Practical P-Chiral Phosphane Ligand for Rh-Catalyzed Asymmetric Hydrogenation

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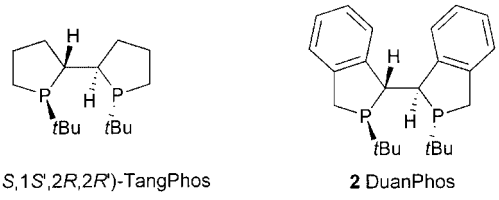
A highly electron-donating and conformationally rigid P-chiral bis(trialkylphospholane) ligand **2** (DuanPhos) has been prepared in both enantiomeric forms through a concise synthesis. Rh-**2** complex has exhibited remarkably high enantioselectivities (up to >99% *ee*) and reactivities (up to 10,000 TON) for the hydrogenation of a wide variety of functionalized prochiral alkenes (5 different types), which provides a very practical catalytic system for the preparation of various synthetically useful chiral compounds.

Transition metal-catalyzed asymmetric hydrogenation of prochiral double bonds using such elements as Rh, Ru and Ir represents one of the most practical and efficient methods for the preparation of chiral building blocks.[1] Tremendous effort has been devoted into this field during the last few decades, especially the development of chiral phosphorus ligands that can provide not only high enantioselectivities, but also high reactivities.[2] However, the substrate scope of hydrogenation for a particular ligand or ligand family is generally very limited with only few exceptions such as BINAP[3] and DuPhos.[4] While there is no universal ligand, the search for more practical ligands with ready availability, high enantioselectivity and reactivity, and broad substrate scope remains an important goal in asymmetric hydrogenation.

P-chiral phosphorus ligands are highly likely to be a superior class of ligands for asymmetric catalysis because of their abilities to bring the chiral environment to the closest proximity to the transition metal centers. Dramatic results by Knowles using P-chiral DIPAMP ligand for Rh-catalyzed hydrogenation in 1970s opened the field of asymmetric catalysis.[5] However, it took nearly two decades for other groups to discover efficient methods to prepare P-chiral phosphane compounds largely due to the synthetic difficulties in construction of stereogenic phosphorus centers.[6,7] Moreover, a major drawback of many P-chiral phosphane synthetic methods developed by Imamoto,[6a] Juge,[6b] Corey,[6c] Evans,[6e] and Livinghouse[6g] is that either only one enantiomer of ligand is readily accessible due to the nature of the chiral auxiliaries they used in the stereogenic center formation step or a tedious diastereomeric derivatization, separation and deprotection sequence was involved. Thus, an overwhelming challenge in this field is to prepare both enantiomers of P-chiral ligands in a practical way.



1 (1*S*,1*S*',2*R*,2*R*')-TangPhos **2** DuanPhos

Figure 1. Structures of a new class of highly electron-donating and conformationally rigid bis(trialkylphospholane) ligands

We have designed many conformationally rigid chiral bis(phosphanes) for achieving high enantioselectivities in asymmetric hydrogenation.[8] To reach high turnover number (TON) and turnover frequency (TOF) as well, we envisioned that bis(trialkylphosphanes), especially with *tert*-butyl groups, would be a particular class of electron-donating ligands and their Rh complexes would be highly active and represent a new generation of hydrogenation catalysts. For instance, a bis(trialkylphosphane) ligand developed by Hoge[9] provided 10 times more turnovers for the hydrogenation of an alkene than the bis(dialkylarylphosphane) DuPhos. Recently, we introduced a highly electron-donating P-chiral bis(trialkylphospholane) ligand (**1**, TangPhos), which is highly enantioselective and reactive for the Rh-catalyzed hydrogenation of a wide variety of alkenes.[10] However, only one enantiomer of **1** (1*S*,1*S*',2*R*,2*R*'-TangPhos, Figure 1) is readily accessible due to the usage of (–)-sparteine, which is available only in one enantiomeric form, as a chiral induction base. Another very effective P-chiral ligand BisP*,[11] introduced by Imamoto, is also only

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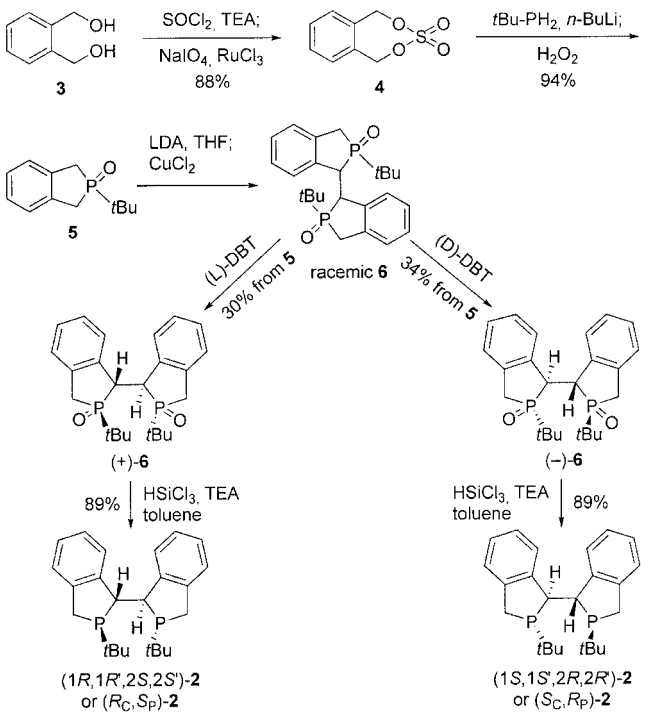
available in one enantiomeric form for the same reason. Herein, we like to report a concise and practical synthesis of a new P-chiral bis(trialkylphospholane) ligand **2** (named as DuanPhos, Figure 1) in both enantiomeric forms and the highly enantioselective hydrogenation of various functionalized alkenes (five different types) using a cationic Rh-**2** complex as the catalyst.

