Asymmetric Synthesis

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Catalytic Enantioselective Reaction of α-Aminoacetonitriles Using Chiral Bis(imidazoline) Palladium Catalysts**

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Abstract: *The catalytic enantioselective reaction of diphenylmethylidene-protected α-aminoacetonitriles with imines has been developed. Good yields and diastereo- and enantioselectivities were observed for the reaction of various imines using chiral bis(imidazoline)/Pd catalysts. The reaction of α-aminonitriles with di-tert-butyl azodicarboxylate afforded chiral α,α-diaminonitriles in high yields with high enantioselectivities.*

Optically active α,β-diaminoacetonitriles and their derivatives are proven useful chiral building blocks for the preparation of various biologically active compounds and synthetic intermediates.[1] Furthermore, the α,β-diaminoacetonitrile backbone is an important structural motif in biologically active compounds such as saframycin A,[2] phthalascidin,[3] and aspeverin[4] (Figure 1).

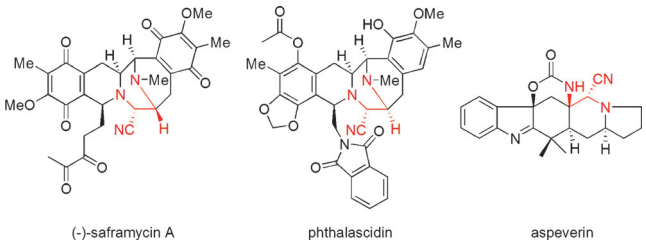

Figure 1. Biologically active α,β-diaminoacetonitriles.

Therefore, their synthetic importance has prompted considerable interest in developing asymmetric methods for their preparation. In this context, the enantioselective reaction of α-cyano carbanions of N-protected α-aminoacetonitriles with imines is attracting a great deal of interest, as it provides efficient access to chiral α,β-diaminoacetonitriles. However the preparation of α-cyano carbanions of α-aminoacetonitriles is not an easy task because of the low acidity of the α protons of N-protected α-aminoacetonitriles caused by the electron-donating effect of the neighboring amino group. Therefore, the preparation of α-cyano carbanions of N-protected α-aminoacetonitriles generally needs a stoichiometric amount of a strong base.[5] One of the solutions for this problem is to use an electron-withdrawing group for the amino group. There are only three reports on the catalytic enantioselective reaction of α-cyano carbanions of N-protected α-aminoacetonitriles. Carretero and co-workers reported the enantioselective 1,3-dipolar cycloaddition of α-carbainon of *N*-benzylidene-α-aminoacetonitriles with α,β-unsaturated carbonyl compounds by using a combination of a chiral silver complex and NaOAc as the base.[6] Recently, Kobayashi and co-workers reported the catalytic enantioselective reaction of *N*-fluorenylidene-α-aminoacetonitrile with *N*-diphenylphosphinoylimine using chiral guanidine as a strong basic organocatalyst to afford a product with 73% *ee*.[7] During the preparation of this manuscript, Shibasaki, Kumagai, and co-workers reported the highly *anti*-selective enantioselective reaction of *N*-fluorenylidene-α-aminoacetonitrile with *N*-thiophosphinoyl ketimines derived from dialkyl ketones (83–95% *ee*).[8] Despite the pioneering progress achieved in the catalytic enantioselective reaction of α-aminoacetonitriles with imines, the development of novel catalyst systems with wide substrate tolerance and acceptable catalytic activity for enantioselective reactions of α-aminoacetonitrile still remains a major challenge.[9] Recently, we developed the highly enantioselective reaction of nitrile compounds with imines using palladium pincer complexes with 1,3-bis(imidazolin-2-yl)benzene (Phebim).[10–12] Herein, we report the highly enantioselective reactions of N-protected α-aminoacetonitriles with imines using bis(imidazoline)/palladium pincer complexes as the chiral Lewis acid catalyst (Figure 2). The coordination of palladium to cyanides in N-protected α-aminoacetonitriles enhances the production of α-cyano carbanions, and the subsequent reaction of α-cyano carbanions with imines to give chiral α,β-diaminoacetonitriles.

We first examined the enantioselective reaction of the α-aminoacetonitrile **2a** (1.2 equiv) with various imines (**1a–d**;

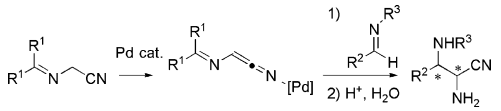

Figure 2. Enantioselective reaction of α-aminoacetonitriles with imines using a palladium catalyst.

