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Catalytic Enantioselective Reaction of α-Phenylthioacetonitriles with Imines using Chiral Bis(imidazoline)–Palladium Catalysts

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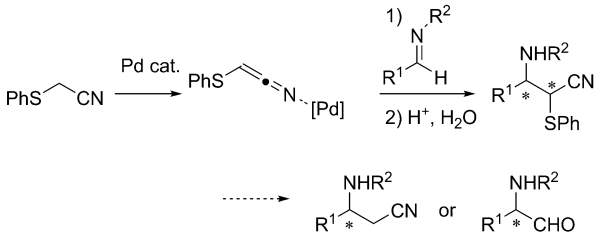
Abstract: The catalytic enantioselective reaction of α-phenylthioacetonitriles with imines has been developed. The reaction of various imines proceeds in good yields and diastereo- and enantioselectivities in the presence of chiral bis(imidazoline)–palladium catalysts. The obtained products can be converted into β-aminonitrile or β-aminoamide compounds without loss of enantiopurity.

The development of catalytic enantioselective C–C bond forming reactions is an important topic in organic chemistry. In particular, the reaction of imines with nucleophiles, which can be easily transformed into various functional groups, has attracted a great deal of interest, as it provides efficient access to various chiral amine derivatives.[1] In this context, α-carbanions of α-thioacetonitriles, which are well known as cyanoalkyl anion equivalents[2] and formyl anion equivalents,[3] are powerful building blocks for the preparation of synthetically useful chiral compounds. Although the racemic reaction of α-thioacetonitriles with electrophiles were reported,[4] there are no reports on enantioselective reactions using α-thioacetonitriles as nucleophiles.[5] Recently, we developed an efficient activating method for nitrile compounds and a highly enantioselective reaction of α-carbanions of nitriles with imines by using palladium pincer complexes with 1,3-bis(imidazolin-2-yl)benzene (Phebim) ligand.[6,7] Herein, we report the first highly enantioselective reaction of α-phenylthioacetonitriles with imines using bis(imidazoline)–palladium pincer complexes as a chiral Lewis acid catalyst (Scheme 1).

The coordination of palladium to cyanides in α-phenylthioacetonitriles enhances their acidity of the α-proton, followed by the reaction of α-cyano carbanions with imines, giving chiral α-thio-β-aminoacetonitriles, which are precursors for some biologically active compounds, such as influenza neuraminidase inhibitor,[8] β-lactamase inhibitor,[9] and botulinum neurotoxin inhibitor (Figure 1).[10]



Scheme 1. Enantioselective reaction of α-phenylthioacetonitriles with imines in the presence of palladium catalyst.

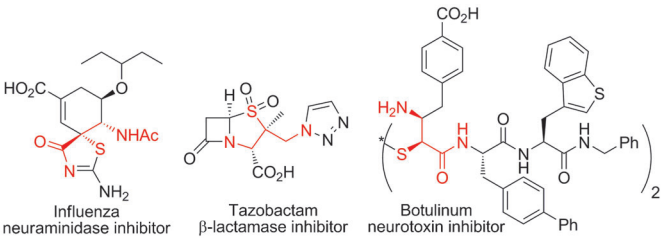


Figure 1. Biologically active compounds incorporating the α-thio-β-aminoacetonitrile moiety.

We first examined the enantioselective reaction of α-phenylthioacetonitrile **2a** (1.5 equiv) with various imines **1a–c** by using 5 mol% of palladium catalysts **4a–e** and AgOAc at 0 °C (Table 1).

Although the reaction of **2a** with *N*-Boc or *N*-diphenylphosphoryl (DPP) imines **1b** or **c** afforded products **3b** and **c** in low yield (Table 1, entries 2 and 3), the reaction with *N*-(*p*-toluenesulfonyl)imine **1a** gave product **3a** in high yield with good enantioselectivity but with low diastereoselectivity (Table 1, entry 1). Encouraged by this result, we next investigated the effect of the catalyst structure on stereoselectivity. The reaction using bis(imidazoline)–palladium catalysts **4b–e**, with R^2 = mesityl or 1-naphthyl and R^1 = acetyl or *p*-tosyl, afforded product **3a** with better diastereo- and enantioselectivity than that from the reaction using **4a** (Table 1, entries 4–7). Catalyst **4b** emerged as the most suitable catalyst for this reaction, yielding product **3a** in good yield and stereoselectivity (80% yield, d.r. = 93:7, 96% *ee*; Table 1, entry 4). The reaction in the presence of silver acetylacetonate (Ag(acac)) instead of AgOAc was carried out at −30 °C, giving **3a** in high yield with high diastereo- and enantioselectivity (Table 1, entry 8). Furthermore, the

