A Highly Enantioselective, Pd–TangPhos-Catalyzed Hydrogenation ofN-Tosylimines

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Palladium-Catalyzed Hydrogenation

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A Highly Enantioselective, Pd–TangPhos-Catalyzed Hydrogenation of *N*-Tosylimines**

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Although significant progress has been made in the catalytic asymmetric reduction of ketones and olefins over the last few decades,[1] the asymmetric reduction of imines remains a major challenge.[2] Enantioselective reductive amination with organocatalysts has recently been reported,[3] and a number of transition-metal-based catalysts, such as those containing Rh,[4] Ru,[5] Ti,[6] Zr,[6d] and Ir,[7] have been applied to the asymmetric hydrogenation of imines. However, this method has been less successful than the hydrogenation of other substrates. The main obstacles in solving the problems in this hydrogenation approach include different enantioselectivities for *E* and *Z* isomers of acyclic imines,[6b,c,8] the instability of some imines prepared from ketones, and the inhibitory effect of the amine products on the metal catalysts. In order to solve these problems, *N*-tosylimines were selected as the hydrogenation substrates since they are relatively stable and can be easily obtained from the corresponding ketones exclusively as the *E* isomer.[9] In addition, the strongly electron-withdrawing character of the tosyl group reduces the inhibitory effect of the reduction product on the catalysts, which might lead to higher reactivity. These advantages of *N*-tosylimines as substrates prompted us to look for a good reduction catalyst for the substrates. To the best of our knowledge, the asymmetric hydrogenation of *N*-tosylimines has rarely been explored, and the best result reported so far is the 84% *ee* reported by the Charette group using a Ru–Binap catalyst.[9] In our search for effective hydrogenation catalysts for the reduction of *N*-tosylimines, we have explored this trans-

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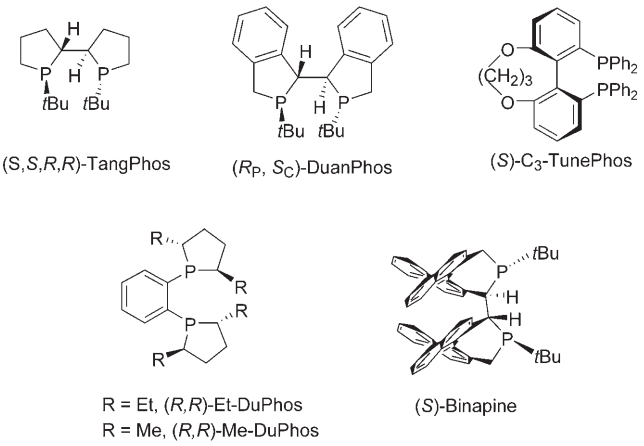
formation with many transition-metal-containing catalysts, in particular Rh, Ru, Ir, and Pd complexes.

Palladium complexes have been extensively employed as catalysts for a wide range of reactions, especially for carbon–carbon and carbon–heteroatom coupling reactions.[10] Although heterogeneous Pd/C catalysts have been used extensively in imine reductions, there are only a few reports of Pd-catalyzed homogeneous and asymmetric hydrogenation. The first asymmetric hydrogenation of imino esters was described by Amii with a $Pd(OCOCF_3)_2$–Binap complex that gave up to 90% *ee*.[11] However, the substrate scope of this system was limited to fluoro-substituted compounds. Raja and Thomas have reported a heterogeneous palladium-catalyzed asymmetric hydrogenation of α-ketoesters,[12] and, very recently, the Zhou group disclosed their results on the hydrogenation of functionalized ketones using $Pd(OCOCF_3)_2$ and Me-DuPhos as catalyst, with a best result of 92% *ee*.[13]

Our group has developed a series of diphosphane ligands, such as TangPhos, DuanPhos, Binapine, and C_n-Tunephos (Scheme 1), which we have successfully employed in the asymmetric hydrogenation of a wide range of substrates.[14] The electron-donating rigid TangPhos ligand was found to be particularly good for highly enantioselective hydrogenation reactions; therefore we anticipated that the combination of Pd precursors with TangPhos could lead to outstanding results in the asymmetric hydrogenation of imines. Here we present our preliminary results on the Pd–TangPhos-catalyzed hydrogenation of *N*-tosylimines, which occurs with up to >99% *ee* and complete conversion.

