JOC Note

Efficient Three-Component Strecker Reaction of Aldehydes/Ketones via NHC-Amidate Palladium(II) Complex Catalysis

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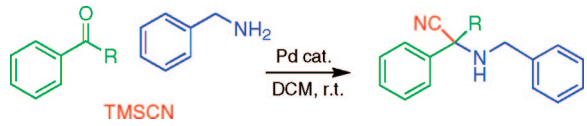

A simple and efficient one-pot, three-component method has been developed for the synthesis of α-aminonitriles. This Strecker reaction is applicable for aldehydes and ketones with aliphatic or aromatic amines and trimethylsilyl cyanide in the presence of a palladium Lewis acid catalyst in dichloromethane solvent at room temperature.

The Strecker reaction, which employs aldehydes or ketones, amines, and a cyanide source, is a well-established route for the preparation of α-aminonitriles, which are versatile intermediate compounds and are particularly useful in the preparation of α-amino acids and other biologically relevant molecules, such as nitrogen-containing heterocycles.[1] Successful examples of this reaction have been demonstrated using titanium,[2] iron,[3] and zirconium[4] catalysts, Schiff bases,[5] Lewis bases,[6] gallium triflate,[7] ionic liquids,[8] β-cyclodextrin,[9] and other nonmetal catalysts.[10] However, most one-pot multicomponent variations of the Strecker reaction involve aldehydes, and the Strecker synthesis applied to ketones and aliphatic amines remains a more difficult reaction. Often with these substrates, the reaction is carried out stepwise using premade imines or under high pressure conditions.[11] Although recently one-pot procedures have been developed for the synthesis of α-aminonitriles using a variety of Lewis acids such as lithium perchlorate,[12] scandium triflate,[13] vanadyl triflate,[14] zinc halides,[15] ytterbium triflate,[16] and montmorillonite;[17] most of these methods involve the use of strong acidic conditions, expensive reagents, extended reaction times, harsh conditions, fast hydrolysis, and tedious workup leading to the generation of a large amount of waste.

Therefore, more general and milder reaction conditions for one-pot multicomponent Strecker reactions, particularly those involving ketones, would be advantageous.

Recently, we found that *N*-heterocyclic carbene (NHC)−amidate palladium(II) complex **1a** acts as an effective catalyst for asymmetric boron−Heck type carbon−carbon bond-forming reactions under mild conditions.[18] In addition, this palladium(II) complex **1a** was converted to the palladium complex **1b** by treating with aqueous $AgBF_4$, and it was found that the subsequent monomer/dimer equilibrium process (**1b** ↔ **1c**) readily occurred in the aqueous solution (Scheme 1). Consequently, the catalytic reaction was not inhibited by coordination of water to palladium metal since the presence of strongly electron-donating groups such as the NHC, amidate N, and O would increase the electron density of palladium and allow for a weak interaction between electrophilic Pd and water. Therefore, due to the stability toward aqueous conditions and easy formation of a palladium open site, we prepared new NHC−amidate palladium(II) analogue **2** having an ester moiety as a portable chelating group. We herein report the results of its application in the synthesis of α-amino nitriles from the corresponding aldehydes or ketones and amines with trimethylsilyl cyanide (TMSCN) in dichloromethane solvent. These reactions required no further purification in most cases.

The preparation of ligand precursor **6** was carried out as illustrated in Scheme 2. Treatment of **4**, derived from the

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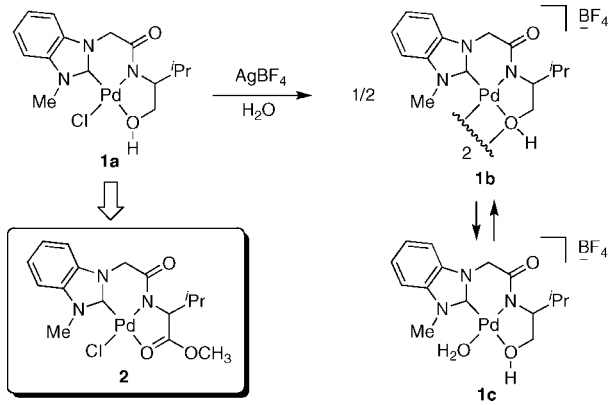
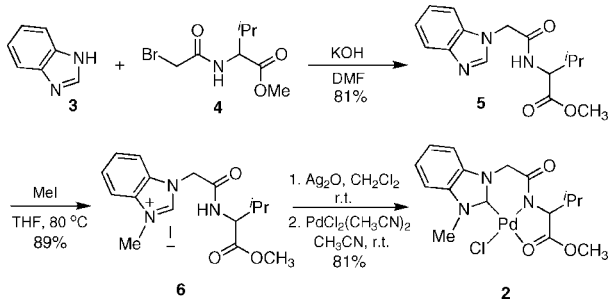
SCHEME 1



SCHEME 2. Preparation of the Palladium Complex 2



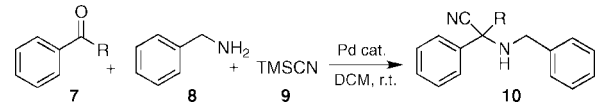
amidation of valine methyl ester and bromoacetyl bromide, with benzimidazole **3** in the presence of KOH in DMF provided compound **5** efficiently. The amido ester-substituted benzimidazolium iodine salt **6** was then obtained by allowing **5** to react with CH_3I in refluxing THF. Formation of **6** was confirmed (^{1}H NMR spectroscopy in $CDCl_3$) by observation of the new peak assigned to the N-C*H*$_3$ at 4.18 ppm, as well as the expected chemical shift change for the imidazole-*H* (7.95 to 10.16 ppm) as an iodine salt.