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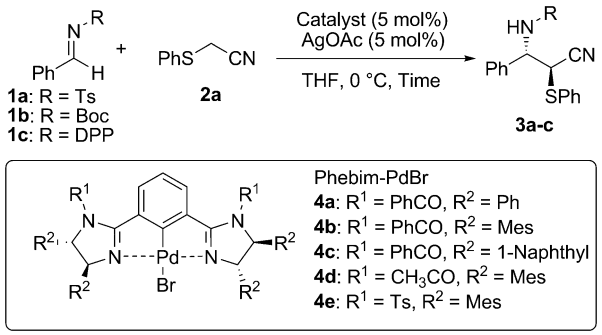
Table 1. Enantioselective reaction of α-phenylthioacetonitriles **2a** with imines **1a–c** using palladium catalysts **4a–e**.



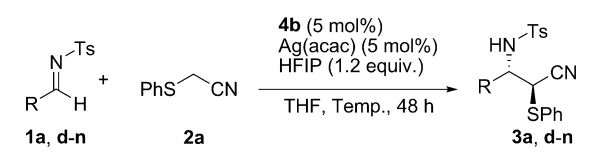
Entry	1	Catalyst	*t* [h]	Yield [%]	d.r. (*anti/syn*)	*ee* (*anti/syn*) [%]
1	**1a**	**4a**	24	94	42:58	85/80
2	**1b**	**4a**	24	64	51:49	70/69
3	**1c**	**4a**	24	–	–	–
4	**1a**	**4b**	48	80	93:7	96/78
5	**1a**	**4c**	48	53	54:46	80/81
6	**1a**	**4d**	48	81	91:9	96/60
7	**1a**	**4e**	48	64	88:12	90/59
8[a]	**1a**	**4b**	48	99	88:12	97/93
9[a,b]	**1a**	**4b**	48	95	91:9	99/89
10[a,b,c]	**1a**	**4b**	96	99	88:12	98/88

[a] The reaction was carried out using Ag(acac) at −30 °C. [b] HFIP (1.2 equiv) was added. [c] 2 mol% each of **4b** and Ag(acac) were used.

addition of 1.2 equivalents of hexafluoro-2-propanol (HFIP) as a protonating reagent slightly improved the yield and stereoselectivity of product **3a** (Table 1, entry 9). The catalyst loading was successfully reduced to 2 mol% without loss of enantioselectivity (Table 1, entry 10).

Having established optimized conditions for the reaction of imine **1a** with **2a**, the reaction of a series of imines **1d–n** and **2a** in the presence of **4b** and Ag(acac) was examined (Table 2).

Table 2. Enantioselective reaction of α-thioacetonitriles **2a** with various imines **1a,d–n** in the presence of palladium catalyst **4b**.

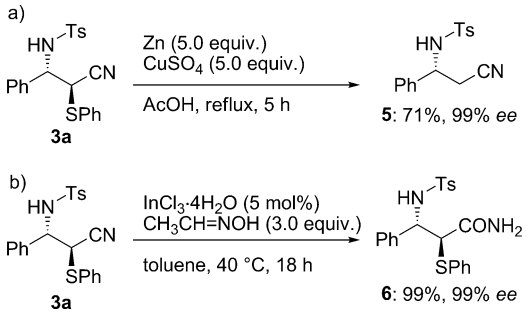


Entry	1	R	*T* [°C]	Yield [%]	d.r. (*anti/syn*)	*ee* (*anti*) [%]
1	**1a**	Ph	−30	95	91:9	99
2[a]	**1d**	4-MeOC$_6$H$_4$	−30	93	91:9	96
3	**1e**	3-MeOC$_6$H$_4$	−30	85	95:5	99
4	**1f**	4-FC$_6$H$_4$	−30	93	92:8	97
5	**1g**	4-ClC$_6$H$_4$	−30	99	88:12	96
6	**1h**	4-BrC$_6$H$_4$	−30	90	86:14	95
7	**1i**	1-naphthyl	−10	90	92:8	95
8	**1j**	2-naphthyl	−10	35	92:8	93
9	**1k**	2-furyl	−30	50	70:30	96
10	**1l**	2-thienyl	−20	96	74:26	98
11[a]	**1m**	PhCH=CH	−30	68	79:21	94
12	**1n**	*n*Pr	−30	99	70:30	90

[a] Without HFIP.

