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Rhodium-Catalyzed Asymmetric Synthesis of Indanones: Development of a New "Axially Chiral" Bisphosphine Ligand

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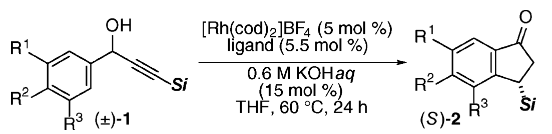
The design and the synthesis of new chiral ligands are of great importance in advancement of asymmetric catalysis.[1] Among the chiral ligands in the literature, chiral bisphosphines based on a biaryl backbone constitute a useful family of ligands in a number of transition-metal-catalyzed asymmetric transformations.[2] Since the first development of binap,[3] various modified binap's have been reported, firmly establishing the utility of this family of ligands. In addition to the substituents on the phosphorus atoms, the change of the dihedral angle of backbone axes has shown a significant impact on the enantioselectivity in some reactions.[4]

Although a large number of chiral ligands are known to date, preparation of a new chiral ligand is still often necessary to achieve high enantioselectivity, particularly in the context of developing a new asymmetric transformation. In this Communication, we describe the development of a rhodium-catalyzed asymmetric isomerization of racemic α-arylpropargyl alcohols to β-chiral indanones[5,6] and the achievement of high enantioselectivity through optimization of axial chirality of bisphosphine ligands.

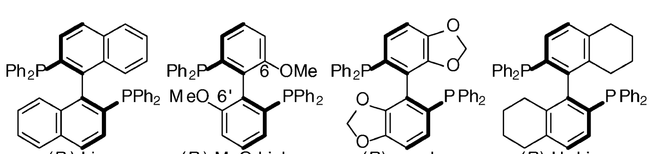
Initially, we conducted an isomerization reaction of (±)-**1a** in the presence of 5 mol % rhodium catalyst to examine the effect of chiral ligands (Table 1). The use of (*R*)-binap produced only 8% yield of indanone **2a** with 41% ee (entry 1). (*R*)-MeO-biphep,[7] which has a smaller dihedral angle around the chiral axis (72° as a free ligand vs 86° for binap),[4a,8] was somewhat more effective, furnishing **2a** in 30% yield with 56% ee (entry 2). The use of (*R*)-segphos[9] (dihedral angle: 67° as a free ligand)[4a,8] gave **2a** in 44% yield with 62% ee (entry 3), whereas the employment of (*R*)-H_8-binap[10] (dihedral angle: 80.3° in a Rh complex[11] vs 74.4° for binap[8]) resulted in 28% yield with 40% ee (entry 4). These results may imply that higher enantiomeric excess can be achieved by the use of an axially chiral bisphosphine with an even smaller dihedral angle, but in fact, (*R*)-segphos has one of the smallest dihedral angles among the readily available axially chiral bisphosphines.[2] We therefore decided to design and synthesize an easily accessible chiral bisphosphine that could potentially exhibit a much smaller dihedral angle.

Table 1. Asymmetric Isomerization of (±)-1-Aryl-2-propyn-1-ols **1**



entry	substrate/product	ligand	yield (%)	ee (%)
1	**1a**/**2a** (R^1=R^2=R^3=H, ***Si*** = $SiEt_3$)	(*R*)-binap	8	41
2	**1a**/**2a**	(*R*)-MeO-biphep	30	56
3	**1a**/**2a**	(*R*)-segphos	44	62
4	**1a**/**2a**	(*R*)-H_8-binap	28	40
5	**1a**/**2a**	(*R*,*R*)-**3**	57	74
6	**1b**/**2b** (R^1=R^2=R^3=H, ***Si***=$SiMe_2Et$)	(*R*)-binap	10	14
7	**1b**/**2b**	(*R*)-segphos	28	29
8	**1b**/**2b**	(*R*,*R*)-**3**	57	99
9	**1c**/**2c** (R^1=R^2=R^3=H, ***Si***=$SiMe_3$)	(*R*,*R*)-**3**	44	92
10	**1d**/**2d** (R^1=R^3=H, R^2=Me, ***Si***=$SiMe_2Et$)	(*R*,*R*)-**3**	60	93
11	**1e**/**2e** (R^1=R^3=H, R^2=OMe, ***Si***=$SiMe_2Et$)	(*R*,*R*)-**3**	57	94
12[a]	**1f**/**2f** (R^1=Me, R^2=R^3=H, ***Si***=$SiMe_2Et$)	(*R*,*R*)-**3**	56	92
13[a]	**1g**/**2g** (R^1=R^2=Me, R^3=H, ***Si***=$SiMe_2Et$)	(*R*,*R*)-**3**	50	95
14[b]	**1h**/**2h** (R^1=H, R^2,R^3=OCH_2O, ***Si***=$SiMe_2Et$)	(*R*,*R*)-**3**	55	96

[a] The regioselectivity of cyclization is >20:1. [b] The regioselectivity of cyclization is 10:1.