Our initial study began with *N*-tosylimine (**1a**) as the model substrate and a rhodium complex of a chiral diphosphane as the catalyst. A number of catalytic systems were tested; the results are summarized in Table 1. First, we investigated the asymmetric hydrogenation of **1a** using the Rh–TangPhos complex **A**, which has been proved to be an efficient hydrogenation catalyst for a number of substrates. Up to 91% *ee* was observed (Table 1, entry 1). Other Rh complexes with chiral diphosphane ligands, such as **B** and **C**, also provided good enantioselectivities (Table 1, entries 2 and 3). A systematic study of the hydrogenation of **1a** was then performed to screen the reaction conditions. The hydrogenation with Rh–(*R*,*R*)-Et-DuPhos (**D**) or Rh–(*R*,*R*)-Met-DuPhos (**E**) proceeded with high conversions; however, the *ee* values of the products were relatively low (63% and 68%, respectively; Table 1, entries 4 and 5). To our delight, the best result was obtained with the Pd–TangPhos complex **L** (up to 99% *ee* and >99% conversion; Table 1, entry 14). In contrast, complexes **I** and **J** did not show any reactivity. These results imply that the weakly coordinating $CF_3CO_2^-$ ion in complex **L** might play an important role in this transformation (Table 1, entries 9 and 10).

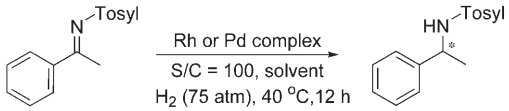


Scheme 1. Structure of ligands for asymmetric hydrogenation.

The effect of reaction temperature and hydrogen pressure on the enantioselectivity and reactivity of the hydrogenation was also tested. We found that both the conversion and the *ee* decreased at a lower hydrogen pressure (Table 1, entry 12). A lower temperature only resulted in a lower conversion; the enantioselectivity remained the same (Table 1, entry 13). Further studies indicated that changing the solvent had no significant effect on the enantioselectivities and conversions (Table 1, entries 15–18).

To demonstrate the efficiency of this Pd–TangPhos catalyst, a series of substituted *N*-tosylimines **1** were synthesized from readily available starting materials according to

Table 1: Enantioselective hydrogenation of *N*-tosylimine **1a**.[a]



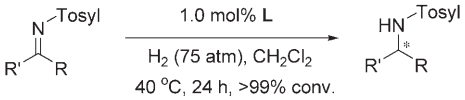
1a **2a**

Entry	Cat. precursor	Ligand	Complex	Solvent	Conv. [%][b]	*ee* [%][c]
1	$[Rh(cod)_2]BF_4$	(*S*,*S*,*R*,*R*)-TangPhos	**A**	CH_2Cl_2	>99	91
2	$[Rh(cod)_2]BF_4$	(R_P,S_C)-DuanPhos	**B**	CH_2Cl_2	>99	82
3	$[Rh(cod)_2]BF_4$	S_P-Binapine	**C**	CH_2Cl_2	>99	88
4	$[Rh(cod)_2]BF_4$	(*R*,*R*)-Et-DuPhos	**D**	CH_2Cl_2	>99	63
5	$[Rh(cod)_2]BF_4$	(*R*,*R*)-Me-Duphos	**E**	CH_2Cl_2	>99	68
6	$[Rh(cod)_2]BF_4$	(*S*)-C_3-Tunephos	**F**	CH_2Cl_2	>99	94
7	$Pd(OCOCF_3)_2$	(*S*)-Binapine	**G**	CH_2Cl_2	15	n.a.
8	$Pd(OCOCF_3)_2$	(*S*)-C_3-Tunephos	**H**	CH_2Cl_2	65	n.a.
9	$Pd(OAc)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**I**	CH_2Cl_2	n.r.	n.a.
10	$[Pd(MeCN)]Cl_2$	(*S*,*S*,*R*,*R*)-TangPhos	**J**	CH_2Cl_2	n.r.	n.a.
11	$[Pd(MeCN)_4](BF_4)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**K**	CH_2Cl_2	>99	98
12[d]	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	CH_2Cl_2	60	93
13[e]	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	CH_2Cl_2	75	99
14	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	CH_2Cl_2	>99	99
15	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	MeOH	>99	99
16	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	*i*PrOH	>99	98
17	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	toluene	>99	98
18	$Pd(OCOCF_3)_2$	(*S*,*S*,*R*,*R*)-TangPhos	**L**	EtOAc	>99	96

[a] cod = 1,5-cyclooctadiene, n.r. = no reaction, n.a. = not analyzed. [b] Conversions (in %) were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Enantiomeric excesses were determined by chiral HPLC. [d] The reaction was carried out under 20 atm hydrogen pressure. [e] The reaction was carried out at 24 °C.

the procedures reported in the literature.[15] The Pd–TangPhos-catalyzed hydrogenation of **1** under optimized conditions was then performed; the results are summarized in Table 2. Both electron-donating and electron-withdrawing

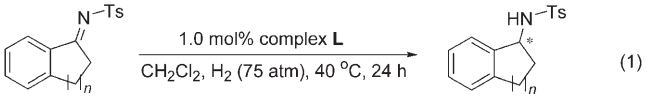
Table 2: Pd-catalyzed asymmetric hydrogenation of *N*-tosylimines **1**.



