DOI: 10.1002/adsc.200900589

Axial Chirality Control by 2,4-Pentanediol for the Alternative Synthesis of C_3*-TunePhos Chiral Diphosphine Ligands and Their Applications in Highly Enantioselective Ruthenium-Catalyzed Hydrogenation of β-Keto Esters

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Received: August 28, 2009; Published online: October 28, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900589.

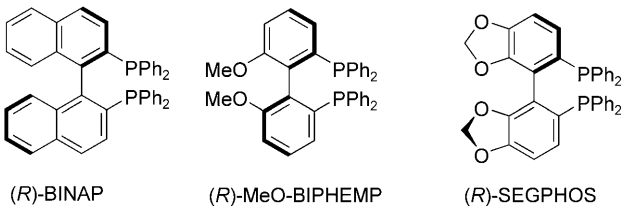
Abstract: A highly efficient strategy for the synthesis of a series of C_3*-TunePhos chiral diphosphine ligands was well established with several remarkable features. The synthetic utility of these ligands was explored for the ruthenium-catalyzed asymmetric hydrogenation of β-keto esters. Up to 99% *ee* values were achieved for the enantioselective synthesis of β-hydroxy acid derivatives, which are very important chiral building blocks for the synthesis of a variety of natural products and biologically active molecules.

Keywords: asymmetric catalysis; enantioselectivity; hydrogenation; ruthenium

As remarkable auxiliaries and scaffolds, chiral biaryls are widely applied in a large number of efficient stereodifferentiating reactions.[1] Particularly, the atropisomeric C_2-symmetric binaphthyl or biphenyl bridged diphosphine ligands BINAP,[2] H_8-BINAP,[3] MeO-BIPHEP,[4] SEGPHOS,[5] P-Phos,[6] and their analogues (Figure 1) are well known as highly efficient chiral ligands for a variety of transition metal-catalyzed asymmetric transformations.

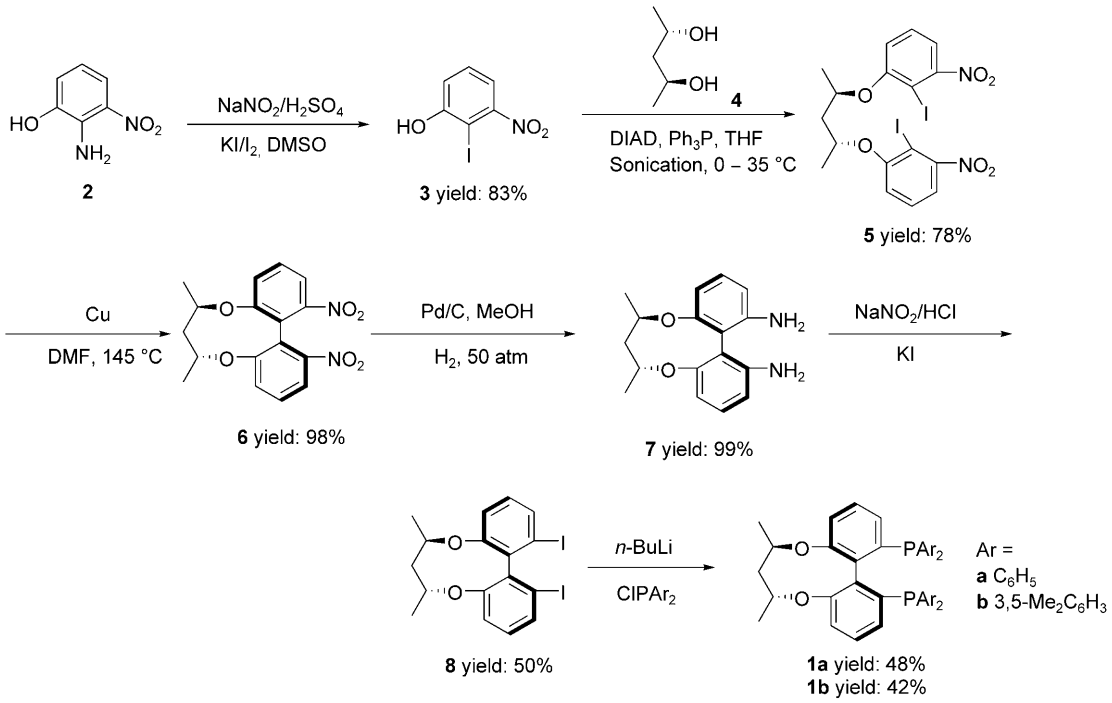
Traditionally, the most convenient access to these chiral bidentate diphosphine ligands proved to be the resolution of the racemic diphosphine oxides with some chiral tartaric acids followed by fractional recrystallization.[7] This resolution step is very tedious and some times difficult for the further optimization to obtain >99.5% a single enantiomer. To tackle these problems, various strategies have been reported and established, including desymmetrization of prochiral biaryls,[8] kinetic resolution of racemic substrates,[9] and chirality transfer from central, axial and planar symmetry.[10] Significant progress was made by Lipshutz et al., who introduced the use of enantiomerically pure 1,2-diphenyl-1,2-ethanediol, 2,3-butanediol, 1,2-amino alcohols and 1,4-di-*O*-benzylthreitol as chiral auxiliaries for copper-medidated intramolecular biaryl couplings *via* higher-order cuprates.[11] Sugimura's group also demonstrated a highly efficient and widely applicable stereocontroller to produce enantiomerically pure materials by utilization of optically active 2,4-pentanediol as a chiral linking bridge between a reagent and a prochiral substrate.[12] The stereochemistries of the products can be strictly controlled by only two small methyl groups or even by a single methyl group in some cases. For instance, optically pure BINOL, trinaphthol derivatives or even some unsymmetrical biaryl alcohols can be obtained after biaryl coupling reactions followed by removal of the chiral tether.[10g,13]

