Palladium-catalyzed Asymmetric Mannich-type Reactions of α-Cyanoketones with *N*-Boc Aldimines

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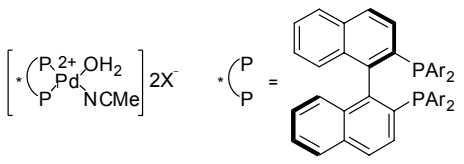
The efficient synthetic construction of β-amino carbonyl compounds is one of the most intensely studied areas in organic synthesis.[1] Chiral α-substituted β-amino nitriles, since cyano group is easily converted to other functional groups, would be versatile synthetic intermediates for the synthesis of β-amino acids and the corresponding chiral diamine derivatives which are employed as medicinal agents or chiral ligands.[2] Enantioselective Mannich reactions are efficient and powerful methods to prepare β-amino carbonyl derivatives.[3] Tremendous efforts have been made in the development of efficient chiral metal and organic catalysts for enantioselective Mannich reactions with pre-formed enolates and enolizable methylenes and methines.[4-7] Recently, Shibasaki *et al.* have reported a highly enantio- and diastereoselective Mannich reaction using α-cyanoketones, catalyzed by chiral amide ligand associated with a rare earth metal complexes.[8] However, a highly enantioselective Mannich reaction of α-cyanoketones with simple imines remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under air- and moisture-tolerant conditions, it could provide a highly attractive, convergent approach toward optically active β-amino nitriles.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we recently reported the catalytic electrophilic amination and fluorination of active methines promoted by chiral palladium complexes with excellent enantioselectivities.[10]

Herein, we wish to describe the direct enantioselective Mannich reaction of α-cyanoketones with simple *N*-Boc imines catalyzed by air- and moisture-stable chiral palladium complexes (Fig. 1).



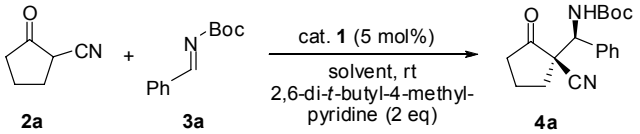
1a : Ar = Ph : (*R*)-BINAP, X = BF_4
1b : Ar = Ph : (*R*)-BINAP, X = OTf
1c : Ar = Ph : (*R*)-BINAP, X = PF_6
1d : Ar = Ph : (*R*)-BINAP, X = SbF_6
1e : Ar = 4-methylphenyl : (*R*)-Tol-BINAP, X = PF_6
1f : Ar = 3,5-dimethylphenyl : (*R*)-Xylyl-BINAP, X = PF_6

Figure 1. Structure of chiral palladium complexes.

To determine suitable reaction conditions for the catalytic enantioselective Mannich reaction of α-cyanoketones, we initially investigated the reaction system with 2-cyano cyclopentanone (**2a**) and *N*-Boc benzaldimine (**3a**) in the presence of 5 mol% of catalyst in THF at room temperature (Table 1). We first examined the impact of the structure of catalysts **1** on enantioselectivity (Table 1, 25-88% ee, entries 1-6). The best results have been obtained with catalysts **1c**. In the presence of 2,6-di-*tert*-butyl-4-methylpyridine as base, the reaction proceeded rapidly without a significant change of enantioselectivity (entries 3 and 7).[10b] Concerning the solvent (entries 7-13), the use of THF and acetone gave the best results in the yield and the enantiomeric excess (entries 7 and 10). The stereochemistry of **4a** was determined by comparing chiral HPLC, optical rotation, and ^{1}H NMR data with literature value.[8]

We then explored the possibility of extending of this reaction to other para-substituted aromatic aldimines **3** with α-cyanoketones **2a** under the optimized reaction conditions. As shown in Table 2, the products **4a-e** was formed in high yields