The synthetic route to both enantiomers of DuanPhos (**2**) is outlined in Scheme 1, in which a conversional resolution of a racemic bis(phosphane) oxide intermediate is applied for the first time for making trialkyl P-chiral phosphorus ligand.[12] From readily available diol **3**, cyclic sulfate **4** was formed in high yield according to the literature procedure.[13] Treatment of **4** with *tert*-butylphosphane[14] in the presence of *n*BuLi, followed by in situ oxidation with H_2O_2, provided phosphane oxide **5** in excellent yield. $CuCl_2$ mediated homo-coupling of **5** in the presence of LDA gave racemic bis(phosphane) oxide **6**. It is noteworthy that the *meso* diastereomer of **6**, as well as all other possible stereoisomers, were not formed in an appreciable amount, which was indicated by the ^{31}P NMR spectra of the crude coupling product. This is probably due to the highly selective deprotonation directed by the bulky *tert*-butyl group and steric hindrance in the coupling step, which only favor the formation of racemic product. To our delight, racemic **6** can be easily resolved with inexpensive (L)-DBT·H_2O (DBT = dibenzoyl tartaric acid) to afford enantiomerically pure (+)-**6** (> 99 % *ee* with one resolution, no further recrystallization needed) in 30 % yield (of expected from **5**). The remainder of **6** was treated with (D)-DBT·H_2O to give (–)-**6** (> 99 % *ee*) in 34 % yield (of expected from **5**). Reduction of (+)-**6** and (–)-**6** with trichlorosilane in the presence of



Scheme 1. Synthesis of ligand **2** (DuanPhos)

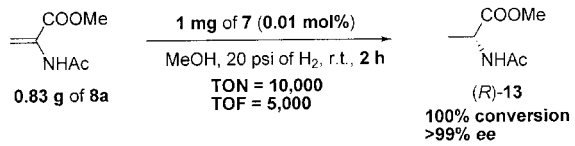
triethylamine afforded (1*R*,1*R*′,2*S*,2*S*′)-**2** [or (R_C,S_P-**2**)] and (1*S*,1*S*′,2*R*,2*R*′)-**2** [or (S_C,R_P-**2**)], respectively, as white solid in high yields. The absolute configurations of both enantiomers of **2** were determined by chemical correlations with the single-crystal X-ray crystallography of the complex of (–)-**6** and (D)-DBT.[15]

In order to examine the catalytic properties of DuanPhos (**2**), a cationic Rh complex {Rh(NBD)[(1*R*,1*R*′,2*S*,2*S*′)-**2**]}-SbF_6 (**7**) (NBD = norbornadiene) was prepared and used as the catalyst precursor in the hydrogenation of various prochiral alkenes. Some preliminary results are summarized in Table 1. Methyl α-(acetamido)acrylate (**8a**) and methyl α-(acetamido)-2-phenylacrylate (**8b**), two widely studied α-dehydroamino acid substrates in literature,[2] were explored with **7** under very mild conditions (methanol as solvent, room temperature, 20 psi of H_2 pressure). After 12 h (this is not optimal) quantitative yields and >99 % enantiomeric excesses of the products were observed (Entry 1 and 2). It is noteworthy that when 0.83 g of **8a** was hydrogenated with only 1 mg (0.01 mol%) of complex **7** under otherwise the same reaction conditions, >99 % *ee* of (*R*)-**13** were obtained quantitatively within 2 h (Scheme 2). Thus, high turnover number (10,000) and high turnover frequency (5,000 h^{-1}) were achieved, indicating the high activity of the Rh-DuanPhos catalyst.

Table 1. Asymmetric hydrogenation of alkenes with Rh-DuanPhos complex **7**

Entry[a]	Substrate		Conversion	ee (%)[b]	Configuration[c]
1		**8a** R = H	100%	>99	*R*
2		**8b** R = Ph	100%	>99	*R*
3		**9a** R = Me, R' = Et (*E*)	100%	>99	*R*
4		**9b** R = Me, R' = Et (*Z*)	100%	97	*R*
5		**9c** R = *p*-MeO-C_6H_4, R' = Me (*Z*)	100%	92	*S*
6		**9d** R = *p*-Cl-C_6H_4, R' = Me (*Z*)	100%	92	*S*
7		**10a** Ar = Ph, R = H	100%	>99	*R*
8		**10b** Ar = Ph, R = *i*Pr	100%	97	*R*
9		**10c** Ar = *p*-MeO-C_6H_4, R = Me	100%	99	*R*
10		**10d** Ar = *p*-CF_3-C_6H_4, R = Me	100%	99	*R*

[a] The hydrogenations were carried out at room temperature in MeOH under 20 psi of hydrogen pressure with **7** (1 mol %) as the catalyst precursor. [b] The *ee* values were determined by chiral GC or chiral HPLC. For separation conditions, see ref.[10] [c] The absolute configurations of the products were determined by comparing the retention times of two enantiomers with reported data.