Pertinent to this concept, Chan's and our groups recently have introduced central-to axial chirality transfer in the bisphosphine ligand synthesis with an ex-



(*R*)-BINAP (*R*)-MeO-BIPHEMP (*R*)-SEGPHOS

Figure 1. Some chiral atropisomeric C_2-symmetric biaryl ligands.



Scheme 1. An alternative synthetic route to the family of the C_3*-TunePhos.

tremely high diastereomeric aryl-aryl coupling reaction (>99.5%) and several other features.[14] The presence of additional chiral centers on the ligand backbones was found to exert significant influence on the enantioselectivity and activity of the catalysts in asymmetric hydrogenations utilizing their highly modular nature. As part of our continuing effort in designing ligand scaffolds for asymmetric catalysts by using this concept, Scheme 1 depicts the diastereoselective Ullmann coupling reaction for a highly efficient alternative synthetic route to the family of air-stable modular C_3-Tunephos-type chiral diphosphine ligands (C_3*-TunePhos **1**).

Starting from 2-amino-3-nitrophenol **2**, selective activation of the amino group was achieved *via* a one-pot diazotization-iodination sequence to give 2-iodonitrophenol **3** in 83% yield.[15] The chiral bis(nitrophenol ether) **5** was prepared by the Mitsunobu reaction with (2*S*,4*S*)-pentanediol and 2-iodonitrophenol. The double Mitsunobu reaction proceeded smoothly and afforded a 78% yield of **5** in one hour under sonication conditions. The intramolecular Ullmann reaction of iodide **5** carried out according to Kornblum and Kendall in DMF solution,[16] proceeded with surprising ease in very high yield (up to 98%) and >99% diastereoselectivity based on ^{1}H NMR analysis. A crystal of intermediate **6** suitable for X-ray diffraction was grown and analyzed, since it is an unknown compound. The axial chirality *S* was assigned when compared to the chiralities of carbon centers C-14 (*R*) and C-16 (*R*) in the single crystal structure (Figure 2).

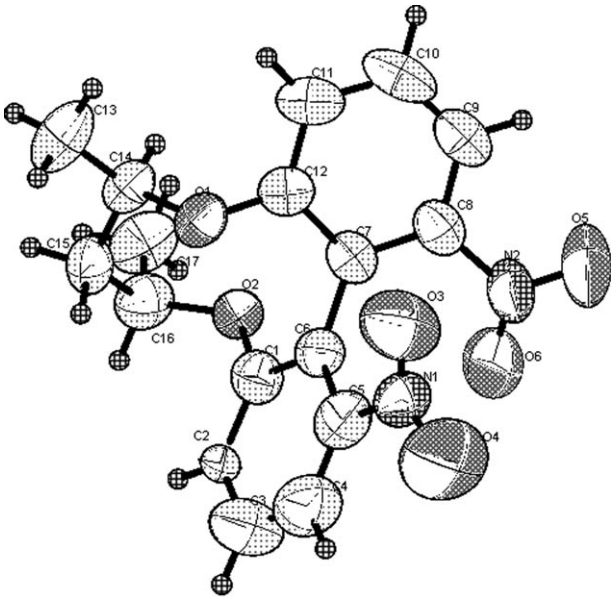


Figure 2. X-ray crystal structure of intermediate **6** (ORTEP drawing).[17]

The optically active intermediate **7**, obtainable by the reduction of the compound **6**, can be converted into the 2,2′-diiodo derivative **8** by diazotization and treatment with potassium iodide. The enantiomer diiodo **8** was readily transformed to optically pure bisphosphine ligands **1a** and **1b** in moderate yields by consec-

utive treatment with *n*-butyllithium and corresponding diarylphosphine chlorides at low temperature.

