Communication

Dynamic Kinetic Resolution in Rhodium-Catalyzed Asymmetric Arylation of Phospholene Oxides

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Dynamic Kinetic Resolution in Rhodium-Catalyzed Asymmetric Arylation of Phospholene Oxides

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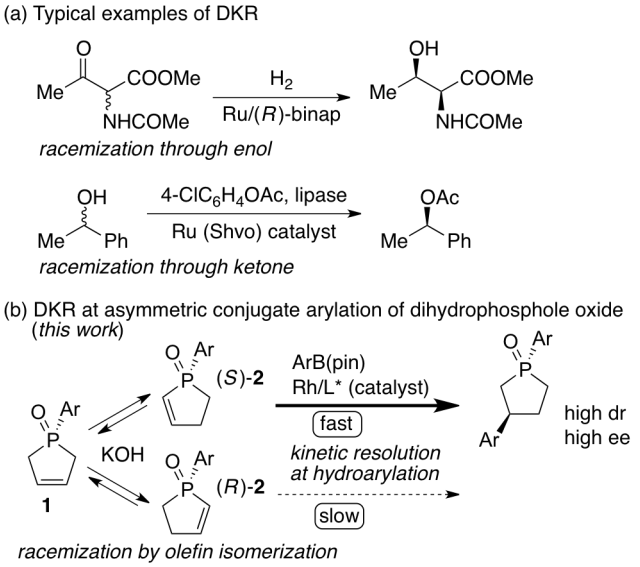
Supporting Information

ABSTRACT: The reaction of 2,5-dihydro-1*H*-phosphole 1-oxide **1** with ArB(pin) **3** in the presence of a chiral (*R*)-segphos–rhodium catalyst under highly basic conditions (10 equiv of KOH) gave high yields of (1*S*,3*S*)-3-arylphospholane 1-oxide **4** with high diastereoselectivity as well as high enantioselectivity. Equilibration of **1** with its 2,3-dihydro isomer **2**, which is chiral and racemic, by base-catalyzed olefin isomerization followed by kinetic resolution of **2** with the chiral rhodium catalyst realized the present dynamic kinetic resolution.

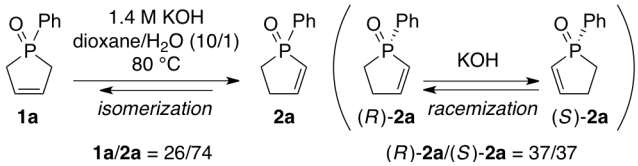
Dynamic kinetic resolution (DKR) in asymmetric synthesis, which is recognized to be an ideal method of synthesizing enantioenriched products from racemic substrates, consists of racemization of a chiral substrate and kinetic resolution of the racemized substrate.[1,2] In most cases, the racemization takes place at sp^3 carbon stereogenic center by way of achiral sp^2 carbon intermediates. Typical examples are racemization through enol formation in ruthenium-catalyzed asymmetric hydrogenation[3] and that through alcohol/ketone interconversion in lipase-catalyzed asymmetric acylation[4] (Scheme 1a). In this communication, we wish to report a dynamic kinetic resolution in rhodium-catalyzed asymmetric conjugate arylation[5,6] where the racemization of starting olefinic substrates takes place by a migration of carbon–carbon double bond. The scenario of the present DKR is as follows (Scheme 1b): The 2,5-dihydrophosphole oxide **1**, which is achiral and is not reactive towards the rhodium-catalyzed conjugate arylation, undergoes olefin isomerization into 2,3-dihydro isomer **2**, which is racemic and is reactive because of the olefin conjugation with electron-withdrawing phosphine oxide.[7] If the racemization of **2** takes place fast by way of **1**, one of the enantiomers **2** is much more reactive than the other enantiomer, and the asymmetric arylation proceeds with high diastereoselectivity, we have a chance to obtain the asymmetric arylation product as a single stereoisomer. As a related asymmetric reaction in that the olefin isomerization generates more reactive olefinic substrates under the reaction conditions, asymmetric arylation of 3-sulfolene has been reported.[8]

