Rhodium-Catalyzed Enantioselective Hydrogenation of β-Acylamino Nitroolefins: A New Approach to Chiral β-Amino Nitroalkanes

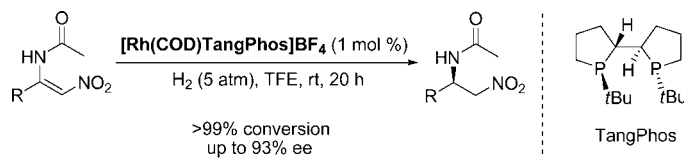**Ming Zhou,[†] Dejun Dong,[†] Baolin Zhu,[†] Huiling Geng,[‡] Yan Wang,*,[†] and Xumu Zhang*,[†]**

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ABSTRACT

An efficient and highly enantioselective catalytic asymmetric hydrogenation of β-acylamino nitroolefins has been realized by using Rh-TangPhos as the catalyst. A series of β-amino nitroalkane products, which are versatile intermediates in organic synthesis, were obtained with high yield and good enantioselectivity.

Chiral nitroalkanes and their derivatives are versatile intermediates in organic synthesis, especially enantiomerically pure β-amino nitroalkanes, which can be readily converted to a variety of other useful building blocks, such as α-amino acids, as well as 1,2-diamines through a Nef reaction[1] or nitro reduction.[2] Moreover, the alkylation with alkyl halides and Henry reaction with aldehydes for β-amino nitroalkanes enable the facile preparation of a myriad of structurally diverse and complex molecules bearing two or three stereocenters (Scheme 1). These derivates are key structural elements and have been widely found in chiral diamine ligands,[3] pharmaceuticals such as clopidogrel,[4] oseltamivir,[5] and asimadoline,[6] and other biologically active molecules[7] (Figure 1).

To date, the preparation of chiral β-amino nitroalkanes mainly relies on asymmetric aza-Henry reactions,[8] in which chiral metal complexes[9] and organocatalysts, such as chiral thiourea,[10] chiral proton catalysts,[11] and chiral phase transfer catalysts,[12] were employed to afford moderate to high enantio-/diastereoselectivities. Recently, Sun and co-workers

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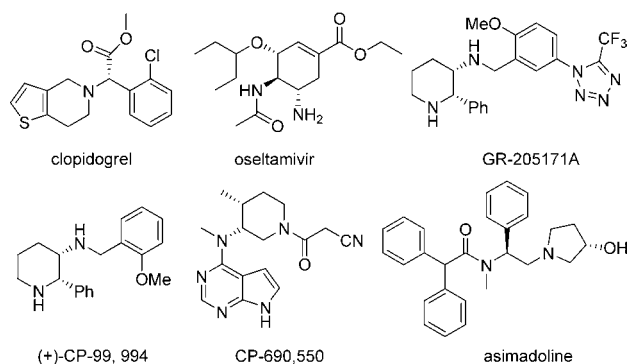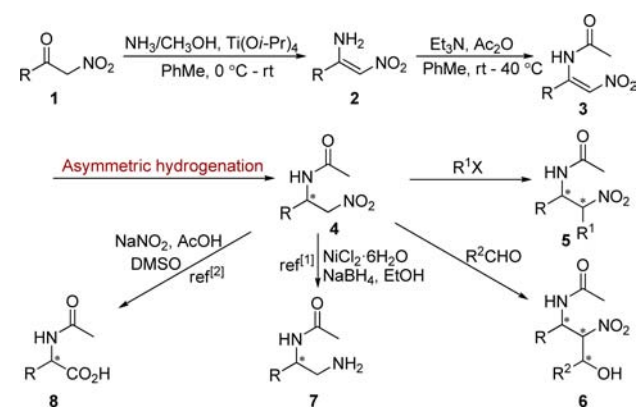
Figure 1. Key structural elements in chiral pharmaceuticals.

developed an asymmetric reduction of β-amino nitroolefins through hydrosilylation with a simple N-sulfinyl urea as a bifunctional catalyst.[13] Nevertheless, among these methods, there is substantial room for increasing catalytic activities and improving the enantioselectivities.