Several features are highlighted in this new C_3*-TunePhos synthetic strategy. First, the low hindered and strong electron-withdrawing bisnitro groups in compound **5** facilitated the Ullmann coupling reaction, giving the desired intermediate **6** in a very high yield. This strategy circumvents the problem in our initial effort to attach bis(diethyl phosphonate) groups in this step, which led to a relatively low oxidative homo-coupling yield.[14c] Second, the introduction of the synthetically flexible intermediate **8** allows for the convenient divergent incorporation of various Ar substituents of the PAr_2 moieties in the last step, avoiding the requisite individual formation of the phosphinic or phosphinous moieties and any phosphine oxide reduction as described in traditional strategies.[1] Third, the chiral linking bridge of the 2,4-pentanediol tether is very simple and just flexible enough for the chirality transfer from central-to-axial in the Ullmann coupling reaction with complete diastereodifferentiation without unwanted intermolecular coupling; this avoids tedious and time-consuming routine resolutions. Finally, the ready availability of the enantiomerically pure diiodide **8** of defined axial chirality has now opened up a possible direct access to asymmetric diphosphines by applying the sequential monolithiation/monophosphination principle demonstrated previously by Murdoch and Achiwa.[18]

To systematically test the synthetic utility of this TunePhos family of ligands in asymmetric hydrogenations, their analogous ligands **1c** (Ar = 4-Me-C_6H_4), **1d** [Ar = 3,5-(*t*-Bu)$_2C_6H_3$] and **1e** [Ar = 4-MeO-3,5-(*t*-Bu)$_2C_6H_2$] were also resynthesized by following our reported procedures.[14c] The catalysts RuL^*Cl_2(DMF)n **9a–e** (where L* is the corresponding chiral ligand **1a–e**, $n = 2$–6) were prepared as reddish brown solids from $[RuCl_2(benzene)_2]_2$ and the corresponding **1a–e** in DMF at 100 °C.[19] The complexes obtained were used directly in the catalytic reactions.

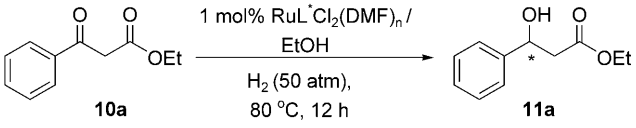
Optically active β-hydroxy acids and their derivatives are very important structural motifs in numerous biologically active compounds, especially medicines and functional materials.[7] Accordingly, tremendous effort has been devoted to their preparation *via* asymmetric synthesis.[1] Although the Ru-BINAP system has been recognized as an efficient and general catalyst for the hydrogenation of β-alkyl-substituted β-keto esters, only inferior *ee* values were obtained for analogous β-aryl-substituted β-keto esters.[20] So far, limited C_2-symmetrical bisphosphine ligands have been reported to show good to excellent *ee* in the Ru-catalyzed hydrogenation of β-aryl-substituted β-keto esters.[21] For example, up to 99% *ee* was achieved with bisphosphinite ligands[21e,f] and 4,4′-substituted BINAP ligands.[21g]

We initiated our studies by screening catalysts **9a–e** on the asymmetric hydrogenation of standard substrate ethyl benzoylacetate **10a**, which potentially leads to the useful pharmaceutical intermediate, ethyl (*S*)-3-hydroxy-3-phenylpropionate (**11a**).[22] The reaction was performed in ethanol at 80 °C under 50 atm hydrogen pressure for 12 h. In the presence of complex **9a**, up to 97% *ee* and 100% conversion were observed (Table 1, entry 1).[14d] A systematic investigation of electronic and steric effects of substituents on ligand **1** indicated that the introduction of somewhat bulky 3,5-dimethyl (**1b**) and 4-methyl (**1c**) groups gave the best results with 98% enantiomeric excesses (Table 1, entries 2 and 3). This enantiomeric excess of **11a** was much higher than when C_3-TunePhos (72% *ee*) was employed as a ligand under the similar conditions.[14b] However, much more hindered 3,5-di-*tert*-butyl (**1d**) and 4-methoxy-3,5-di-*tert*-butyl (**1e**) groups on the P-phenyl rings dramatically diminished the enantioselectivities (Table 1, entries 4 and 5).

