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Convenient Divergent Strategy for the Synthesis of TunePhos-Type Chiral Diphosphine Ligands and Their Applications in Highly Enantioselective Ru-Catalyzed Hydrogenations

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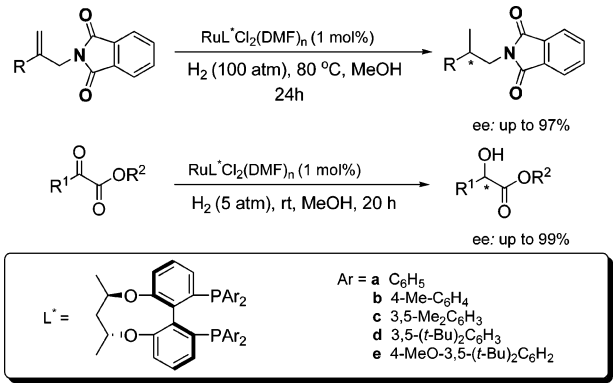

A convenient, divergent strategy for the synthesis of a series of modular and fine-tunable C_3-TunePhos-type chiral diphosphine ligands and their applications in highly efficient Ru-catalyzed asymmetric hydrogenations were explored. Up to 97 and 99% ee values were achieved for the enantioselective synthesis of β-methyl chiral amines and α-hydroxy acid derivatives, respectively.

The biological activity of many pharmaceutical compounds, agrochemicals, flavors, and fragrances is associated with absolute molecular configuration, which makes the enantioselective synthesis of chiral compounds an important topic.[1] The development of efficient methods to achieve this goal has been a substantial challenge for chemists in both academia and industry. Among various strategies, catalytic asymmetric hydrogenation mediated by transition metal complexes provides one of the most practical and powerful routes due to its remarkable features, including high stereoselectivity, high reactivity, atom economy, and operational simplicity.[2] Owing to the decisive role of chiral ligands for both catalytic activity and high level of enantioselectivity, considerable efforts have been devoted to the design and synthesis of a variety of chiral ligands.[3] Inspired by the tremendous success achieved in the use of Rh- and Ru-BINAP-catalyzed asymmetric reactions,[4] many atropisomeric C_2-symmetric biaryl diphosphine ligands, such as H_8-BINAP,[5] MeO-BIPHEP,[6] SEGPHOS,[7] P-Phos,[8] and other important biaryl phosphine ligands, have been developed in the past two decades (Figure 1).[3]

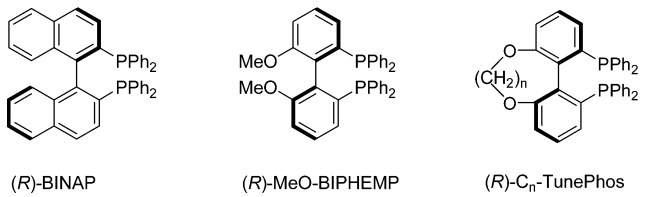

FIGURE 1. Some atropisomeric C_2-symmetric biaryl ligands.

Although these atropisomeric biaryl ligands are highly effective for many asymmetric transformations, the search for more practical and efficient ligands in terms of ease of preparation, high enantioselectivity, and high turnover number (TON) remains an important goal in asymmetric hydrogenation.

Recently, we have developed a novel class of conformationally rigid C_n-TunePhos (Figure 1, $n = 1-6$) ligands, by introducing a bridge with variable length to link the chiral atropisomeric biaryl groups.[9] This family of TunePhos ligands has proven highly efficient in a variety of asymmetric reactions.[10] Apart from optimization in length of these alkyl linkers, we envision that changes of the phosphorus substituents of TunePhos ligands are also important structural modifications, which may endow these new ligands with unique steric and electronic properties. With respect to the efficient synthesis of a class of such ligand analogues, the established synthetic routes from MeO-BIPHEP and its derivatives have some disadvantages, as described in Schmid's report.[6] Specifically, the phosphinous or phosphinic acid derivatives or the secondary phosphines have to be synthesized separately in each case (typically starting from a phosphorus trichloride) which elon-

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(1) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999. (c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994.

(2) Noyori, R. *Angew. Chem.* **2002**, *114*, 2108; *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(3) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(4) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Tto, I.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7935.

(5) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

(6) Schmid, R.; Broger, E. A.; Cereghtti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.

(7) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, 343.

(8) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513.

(9) (a) Zhang, X. U.S. Patent 6521769, 2003 (filed 1999). (b) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.

(10) (a) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495. (b) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (c) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626. (d) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem.* **2005**, *117*, 5013; *Angew. Chem., Int. Ed.* **2005**, *44*, 4933. (e) Wang, C.-J.; Sun, X.; Zhang, X. *Synlett* **2006**, 1169. (f) Raghunath, M.; Zhang, X. *Tetrahedron Lett.* **2005**, *46*, 7017.