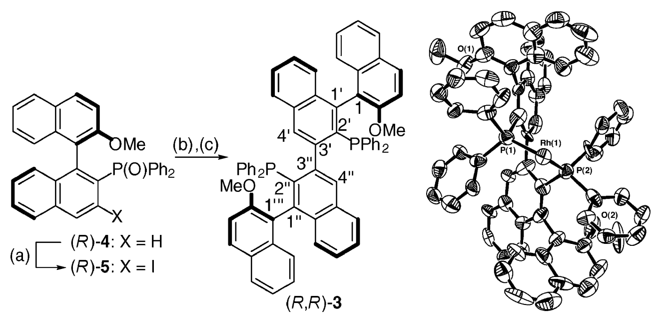
(*R*)-binap (*R*)-MeO-biphep (*R*)-segphos (*R*)-H_8-binap

As described by Genêt[4a] and Saito,[9] smaller substituents at 6,6′-positions of axially chiral bisphosphines provide smaller dihedral angles both in free ligands and in their metal complexes, but if these substituents are too small, the bisphosphines no longer possess a stable axial chirality due to a free rotation around the axis. To overcome this problem with maintaining the smallness of the 6,6′-substituents, we chose (*R*,*R*)-**3** as the target, a dimer of (*R*)-MeO-mop[12] (Scheme 1). This is expected to have a free rotation around the 3′−3″ axis at ambient temperature due to the lack of substituents at 4′,4″-positions, but the existence of fixed axes at 1−1′ and 1″−1‴ in (*R*)-configurations might control the three-dimensional structure upon complexation to a transition metal.[13]

Starting with (*R*)-MeO-mop oxide (**4**),[14] phosphine oxide-directed ortho-lithiation,[15] followed by electrophilic quench with I_2, produces 3-iodo species (*R*)-**5**. Copper-mediated reductive dimerization of (*R*)-**5**, followed by reduction of the phosphine oxides, affords the desired bisphosphine (*R*,*R*)-**3**. Consistent with our hypothesis, a 1:1 mixture of $[Rh(cod)_2]BF_4$ and (*R*,*R*)-**3** (^{31}P NMR: 1.8 ppm (s)) in $CDCl_3$ generated a single species (^{31}P NMR: 25.1 ppm (d, J = 148 Hz)). We also obtained an X-ray crystal structure of a related Rh/(*R*,*R*)-**3** complex, and the absolute configuration of the 3′−3″ axis was determined to be (*R*) with its dihedral angle being 72.8° (Scheme 1; see Supporting Information).[8]

We then conducted an isomerization reaction of (±)-**1a** in the presence of (*R*,*R*)-**3**, obtaining indanone **2a** in higher yield and

Scheme 1. Synthesis of (*R*,*R*)-**3** (left)[a] and ORTEP Illustration of $[Rh((R,R)\text{-}\mathbf{3})(MeCN)_2]PF_6$ (right; MeCN, PF_6, hydrogens are omitted)



[a] Conditions: (a) *t*-BuLi (5.0 equiv), THF, −96 °C; then I_2 (3.5 equiv), 51%; (b) Cu powder (3.7 equiv), DMF, reflux, 83%; (c) MeOTf (6.0 equiv), DME, 60 °C; then $LiAlH_4$ (15 equiv), 60 °C, 89%.