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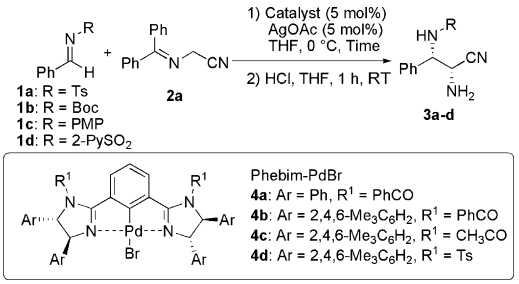
Table 1: Enantioselective reaction of the α-aminoacetonitrile **2a** with the imines **1a–d** using palladium catalysts **4a–d**.



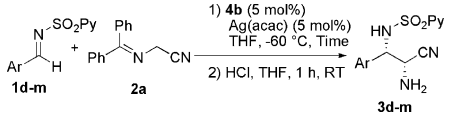
Entry	**1**	Cat.	*t* [h]	Yield [%]	d.r.[a] (*syn*/*anti*)	*ee* [%] (*syn*)
1	**1a**	**4a**	12	88	75:25	9
2	**1a**	**4b**	72	82	78:22	94
3	**1a**	**4c**	72	81	73:27	94
4	**1a**	**4d**	72	65	66:34	4
5	**1b**	**4b**	72	69	63:37	75
6	**1c**	**4b**	72	–	–	–
7	**1d**	**4b**	72	86	86:14	99
8[b]	**1d**	**4b**	72	86	92:8	99
9[b,c]	**1d**	**4b**	24	89	95:5	99

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis. [b] The reaction was carried out using **2a** (2.0 equiv) and Ag(acac) instead of AgOAc at −60 °C. [c] TMSOH (20 mol %) was added. acac = acetylacetonate, Boc = *tert*-butoxycarbonyl, PMP = *para*-methoxyphenyl, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

1.0 equiv) using 5 mol % of the palladium catalysts **4a–d** at 0 °C (Table 1). The reaction of **2a** with **1a** using **4a**/AgOAc afforded the product **3a** in high yield with moderate *syn* selectivity but with low enantioselectivity (entry 1). To improve stereoselectivity, we next optimized the structure of the bis(imidazoline) catalysts **4b–d** (entries 2–4). When the substituent on the imidazoline was changed to a 2,4,6-trimethylphenyl group, the reaction gave **3a** with good diastereoselectivity and excellent enantioselectivity. As a result, the bis(imidazoline) **4b** was found to be the best catalyst (entry 2). Next, we examined a change to the activating group for imines (entries 5–7). Although the reaction of *p*-methoxyphenyl imine could not afford the product **3c**, the reaction of the Boc-imine **1b** gave **3b** with moderate enantioselectivity. In contrast, we recently developed enantioselective reactions of imines having a 2-pyridinesulfonyl group as a highly functional activating group for imines.[13] Therefore we attempted to use the *N*-(2-pyridinesulfonyl)imine **1d**. The reaction of **1d** afforded the product **3d** in high yield with high diastereo- and enantioselectivity (entry 7). We also examined various silver salts, and **4b**/Ag(acac) afforded **3d** with high diastereoselectivity (entry 8). The addition of 20 mol % of trimethylsilylalcohol (TMSOH) slightly improved the yield and diastereoselectivity of the product (entry 9). The absolute configuration of **3d** was assigned as (2*R*,3*S*) by X-ray crystallographic analysis, and the configuration of other products was tentatively assumed by analogy.

With these optimized reaction conditions, the reaction of a series of imines (**1d–m**) in the presence of **4b**/Ag(acac) was examined (Table 2). The imines **1d–g**, carrying either electron-donating or electron-withdrawing substituents, gave the corresponding products **3d–g** in good yield with high enantioselectivity (entries 1–4). The reaction of the naphthylimines **1h**,**i** also gave the products **3h**,**i** with high enantioselectivity (entries 5 and 6). Imines having either a furyl or a thiophene group as heteroaryl groups also afforded the products **3j–m** in high yield with good diastereo- and enantioselectivity, although it is difficult to coordinate the metal catalyst to **2a** selectively in the presence of heteroatoms (entries 7–10). To the best of our knowledge, the levels of enantioselectivity and substrate generality reported herein are the highest among those previously reported.

