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Highly Efficient Rh^I-Catalyzed Asymmetric Hydrogenation of β-Amino Acrylonitriles

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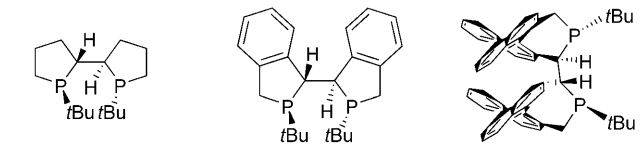
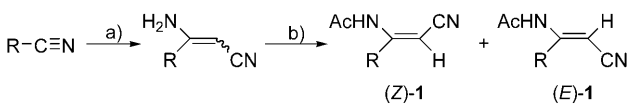
Enantiomerically pure β-amino nitriles and their derivatives are important intermediates in organic synthesis and pharmaceutical chemistry. The nitrile group is one of the most versatile functional groups in organic chemistry and can be readily transformed into a variety of valuable functionalities,[1] including carboxyl; aldehyde; and amino groups, and, hence, β-amino nitriles enable facile approaches to β-amino acids, aldehydes, and 1,3-diamines. Therefore, the synthesis of β-amino nitriles has attracted much attention in recent decades. The early preparation of β-amino nitriles started from β-amino alcohols and involves a reaction with toxic cyanic reagents.[2] Some recent progress[3] includes addition reactions of alkyl nitriles to imines catalyzed by Cu,[4] Pd,[5] Ru,[6] or Lewis base[7] complexes, with good yields. An alternative approach to β-amino nitriles is the ring-opening of aziridines with trimethylsilyl cyanide (TMSCN).[8]

To the best of our knowledge, there are few reports of the direct preparation of chiral β-amino nitriles by asymmetric hydrogenation of the corresponding β-amino acrylonitriles.[9] This is mainly due to the electronic structure of nitriles, which prefer the end-on coordination of metal ions, making the conjugated double bond unsuitable for hydrogenation reactions. Another challenge in the direct hydrogenation of β-amino acrylonitriles is achieving chemoselectivity between the olefinic double bond and the nitrile group.[10]

Asymmetric hydrogenation catalyzed by transition metals has proved to be a highly efficient method for the synthesis of chiral amines. A number of chiral phosphine ligands have been developed that improve the chemo- and enantioselectivity of the hydrogenation reaction.[11] We envisioned that the electron-donating, rigid, chiral ligands, such as TangPhos, DuanPhos, and Binapine (shown here), developed in our research group,[11d] could be efficient ligands for the hydrogenation of β-amino acrylonitriles. Herein, we report the first direct asymmetric hydrogenation of β-amino acrylonitriles with a Rh–TangPhos catalyst, providing the corresponding β-amino nitriles in excellent enantioselectivities (up to 99.4% *ee*) and tolerating *E*/*Z* mixtures of substrate.[11a]



β-Amino acrylonitriles can be readily prepared in two steps with good yield (Scheme 1).[12] With (*E*)-3-acetylamino-3-phenylacrylonitrile [(*E*)-**1a**)] as a model substrate, we screened several electron-donating ligands developed in our group, and some commercially available chiral ligands, such



Scheme 1. Synthesis of β-acetylamino acrylonitriles. Reagents and conditions: a) CH_3CN, *t*BuOK, toluene, ultrasound, 4 h; b) Ac_2O, Et_3N, toluene, reflux, overnight.

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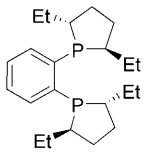
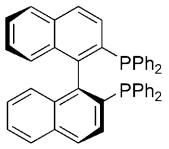
as 1,2-bis(2,5-dialkylphospholano)benzene (DuPhos) and BINAP (shown). DuanPhos, Binapine, Et-DuPhos, and



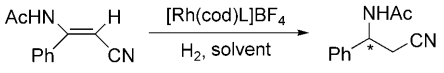
(*R,R*)-Et-DuPhos



(*S*)-BINAP

BINAP only showed low conversions and enantioselectivities (Table 1, entries 2–5). To our delight, the Rh–TangPhos complex proved to be highly enantioselective. However, by

Table 1. Rhodium-catalyzed asymmetric hydrogenation of (*E*)-**1a** under various conditions.[a]



(*E*)-**1a** **2a**

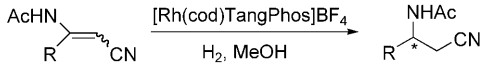
Entry	Ligand	Solvent	P_{H_2} [atm]	T [°C]	Conversion [%][b]	*ee* [%][c]
1	(*S*, *S*, *R*, *R*)-TangPhos	CH_2Cl_2	70	60	64	93
2	(S_P, R_C)-DuanPhos	CH_2Cl_2	70	60	38	80
3	(*R*, *R*)-Et-DuPhos	CH_2Cl_2	70	60	24	20
4	(*S*)-BINAP	CH_2Cl_2	70	60	22	59
5	(*S*)-Binapine	CH_2Cl_2	70	60	3	29
6	(*S*, *S*, *R*, *R*)-TangPhos	MeOH	70	60	100	93
7	(*S*, *S*, *R*, *R*)-TangPhos	THF	70	60	84	36
8	(*S*, *S*, *R*, *R*)-TangPhos	toluene	70	60	100	19
9	(*S*, *S*, *R*, *R*)-TangPhos	dioxane	70	60	70	8
10	(*S*, *S*, *R*, *R*)-TangPhos	MeOH	30	60	100	94
11	(*S*, *S*, *R*, *R*)-TangPhos	MeOH	10	60	100	96
12	(*S*, *S*, *R*, *R*)-TangPhos	MeOH	10	40	100	96
13	(*S*, *S*, *R*, *R*)-TangPhos	MeOH	10	25	94	94

