Asymmetric Synthesis

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Enantioselective Aza-Morita–Baylis–Hillman Reactions of Acrylonitrile Catalyzed by Palladium(II) Pincer Complexes having C_2-Symmetric Chiral Bis(imidazoline) Ligands**

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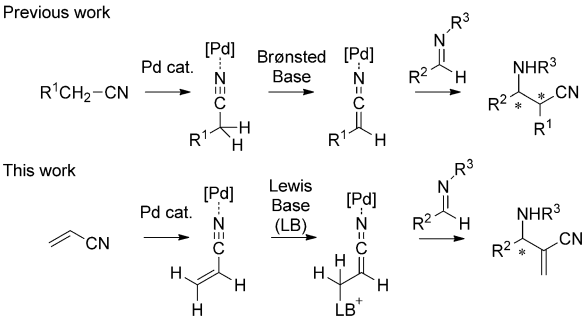
The enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction of α,β-unsaturated carbonyl compounds or nitriles with imines is a powerful method for the preparation of synthetically useful chiral α-methylidene-β-amino carbonyl compounds or nitriles. Therefore, there are many reports on the catalytic enantioselective aza-MBH reaction for α,β-unsaturated carbonyl compounds.[1] However, the catalytic enantioselective aza-MBH reaction with acrylonitriles is still not fruitful,[2] even though the obtained β-amino nitriles are chiral precursors to β-amino carboxylic acids and 1,3-diamines.[3,4] The first enantioselective aza-MBH reaction of acrylonitrile with imines was reported by Shi and co-workers.[5] They reported that using organocatalysts derived from cinchona alkaloids for the reaction of imines with acrylonitrile afforded α-methylidene-β-aminonitriles in moderate yield (32–40%) with up to 68% *ee*. Adolfsson and Balan reported the three-component aza-MBH reaction between benzaldehyde, tosylamide, and acrylonitrile with 15 mol% of the same organocatalyst and 2 mol% of $Ti(OiPr)_4$ to give the product in 45% yield with 53% *ee*.[6] Despite the pioneering results achieved for the enantioselective aza-MBH reaction of acrylonitrile with imines, a more efficient catalytic system with regards to reactivity and selectivity is still highly desirable. However, the enantioselective aza-MBH reaction of acrylonitrile with imines is not a trivial task because of the low reactivity and high polymerization ability of acrylonitrile in comparison with α,β-unsaturated carbonyl compounds. Therefore, the enhancement of the electrophilicity of acrylonitrile by coordination of transition metal catalysts to the cyano group has become an attractive approach for the activation of acrylonitrile. Although there are many reports for the enantioselective aza-MBH reaction using chiral Lewis bases, to the best of our knowledge, there is only one report for the catalytic enantioselective aza-MBH reaction using chiral Lewis acids together with achiral Lewis bases. In 2010, Shibasaki and co-workers reported a highly enantioselective aza-MBH reaction of acrylates using $La(OiPr)_3$/linked-binol complexes in combination with an achiral nucleophilic Lewis base.[7] On the other hand, we recently developed a highly enantioselective reaction of α-cyano carbanions with imines catalyzed by chiral bis(imidazoline)/palladium(II) pincer complexes.[8–10] In this catalyst system, palladium pincer complexes enhance the acidity of the α-protons of alkylnitriles to give palladium ketenimides, which react with imines (Scheme 1). We expected that the bis(imidazoline)/palladium system can be applied to the aza-MBH reaction of acrylonitrile with imines; the chiral palladium pincer complexes should coordinate to acrylonitrile, thus increasing its electrophilicity, then an achiral Lewis base would attack the β-position of acrylonitrile. The generated palladium ketenimide should react with imines to give chiral α-methylene-β-amino nitriles. We herein report the first highly enantioselective aza-MBH reaction of acrylonitrile and imines with palladium(II) pincer complexes with chiral bis(imidazoline) ligands as chiral Lewis acid catalysts.