To assess the general efficiency of this catalytic system, the asymmetric hydrogenation reactions were performed on a variety of 3-oxo-3-arylpropionic acid ethyl esters using **9b** as the catalyst (Table 2, entries 1–9). Quantitative conversions with excellent enantioselectivities (95–99% *ee*) were achieved. Hydrogenation of **10** was not sensitive to the substituents (*o*, *p*, electron-donating or electron-withdrawing) on the aromatic ring. The $RuCl_2L^*(DMF)_n$ **9b** catalyst was also successfully applied to the asymmetric reduction of alkyl acetoacetates regardless of the bulkiness of the alkyl group (Table 2, entries 10–12) giving up to 99% *ee*s.

In conclusion, a novel alternative route to a series of chiral C_3*-TunePhos bisphosphines has been de-

Table 1. Ligand screenings for asymmetric hydrogenation of ethyl benzoylacetate **10a**.



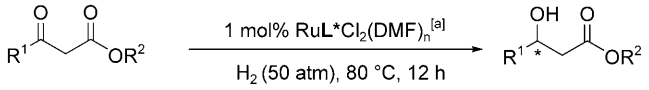
10a **11a**

Entry	Catalyst	Conv.	*ee* [%][a]	Config.[b]
1	**9a**	100	97	*R*
2	**9b**	100	98	*R*
3	**9c**	100	98	*R*
4	**9d**	100	89	*R*
5	**9e**	100	56	*R*

[a] The *ee* values were determined by GC on a chiral Beta dex 390 capillary column.

[b] The absolute configuration of **11a** was assigned by comparison of the observed optical rotation with reported data.

Table 2. Ru-catalyzed asymmetric hydrogenation of β-keto esters.



10a – l **11a – l**

Entry	Sub.	R^1	R^2	Prod.	*ee* [%][b]	Config.[c]
1	**10a**	Ph	Et	**11a**	98	*R*
2	**10b**	4-F-C_6H_4	Me	**11b**	98	*R*
3	**10c**	4-Cl-C_6H_4	Me	**11c**	97	*R*
4	**10d**	4-Cl-C_6H_4	Et	**11d**	97	*R*
5	**10e**	4-Br-C_6H_4	Me	**11e**	96	*R*
6	**10f**	4-Br-C_6H_4	Et	**11f**	96	*R*
7	**10g**	4-Me-C_6H_4	Et	**11g**	99	*R*
8	**10h**	2-Me-C_6H_4	Et	**11h**	97	*R*
9	**10i**	2-MeO-C_6H_4	Et	**11i**	95	*R*
10	**10g**	Me	Me	**11g**	99	*S*
11	**10k**	Me	*i*-Pr	**11k**	99	*S*
12	**10l**	Me	*t*-Bu	**11l**	99	*S*

[a] Reactions were carried out in methanol or ethanol solvent with 1 mol% **9b** as a catalyst precursor for 12 h. All reactions were completed in full conversions.

[b] Enantiomeric excesses were determined by GC using chiral Beta dex 390 and Gama dex 225 columns or HPLC using a Chiralpak AS column.

[c] The absolute configuration of **11** was assigned by comparison of the observed optical rotation with reported data.

signed and carried out with several highlighted features. The Ru-catalyzed enantioselective hydrogenation of aryl- and alkyl-substituted β-keto ester was achieved with very high enantioselectivities, which provides an efficient access to a variety of chiral β-hydroxy esters and their derivatives. Future work on the applications of these new types of ligands will focus on achieving new transition metal-catalyzed enantioselective reactions and extending the scope of substrates in many existing enantioselective transformations.

Experimental Section

General Hydrogenation Procedure

$[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and chiral ligand **1** (0.021 mmol) were dissolved in degassed DMF (3 mL) in a Schlenk tube and heated to 100 °C under N_2. After the mixture had cooled to 50 °C, the solvent was removed under vacuum to give the catalysts as a reddish brown solid. The catalyst was taken into a glovebox, dissolved in degassed methanol (16 mL), and distributed equally among eight vials. To the catalyst solution was added the substrate (0.25 mmol). The resulting mixture was transferred into an autoclave and charged with H_2 at 50 atm. The autoclave was heated at 80 °C for 12 h. The autoclave was then cooled to room temperature and the H_2 was carefully released. The reaction solution was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then directly analyzed by GC (chiral Beta dex 390 or Gamma dex 225) or HPLC (Chiralpak AS) to determine the enantiomeric excess.

Acknowledgements

We would like to acknowledge the National Institutes of Health (GM58832) and Merck & Co., Inc. for financial support. We would like to thank Dr. H. Yennane at The Pennsylvania State University for the X-ray analyses. The assistance of Dr. C. Pabba and Mr. R. Davis at Albany Molecular Research Inc. in the preparation of the manuscript is also gratefully acknowledged.

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