Catalytic Asymmetric Electrophilic α-Amination of α-Cyanoketones in the Presence of Chiral Palladium Complexes

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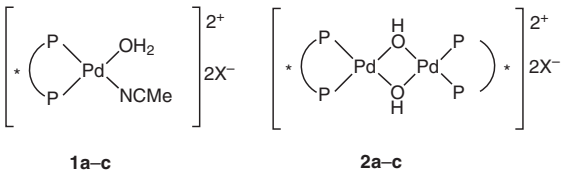
Abstract: The catalytic enantioselective electrophilic α-amination promoted by chiral palladium complexes is described. Treatment of α-cyanoketones with azodicarboxylates as electrophilic amination reagents under mild reaction conditions afforded the corresponding α-amino α-cyanoketones with excellent enantiomeric excesses (81–95% ee).

Key words: electrophilic amination, asymmetric catalysis, chiral palladium catalysts, α-cyanoketones

Chiral α-amino nitriles are very useful bifunctional compounds for a large number of synthetic applications.[1] The most popular and wide use of chiral α-amino nitrile involves hydrolysis of the nitrile group to generate chiral α-amino acids,[2] which are often used as key building blocks in pharmaceuticals. In addition, since the cyano group is easily converted into other functional groups, chiral α-substituted α-amino nitriles would be versatile synthetic intermediates for the synthesis of nitrogen-containing heterocycles[3] and chiral 1,2-diamine derivatives, which are employed as medicinal agents or chiral ligands.[4] The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most popular methods for the synthesis of chiral α-amino nitriles and their derivatives. Several successful achievements in catalytic asymmetric Strecker reaction were reported.[5] However, most of the known asymmetric Strecker reactions rely on the use of toxic and anhydrous cyanide reagents. The catalytic asymmetric electrophilic amination of α-substituted nitriles seems to be an alternate method for the synthesis of chiral α-amino nitrile derivatives. The catalytic, enantioselective, direct C–N bond-formation reaction of active methine compounds represents an efficient and simplest procedure to generate stereogenic carbon center attached to a nitrogen atom.[6] Recently, several groups presented the direct enantioselective amination of active methine compounds in the presence of chiral metal complexes or organocatalysts.[7–9] To the our best knowledge, although electrophilic amination of active methines such as β-ketoester,[7] β-ketophosphonates,[8] and α-cyanoacetates[9] have been reported, up to now there are no examples of these reactions with α-cyanoketones.[10]



1a–c **2a–c**

a Ar = Ph: (*R*)-BINAP
b Ar = 4-methylphenyl: (*R*)-Tol-BINAP
c Ar = 3,5-dimethylphenyl: (*R*)-Xylyl-BINAP

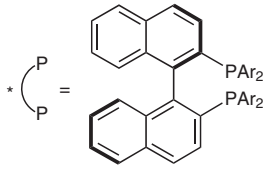


Figure 1

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[11] we report the catalytic enantioselective functionalization of ester derivatives promoted by air- and moisture-stable chiral palladium complexes.[12e–g] In this letter, we report the direct α-amination of cyclic and acyclic α-cyanoketones **3** catalyzed by palladium complexes **1** and **2**[12] (Figure 1) with azodicarboxylates **4** as the electrophilic nitrogen source.

Our investigation began with the catalytic enantioselective electrophilic amination of 2-cyanoindanone **3a** with azodicarboxylates **4** as the electrophilic aminating reagent in MeOH at room temperature in the presence of 5 mol% of catalyst **1a** (BF_4). We examined the impact of the structure of azodicarboxylates **4** on enantioselectivity (Table 1, entries 1–4). The best results were obtained with *tert*-butyl ester of azodicarboxylate. Concerning the solvent (entries 4–13), the use of acetone gave the best results in the yield and the enantiomeric excess (entry 10). Catalysts **1a** (BF_4) and **1a** (PF_6) were more effective than other catalysts (entries 10 and 15).

To examine the generality of the catalytic enantioselective amination of α-cyanoketones **3** by using chiral palladium complexes **1**, we studied the amination of various α-cyanoketones **3a–g**.[13] As it can be seen by the results summarized in Table 2, the corresponding α-aminated α-cyanoketones **5a–g** were obtained in excellent yields and enantioselectivities.