The reaction of imines **1d** and **e**, bearing an electron-donating methoxy group in the *para* or *meta* position, gave the corresponding products **3d** and **e** in high yield with high diastereoselectivity and excellent enantioselectivity (Table 2, entries 2 and 3). The electron-deficient imine substrates **1e–h**, having fluoro, chloro, or bromo groups, were tolerated under these reaction conditions to give products **3e–h** with good stereoselectivity (Table 2, entries 4–6). Imines **1i–l**, having a naphthyl or a heteroaryl group, also afforded products **3i–l** with high enantioselectivities (Table 2, entries 7–10). These reaction conditions were also applicable to the reaction of alkenylimine **1m** and alkylimine **1n** (Table 2, entries 11 and 12). The absolute configuration of **3a** was assigned as (*2S,3S)* by X-ray crystallographic analysis, and the configuration of other products was tentatively assumed by analogy. To our knowledge, these results are the first reported highly enantioselective reactions of α-thioacetonitriles as nucleophiles.

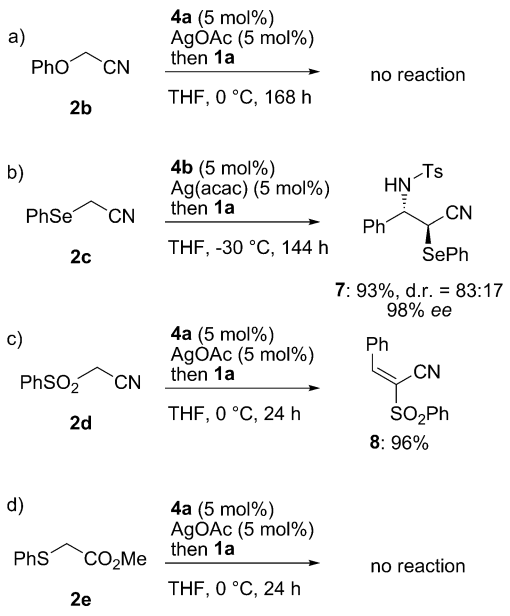
Chiral α-thio-β-aminoacetonitrile products **3** are versatile intermediates in organic synthesis that can be readily converted into important chiral building blocks (Scheme 2). For example, removal of the phenylthio group of **3a** by using Zn and $CuSO_4$



Scheme 2. Transformation of **3a** to chiral β-aminonitrile **5** (a) and α-thio-β-aminoamide **6** (b).

afforded β-aminonitrile **5** in high yield without loss of enantiopurity (Scheme 2a).[11] Hydrolysis of the cyano group of **3a** by using $InCl_3{\cdot}4H_2O$ in toluene at 40 °C afforded α-phenylthio-β-tosylaminopropionamide **6** in high yield without any epimerization (Scheme 2b).[12]

The reaction of α-phenylselenoacetonitrile **2c** with **1a** in the presence of the palladium pincer complex **4b** and Ag(acac) also gave product **7** in high yield with high enantioselectivity, although the reactions of α-phenyloxyacetonitrile **2b** did not afford any product (Scheme 3a,b). This reactivity is in sharp contrast with the reaction of α-phenylthioacetonitrile **2a** with **1a**. However, the reaction of α-benzenesulfonylacetonitrile **2d** with **1a** afforded α,β-unsaturated α-benzenesulfonyl acrylonitrile **8** (Scheme 3c), which was obtained through the elimination of toluenesulfonamide from the addition product. This result shows the clear superiority of the reaction of α-thioacetonitriles in comparison to that of sulfonyl derivatives. We next examined the activation ability of the palladium catalyst for nitrile compounds. The reaction of α-phenylthioacetate **2e** in the presence of **4a** and AgOAc did not give a product