Over the past decade, transition-metal-catalyzed enantioselective hydrogenation of functionalized olefins has attracted a great deal of attention and catalytic asymmetric hydrogenation has emerged as a powerful and environmentally friendly methodology for preparing chiral compounds.[14] With the rapid development of catalytic systems, many types of olefins bearing functional groups such as acylamino,[14a] carbonyl,[14c,15] phosphate,[14d,16] and the cyano group[17] were hydrogenated in high ee's and activities. In principle, the enantioselective hydrogenation

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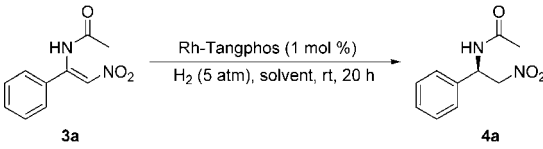
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Scheme 1. Synthetic Route for Chiral β-Amino Nitroalkanes and Their Derivatization

strategy can also be utilized for the formation of chiral β-amino nitroalkanes from new substrates β-acylamino nitroolefins. However, highly enantioselective hydrogenation of nitroolefins remains a challenging task. To the best of our knowledge, there has been no successful catalytic method reported for this transformation. This may be due to the extremely electron-withdrawing nitro group that can reduce the strength of chelation between C=C double bond of the substrate and metal catalyst. Considering the significant role played by transition metal complex bearing chiral phosphine ligands in the asymmetric hydrogenation of C=C, C=O, and C=N double bonds, we envisioned that a Rh-catalyzed highly enantioselective hydrogenation of β-acylamino nitroolefin may serve as an efficient way to afford the desired enantiomerically pure β-amino nitroalkane from a new substrate with highly electron-donating bisphosphine ligands under the right conditions. Recently, we have reported the asymmetric hydrogenation of β,β-disubstituted nitroalkenes for the synthesis of chiral nitroalkanes with excellent efficiency and enantioselectivity.[18] Herein, we document a new strategy to generate chiral β-amino nitroalkanes in high yields and good enantioselectivities *via* Rh-catalyzed asymmetric hydrogenation of β-acylamino nitroolefins.

β-Acylamino nitroolefins can be easily prepared in two steps from readily accessible corresponding α-nitro ketones **1** under mild conditions (Scheme 1), and only *Z* isomers were observed for product **3**. Initially, we used (*Z*)-*N*-(2-nitro-1-phenylvinyl) acetamide **3a** as a model substrate to optimize the reaction conditions. As shown in Table 1, the solvent played a critical role in this catalytic reaction. When the Rh-TangPhos complex was employed as the catalyst, poor conversions were observed in MeOH, CH$_2$Cl$_2$, ethyl acetate, and toluene, *albeit* with promising enantioselectivities (57−85% ee, Table 1, entries 1−4). The catalyst almost showed no activity in THF, dioxane, and EtOH (Table 1, entries 5−7). To our delight, the transformation

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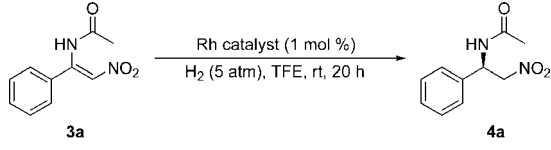
Table 1. Solvent and Metal Precursor Screening for Rh-Catalyzed Asymmetric Hydrogenation of (Z)-N-(2-Nitro-1-phenylvinyl)acetamide **3a**[a]