[a] All reactions were carried out with a substrate/catalyst ratio of 100:1, for 24 h. [b] Determined by GC methods. [c] The *ee* of **2a** was determined by chiral phase GC.

using 70 atm of H_2, at room temperature, in dichloromethane, TangPhos only gave a very poor result with $<5\%$ conversion (result not shown). However, when this reaction was performed at 60 °C, very promising results were obtained (64 % conversion, 93 % *ee*) (Table 1, entry 1). Subsequently, the effect of the solvent was investigated. It was found that only in MeOH was substrate **1a** converted to the desired product with full conversion and good enantioselectivity (93 % *ee*; Table 1, entry 6). Other solvents, such as THF and dioxane, gave much lower enantioselectivities (Table 1, entries 7–9). Although the hydrogenation proceeded smoothly in toluene, the enantioselectivity decreased dramatically (Table 1, entry 8). The effect of the pressure of H_2 was also tested; if the hydrogen pressure was reduced to 10 atm, the milder reaction conditions gave a slightly higher *ee* (96 % *ee*; Table 1, entry 11). Finally, we attempted to decrease the reaction temperature to further improve the enantioselectivity; this had no evident effect on the enantioselectivity of the product, but at 25 °C, incomplete conversion was observed (Table 1, entry 12 and 13).

In asymmetric hydrogenation, lower enantioselectivities are often observed for *E* and *Z* stereoisomers of substrates.[11,13] It is notable that the Rh–TangPhos catalytic system is efficient for the hydrogenation of both the *E* and *Z* isomers of substrates. For example, under the optimized reaction conditions, both (*Z*)-**1a** and (*Z*)-**1b** are hydrogenated by the Rh–TangPhos catalyst to the desired products with higher enantioselectivities (>99 % *ee*, Table 2, entries 2 and 5) than the corresponding *E* isomers (Table 2, entries 1 and 4). Even the hydrogenation of an *E*/*Z* mixture of **1a** or **b** still retains comparable *ee* (Table 2, entries 3 and 6), which makes it unnecessary to isolate the isomers to produce high enantioselectivities and is a more practical method for organic synthesis.

Table 2. Rhodium-catalyzed asymmetric hydrogenation of β-amino acrylonitriles **1**.[a]



1 **2**

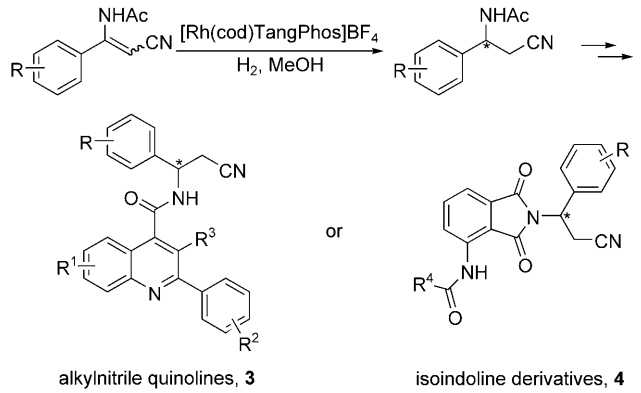
Entry	Substrate	*E*:*Z*[b]	R	Product	*ee* [%][c]	+/−[d]
1	(*E*)-**1a**	–	C_6H_5	**2a**	96	–
2	(*Z*)-**1a**	–	C_6H_5	**2a**	99	–
3	**1a**	2.3:1	C_6H_5	**2a**	98	–
4	(*E*)-**1b**	–	*p*-ClC_6H_4	**2b**	95	–
5	(*Z*)-**1b**	–	*p*-ClC_6H_4	**2b**	99.4	–
6	**1b**	2.2:1	*p*-ClC_6H_4	**2b**	96	–
7	**1c**	>99:1	*p*-MeC_6H_4	**2c**	95	–
8	**1d**	>99:1	*p*-$MeOC_6H_4$	**2d**	96	–
9	**1e**	50:1	*p*-FC_6H_4	**2e**	96	–
10[e]	**1f**	12.5:1	*p*-BrC_6H_4	**2f**	92	–
11	**1g**	0.8:1	*p*-$CF_3C_6H_4$	**2g**	98	–
12	**1h**	>99:1	*m*-MeC_6H_4	**2h**	97	–
13	**1i**	>99:1	*m*-ClC_6H_4	**2i**	94	–
14[f]	**1j**	>99:1	*o*-ClC_6H_4	**2j**	33	–
15[f]	**1k**	>99:1	*o*-MeC_6H_4	**2k**	20	–
16	**1l**	50:1	2-naphthyl	**2l**	93	–
17	**1m**	>99:1	thiophen-2-yl	**2m**	97	–
18	**1n**	>99:1	Me	**2n**	82	+
19[g]	**1a**	2.3:1	C_6H_5	**2a**	93	–

