was examined with a Pd catalyst system employing ligands **1a** and **1b**, which have a cyclohexanediamine backbone. However, only moderate selectivities (k_{rel} = 11 and 10) were observed (Table 1, entries 1 and 2). The tetraphenylphenyl substituent[7d,g,10] was not effective in this case. When the diamine backbone was changed to diphenylethanediamine (**1c**), a higher selectivity (k_{rel} = 19) and catalytic activity were achieved (entry 3). On introducing a bulky substituent at the *meta*-position of the N-phenyl group (**1d**), the k_{rel} value reached 51 (entry 4). Optically active **3a** (80% *ee*) in 48% yield and unreacted **2a** (99% *ee*) in 45% yield were obtained.

The substrate generality was examined with various P-chirogenic substrates (**2b**–**j**). These were synthe-



Scheme 1.

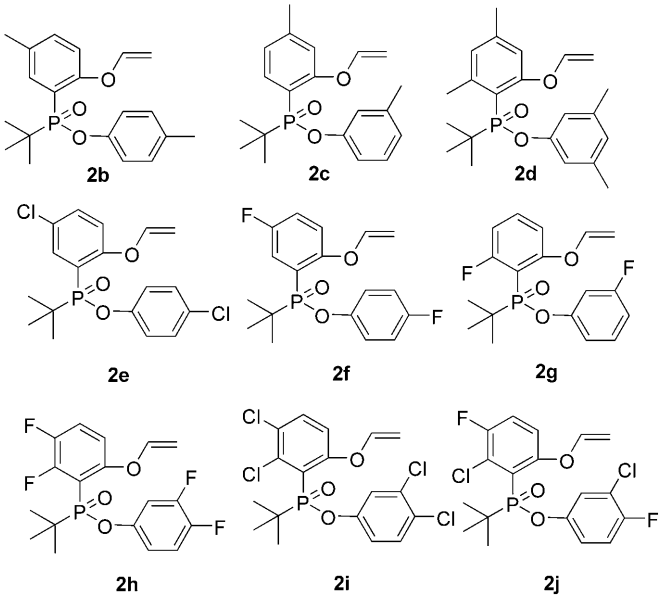
Table 1. Kinetic resolution of a P-chirogenic compound **2a** by Pd-catalyzed alcoholysis of vinyl ethers.



Entry	Ligand	t [h]	Conversion [%][a]	*ee* of **2**[b] [%] (Yield [%])[c]	*ee* of **3**[b] [%] (Yield [%])[c]	k_{rel}[d]
1	**1a**	8	19.6	20 (81)[e]	80 (16)[f]	11.0
2	**1b**	8	13.4	12 (85)[e]	80 (11)[f]	10.1
3	**1c**	4	45.1	67 (53)[e]	81 (36)[f]	19.2
4	**1d**	4	55.3	99.3 (45)	80 (48)	50.8

[a] Calculated with equation: conversion $= ee_{sub}/(ee_{sub}+ee_{pro})$.
[b] Determined by HPLC analysis.
[c] Isolated yield.
[d] Calculated with equation: $k_{rel} = \ln[1-\text{conv}(1+ee_{pro})]/\ln[1-\text{conv}(1-ee_{pro})]$.
[e] (*S*)-**2a** was obtained.
[f] (*R*)-**3a** was obtained.

sized by the same route as described in Scheme 1. When *meta*-substituted phenyl esters underwent phosphinate formation reaction by *ortho*-mono-lithiation, only one of the two possible isomers was obtained. The *m*-tolyl ester afforded *p*-methyl-*o*-hydroxyphenylphosphinate (**3c**), on the other hand *m*-halophenyl esters furnished *o*-halo-*o*-hydroxyphenylphosphinate (**3g**–**j**), respectively. The kinetic resolution with $Pd(OAc)_2$+**1d** as catalyst generally exhibited high selectivities (k_{rel} = 12–196) (Table 2). Among the methyl-substituted phosphinates (**2b**–**d**), the *p*-methyl substrate (**2c**) showed a selectivity value of k_{rel} = 52 (entry 2), which is similar to that of the unsubstituted one (**2a**). However, the *m*-methyl and *m*-dimethyl substrates (**2b** and **d**) gave lower k_{rel} values (12 and 19, entries 1 and 3). The *p*-chloro-, *p*-fluoro-, and *m*-fluorophosphinate esters (**2e**, **2f** and **2g**) also afforded high selectivities (k_{rel} = 37, 56, and 31; entries 4, 5 and 6). Dihalo-substituted substrates, particularly *m*,*p*-dichloro and *m*-chloro-*p*-fluoro esters (**2i** and **2j**) presented selectivities of over 100 (k_{rel} = 110, and 196; entries 8 and 9). For instance, unreacted **2i** was obtained with 99.8% *ee* in 45% yield. A 1-g scale reaction using **2a** proceeded without any difficulty and essen-



tially the same selectivity was observed ($k_{rel}=50$, entry 10).

A single recrystallization of **3a** (80% *ee*) afforded enantiopure (>99% *ee*) crystals. The absolute structure of **3a** obtained with (*S*,*S*)-**1d**/Pd catalyst was found to have the (*S*)-configuration by X-ray crystallographic analysis, in which the absolute structure was unambiguously determined based on the Flack parameter (0.03) refined for the reported configuration (Figure 1).