Scheme 1. Palladium pincer complexes activate alkylnitriles and acrylonitrile.

The enantioselective reaction of acrylonitrile **2** (3.0 equiv) with *N*-(4-methylbenzylidene)-4-methybenzenesulfonamide **1a** (1.0 equiv) was carried out by using 5 mol% of palladium catalysts **4a–f** and 5 mol% of AgOAc (Table 1). Although the reaction using only **4a** and AgOAc did not afford product **3a**, the addition of 20 mol% of DABCO, as a Lewis base, enhanced the reactivity of acrylonitrile to give product **3a** in good yield with moderate enantioselectivity (Table 1, entries 1 and 2).[11] The reaction without AgOAc resulted in decreased enantioselectivity of the product (Table 1, entry 3).[12] To improve enantioselectivity, we optimized the structure of the bis(imidazoline)/palladium catalysts **4b–f** (Table 1, entries 4–8). When catalyst **4f**, having acetyl (R^1)

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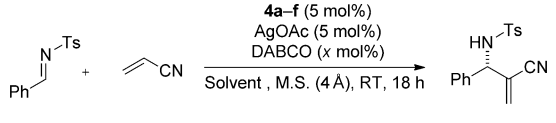
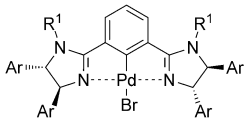
Table 1: Optimization of reaction conditions.



1a **2** (3.0 equiv) **3a**

Entry	4	Ar	R^1	DABCO [mol%]	Solvent	Yield[a] [%]	*ee* [%]
1	**4a**	Ph	Ac	0	CH_3CN	–	–
2	**4a**	Ph	Ac	20	CH_3CN	83	66
3[b]	**4a**	Ph	Ac	20	CH_3CN	81	49
4	**4b**	Ph	Bz	20	CH_3CN	82	57
5	**4c**	Ph	Ms	20	CH_3CN	74	62
6	**4d**	Ph	Ts	20	CH_3CN	79	62
7	**4e**	Mes	Ac	20	CH_3CN	74	65
8	**4f**	1-Nap	Ac	20	CH_3CN	81	76
9	**4e**	Mes	Ac	20	*i*PrCN	92	85
10	**4f**	1-Nap	Ac	20	*i*PrCN	91	87
11	**4f**	1-Nap	Ac	5	*i*PrCN	99	92
12[c,d]	**4f**	1-Nap	Ac	5	*i*PrCN	93	94
13[c,e]	**4e**	Mes	Ac	5	*i*PrCN	58	93
14[f]	**4f**	1-Nap	Ac	2.5	*i*PrCN	97	92
15[g,h]	**4f**	1-Nap	Ac	1	*i*PrCN	91	89

[a] Yield of the isolated product. [b] Without AgOAc. [c] The reaction was carried out at −10 °C. [d] Reaction time is 48 h. [e] 96 h. [f] 2.5 mol% of **4f** and AgOAc was used. [g] 1 mol% of **4f** and AgOAc was used. [h] 168 h. Bz = benzoyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, Mes = 2,4,6-trimethylphenyl, Ms = methanesulfonyl, M.S. = molecular sieves, Nap = naphthyl, Ts = p-toluenesulfonyl.



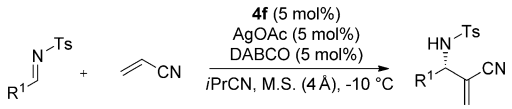
[phebimPdBr] (**4**)

4a: Ar = Ph, R^1 = Ac
4b: Ar = Ph, R^1 = Bz
4c: Ar = Ph, R^1 = Ms
4d: Ar = Ph, R^1 = Ts
4e: Ar = Mes, R^1 = Ac
4f: Ar = 1-Nap, R^1 = Ac

and 1-naphthyl groups (Ar), was used as the catalyst, to our delight, good enantioselectivity was obtained (Table 1, entry 8). When the reaction was carried out with 5 mol% of DABCO in isobutyronitrile (*i*PrCN) as a solvent, the enantioselectivity improved slightly (Table 1, entries 9–11). The best enantioselectivity was obtained when the reaction was carried out at −10 °C in *i*PrCN using **4f** (Table 1, entry 12). The reaction with 2.5 mol% of **4f** and DABCO worked efficiently, and the reaction with 1 mol% of **4f** and DABCO gave the product with slightly lower enantioselectivity and yield (Table 1, entries 14 and 15).