[a] Unless mentioned otherwise, reactions were carried out with a substrate/catalyst ratio of 100:1, in MeOH, at 40 °C, under 10 atm of hydrogen, for 24 h and resulted in 100 % conversion. [b] Determined by ^{1}H NMR spectroscopy. [c] The *ee* was determined by GC or HPLC on a chiral phase. [d] The sign of the optical rotation. [e] 50 atm of H_2, 48 h, 100 % conversion. [f] 50 atm of H_2, 72 h, 100 % conversion. [g] Substrate/catalyst = 1000.

Encouraged by the promising results obtained for the hydrogenation of **1a** and **b**, we applied the Rh–TangPhos-catalyzed asymmetric hydrogenation to a variety of β-amino acrylonitriles, with various *E*/*Z* isomer ratios, **1c**–**n**. The desired β-amino nitriles, were obtained in full conversion and excellent enantioselectivity (Table 2). The electronic properties of the substituents on the aryl group of β-amino acrylo-

nitriles **1** have limited influence on the conversion and the enantioselectivity of the products. Very high enantioselectivities were obtained with substrates bearing either an electron-donating or an electron-withdrawing group at the *para* or *meta* position of the benzene ring (92–98% *ee*; Table 2, entries 7–13). Both 2-naphthyl and thiophen-2-yl β-amino acrylonitriles afforded the β-amino nitrile products, with 93 and 97% *ee*, respectively (Table 2, entries 16 and 17). In contrast, we found that the presence of either a methyl or chloro substituent at the *ortho*-position resulted in dramatically reduced reactivity and enantioselectivity, which may be due to the steric hindrance caused by the *ortho*-substituents. Notably, 82% *ee* was achieved for the hydrogenation of an alkyl β-amino acrylonitrile **1n** (Table 2, entry 18).

To explore the potential of the Rh–TangPhos-catalyzed asymmetric hydrogenation of β-amino acrylonitriles as a practical method to synthesize chiral β-amino nitriles, the catalyst loading was decreased to 0.1 mol% (turnover number = 1000). The model substrate **1a** is still smoothly hydrogenated under these mild reaction conditions albeit with a slightly lower enantioselectivity of 93% *ee*, (Table 2, entry 19). Hence, this Rh–TangPhos catalyst system provides an efficient enantioselective catalytic approach to chiral β-amino nitriles, which frequently occur in pharmaceutical and biological molecules. For example, in important chiral drugs like alkylnitrile quinolines **3**,[14] which are NK-3 receptor ligands used for the treatment of peripheral and central nervous system diseases or disorders, and isoindoline compounds **4**,[15] which are used for the treatment, prevention, and management of diseases mediated by PDE4 inhibition or associated with abnormal TNF-α levels, can be readily prepared by using this methodology (Scheme 2).



Scheme 2. Potential application of this asymmetric hydrogenation for the preparation of chiral alkylnitrile quinolines, **3**, and isoindoline derivatives, **4**.

In conclusion, a highly enantioselective hydrogenation of β-amino acrylonitriles catalyzed by a Rh^I complex of the electron-donating, chiral ligand TangPhos has been developed that provides a straightforward method for the synthesis of chiral β-amino nitriles in excellent *ee*. Further exploration of this method for the preparation of various chiral amine compounds is currently in progress and will be reported in a due course.

Experimental Section

General procedure for the synthesis of compounds 1: Et_3N (2.0 equiv) was added dropwise to a solution of a β-enaminonitrile (1.0 equiv) and Ac_2O (5.0 equiv) in toluene under stirring. The reaction mixture was then heated to reflux and stirred for 24 h. After it was cooled to room temperature, the reaction solution was consecutively washed with saturated sodium carbonate, water, and brine and then dried over anhydrous Na_2SO_4. After removing the solvent, the crude product was purified by column chromatography using ethyl acetate and hexane as the eluent.

General procedure for the hydrogenation of 1: A stock solution of the catalyst was made by mixing $[Rh(cod)_2]BF_4$ with TangPhos (1:1.1 molar ratio) in MeOH, at room temperature, for 10 min, in a nitrogen-filled glovebox. This catalyst solution (0.1 mL, 0.001 mmol) was then transferred, by syringe, into vials charged with different substrates (0.1 mmol each) in MeOH (2.9 mL). All the vials were placed in a steel autoclave and then hydrogen gas was added. After stirring at 40 °C for 24 h (except **1f** (48 h), **j** (72 h) and **k** (72 h)), the hydrogen was released slowly, the solution concentrated and subjected to a short silica gel column to remove the metal complex. The purified solution was analyzed by chiral GC or HPLC to determine the *ee*.

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Keywords: acrylonitriles · enantioselectivity · hydrogenation · P ligands · rhodium

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