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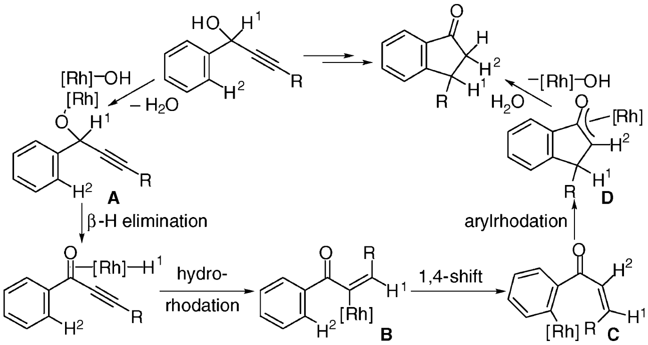
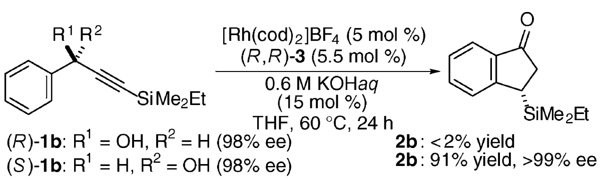


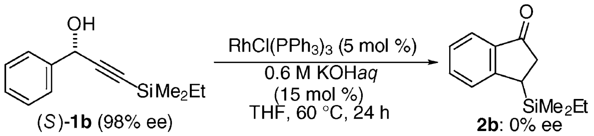
Figure 1. Catalytic cycle of the rhodium-catalyzed isomerization of α-arylpropargyl alcohols to indanones.

enantiomeric excess (57% yield, 74% ee; entry 5). We subsequently identified that the use of a substrate with $EtMe_2Si$ or Me_3Si group instead of Et_3Si group on the alkyne leads to further enhancement of enantiomeric excess (92−99% ee (*S*); entries 8 and 9).[16] Under these conditions, several (±)-α-arylpropargyl alcohols bearing substituents on the aromatic ring are also isomerized to indanones in high enantiomeric excess (92−96% ee; entries 10−14).

A catalytic cycle of this process is illustrated in Figure 1.[5] β-H elimination of alkoxorhodium intermediate **A**, followed by conjugate hydrorhodation, destroys the stereocenter of the substrate to give alkenylrhodium species **B**. After 1,4-rhodium migration (**B** → **C**), a new stereocenter is created at the step of intramolecular 1,4-addition of intermediate **C**. This sequence indicates that a racemic substrate could undergo a full conversion to provide the corresponding indanone, and its stereochemical outcome is controlled at the step of **C** to **D**, independent of the original stereochemical information of the substrate. In reality, however, ∼20% of starting propargyl alcohols always remain under the conditions we employed, and we found that these remaining substrates are enantioenriched. For example, 24% of starting material **1b** was recovered in 89% ee (*R*) in Table 1, entry 8.



(2)



(3)

To gain insight into these isomerizations catalyzed by Rh/(*R*,*R*)-**3**, we employed optically active propargyl alcohol **1b** (eq 2). The use of (*R*)-**1b** (98% ee) did not provide indanone **2b** under our standard conditions, and **1b** was recovered in 48% yield and 98% ee (*R*). In contrast, (*S*)-**1b** (98% ee) was smoothly converted to (*S*)-**2b** in 91% yield with >99% ee. These results, along with the fact that (*S*)-**1b** provides **2b** as a racemate by using an achiral catalyst ($RhCl(PPh_3)_3$; eq 3), indicate that the Rh/(*R*,*R*)-**3** catalyst plays two different roles in one catalytic cycle. Thus, as is the case with a typical kinetic resolution, the first role is to distinguish the (*S*)-substrate from the (*R*)-substrate, preferentially incorporating the (*S*)-isomer into the catalytic cycle.[17] The second role, which is more important, is to differentiate the enantiotopic faces of an olefin of intermediate **C** during the intramolecular 1,4-addition step, creating a new stereocenter with very high stereocontrol. This conclusion is consistent with the moderate yield of indanones from racemic propargyl alcohols in Table 1 (up to 60% yield) and the enantioenrichment of the remaining starting materials.

In summary, we have developed a rhodium-catalyzed asymmetric synthesis of indanones by isomerization of racemic α-arylpropargyl alcohols. High enantioselectivity has been achieved by the use of a newly developed axially chiral bisphosphine ligand ((*R*,*R*)-**3**). This ligand is unique in the sense that its axial chirality is fixed to a single configuration upon complexation to a transition metal due to the chiral axes existing at other positions within the molecule. Future studies will explore further development and application of this class of chiral ligands.

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

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(16) The absolute configuration of indanone **2b** was determined by converting it to 1-indanol via *cis*-selective reduction with $LiAlH_4$ and then desilylation with TBAF (see Supporting Information for details).

(17) In the reaction of *rac*-substrates, (*R*)-isomer must also be isomerized to indanone to some extent since the yields are typically >50% (Table 1).

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