Entry	R′ in **1**	R	Prod.	*ee* [%][a]	Config.[b]
1	C_6H_5 (**1a**)	CH_3	**2a**	99	*R* (+)
2	4-$CH_3C_6H_4$ (**1b**)	CH_3	**2b**	96	(+)
3	4-FC_6H_4 (**1c**)	CH_3	**2c**	99	(+)
4	4-$CH_3OC_6H_4$ (**1d**)	CH_3	**2d**	99	(+)
5	3-$CH_3OC_6H_4$ (**1e**)	CH_3	**2e**	>99	(+)
6	2-naphthyl (**1f**)	CH_3	**2f**	>99	(+)
7	1-naphthyl (**1g**)	CH_3	**2g**	99	(−)
8	4-ClC_6H_4 (**1h**)	CH_3	**2h**	99	(+)
9	3-ClC_6H_4 (**1i**)	CH_3	**2i**	>99	(+)
10	C_6H_5 (**1j**)	C_2H_5	**2j**	93	*R* (+)
11	*t*Bu (**1k**)	CH_3	**2k**	98	*R* (+)
12	cyclopropyl (**1l**)	CH_3	**2l**	75	(+)

[a] Enantiomeric excesses were determined by chiral HPLC. [b] The absolute configuration was determined by comparison of the sign of the optical rotation with the reported data.[16]

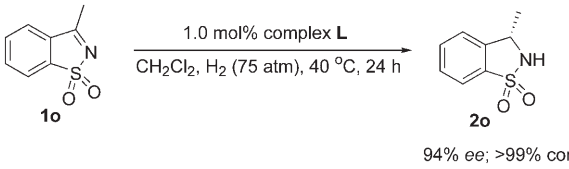
substituents on the aryl unit of the imines gave excellent enantioselectivities (96–99% *ee*; Table 2, entries 1–9). The *ee* value decreased from 99% to 93% when a methyl group was replaced by an ethyl group (Table 2, entry 10). The doubly alkyl substituted *N*-tosylimines **1k** and **1l** were also used as substrates. Up to 98% *ee* was achieved for the *tert*-butyl-substituted imine **1k** (Table 2, entry 11), while a lower *ee* was observed with **1l** (75% *ee*; Table 2, entry 12). It is worth noting that the Pd–TangPhos-catalyzed hydrogenation of cyclic imines **1m** and **1n** also proceeded with high enantioselectivities (98% and 94% *ee*, respectively) to produce α-aminotetralin (**2m**) and α-aminindanes (**2n**), respectively, which are important structural motifs in biologically active compounds [Eq. (1)]. Surprisingly, we found that *N*-tosyli-



(1)

mines **1l, 1m**, and **1n** could be prepared from the corresponding ketones and readily available *p*-toluenesulfonamide in one step in up to 75% yield. The feasibility of this method for the synthesis of other *N*-tosylimine substrates is still under investigation.

Substituted sultams are important chiral auxiliaries that were first introduced in 1990 by Oppolzer[17] and have since been successfully applied to a number of asymmetric transformations. Asymmetric hydrogenation of the corresponding *N*-tosylimine is one of their most widely used synthetic transformations. To examine the efficiency of the Pd–TangPhos catalysts on this transformation, compound **1o** was synthesized and hydrogenated with complex **L** to give the methyl-substituted sultam **2o** with good enantioselectivity [Eq. (2)].[17] To examine the synthetic potential of this



(2)

methodology, a reductive cleavage of the tosyl group in **2a** was performed according to a literature procedure.[18] (*R*)-α-Methylbenzylamine was obtained in 92% yield with retention of the previous *ee*.

In conclusion, we have developed an efficient Pd-catalyzed asymmetric hydrogenation of *N*-tosylimines, which are stable and can be prepared from aromatic, aliphatic, and cyclic ketones exclusively with the *E* configuration. A highly enantioselective hydrogenation of *N*-tosylimines has been achieved in the presence of $Pd(OCOCF_3)_2$–TangPhos, with enantioselectivities of up to 99% *ee* and conversions of more than 99%. However, a relatively high hydrogen pressure and catalytic loading are important limitations of this work. Further studies to improve the turnover number and characterize the catalytic species are underway and will be reported in due course.

Experimental Section

General hydrogenation procedure: $Pd(OCOCF_3)_2$ (3.3 mg, 0.01 mmol) and (*S*,*S*,*R*,*R*)-TangPhos (3.4 mg, 0.012 mmol) were dissolved in degassed acetone in a Schlenk tube under N_2. After stirring the solution at room temperature for 0.5 h, the solvent was removed under vacuum to give the complex as a brown solid. The solid was dissolved in degassed dichloromethane (10 mL) in a glovebox and divided equally between 10 vials. To each vial, substrate (0.1 mmol, S/C = 100) was then added to the catalyst solution and the resulting mixture was transferred to an autoclave, which was charged with H_2 (75 atm). The autoclave was stirred at 40 °C for 12–24 h, before cooling it to room temperature and carefully releasing the H_2. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then analyzed directly by HPLC to determine the enantiomeric excess.

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