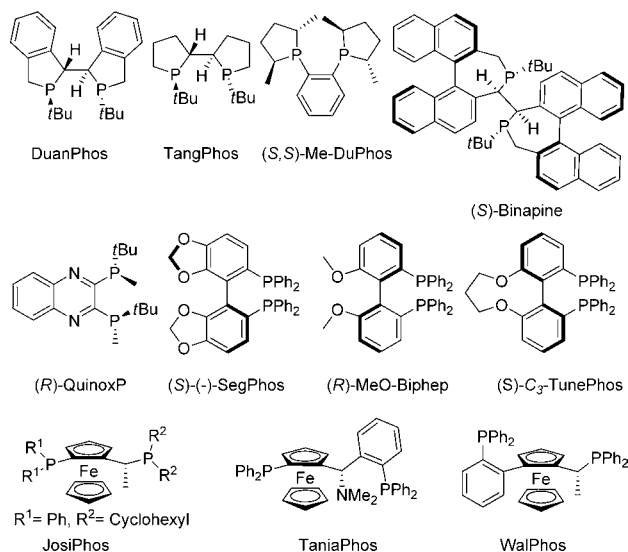| entry	metal	solvent	conversion (%)[b]	ee (%)[c]
1	Rh(COD)$_2$BF$_4$	MeOH	54	81
2	Rh(COD)$_2$BF$_4$	CH$_2$Cl$_2$	48	85
3	Rh(COD)$_2$BF$_4$	ethyl acetate	22	57
4	Rh(COD)$_2$BF$_4$	toluene	28	80
5	Rh(COD)$_2$BF$_4$	THF	<5	NA
6	Rh(COD)$_2$BF$_4$	dioxane	<5	NA
7	Rh(COD)$_2$BF$_4$	EtOH	<5	NA
8	Rh(COD)$_2$BF$_4$	TFE	>99	90
9	[Rh(COD)Cl]$_2$	TFE	34	90
10	Rh(COD)$_2$SbF$_6$	TFE	>99	88
11	Rh(NBD)$_2$BF$_4$	TFE	>99	89

[a] Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)$_2$]BF$_4$/TangPhos/substrate ratio of 1:1.1:100, in 1 mL of solvent, at room temperature, under hydrogen (5 atm) for 20 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. COD = 1,5-cyclooctadiene, NBD = 2,5-norbornadiene, NA = not available, TFE = trifluoroethanol.

Figure 2. Structures of the phosphine ligands for hydrogenation of (Z)-N-(2-nitro-1-phenylvinyl) acetamide **3a**.

could proceed smoothly in trifluoroethanol (TFE), and an excellent result was achieved in terms of both selectivity and reactivity under mild conditions (90% ee, Table 1, entry 8). Some other metal precursors were also tested, and low activity and comparable enantioselectivity were observed when using [Rh(COD)Cl]$_2$ as the Rh source (Table 1, entry 9).

Table 2. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of (Z)-N-(2-Nitro-1-phenylvinyl)acetamide **3a**[a]

entry	ligand	conversion (%)[b]	ee (%)[c]
1	TangPhos	>99	90
2	(R)-QuinoxP	>99	4
3	DuanPhos	>99	1
4	(S)-Binapine	69	15
5	(S, S)-Me-DuPhos	15	21
6	(R)-Binap	76	33
7	(R)-MeO-Biphep	>99	23
8	(S)-SegPhos	>99	39
9	(S)-C$_3$-TunePhos	>99	8
10	DTBM-Biphep	>99	45
11	JosiPhos	>99	23
12	WalPhos	26	23
13	TaniaPhos	10	24

[a] Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)$_2$]BF$_4$/ligand/substrate ratio of 1:1.1:100, in TFE (TFE = trifluoroethanol) at room temperature under hydrogen (5 atm) for 20 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase.

Full conversion and a slight decrease in selectivity were observed when using Rh(COD)$_2$SbF$_6$ and Rh(NBD)$_2$BF$_4$ (Table 1, entries 10, 11).

Inspired by these promising results, a variety of diphosphine ligands developed in our group and some commercially available chiral ligands (Figure 2) were screened in Table 2. Except for TangPhos, other chiral ligands with stereogenic P centers, such as DuanPhos, Binapine, and (R)-QuinoxP showed very low enantioselectivities, although the conversions were good (Table 2, entries 1−4). We reasoned that TangPhos is a highly electron-donating trialkylated biphosphine that facilitates the reaction. Some chiral biaryl bisphosphorus ligands such as (R)-MeO-Biphep, (S)-SegPhos, and (S)-C$_3$-TunePhos, and Binap gave high conversion and 8−39% ee (Table 2, entries 6−9). When the phenyl group on the phosphine of (R)-MeO-Biphep was changed to a bulkier and electron-rich 4-MeO-3,5-^{t}Bu$_2$phenyl group, a slight increase in enantioselectivity was obtained (45% ee, Table 2, entry 10). To investigate the performance of the chiral ferrocene ligand in this transformation, we selected the Rh-JosiPhos, WalPos, and TaniaPhos complex as the catalyst; however, low enantioselectivities were detected (~24% ee, Table 2, entries 11−13).