For coordination of **6** as an NHC to palladium, compound **6** was reacted with Ag_2O in dichloromethane at room temperature for 3 h and then the solvent was filtered under reduced pressure to give the silver NHC complex as a light gray color solid. This reaction could be carried out without any purification of the intermediate. Subsequent treatment of the silver compound with $PdCl_2(CH_3CN)_2$ in CH_3CN at room temperature for 3 h afforded palladium complex **2** in 83% yield. The structure was confirmed by ^{1}H NMR spectroscopic analysis and HRMS data (molecular peak at *m*/*z* 445.0371 [M + H]).

As shown in Table 1, an initial screening of palladium catalysts was conducted. Using TMSCN as a cyanide source and sodium sulfate as a desiccant, reactions were conducted in dichloromethane solvent at room temperature. In the absence of a palladium catalyst, reactivity was poor and provided low conversion for the reaction between acetophenone and benzylamine at room temperature (entry 1). While the use of $PdCl_2$ led to low conversion for reactions involving ketone and aldehyde (entries 2 and 5), optimal conversion (>95%) was obtained using a 3 mol % loading of NHC−palladium complex **2** in reactions employing both carbonyl sources (entries 4 and 6).

In the initial screening, both $PdCl_2$ and **2** were demonstrated to be suitable catalysts for reactions involving aldehydes. However, due to its stability in water released during the course of the reaction, **2** appeared to promote better reactivity compared

TABLE 1. Screening of Palladium Source and Catalyst Loading[a]



entry	R	catalyst (mol %)	time (h)	yield[b] (%)
1	Me		72	15
2	Me	$PdCl_2$ (5)	24	11
3	Me	**2** (5)	24	99
4	Me	**2** (3)	24	99
5	H	$PdCl_2$ (5)	24	68
6	H	**2** (3)	24	95

[a] To a mixture of palladium catalyst, sodium sulfate (100 mg, 0.7 mmol), **7** (0.2 mmol), and **8** (0.2 mmol) in 1 mL of CH_2Cl_2 in a Schlenk tube was added dropwise **9** (0.4 mmol). The mixture was stirred for 24 h at room temperature. [b] Conversion yield.

to $PdCl_2$ for reactions employing ketones. Therefore, complex **2** was evaluated for potential application to a wider scope of substrates for the Strecker reaction, shown in Table 2. Reactions were carried out with aliphatic and aromatic aldehyde and amine substrates, and in all cases, regardless of differences in electronic character of the aldehyde substrates, reactions were able to proceed with high yields. For example, an electron-withdrawing substituent (entries 2 and 9) was compatible with these conditions, as were heteroatom-containing aldehydes (entries 3−5 and 10−12) and aliphatic aldehydes (entries 7, 14, and 15). Similar to previous reports using other Lewis acid catalysts, aromatic (entries 1−7) and aliphatic (entries 8−15) amines were compatible with these reactions as well.[7,12−17] Without the use of a desiccating agent, the formation of the imine intermediate was hindered, and low conversion to the α-aminonitrile produt was observed (not shown).

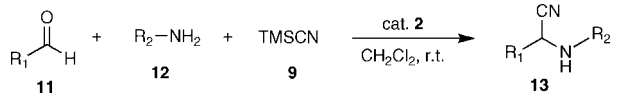
Due to the encouraging reactivity of complex **2** as a Lewis acid catalyst for the Strecker reaction employing aldehydes, its feasibility to promote reactions involving ketones was then evaluated. In the presence of **2**, good reactivity was observed for reactions involving an aromatic amine and ketones with electron-donating (entry 2) substituents, as indicated in Table 3. A bromo substituent was tolerated as well (entry 3), but the electron-withdrawing nitro group (entry 4) was not a feasible substrate. Lower yield with this substrate may be attributed to low conversion to the imine intermediate. In general, reactions employing aniline as the amine provided the α-aminonitrile products in better conversion than did those using benzylamine. Again, electron-withdrawing substituents on the ketone substrate were not well-tolerated, although electron-donating (entry 8) and heteroatom (entry 10) substituents provided modest reactivities.