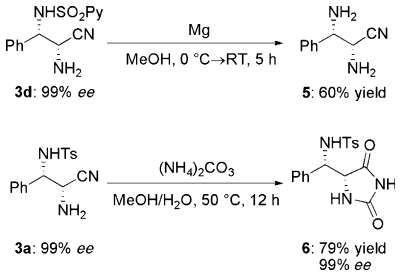
Table 2: Enantioselective reaction of **2a** with various imines (**1d–m**) using the palladium catalyst **4b**.



Entry	**1**	Ar	**3**	*t* [h]	Yield [%]	d.r. (*syn*/*anti*)	*ee* [%] (*syn*)
1[a]	**1d**	Ph	**3d**	24	89	95:5	99
2[b]	**1e**	4-MeOC$_6$H$_4$	**3e**	72	73	91:9	99
3[a]	**1f**	4-ClC$_6$H$_4$	**3f**	72	83	77:23	99
4	**1g**	3-ClC$_6$H$_4$	**3g**	72	86	72:28	99
5[a]	**1h**	1-naphthyl	**3h**	72	84	99:1	99
6[b]	**1i**	2-naphthyl	**3i**	72	82	81:19	99
7[b]	**1j**	2-furyl	**3j**	24	73	89:11	99
8[b]	**1k**	3-furyl	**3k**	60	71	85:15	99
9	**1l**	2-thienyl	**3l**	96	86	92:8	99
10[a]	**1m**	3-thienyl	**3m**	54	95	97:3	99

[a] TMSOH (20 mol %) was added. [b] At −30 °C.

The products **3** are versatile intermediates in organic synthesis and can be readily converted into important chiral building blocks (Scheme 1). Removal of the pyridinesulfonyl group from **3d** using magnesium in methanol afforded the α,β-diaminonitrile **5**. The hydantoin **6** was also prepared from **3a** through a Bucherer–Bergs-type reaction, using ammonium carbonate, in high yield without loss of the enantiopurity.[14]



Scheme 1. Transformation of **3d** and **3a** into the chiral diamine **5** and hydantoin **6**.

Furthermore, α,α-diaminonitrile compounds and their derivatives have also received considerable attention because of their wide application in biologically active compounds, such as Devacade,[15] BRL 36650,[16] and other compounds

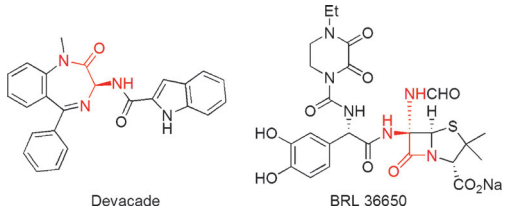
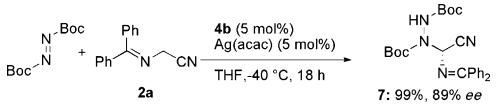


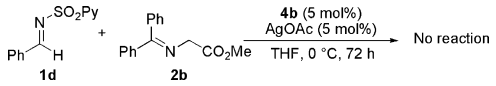
Figure 3. Biologically active α,α-diaminoacetonitrile derivatives.



Scheme 2. Enantioselective amination of α-aminoacetonitrile **2a**.

(Figure 3).[17] Therefore, we also examined the reaction of the α-aminonitrile **2a** with di-*tert*-butyl azodicarboxylate. The reaction using the **4b**/Ag(acac) catalyst afforded the product **7** in high yield with high enantioselectivity (Scheme 2).

To clarify the ability of the palladium catalyst to activate nitrile compounds, the reactions of the iminoester **2b** using the palladium-pincer complex were examined (Scheme 3).



Scheme 3. Reaction of iminoester **2b** with **1d** using the **4b**/AgOAc catalyst.

However, the reaction of **2b** with **1d** in the presence of the **4b**/AgOAc catalyst did not afford any product. This reactivity is in sharp contrast with the reaction of **2a** with **1d**. This result indicates that the palladium-pincer complex selectively coordinates to the cyano group in **2a** to activate the deprotonation of **2a**.