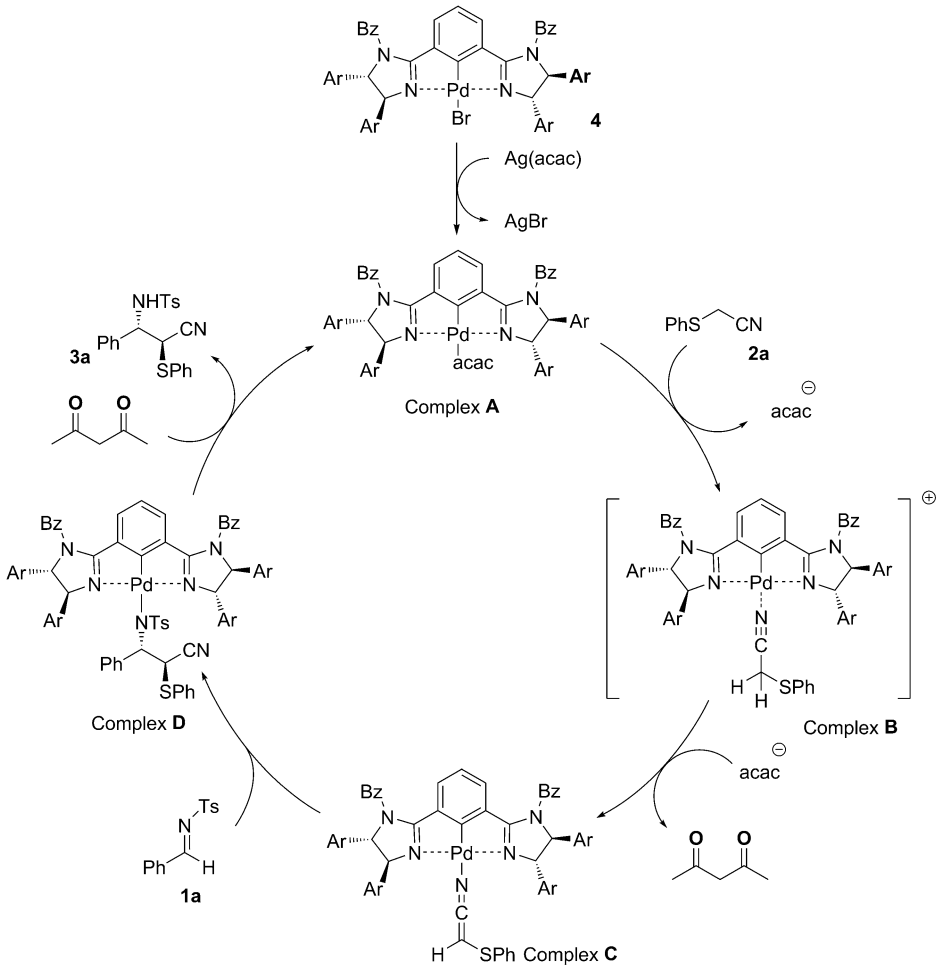
Scheme 3. Reaction of nucleophiles **2b**–**e** with imine **1a** using the catalyst system **4**/Ag.

(Scheme 3d). This result indicates that the palladium-pincer complex selectively coordinates to the cyano group in **2a** to activate the deprotonation of the α-proton for **2a**.

A proposed catalytic cycle for the reaction of α-phenylthioacetonitrile **2a** with **1a** with catalyst **4** is shown in Scheme 4. The addition of Ag(acac) to **4** causes the exchange of bromide on **4** to acetylacetonate (complex **A**). Coordination of the cyano group in **2a** to the palladium atom of complex **A** affords cationic complex **B**, which can be deprotonated by a weak base, such as acetylacetonate, to give palladium ketenimide (complex **C**). The next step is the nucleophilic reaction of complex **C** with imine to give complex **D**, which subsequently undergoes protonation and decomplexation to give the adduct and to regenerate complex **A**. To further investigate the reaction mechanism, we carried out ESI mass spectrometry on the mixture of **2a**, Ag(acac), and **4b** in a 1:1:1 ratio. Complex **B** or $[\mathbf{C}+\mathrm{H}]^+$ could be observed in this mixture (cationic mode, calcd for $C_{70}H_{68}N_5O_2SPd$ as complex **B** or $\mathbf{C}+H^+$: 1148.4; found: 1148.4; see the Supporting Information). This signal supports our proposed reaction mechanism.

We next calculated the complex **C** between **4b** and carbanion of **2a** by using Gaussian 09[13] at the B3LYP/LANL2DZ level of theory (Figure 2a).[14] The calculation showed that the cyano group in **2a** coordinates to palladium to form a ketenimide structure. The natural bond orbital (NBO) analysis[15] for complex **C** shows the interaction between the σ* orbital of the C–S bond and a π bonding orbital of the ketenimide. The stabilization energy for their interaction was estimated to be 7.91 kcal mol^{-1}. Based on the absolute configuration of products, the proposed transition state for the enantioselective reaction of palladium ketenimide with imine **1a** is shown in Scheme 4. Avoiding steric repulsion between the mesityl group on imidazoline and imine and electronic repulsion between of π-orbital of imine and ketenimide, imine **1a** approaches from the *Re*-face of the imine to react with palladium ketenimide to give the (2*S*,3*S*)-isomer (Figure 2b). Further studies are required to fully elucidate the mechanism of the reaction.[16]

In conclusion, we have developed the first highly enantioselective reaction of α-thioacetonitriles with imines in the pres-



Scheme 4. Proposed catalytic cycle for the reaction of phenylthioacetonitrile **2a** with imine **1a** catalyzed by **4**.