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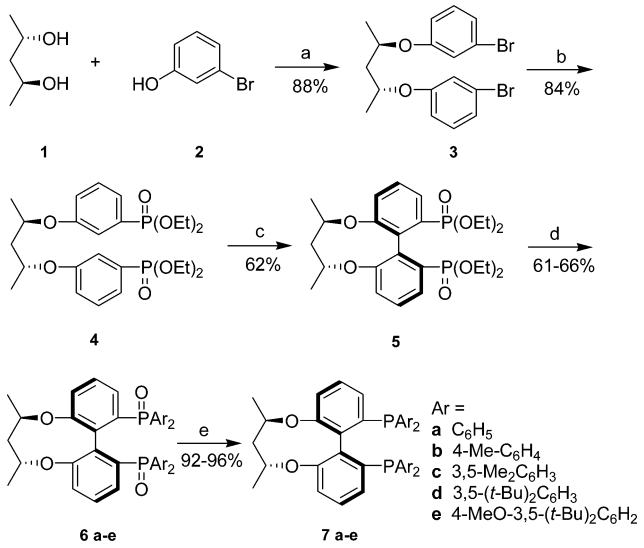
SCHEME 1. Synthesis of Ligands[a]



[a] Reagents and conditions: (a) DIAD, Ph_3P, THF, sonication, 0−35 °C, 1 h; (b) i. Mg, THF, reflux; ii. $(EtO)_2OPCl$, THF, −78 °C to rt; (c) i. LTMP, THF, −78 °C; ii. $FeCl_3$, THF, −78 °C to rt; (d) i. $SOCl_2$, cat. DMF, reflux for 30 h; ii. ArMgX, −78 °C; (e) $HSiCl_3$, Bu_3N, xylene, reflux.

gates the synthetic route. It could also be difficult to attach bulky diaryl groups to the phosphorus atoms due to steric hindrance. Moreover, cumbersome individual resolution procedures have to be performed for each new derivative in the case of routes involving the phosphine oxide.[6,11]

As part of our continued interest in the synthesis and use of new chiral diphosphine ligands in asymmetric catalysis, we have developed the idea of using a chiral linker to make enantiomerically pure TunePhos-type ligands. The designed ligands **7** were first documented by us in the invention disclosure along with a suggested route of using a chiral linker to control the formation of biaryl phosphines in 1999.[9a] Though this attractive pathway to make **7a** was then demonstrated by Chan's group, long synthetic routes, moderate yields, and hard modifications on P-aryl groups restrict their potential applications.[12]

Herein, a truly general, divergent way to make modular C_3-TunePhos-type of phosphine ligands is discovered (Scheme 1). The synthetic route was condensed and straightforward: the chiral bis(bromoether) **3** was prepared by the Mitsunobu reaction with (2*S*,4*S*)-pentanediol and 3-bromophenol. The double Mitsunobu reaction proceeded smoothly and afforded 88% yield of **3** in 1 h under sonication conditions. The phosphate **4** was conveniently obtained after the generation of bis-Grignard reagent followed by quenching with diethyl chlorophosphate. A sequence of thermodynamically controlled ortho-lithiation with in situ LTMP followed by oxidative homocoupling with anhydrous ferric chloride afforded bis(diethyl phosphonates) **5** in a good yield and >99% diastereoselectivity based on ^{1}H NMR analysis. The axial chirality *S* was assigned when compared to the data reported in the literature.[12] The bis-(phosphonic dichlorides), readily formed in situ from intermediate **5** by the treatment with thionyl chloride, underwent tetrasubstitution with a wide variety of Grignard reagents to give compounds **6a**−**e**. Completion of the synthesis of the series of chiral ligands (S_{ax},*RR*)-**7a**−**e** was accomplished after reduction with trichlorosilane and tributylamine in refluxing xylene. Complete retention of the biphenyl stereochemistry was confirmed by ^{1}H NMR analysis and optical rotation measurement.

Several features are highlighted in our new synthetic strategy. First, the small hindrance of bis(diethyl phosphonate) in compound **4** facilitated the followed oxidative coupling reaction to give the desired product **5** in a high yield. This strategy circumvents the problem in our initial attempt to attach Ar groups in this step, which led to extremely low homocoupling yields. For some bulky substituents, even no coupling products were detected due to high steric hindrance. Second, the introduction of the synthetically flexible intermediate **5** allows for the convenient divergent incorporation of various Ar substituents of the PAr_2 moieties in the penultimate step, avoiding the requisite individual formation of the phosphinic or phosphinous moieties as described in traditional strategies.[3] 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 homocoupling reaction with complete diastereodifferentiation without unwanted intermolecular coupling. This avoids tedious routine resolutions.[13] Last, only five steps are necessary in this procedure, and the overall synthesis steps are easy to handle.