Under the optimized conditions, Rh(COD)$_2$BF$_4$/TangPhos/TFE/rt, a variety of β-acylamino nitroolefins **3** were employed as substrates for the hydrogenation reaction to yield the desired β-amino nitroalkanes, and the results are summarized in Table 3. Excellent yield and enantioselectivity were achieved in most cases. It was found that electron-withdrawing groups such as halogen atoms on

Table 3. Rh-Catalyzed Asymmetric Hydrogenation of
β-Acylamino Nitroolefins (**3**)[a]

| entry	substrates	product	conversion (%)[b]	ee (%)[c]
1	R = Ph (**3a**)	**4a**	>99(97)	90
2	R = 4-F-Ph (**3b**)	**4b**	>99(98)	90
3	R = 4-Cl-Ph (**3c**)	**4c**	>99(96)	93
4	R = 4-Br-Ph (**3d**)	**4d**	>99(95)	93
5	R = 4-MeO-Ph (**3e**)	**4e**	>99(95)	84
6	R = 4-Me-Ph (**3f**)	**4f**	>99(96)	84
7	R = 4-^{t}Bu-Ph (**3g**)	**4g**	>99(94)	81
8	R = 3-Cl-Ph (**3h**)	**4h**	>99(96)	93
9	R = 3-Br-Ph (**3i**)	**4i**	>99(98)	93
10	R = 3-Me-Ph (**3j**)	**4J**	>99(97)	89
11	R = 3-MeO-Ph (**3k**)	**4k**	>99(98)	89
12	R = 2-napthyl (**3l**)	**4l**	>99(93)	89
13	R = isopropyl (**3m**)	**4m**	>99(96)	18
14	R = cyclohexyl (**3n**)	**4n**	67	22

[a] Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)$_2$]BF$_4$/TangPhos/substrate ratio of 1:1.1:100, in TFE (TFE = trifluoroethanol) at room temperature under hydrogen (5 atm) for 20 h. [b] Determined by ^{1}H NMR spectroscopy; data in parentheses are the yields of the isolated product based on consumed starting material. [c] Determined by HPLC analysis using a chiral stationary phase.

the aromatic ring had a positive effect on the enantioselectivities regardless of the substitution position (90−93% ee, Table 3, entries 2−4, 8, 9). Substrates bearing electron-donating groups in the *para* position of the phenyl ring resulted in slightly lower ee's (81−84%, Table 3, entries 5−7), while little effect was observed on the enantioselectivity in the *meta* position (89% ee, Table 3, entries 10, 11). 2-Naphthyl substituted nitroalkene **3l** also afforded **4l** in 89% ee with excellent conversion (Table 3, entry 12). However, alkyl

Scheme 2. Conversion of the β-Amino Nitroalkane Product **4l** into Diamine **9l**
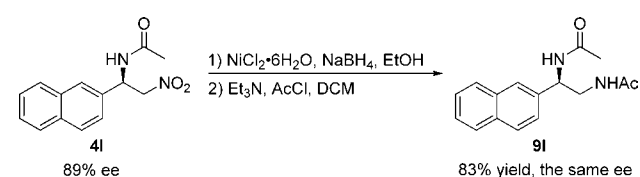
β-acylamino nitroolefins led to disappointed enantioselectivities (Table 3, entries 13, 14).

To illustrate the utility of this catalytic asymmetric hydrogenation, the resulting product **4l** was subjected to known nitro reduction for the preparation of the 1,2-diamine derivative (Scheme 2). The corresponding product **9l** was obtained in good yield without any loss of the enantiopurity.

In summary, we have developed a strategy for the highly enantioselective Rh-catalyzed hydrogenation of β-acylamino nitroolefins for direct synthesis of enantiomerically pure β-amino nitroalkanes, which are versatile precursors in chemical synthesis. Meanwhile, the transformation of β-amino nitroalkane **4l** into diamine **9l** was conducted by nitro reduction in good yield without loss of enantiopurity. Further investigations to improve the enantioselectivity and develop more efficient systems for this hydrogenation are underway in our laboratory.

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