Prior to the asymmetric arylation, 1-phenyl-2,5-dihydro-1*H*-phosphole 1-oxide (**1a**),[9] which is readily prepared through ring-closing metathesis of a (diallyl)phosphine oxide,[10] was examined for its isomerization into 2,3-dihydro isomer **2** under basic conditions (Scheme 2). It was found that the isomerization takes place quickly with 1.4 M KOH in dioxane/H_2O (10/1) at 80 °C to reach the equilibration in 3 h. The equilibrated ratio of **1a** to **2a** determined by ^{31}P NMR is 26:74, indicating that each enantiomer of **2a** exists in 37% at equilibration.

Scheme 1. Dynamic Kinetic Resolution (DKR) at Catalytic Asymmetric Transformations



Scheme 2. KOH-Catalyzed Isomerization–Racemization of Dihydrophosphole Oxides 1a and 2a



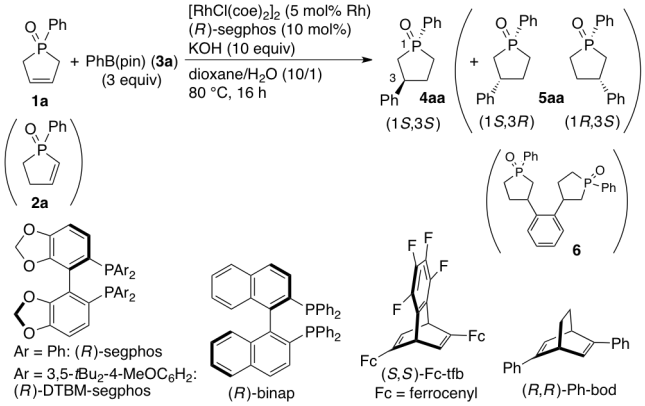
Under the scenario in Scheme 1b with the isomerization conditions in hand, we examined several reaction conditions for the asymmetric hydrophenylation of 2,5-dihydrophosphole oxide **1a** and found that the target phenylation product **4aa** is obtained in a high yield with both high diastereoselectivity and high enantioselectivity under the conditions shown in the reaction scheme in Table 1. Thus, **1a** was allowed to react with PhB(pin)[11] (**3a**. 3 equiv to **1a**) in the presence of KOH (10 equiv) and a rhodium catalyst generated from $[RhCl(coe)_2]_2$ (5

mol % of Rh) and (*R*)-segphos[12] (10 mol %) in dioxane/H_2O (10/1) at 80 °C for 16 h (Table 1, entry 1). ^{31}P NMR analysis of the reaction mixture showed that **1a** was all converted into the hydrophenylation products with high diastereoselectivity (**4aa**:**5aa** = 97:3), and the main diastereoisomer **4aa** was determined to be a (1*S*,3*S*) isomer of 96% ee (see Figure 1). The absolute configuration (1*S*,3*S*) with the high % ee indicates that (*S*)-**2a** is more reactive than its enantiomer (*R*)-**2a** under the present conditions using (*R*)-segphos as a chiral ligand and that the carbon–carbon double bond of (*S*)-**2a** undergoes the phenylation from the side opposite to the phenyl group on phosphine oxide to avoid the steric repulsion. The diastereoselectivity in giving **4aa** over **5aa** is always high irrespective of the reaction conditions examined (vide infra).