We next examined the reaction of **2** with various imines **1a–o** in the presence of **4f**, AgOAc, and DABCO (Table 2). The reaction of various imines **1a–o** gave products **3a–o** in high yield with high enantioselectivity (Table 1, entries 1–15), although the reaction of *ortho*-substituted imine **1d** proceeded with relatively lower enantioselectivity (Table 1, entry 4). For the reactions of *para*-substituted imines **1b**, **1f**, **1h**, and **1k**, higher enantioselectivity could be achieved with 2,4,6-trimethylphenyl-substituted phebim/palladium complex **4e** instead of **4f** (entries 2, 6, 8, and 11; see also the Supporting Information). Imines with naphthyl- and heteroatom-containing substituents (**1j–o**) also afforded products

Table 2: The aza-MBH reaction of acrylonitrile with various imines **1a–o** catalyzed by **4f**.



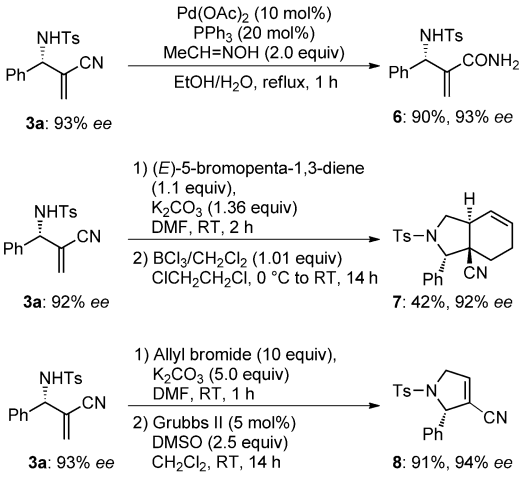
1a–o **2** (3.0 equiv) **3a–o**

Entry	1	R^1	3	*t* [h]	Yield[b] [%]	*ee* [%]
1	**1a**	Ph	**3a**	48	93	94
2[a]	**1b**	4-FC_6H_4	**3b**	72	84	91
3	**1c**	3-FC_6H_4	**3c**	24	97	93
4	**1d**	2-FC_6H_4	**3d**	24	89	76
5	**1e**	3,5-FC_6H_4	**3e**	24	87	90
6[a]	**1f**	4-ClC_6H_4	**3f**	96	97	90
7	**1g**	3-ClC_6H_4	**3g**	36	98	95
8[a]	**1h**	4-$MeOC_6H_4$	**3h**	168	75	77
9	**1i**	3-$MeOC_6H_4$	**3i**	84	96	93
10	**1j**	1-$C_{10}H_7$	**3j**	72	89	97
11[a]	**1k**	2-$C_{10}H_7$	**3k**	72	98	91
12	**1l**	2-C_4H_3O	**3l**	72	88	94
13	**1m**	3-C_4H_3O	**3m**	72	87	96
14	**1n**	2-C_4H_3S	**3n**	96	93	90
15	**1o**	3-C_4H_3S	**3o**	72	88	98

[a] The reaction was carried out using 5 mol% of **4e** and 20 mol% DABCO at −20 °C. [b] Yield of the isolated product.

3j–o with high enantioselectivity (entries 10–15).[13] The absolute stereochemistry of product **3a** was assigned to be *S* by comparison with the value of the specific rotation reported in the literature.[5c] To the best of our knowledge, the levels of enantioselectivity and substrate generality reported herein are the highest among those previously reported.