Scheme 2. Asymmetric hydrogenation of **8a** with low catalyst loading

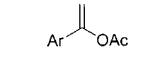
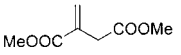
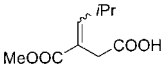
Asymmetric hydrogenation of β-(acetamido)acrylate derivatives, one of the most efficient and practical ways to obtain unnatural enantiomerically enriched β-amino acids, remains much less successful compared to the hydrogenation of their α-analogues. Few catalysts can provide high

enantioselectivities for both *E* and *Z* isomers of β-(acetamido)acrylate derivatives,[16] which are formed simultaneously in most synthetic protocols. As shown in Entries 3 and 4, using Rh complex **7** as the catalyst precursor, both ethyl (*E*)- and (*Z*)-3-acetamido-2-butenoate (**9a** and **9b**) were hydrogenated in remarkably high *ee* values (>99 % and 97 %, respectively). For more challenging β-aryl-substituted substrates **9c** and **9d**, high *ee* values (92 %) were also obtained (Entry 5 and 6).

Enantioselective hydrogenation of α-arylenamides **10** has also been investigated with many phosphorus ligands. As shown in Entries 7–10, Rh complex **7** provided excellent enantioselectivities (97->99 % *ee*) for the hydrogenation of enamides **10** regardless of the *E*/*Z* mixture of tri-substituted substrates or the substituents on the phenyl ring. These results are comparable to the best reported to date.

Compared to TangPhos, DuanPhos is expected to be more conformationally rigid due to the fused benzene rings on the phospholane rings. It has been demonstrated that increasing the conformational rigidity would improve the enatioselectivity.[8,17] Indeed, some preliminary results showed that, for the hydrogenation of another two types of functionalized alkenes enol acetates **11** and itaconic acid derivatives **12**, Rh-DuanPhos complex delivered higher enantioselectivities than Rh-TangPhos complex[10c] (Table 2). Especially for an electron-rich enol acetate **12b**, significant increase in enantioselectivity (from 80 % to 96 % *ee*) was observed with Rh-DuanPhos complex (Entry 2).

Table 2. Asymmetric hydrogenation of enol acetate and itaconic acid derivatives

Entry	Substrate		*ee* (%)	
			Rh-DuanPhos (7)[a]	Rh-TangPhos[b]
1		**11a** Ar = Ph	97(*R*)	96(*R*)
2		**11b** Ar = *p*-MeO-C_6H_4	**96(*R*)**	**80(*R*)**
3		**11c** Ar = *p*-F-C_6H_4	97(*R*)	92(*R*)
4		**11d** Ar = 2-naphthyl	98(*R*)	97(*R*)
5		**11d** Ar = 2-naphthyl	98(*R*)	95(*R*)[c]
6		**12a**	>99(*S*)	99(*S*)[c]
7		**12b** (*E*/*Z* mixture)	>99(*S*)	96(*S*)[c]

[a] The hydrogenations were carried out at room temperature in THF under 20 psi of hydrogen pressure with 1 mol % of Rh-DuanPhos complex 7 as the catalyst precursor. All reactions proceeded completely. [b] The hydrogenations were carried out at room temperature in EtOAc under 20 psi of hydrogen pressure with 1 mol % of [Rh(TangPhos)(NBD)]SbF_6 as the catalyst precursor. All reactions proceeded completely. [c] THF was used as the solvent.

It is worthy of mentioning that while TangPhos is very useful for hydrogenation of a variety of alkene substrates to offer one enantiomer of products, introduction of DuanPhos is a significant improvement because that: 1) Both enantiomers of ligand are readily available; 2) preliminary study shows that, unlike TangPhos, DuanPhos is not particularly air sensitive, which makes its preparation and handling more practical;[18] 3) increased conformational rigidity makes DuanPhos an overall more enantioselective ligand than TangPhos.

In conclusion, a concise and practical synthesis of a P-chiral bis(phospholane) ligand **2** (DuanPhos) has been developed. Both enantiomers of this highly electron-donating and conformationally rigid ligand are easily accessible through a simple resolution procedure. Rh-DuanPhos complex has exhibited remarkably high enantioselectivity and reactivity in the hydrogenation of a wide variety of functionalized prochiral olefins, which provides a very practical catalytic system for the preparation of various synthetically useful chiral compounds. Optimization of DuanPhos synthesis and further substrate scope expansion of hydrogenation are currently ongoing.

Acknowledgments

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