The use of 10 mol % (2 equiv to Rh) of segphos ligand is essential for the high conversion of **1a**. The reaction was not completed with 5 mol % (1 equiv to Rh) of segphos (Table 1, entries 2 and 3). Monitoring the reaction progress showed that the catalyst with 5 mol % of the ligand loses its catalytic activity in a short time (2 h). At 60 °C, the phenylation reaction is much slower (entry 4). Rhodium complex with binap ligand is as catalytically active as that with segphos, but the enantioselectivity is lower (entry 5). Chiral dienes[13] are not ligands of choice for the present reaction. The enantiomeric purities of **4aa** are low, while catalytic activity of the diene–rhodium complexes is high to promote the reaction to 100% conversion (entries 7 and 8). Interestingly, the reaction with the diene ligands gave 16% of side product **6**, which is assumed to be formed through a reaction pathway involving the 1,4-shift of rhodium from an alkyl-Rh intermediate to an aryl-Rh intermediate.[14] The asymmetric phenylation also proceeded with high diastereo- and enantioselectivity with $PhB(OH)_2$ or $PhBF_3K$ instead of PhB(pin), but the yield of **4aa** was lower (entries 9 and 10). It is noted that, when the reaction was not completed, the unreacted starting compound **1a** was recovered as a mixture of **1a** and **2a** in an equilibrated ratio (ca. 1:3) under the reaction conditions using 10 equiv of KOH in all the entries. With 5 equiv of KOH, the reaction is slower to leave 18% of a mixture of alkenes **1a** and **2a** unreacted (entry 11). With 0.5 equiv of KOH, the isomerization of **1a** into **2a** is very slow, and most of the starting **1a** was recovered as it was without isomerization into **2a** (entry 12). The reaction of racemic **2a** instead of **1a** under the same conditions as entry 1 gave essentially the same result as that in entry 1, that is, 95% yield, 98:2 dr, and 96% ee of **4aa** (entry 13). It follows that the isomerization between **1a** and **2a** with 10 equiv of KOH is fast enough for the equilibrium to be reached under the standard conditions for the present asymmetric arylation.

The reaction of racemic and enantiomerically pure **2a**[15,16] in the presence of 0.5 equiv of KOH which promotes the Rh-catalyzed arylation[5] but does not promote the fast isomerization (see entry 12 in Table 1) gave us further insight into the kinetic resolution of the present asymmetric reaction (Scheme 3). The reaction of (*S*)-**2a** (>99% ee) gave a high yield (96%) of (1*S*,3*S*)-**4aa** (>99% ee) with high dr (**4aa**:**5aa** = 96:1). On the other hand, the reaction of (*R*)-**2a** (>99% ee) gave **4aa** in a low yield (10%) with low enantioselectivity (36% ee) and low dr (**4aa**:**5aa** = 10:3). These results demonstrate that (*S*)-**2a** is much more reactive than its enantiomer (*R*)-**2a** under the catalysis by (*R*)-segphos/Rh to realize efficient kinetic resolution. It is noted that racemization of recovered **2a** was observed to some extent in the reaction of both enantiomers. The formation of isomer **1a** together with the racemization of **2a** indicates that a slow racemization **2a** by way of **1a** is taking place even with a small amount (0.5 equiv) of KOH. The result obtained for racemic **2a** is consistent with those for enantiopure (*S*)- and (*R*)-**2a**. Thus, (*S*) isomer was consumed selectively to give (1*S*,3*S*)-**4aa** (97% ee) and to leave (*R*) isomer unreacted.

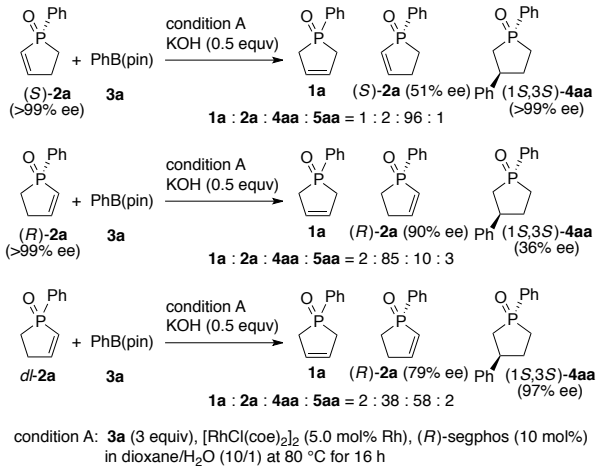
Table 1. Rhodium-Catalyzed Asymmetric Phenylation of 1-Phenyl-2,5-dihydro-1*H*-phosphole 1-Oxide (1a) [a]