The proposed catalytic cycle for the reaction of **2a** with **1d** using the catalyst **4** is shown in Figure 4. The addition of Ag(acac) to **4** causes the exchange reaction of bromide on **4** to acetylacetonate (**A**). Coordination of the cyano group in **2a** to the palladium atom of **A** affords the cationic complex **B**, which can be deprotonated by a weak base, such as acetylacetonate, to give palladium ketenimide (**C**). The next step is the nucleophilic reaction of **C** with imines to give **D**, which subsequently undergoes protonation and decomplexation to give the adduct and regenerate **A**. To clarify the assumed reaction mechanism, we investigated the ESI-mass spectroscopic analysis for the mixture of **2a**, Ag(acac), and **4b** in a 1:1:1 ratio. The complex **B** was observed in this mixture (cation mode, calcd for $C_{77}H_{73}N_6O_2Pd$ as complex **B**: 1219.5, found: 1219.4; see the Supporting Information). This signal supports our proposed reaction mechanism.

To clarify the reaction mechanism, we next examined the MO calculation of the complex between **2a** and **4b** using a Gaussian 09[18] B3LYP/LANL2DZ level.[19] The most stable intermediate for the complex between **2a** and **4b** is shown in Figure 5. The α-carbanion of **2a** forms a palladium keteni-

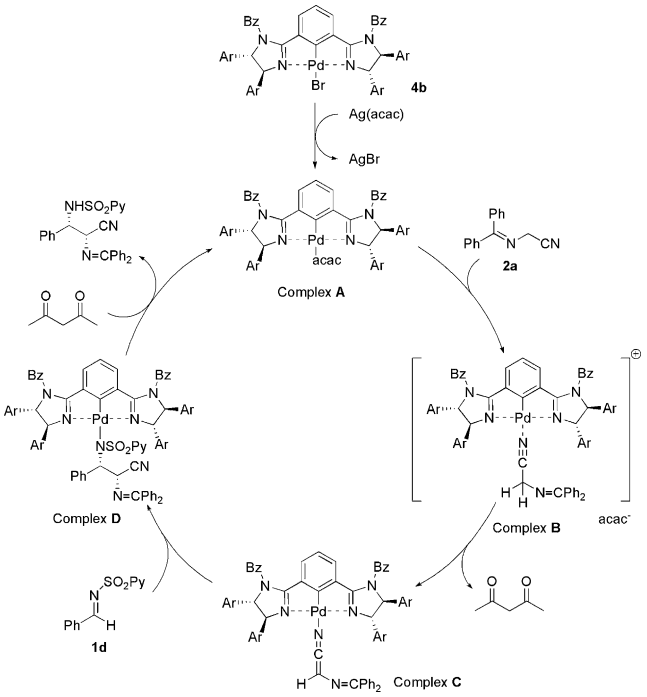


Figure 4. Proposed reaction cycle of the reaction of the α-aminoacetonitrile **2a** with the imine **1d** and the catalyst **4**. Bz = benzoyl.

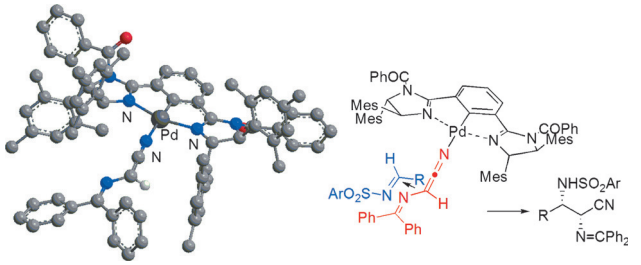


Figure 5. MO calculation of the complex between **2a** and **4b** using Gaussian 09 B3LYP/LANL2DZ and the transition state for this reaction. H atoms have been omitted for clarity.

mide intermediate, and the diphenylmethylidenamino group in **2a** directs to the less steric hindered site for the substituent on bis(imidazoline). Based on this structure and on the absolute configuration of the products, imine **2a** would approach the *Re*-face of the imine to react with palladium ketenimide to give the (2*R*,3*S*)-isomer. Further studies are required to fully elucidate the mechanistic detail of this reaction.

In conclusion, we developed a highly *syn*-selective enantioselective reaction of N-protected α-aminoacetonitriles with imines using bis(imidazoline)/palladium pincer complexes as a chiral Lewis acid catalyst. The reaction was screened for a broad range of imines. This process offers a simple and efficient route for the synthesis of α,β- and α,α-diaminoacetonitriles. Additional experiments are in progress to study the scope of this process and the potential application of the bis(imidazoline)/palladium pincer catalyst to other reactions.

Keywords: asymmetric catalysis · diastereoselectivity · palladium · silver · synthetic methods

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