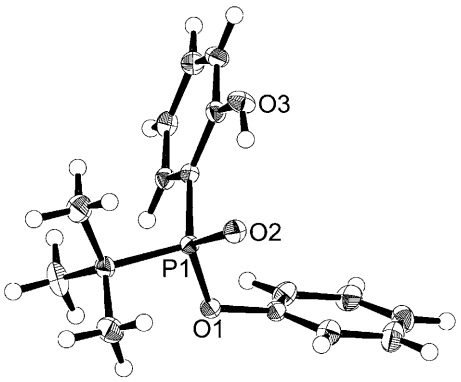
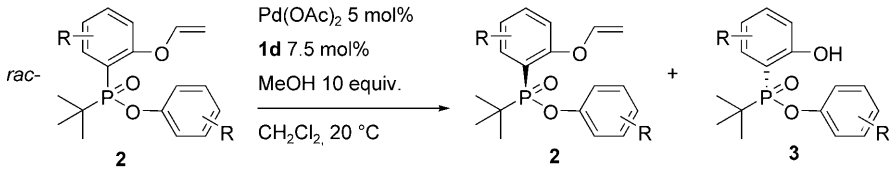


Figure 1. ORTEP drawing for (*S*)-**3a** (product of Table 1, entry 4, recrystallization from hexane/diethyl ether).

A transformation of optically active **2a** (>99% *ee*) was carried out (Scheme 2). Hydrogenation of (*R*)-**2a** gave an ethyl ether and *ortho*-lithiation to make a P–C bond afforded a phosphine oxide. In both cases, the enantiomeric excesses of the products were maintained (>99% *ee*). The absolute configuration of the phosphine oxide was again confirmed by the X-ray crystallographic analysis.

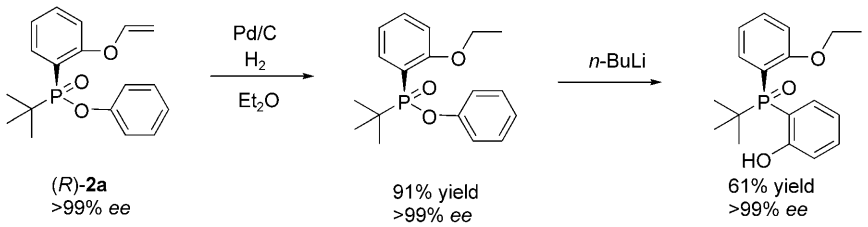
In conclusion, we have accomplished a kinetic resolution of P-chirogenic vinyl ethers (**2a**–**j**) with high selectivities (k_{rel} up to 196) by an alcoholysis reaction with $Pd(OAc)_2$/**1d** as a catalyst. These chiral compounds (**2** and **3**) provide potential building blocks for novel chiral ligands and bioactive compounds. Extended studies utilizing this strategy are now under way.

Table 2. Kinetic resolution of P-chirogenic compounds **2** *via* $Pd(OAc)_2$/**1d**-catalyzed alcoholysis.



Entry	Substrate	t [h]	Conversion [%][a]	*ee* of **2**[b] [%] (Yield [%])[c]	*ee* of **3**[b] [%] (Yield [%])[c]	k_{rel}[d]
1	**2b**	1	44.4	60 (46)	75 (42)	12.4
2	**2c**	5	53.4	97 (41)	85 (50)	52.3
3	**2d**	5	30.3	37 (62)	86 (30)	18.5
4	**2e**	4	53.1	94 (43)	83 (43)	37.4
5	**2f**	4	50.8	92 (47)	89 (46)	56.2
6	**2g**	4	48.9	81 (43)	85 (48)	30.6
7	**2h**	4	30.2	41 (65)	94 (29)	49.0
8	**2i**	4	52.9	99.8 (45)	89 (51)	110
9	**2j**	5	41.5	70 (56)	98 (41)	196
10[e]	**2a**	4	49.6	88 (52)	89 (48)	50.4

[a] Calculated with equation: conversion = $ee_{sub}/(ee_{sub}+ee_{pro})$.
[b] Determined by HPLC analysis.
[c] Isolated yield.
[d] Calculated with equation: $k_{rel}=\ln[1-conv(1+ee_{pro})]/\ln[1-conv(1-ee_{pro})]$.
[e] A 3.67 mmol (1.16 g) scale reaction.



Scheme 2.

Experimental Section

Typical Procedure for the Kinetic Resolution of 2a

A mixture of $Pd(OAc)_2$ (40.5 mg, 0.180 mmol) and **1d** (205.9 mg, 0.264 mmol) in CH_2Cl_2 (3.5 mL) was stirred at room temperature under air. After 1 h, the mixture was concentrated under reduced pressure and dried under vacuum. To this residue was added a CH_2Cl_2 (anhydrous, 2.1 mL) solution of **2a** (1.1607 g, 3.67 mmol) and methanol (anhydrous, 1.4 mL, 35 mmol), and the mixture was stirred at 20 °C under ambient atmosphere for 4 h. Silica-gel column chromatography was carried out to give (*S*)-**3a** (yield: 508.1 mg, 47.7% yield, 89.2% *ee*) and (*R*)-**2a** (yield: 598.9 mg, 51.6% yield, 87.8% *ee*).

CCDC 724711 [(*S*)-**3a**] and CCDC 724712 {(*S*)-2-[*tert*-butyl(2-ethoxyphenyl)phosphinoyl]phenol} contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information

Additional experimental procedures and spectral data are available as Supporting Information.

Acknowledgements

The present work is supported by a Grant-in-Aid for Global-COE program, "Science for Future Molecular Systems" from the Ministry of Education, Culture, Science, Sports and Technology of Japan.

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