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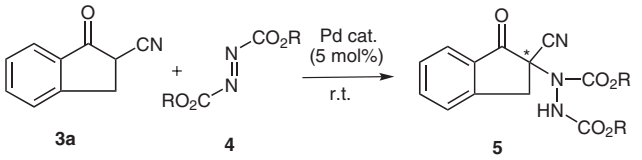
Table 1 Optimization of the Reaction Conditions



3a 4 5

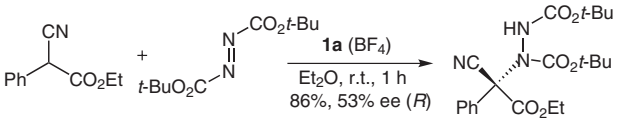
Entry	4, R	Catalyst	Solvent	Time (min)	Yield (%)	ee (%)[a]
1	**4a**, Et	**1a** (BF_4)	MeOH	5	93	37
2	**4b**, Bn	**1a** (BF_4)	MeOH	20	90	40
3	**4c**, *i*-Pr	**1a** (BF_4)	MeOH	10	93	60
4	**4d**, *t*-Bu	**1a** (BF_4)	MeOH	10	95	73
5	**4d**, *t*-Bu	**1a** (BF_4)	EtOH	20	95	73
6	**4d**, *t*-Bu	**1a** (BF_4)	*t*-BuOH	20	93	81
7	**4d**, *t*-Bu	**1a** (BF_4)	THF	15	94	75
8	**4d**, *t*-Bu	**1a** (BF_4)	MeCN	24 h	0	–
9	**4d**, *t*-Bu	**1a** (BF_4)	CH_2Cl_2	6 h	90	60
10	**4d**, *t*-Bu	**1a** (BF_4)	acetone	10	95	92
11[b]	**4d**, *t*-Bu	**1a** (BF_4)	acetone–THF	40	93	85
12[c]	**4d**, *t*-Bu	**1a** (BF_4)	acetone–PhMe	30	95	83
13[d]	**4d**, *t*-Bu	**1a** (BF_4)	acetone–H_2O	10	94	79
14	**4d**, *t*-Bu	**1a** (OTf)	acetone	15	95	83
15	**4d**, *t*-Bu	**1a** (PF_6)	acetone	15	93	92
16	**4d**, *t*-Bu	**1b** (PF_6)	acetone	15	93	79
17	**4d**, *t*-Bu	**1c** (PF_6)	acetone	15	90	83
18	**4d**, *t*-Bu	**2a** (BF_4)	acetone	10	96	85
19	**4d**, *t*-Bu	**2b** (BF_4)	acetone	10	94	85
20	**4d**, *t*-Bu	**2c** (BF_4)	acetone	10	95	77

[a] Enantiopurity of **5** was determined by HPLC analysis with Chiralpak AD column.
[b] Acetone–THF, 4:1.
[c] Acetone–PhMe, 4:1.
[d] Actone–H_2O, 19:1.

The cyclic α-cyanoketones **3a–d** reacted with *tert*-butyl azodicarboxylate (**4d**) to give the corresponding α-aminated α-cyanoketones **5a–d** in 90–95% yields and 83–95% ee (Table 2, entries 1–5). Acyclic α-cyanoketones **3e–g** reacted with *tert*-butyl azodicarboxylate (**4d**) or ethyl azodicarboxylate (**4a**) to afford the α-aminated adducts **5e–g** in alcoholic solvents with 81–91% ee in the presence of catalyst **2c** (Table 2, entries 6–8).

We examined the catalytic enantioselective electrophilic amination of α-cyanoacetate **6** with *tert*-butyl azodicarboxylate (**4d**) using palladium complexes **1** and **2** at room temperature. In the presence of 5 mol% of catalyst **1a** (X = BF_4), the reaction proceeded to afford the α-aminated product **7** after one hour with 86% yield and 53% ee (Scheme 1). The absolute configuration of **7** was determined to be *R* by comparing specific rotation and chiral HPLC data with an authentic sample.[9b,c]