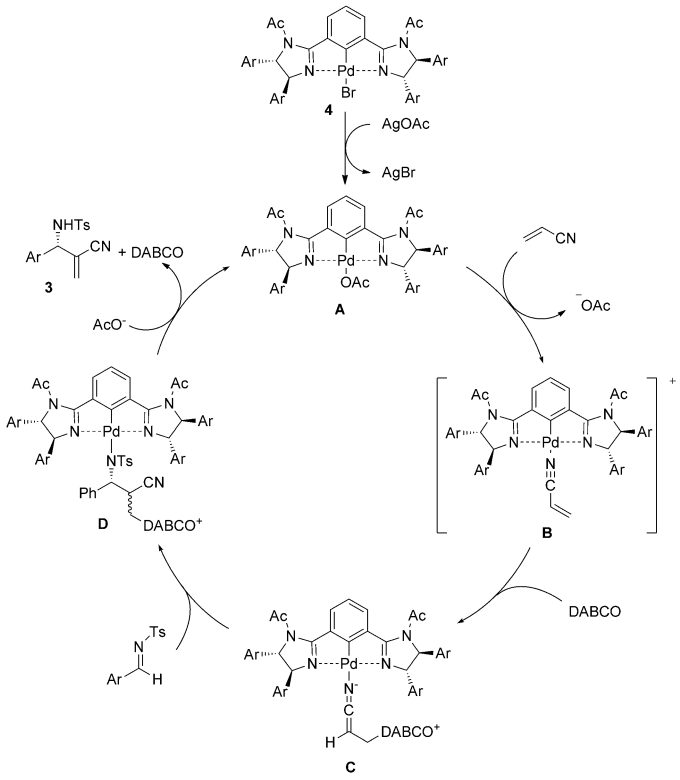
We next examined the transformation of product **3a** to amide, tetrahydroisoindoline, and pyrroline derivatives (Scheme 2). Hydrolysis of **3a** using $Pd(OAc)_2$, PPh_3, and $CH_3CH{=}NOH$ in aqueous EtOH, heated to reflux, gave α-methylidene-β-amino amide **6** in high yield.[14] In addition, the reaction of **3a** with (*E*)-5-bromopenta-1,3-diene in the presence of K_2CO_3 gave the *N*-alkylated product. A subse-



Scheme 2. Transformation of α-methylidene-β-aminonitriles. DMF = *N*,*N*′-dimethylformamide, DMSO = dimethylsulfoxide.

quent intramolecular Diels–Alder reaction using BCl_3 afforded the corresponding 1-aryl-substituted tetrahydroisoindoline derivative **7** without loss of enantiopurity.[15] Furthermore, the reaction of **3a** with allyl bromide using K_2CO_3 gave *N*-allylated product. Then, ring-closing metathesis of the *N*-allylated product in the presence of 5 mol% of Grubbs II type catalyst in CH_2Cl_2 afforded pyrroline **8** in high yield.

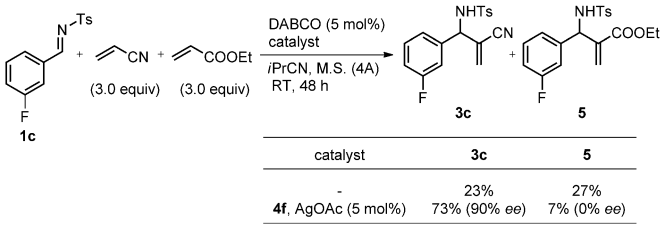
The proposed catalytic cycle for the reaction of acrylonitrile with imines is shown in Scheme 3. The addition of AgOAc causes the exchange reaction of bromide in **4** to



Scheme 3. Proposed reaction cycle of the aza-MBH reaction of acrylonitrile with imines catalyzed by **4**.

acetate (**A**). Coordination of the cyano group in acrylonitrile to the palladium atom of **A** affords cationic **B**, which was observed by APCI–MS analysis of a 1:1:1 mixture of **4a**, AgOAc, and acrylonitrile (cation mode, calcd. for $C_{43}H_{36}N_5O_2Pd$: 760.19, found: 760.19, see the Supporting Information). DABCO attacks the β-position of acrylonitrile in the **B** to give palladium ketenimide (**C**). Then the **C** reacts with *N*-sulfonylimines to give **D**, which subsequently undergoes deprotonation and decomplexation giving products **3** and regenerated **A**.