To test the synthetic utility of these ligands, we have explored the Ru-catalyzed hydrogenations of allylphthalimides and α-keto esters. The catalysts $RuL^*Cl_2(DMF)_n$ **8a**−**e** (where L* is the chiral ligand **7a**−**e**, $n = 2-6$) were prepared as reddish brown solids from $[RuCl_2(benzene)_2]_2$ and the corresponding **7a**−**e** in DMF at 100 °C.[14] The complexes, thus obtained, were used directly in the catalytic reactions.

Asymmetric hydrogenation of α-phthalimide ketones and disubstituted allylphthalimides demonstrates an efficient approach to access chiral amino alcohols and *β*-methyl chiral amines after deprotection.[10,15] Chiral amines bearing a *β*-methyl group on the chiral center and their derivatives are key structural elements in both natural products and pharmaceuticals.[16] We initiated our studies by screening catalysts **8a**−**e** on the asymmetric hydrogenation of the *N*-2-ethylallylphthalimide. In the presence of the **8a** complex, up to 94% ee and 100% conversion was observed at 80 °C under 100 atm hydrogen pressure in 24 h (Table 1, entry 1). A systematic investigation of the effect of substituents on ligand **7** indicated that the introduction of somewhat bulky 4-methyl (**7b**) and 3,5-dimethyl (**7c**) groups or much more hindered 3,5-di-*tert*-butyl (**7d**) and 4-methoxyl-3,5-di-*tert*-butyl (**7e**) groups to P-phenyl rings dramatically decreased the enantioselectivities (Table 1, entries 2−5).

To assess the general efficiency of this catalytic system, the asymmetric hydrogenation reactions were performed on a variety of substrates using **8a** as a catalyst (Table 1, entries 6−12).

(11) (a) Broger, E. A.; Foricher, J.; Heiser, B.; Schmid, R. U.S. Patent 5274125, 1993. (b) Foricher, J.; Heiser, B.; Schmid, R. U.S. Patent 5302738, 1994. (c) Lalonde, M.; Schmid, R. U.S. Patent 5536858, 1996.

(12) (a) Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5815. (b) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955.

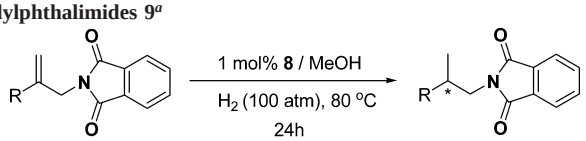
(13) Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 649.

(14) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1993**, *71*, 57.

(15) Brunner, H.; Wachter, J.; Schmidbauer, J. *Organometallics* **1986**, *5*, 2212.

(16) (a) Lazarevski, G.; Kobrehel, G.; Metelko, B.; Duddeck, H. *J. Antibiot.* **1996**, *49*, 1066. (b) Nicholas, G. M.; Molinski, T. F. *Tetrahedron* **2000**, *56*, 2921.

TABLE 1. Asymmetric Hydrogenation of *N*-2-Substituted Allylphthalimides 9[a]



9a-h **10a-h**

entry	catalyst	sub.	R	prod.	ee %[b]	config.[c]
1	**8a**	**9a**	Et	**10a**	94	*S* (−)
2	**8b**	**9a**	Et	**10a**	84	(−)
3	**8c**	**9a**	Et	**10a**	72	(−)
4	**8d**	**9a**	Et	**10a**	24	(−)
5	**8e**	**9a**	Et	**10a**	76	(−)
6	**8a**	**9b**	*n*Bu	**10b**	95	(−)
7	**8a**	**9c**	Bn	**10c**	92	(−)
8	**8a**	**9d**	*i*Bu	**10d**	86	(−)
9	**8a**	**9e**	*t*Bu	**10e**	66	(+)
10	**8a**	**9f**	cyclohexyl	**10f**	97	(−)
11	**8a**	**9g**	cyclopentyl	**10g**	93	(−)
12	**8a**	**9h**	Cl	**10h**	94	(−)

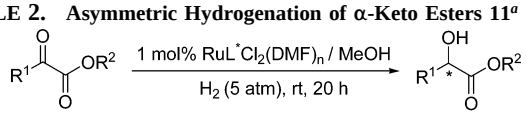
[a] Complete conversions were indicated by ^{1}H NMR spectroscopy in all entries. [b] The enantiomeric excesses were determined by chiral HPLC or chiral GC (see the Supporting Information). [c] The absolute configuration of **10a** was assigned by comparison of the observed optical rotation with reported data.[10d]