entry	Variations from standard conditions	ratio[b] of **1**:**2**:(**4**+**5**)	yield (%)[c] **4**+**5**	dr[b] **4**:**5**	% ee[d] **4** (**5**)
1	None	0:0:100	99	97:3	96 (33)
2	(*R*)-segphos (5 mol %)	3:7:90	81	97:3	90 (61)
3	(*R*)-segphos (5 mol %), at 100 °C	4:11:85	73	97:3	73 (63)
4	At 60 °C	8:24:68	56	99:1	99 (0)
5	(*R*)-binap (10 mol %)	0:0:100	99	96:4	87 (42)
6	(*R*)-DTBM-segphos (10 mol %)	6:19:75	65	99:1	8 (–15)
7	(*S*,*S*)-Fc-tfb (10 mol %)[e]	0:0:84[f]	82	94:6	46 (83)
8	(*R*,*R*)-Ph-bod (10 mol %)[e]	0:0:84[f]	84	98:2	31 (18)
9	$PhB(OH)_2$ instead of PhB(pin)	3:7:90	86	97:3	96 (55)
10	$PhBF_3K$ instead of PhB(pin)	6:15:79	72	97:3	96 (0)
11	KOH (0.75 mmol, 5 equiv)	4:14:82	79	97:3	89 (56)
12	KOH (0.08 mmol, 0.5 equiv)	90:5:5	—	—	—
13	*rac*-**2a** instead of **1a**	0:0:100	95	98:2	96 (38)

[a] Standard reaction conditions: **1a** (0.15 mmol), PhB(pin) (**3a**, 0.45 mmol), KOH (1.50 mmol, 10 equiv to **1a**), $[RhCl(coe_2)]_2$ (3.75 μmol, 5.0 mol % of Rh), (*R*)-segphos (15 μmol, 10 mol %) in dioxane/H_2O (0.70/0.07 mL) at 80 °C for 16 h. [b] Determined by ^{1}H and ^{31}P NMR of the crude reaction mixture. [c] Isolated yield of a mixture of **4aa** and **5aa**. [d] The % ee was determined by HPLC on a chiral stationary phase column. The absolute configuration of **4aa** was assigned by analogy to **4ab** (see Figure 1). [e] $[RhCl(diene)]_2$ (5 mol % Rh) + diene (5 mol %). [f] Compound **6** was formed in 16%.

Scheme 3. Asymmetric Phenylation of Enantiomerically Pure and Racemic 2a Catalyzed by Rh/(*R*)-segphos



condition A: **3a** (3 equiv), $[RhCl(coe)_2]_2$ (5.0 mol% Rh), (*R*)-segphos (10 mol%) in dioxane/H_2O (10/1) at 80 °C for 16 h

The optimized condition for the dynamic kinetic resolution of **1a** with PhB(pin) (**3a**) (entry 1 in Table 1) was applied to several other phospholene oxides **1** and arylboron reagents **3**. The results summarized in Table 2 show that the efficient dynamic kinetic resolution takes place for ArB(pin) reagents **3b**-**3e** where Ar groups are phenyls substituted with methyl or methoxy group at para or meta position, the corresponding hydroarylation products **4** being produced with high diastereo- and enantioselectivity (entries 2–5). The selectivity was also high for the arylboron reagents **3f** and **3g** bearing fluoride(s) on the phenyl ring, although the yields are lower (entries 6 and 7). The same level of high dr (99:1 or higher) and ee (≥95% ee) were observed in the hydroarylation of phospholene oxides **1b**-**1e** where substituents R on the phosphine oxide are para- or meta-substituted aryl groups (entries 8–12). Those with secondary alkyl groups on the phosphine oxide can be also used as starting substrates, although they are less reactive (entries 13–15). By increasing the amount of the (*R*)-segphos/Rh catalyst to 10 mol %, the arylation products **4fb** and **4gb**, which are substituted with 2-propyl and cyclohexyl groups, respectively, were obtained with high selectivity (dr = >99:1, 97–98% ee). The diastereoselectivity was low (dr = 82:18) for 1-hexyl-substituted phospholene oxide **1h** (entry 16) and the reactivity of *tert*-butyl-substituted one was too low to give only a low yield of the arylation product (entry 17). It is noted that an alkenyl group is also successfully introduced with high selectivity (entries 18 and 19).