Table 1. Optimazation of the reaction conditions

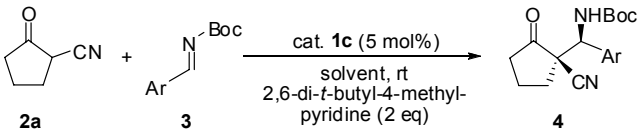


2a **3a** **4a**

entry	cat. **1**	solvent	time (h)	yield (%)[a]	*syn/anti*[b]	ee (%)[c]
1[d]	**1a**	THF	48	55	50/50	52
2[d]	**1b**	THF	48	80	50/50	25
3[d]	**1c**	THF	90	65	75/25	88
4[d]	**1d**	THF	48	79	50/50	25
5[d]	**1e**	THF	36	75	25/75	37
6[d]	**1f**	THF	36	60	66/33	55
7	**1c**	THF	10	78	83/17	91
8	**1c**	MTBE	24	40	70/30	52
9	**1c**	DCM	7.5	96	40/60	50
10	**1c**	acetone	24	85	90/10	89
11	**1c**	CH_3CN	3.5	65	70/30	76
12	**1c**	MeOH	3.5	70	60/40	0
13	**1c**	PhMe	7.5	51	50/50	0

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the *syn* diastereomer, determined by chiral HPLC. [d]Reactions were carried out without base (2,6-di-*t*-butyl-4-methylpyridine).

Table 2. Variation of the *N*-Boc imine

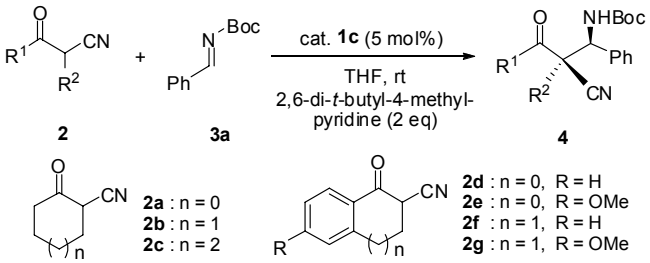


2a **3** **4**

entry	**3**, Ar	solvent	time (h)	yield (%)[a]	*syn/anti*[b]	ee (%)[c]
1	**3a**, C_6H_5	THF	10	**4a**, 78	83/17	91
2	**3b**, 2-naphthyl	THF	4	**4b**, 95	100/0	77
3	**3b**, 2-naphthyl	acetone	4	**4b**, 94	100/0	88
4	**3c**, 2-F-C_6H_4	acetone	3	**4c**, 95	100/0	81
5	**3d**, 2-Cl-C_6H_4	acetone	3	**4d**, 92	75/25	80
6	**3e**, 4-Cl-C_6H_4	acetone	4	**4e**, 72	73/27	80

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the *syn* diastereomer, determined by chiral HPLC.

Table 3. Variation of the α-cyanoketone



2 **3a** **4**

entry	**2**	time (h)	yield (%)[a]	*syn/anti*[b]	ee (%)[c]
1	**2a**	10	**4a**, 78	83/17	91
2[d]	**2b**	6	**4f**, 81	100/0	90
3	**2c**	10	**4g**, 82	82/18	91
4	**2d**	4	**4h**, 95	97/13	83
5	**2e**	12	**4i**, 72	88/12	83
6	**2f**	7	**4j**, 80	100/0	73
7	**2g**	7	**4k**, 71	100/0	70

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the *syn* diastereomer, determined by chiral HPLC. [d]This reaction was carried out using cat. **1f**.

(72-95%), excellent diastereoselectivity (73/27-100/0), and high enatioselectivity (77-91%).

To examine the generality of the catalytic enantioselective Minnich reaction of α-cyanoketones **2** by using chiral palladium complex **1c**, we studied the Mannich reaction of various α-cyanoketones **2** with *N*-Boc benzaldimine (**3a**). As it can be seen by the results summarized in Table 3, the corresponding β-aminated α-cyanoketones **4a**, and **4f-k** were obtained in excellent yields (71-95%) and enantioselectivities (70-91%). The absolute configuration of adducts **4** has been determined for some derivatives by comparison of their optical and HPLC data with literature values.[8]

In conclusion, we have developed a highly efficient catalytic enantioselective Mannich reaction of cyclic α-cyanoketones using air- and moisture-stable chiral palladium complexes. The desired β-aminated products were obtained in high yields and high enantioselectivities (70-91% ee) for various substrates.

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