Substrates with a primary *n*-alkyl substituent such as an ethyl, *n*-butyl, or benzyl group at the 2-position of the allylphthalimides afforded products with high ee values (Table 1, entries 1, 6, and 7). The enantioselectivities decreased gradually as the steric hindrance of the substituents in the substrates increased (Table 1, entries 6−9). However, the hydrogenation of a cyclohexyl- and cyclopentyl-substituted substrates (**9f** and **9g**) still afforded the desired products in 97 and 93% ee (Table 1, entries 10 and 11). In addition, the electron-deficient 2-chloroallylphthalimide can also be hydrogenated with good enantioselectivity using this system (Table 1, entry 12). These enantioselectivities for the corresponding products were comparable with the results achieved with Ru[(*S*)-C$_n$-TunePhos]Cl$_2$(DMF)$_n$ systems.[10d]

Asymmetric hydrogenation of the corresponding α-keto esters provides one of the most efficient approaches to enantiomerically pure α-hydroxy acid derivatives, which are very important structural motifs in numerous biologically active compounds and are often utilized as resolving agents.[1,17] Optimization proved that complex **8c** showed superior efficiency in the asymmetric hydrogenation of α-keto esters at room temperature under low hydrogen pressure.

As shown in Table 2, a variety of α-keto esters were reduced to form chiral α-hydroxy esters with excellent enantioselectivity (96−99%). The electronic and steric nature of a substituent on the phenyl ring of the substrate had little influence on the enantioselectivity and reactivity of the reaction. The enantiomeric excesses of **12** were better than those obtained when their parent ligand C$_3$-TunePhos was used under the same conditions (Table 2).[10e] It was noteworthy that, even without acidic additives,[18] ligand **7c** showed a marked superiority in selectivity to BINAP in the hydrogenation of **11**. A key intermediate for the synthesis of ACE inhibitors Benazepril and Delapril

TABLE 2. Asymmetric Hydrogenation of α-Keto Esters 11[a]



11a-j **12 a-j**

					ee %[b]	
entry	sub.	R^1	R^2	prod.	(S_{ax},*RR*)-**7c**	(*S*)-C$_3$-TunePhos
1	**11a**	Ph	Me	**12a**	99	97
2	**11b**	4-F−C$_6$H$_4$	Me	**12b**	98	95
3	**11c**	3-F−C$_6$H$_4$	Me	**12c**	98	94
4	**11d**	4-Cl−C$_6$H$_4$	Me	**12d**	98	93
5	**11e**	4-Br−C$_6$H$_4$	Me	**12e**	96	92
6	**11f**	4-Me−C$_6$H$_4$	Me	**12f**	99	96
7	**11g**	4-MeO−C$_6$H$_4$	Me	**12g**	98	96
8	**11h**	3-MeOC$_6$H$_4$	Me	**12h**	98	95
9	**11i**	2-furyl	Me	**12i**	97	85
10	**11j**	Ph(CH$_2$)$_2$	Et	**12j**	98	96

[a] Conversions were >99% as indicated by ^{1}H NMR for all entries. [b] The enantiomeric excesses were determined by chiral GC (see the Supporting Information); the absolute configurations of products were assigned as *S* by comparison of the observed optical rotation with reported data.[10e]

hydrochloride[19] was readily accessible via the hydrogenation of ethyl 2-oxo-4-phenylbutyrate with up to 98% ee (Table 2, entry 10). To our knowledge, these results represent one of the highest enantioselectivities yet achieved for the preparation of optically active α-hydroxy acid derivatives using direct asymmetric hydrogenations.

In conclusion, we have developed a remarkably versatile route for the synthesis of a family of C$_3$-TunePhos derivative diphosphine ligands for highly efficient Ru-catalyzed asymmetric hydrogenations. These highly enantioselective hydrogenation reactions provide facile access to optically active amines and α-hydroxy acid derivatives, which are very important chiral building blocks for the synthesis of a variety of natural products and biologically active molecules. Further exploration of the general applications of this class of ligands in transition-metal-catalyzed asymmetric reactions will be reported in due course.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenations. [Ru(benzene)Cl$_2$]$_2$ (5 mg, 0.01 mmol) and chiral ligand **7** (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 was 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$_2$ (100 atm for allylphthalimides and 5 atm for α-keto esters). The autoclave was heated at 80 °C for 24 h for allylphthalimide substrates or at room temperature for α-keto ester substrates for 20 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,

(17) Kinbara, K. *Synlett* **2005**, 732.

(18) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

(19) (a) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511. (b) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1988**, *31*, 422. (c) Ogihara, T.; Nakamaru, M.; Higaki, J.; Kumahara, Y.; Hamano, Y.; Minamino, T.; Nakamura, N. *Curr. Ther. Res.* **1987**, *41*, 809. (d) Miyake, A.; Itoh, K.; Oka, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2852.

which was then directly analyzed by chiral GC (Gamma dex 225) or chiral HPLC (Chiralpak AD) to determine the enantiomeric excess.

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Supporting Information Available: Complete description of ligand synthesis, asymmetric hydrogenation, and product characterization together with photocopies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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