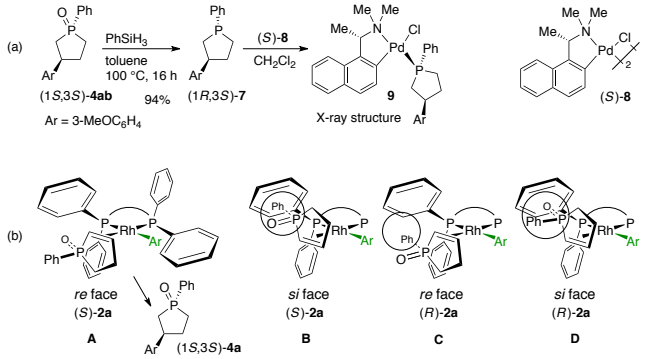
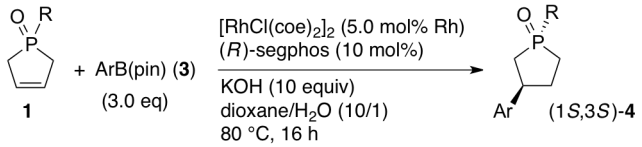


Figure 1. Absolute configuration of product **4** and proposed stereochemical pathway.

The relative and absolute configuration of the arylation product **4ab** was determined unequivocally to be (1*S*,3*S*) by X-ray crystallographic analysis of its palladium complex **9**,[17] which is obtained by reduction of **4ab**[18] followed by treatment of the phosphine **7** with enantiopure palladacycle (*S*)-**8**[19] (Figure 1a). Metal complexes coordinated with axially chiral (*R*)-biarylbisphosphine ligands including (*R*)-segphos are well-known to have a structure where the 2nd and 4th quadrants are occupied by phenyl rings on the phosphino groups.[20] The (1*S*,3*S*) configuration of the product **4** with the (*R*)-segphos ligand is rationalized by the selective coordination of (*S*)-isomer of **2a** to an aryl–rhodium intermediate with its *re* face where the steric repulsions between **2a** and phenyl rings of segphos ligand are minimized (**A** in Figure 1b). Arylrhodation on the intermediate **A** will lead to the product (1*S*,3*S*)-**4a**. There would be serious steric repulsions at coordination of (*S*)-**2a** with the other enantioface *si* between the phenyl group on the ligand and the phosphine oxide moiety of **2a** (**B**). The (*R*)-isomer of **2a** would suffer from repulsions at both *re* face and *si* face coordination as shown in **C** and **D**, respectively.

Table 2. Rhodium-Catalyzed Asymmetric Arylation of 2,5-Dihydro-1*H*-phosphole Oxide 1 with ArB(pin) 3[a]