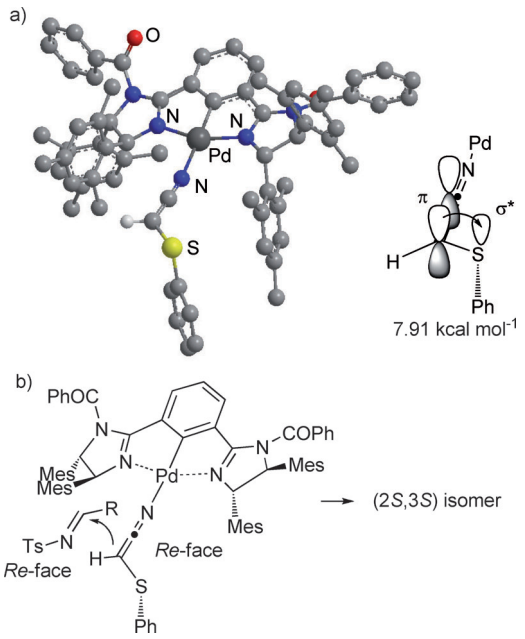


Figure 2. a) MO calculation of complex between **4b** and **2a** by using Gaussian 09 B3LYP/LANL2DZ and NBO analysis. b) Proposed transition state for the reaction. H atoms have been omitted for clarity.

ence of bis(imidazoline)-palladium pincer complexes as a chiral Lewis acid catalyst. The reaction was screened for a broad range of imines. The obtained products can be converted to β-aminonitrile or β-aminoamide compounds without loss of enantiopurity. Further 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.

Experimental Section

Typical procedure

(2*S*,3*S*)-3-Phenyl-2-phenylthio-3-(toluenesulfonyl)aminopropionitrile: Compound **2a** (15 μL, 0.116 mmol), *N*-sulfonylimine **1a** (20.4 mg, 0.0788 mmol), and HFIP (10 μL, 0.095 mmol) were added to a mixture of Ag(acac) (0.8 mg, 3.94 μmol) and **4b** (4.3 mg, 3.94 μmol) in THF (0.5 mL) at −30 °C. After disappearance of *N*-sulfonylimine **1a**, as indicated by TLC, the reaction was quenched by saturated aqueous NH_4Cl (1.0 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layer was dried over Na_2SO_4. Filtration and removal of solvent under reduced pressure gave a residue, which was purified by column chromatography on silica (benzene/CH_3CN, 98:2 v/v) giving **3a** (30.5 mg, 95%) as a white solid.

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Keywords: asymmetric catalysis · imidazoline · nitriles · palladium · pincer-type complexes

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[16] We also checked the retro reaction of product **3a**, in which the treatment of racemic **3a** with chiral **4b** and Ag(acac) did not change the diastereo- or enantioselectivity, indicating that the stereoselectivity of the reaction is kinetically controlled.

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Asymmetric Synthesis

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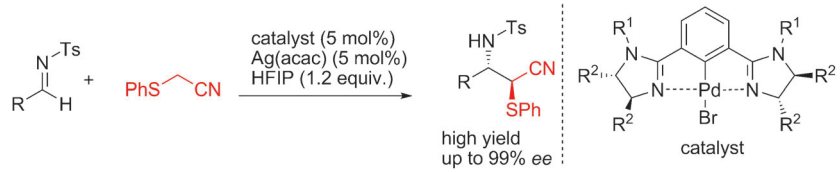
Catalytic Enantioselective Reaction of α-Phenylthioacetonitriles with Imines using Chiral Bis(imidazoline)–Palladium Catalysts



The catalytic enantioselective reaction of α-phenylthioacetonitriles with various imines proceeds in good yields and diastereo- and enantioselectivities with chiral bis(imidazoline)–palladium catalysts. The obtained products can be converted into β-aminonitrile or β-aminoamide without loss of enantiopurity.