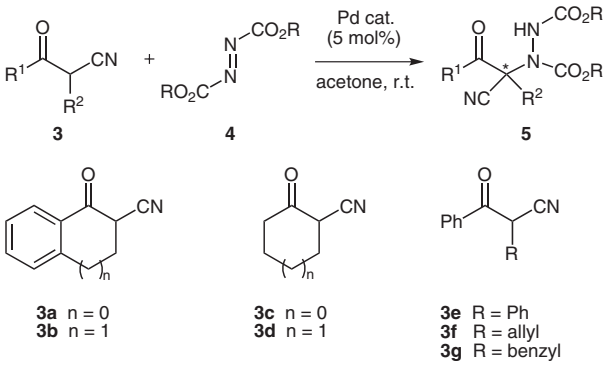
In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of cyclic and acyclic α-cyanoketones using air- and moisture-stable chiral palla-



6 4d 7

Scheme 1 Catalytic enantioselective amination of α-cyanoacetate **6**

Table 2 Catalytic Enantioselective Amination of α-Cyanoketones



Entry	**3**	**4**, R	Catalyst	Time (min)	Yield (%)[a]	ee (%)[b]
1	**3a**	**4d**, *t*-Bu	**1a** (PF_6)	15	**5a**, 93	92
2	**3a**	**4d**, *t*-Bu	**1a** (BF_4)	10	**5a**, 95	92
3	**3b**	**4d**, *t*-Bu	**1a** (BF_4)	10	**5b**, 95	95
4	**3c**	**4d**, *t*-Bu	**1a** (BF_4)	10	**5c**, 95	85
5	**3d**	**4d**, *t*-Bu	**1a** (BF_4)	2.5 h	**5d**, 90	83
6[c]	**3e**	**4d**, *t*-Bu	**2c** (BF_4)	20 h	**5e**, 87	86
7[d]	**3f**	**4d**, *t*-Bu	**2c** (BF_4)	1 h	**5f**, 94	91
8[d]	**3g**	**4a**, Et	**2c** (BF_4)	5 h	**5g**, 90	81

[a] Yield of isolated product.
[b] Enantiopurity of **5** was determined by HPLC analysis with Chiralpak AD (for **5a**,**c**,**f**,**g**), AS (for **5b**), (*S*,*S*)-Whelk-O1 (for **5d**) and Chiralcel OD-H (for **5e**) columns.
[c] Reaction carried out in *t*-BuOH–*i*-PrOH, 1:1.
[d] Reaction carried out in *t*-BuOH.

dium complexes. The desired α-aminated products were obtained in good to high yields, and excellent enantioselectivities (81–95% ee) were observed for all the substrates examined in this work. To our knowledge, these results constitute the first examples of the direct catalytic asymmetric amination of α-cyanoketones. We believe that this report provides a practical method for the preparation of chiral α-amino α-cyanoketones derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this amination will be presented in due course.

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(13) **General Procedure for the Amination of α-Cyanoketone**

To a stirred solution of α-cyanoketone **3** (0.2 mmol) and catalyst **1a** (BF_4) (9.6 mg, 0.01 mmol) in acetone (2 mL) was added *tert*-butyl azodicarboxylate (**4d**, 46 mg, 0.2 mmol) at r.t. The reaction mixture was stirred for 10 min to 20 h at r.t. The mixture was diluted with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (EtOAc–hexane, 1:3) to afford the α-aminated α-cyanoketone **5**.

2-Aminated 2-Cyano-1-indanone 5a

$[\alpha]_D^{22}$ –21.5 (*c* 1.45, $CHCl_3$, 92% ee). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.90–7.82 (m, 1 H), 7.74–7.66 (m, 1 H), 7.56–7.43 (m, 2 H), 7.01 (br s, 1 H), 4.07–3.83 (m, 2 H), 1.62–1.22 (m, 18 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.1, 155.5, 149.3, 136.9, 136.6, 132.2, 128.6, 126.5, 125.9, 115.6, 84.3, 82.2, 68.4, 40.9, 28.2, 27.8. MS (MSI): *m/z* (%) = 387 [M^+], 356 (10), 332 (70), 275 (32), 232 (8), 213 (12), 188 (7.5), 158 (8). ESI-HRMS: *m/z* calcd for $C_{20}H_{25}N_3O_5$ [$M]^+$: 387.1794; found: 387.1802. HPLC (hexane–*i*-PrOH, 8:2, 254 nm, 1.0 mL/min, Chiralpak AD column): t_R = 5.8 min (minor), t_R = 7.7 min (major).