To clarify the activation ability of **A**, the reactions of mixtures of acrylonitrile and ethyl acrylate to imine **1c** with or without **4f** and AgOAc were examined (Scheme 4). The reaction without **4f** and AgOAc afforded both products **3c** and **5**, and the reactions showed similar reactivity. On the other hand, the aza-MBH reaction using **4f** and AgOAc preferably afforded product **3c**. The rate for the reaction with



Scheme 4. Aza-MBH reactions of **1c** with acrylonitrile and ethyl acrylate.

acrylonitrile in the presence of catalyst is at least 10 times faster than that for the reaction with ethyl acrylate. These results indicate that the palladium/pincer complex selectively coordinates to the cyano group and that it activates acrylonitrile.

Based on previous X-ray crystallographical analysis of the palladium pincer complexes,[8a] and the absolute configuration of the products, we propose the structure shown in Figure 1 for palladium ketenimide intermediate and transi-

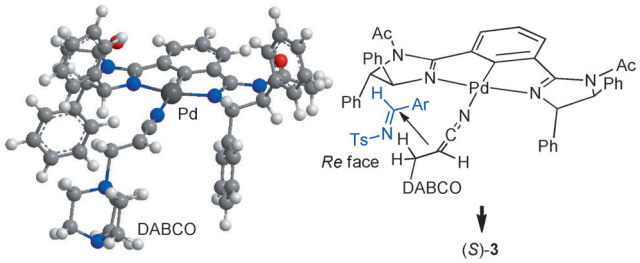


Figure 1. The structure of the complex and the assumed transition state for the addition reaction of activated acrylonitrile with an imine in the presence of **4a**.

tion state of the enantioselective reaction of palladium ketenimide with imine in the presence of **4a**. We believe imine **1** approaches from the opposite side to DABCO, thus avoiding steric repulsion; the *Re* face of the imine reacts with palladium ketenimide to give the *S* isomer. Further studies are required to fully elucidate the mechanistic detail of the aza-MBH reaction of acrylonitrile with imines.[16]

In conclusion, we have developed the first highly enantioselective aza-MBH reaction of acrylonitrile with imines using chiral pincer complexes of 1,3-bis(imidazolin-2-yl)benzene bearing a bulky substituent and Pd^{II}. A range of imines can be tolerated in this process. This process offers a simple and efficient route for the synthesis of functionalized α-methylene-β-aminonitriles and their derivatives. 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 for aza-Morita–Baylis–Hillman reaction of acrylonitrile catalyzed by chiral phebim/Pd^{II} complexes: *N*-[(*1S*)-2-Cyano-

1-phenylpropen-3-yl]-4-methylbenzenesulfonamide (**3a**): DABCO (1.2 mg, 11.7 μmol), and **2** (46.5 μL, 0.504 mmol) were added to a mixture of AgOAc (1.8 mg, 11.7 μmol), **4f** (12.6 mg, 11.7 μmol), and molecular sieves (4 Å; 90 mg) in *i*PrCN (0.75 mL) at −10 °C. Then, *N*-sulfonylimine **1a** (61.5 mg, 0.237 mmol) was added. After disappearance of *N*-sulfonylimine in the reaction mixture, as monitored by TLC, the crude mixture was filtered through a pad of silica gel and washed with CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (benzene/CH_3CN = 95:5) giving **3a** (68.9 mg, 93%) as a white solid.

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