entry	**1**: R	**3**: Ar	yield (%)[b]	dr[c] **4**:**5**	ee (%)[d] **4**
1	**1a**: Ph	**3a**: Ph	**4aa**: 99	97:3	96
2	**1a**: Ph	**3b**: 3-$MeOC_6H_4$	**4ab**: 90	98:2	95
3	**1a**: Ph	**3c**: 3-MeC_6H_4	**4ac**: 95	98:2	94
4	**1a**: Ph	**3d**: 4-MeC_6H_4	**4ad**: 99	>99:1	94
5	**1a**: Ph	**3e**: 4-$MeOC_6H_4$	**4ae**: 80	98:2	95
6	**1a**: Ph	**3f**: 4-FC_6H_4	**4af**: 73	>99:1	96
7	**1a**: Ph	**3g**: 3,5-$F_2C_6H_4$	**4ag**: 74	97:3	97
8	**1b**: 4-$CF_3C_6H_4$	**3a**: Ph	**4ba**: 99	>99:1	>99
9	**1b**: 4-$CF_3C_6H_4$	**3b**: 3-$MeOC_6H_4$	**4bb**: 90	99:1	95
10	**1c**: 4-$MeOC_6H_4$	**3b**: 3-$MeOC_6H_4$	**4cb**: 74	>99:1	97
11	**1d**: 3-MeC_6H_4	**3b**: 3-$MeOC_6H_4$	**4db**: 95	>99:1	97
12	**1e**: 3,5-Me_2-4-$MeOC_6H_2$	**3b**: 3-$MeOC_6H_4$	**4eb**: 94	>99:1	97
13	**1f**: 2-propyl	**3b**: 3-$MeOC_6H_4$	**4fb**: 24	>99:1	97
14[e]	**1f**: 2-propyl	**3b**: 3-$MeOC_6H_4$	**4fb**: 71	>99:1	97
15[e]	**1g**: cyclohexyl	**3b**: 3-$MeOC_6H_4$	**4gb**: 63	>99:1	98
16	**1h**: 1-hexyl	**3b**: 3-$MeOC_6H_4$	**4hb**: 82	82:18	90
17	**1i**: *t*-butyl	**3b**: 3-$MeOC_6H_4$	**4ib**: 7	>99:1	—
18[f]	**1a**: Ph	**3h**: *c*-hexenyl	**4ah**: 95	>99:1	97
19[f]	**1b**: 4-$CF_3C_6H_4$	**3h**: *c*-hexenyl	**4bh**: 89	>99:1	93

[a] Reaction conditions: **1** (0.15 mmol), ArB(pin) **3** (0.45 mmol), KOH (1.5 mmol), $[RhCl(coe)_2]_2$ (5 mol% of Rh), (*R*)-segphos (10 mol%), dioxane/H_2O (0.7/0.07 mL) at 80 °C for 16 h. [b] Isolated yield. c Determined by ^1H and ^{31}P NMR of the crude reaction mixture. [d] The % ee was determined by HPLC on chiral stationary phase columns. The absolute configurations of products **4** were assigned by analogy to **4ab**. [e] With 10 mol% of Rh and 20 mol% of segphos. [f] With 7 mol% of Rh and 14 mol% of segphos.

In summary, we have succeeded in developing a new type of dynamic kinetic resolution in rhodium-catalyzed asymmetric arylation which gives high yields of the hydroarylation products with high dr and high ee. The reaction opened a new synthetic route to chiral organophosphorus compounds containing two stereogenic centers, one on phosphorus and the other on carbon.[21,22]

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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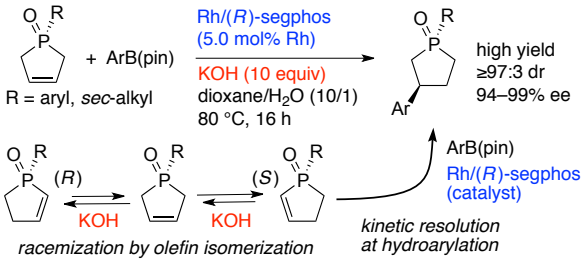
+ ArB(pin)
R = aryl, sec-alkyl
Rh/(R)-segphos
(5.0 mol% Rh)
KOH (10 equiv)
dioxane/H2O (10/1)
80 °C, 16 h
high yield
≥97:3 dr
94–99% ee
Ar
(R)
KOH
(S)
KOH
racemization by olefin isomerization
ArB(pin)
Rh/(R)-segphos
(catalyst)
kinetic resolution
at hydroarylation