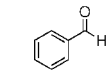
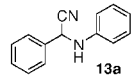
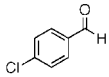
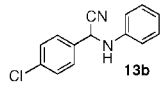
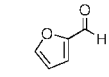
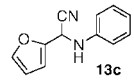
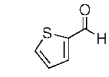
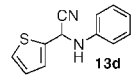
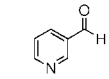
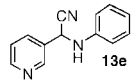
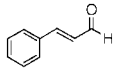
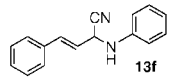
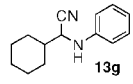
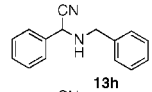
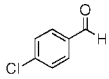
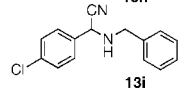
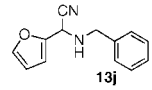
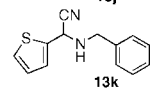
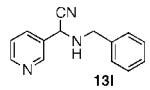
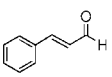
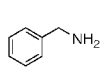
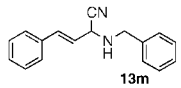
In summary, NHC−amidate ester palladium(II) complex **2** has been demonstrated to be a useful Lewis acid catalyst to promote one-pot multicomponent Strecker reactions for the synthesis of α-aminonitriles. Additionally, the application of **2** in reactions involving ketone substrates allowed for the formation of α-aminonitrile products containing a quaternary carbon. The benefit of this methodology is the simplicity of the procedure involved, which often avoided the use of tedious chromatographic purification of products. Future studies involving optically active forms of **2** may allow for the formation of α-aminonitriles in an enantioselective manner.

Experimental Section

Palladium(II) Complex (2). The suspension of benzimidazolium iodine salt **6** (500 mg, 1.16 mmol) and silver(I) oxide (185 mg, 0.8

TABLE 2. Strecker Reactions of Various Aldehydes and Amines in the Presence of Palladium Complex 2[a]



Entry	Aldehyde	Amine	Product	Conv.(Yield) (%)
1			 **13a**	99 (79)
2			 **13b**	99 (84)
3			 **13c**	99 (79)
4			 **13d**	99 (91)
5			 **13e**	99 (95)
6			 **13f**	99 (83)
7			 **13g**	99 (88)
8			 **13h**	99 (95)
9			 **13i**	99 (90)
10			 **13j**	99 (86)
11			 **13k**	99 (91)
12			 **13l**	99 (87)
13			 **13m**	99 (98)
14			**13n**	99 (70)
15			**13o**	99 (62)

[a] To a mixture of palladium catalyst, sodium sulfate (100 mg, 0.7 mmol), **7** (0.2 mmol), and **8** (0.2 mmol) in 1 mL of CH_2Cl_2 in a Schlenk tube was added dropwise **9** (0.4 mmol). The mixture was stirred for 24 h at room temperature. [b] Isolated yields.

mmol) in CH_2Cl_2 (20 mL) was stirred for 3 h in the dark at room temperature. The reaction mixture was concentrated under reduced pressure to give a gray solid. To a suspension of the silver complex in CH_3CN (20 mL) was added $PdCl_2(CH_3CN)$ (301 mg, 1.16 mmol) in the dark at room temperature. Then, the resulting suspension

TABLE 3. Strecker Reactions of Various Ketones and Amines in the Presence of Palladium Complex 2[a]

Entry	Aldehyde	Amine	Product	Conv.(Yield) (%)
1			**15a**	99 (92)
2			**15b**	86 (74)
3			**15c**	95 (88)
4			**15d**	17 (15)
5			**15e**	44 (40)
6			**15f**	85 (83)
7			**15g**	49 (33)
8			**15h**	58 (35)
9			**15i**	62 (55)
10			**15j**	68 (60)

[a] To a mixture of palladium catalyst, sodium sulfate (100 mg, 0.7 mmol), **7** (0.2 mmol), and **8** (0.52 mmol) in 1 mL of CH_2Cl_2 in a Schlenk tube was added dropwise **9** (0.4 mmol). The mixture was stirred for 24 h at room temperature. If necessary, compounds were purified by column chromatography on silica gel with a gradient elution of hexanes/ethyl acetate. [b] Isolated yields.

was stirred for 2 h and filtered through a plug of glass fiber filter paper. The filtrate was evaporated to dryness in vacuo to afford product **2** (418 mg, 81% yield) as an orange solid: ^{1}H NMR (CD_3OD, 250 MHz) δ 7.63−7.59 (m, 1H), 7.51−7.48 (m, 1H), 7.38−7.33 (m, 2H), 5.82 (d, J = 16.5 Hz, 1H), 5.63 (d, J = 16.5 Hz, 1H), 4.41 (brs, 1H), 4.35 (s, 3H), 3.66 (s, 3H), 2.23−2.09 (m, 1H), 0.95 (d, J = 2.5 Hz, 3H), 0.92 (d, J = 2.5 Hz, 3H); ^{13}C NMR (CD_3OD, 63 MHz) δ 18.6, 19.4, 31.7, 35.3, 52.0, 52.4, 59.6; Anal. Calcd for $C_{16}H_{21}ClN_3O_3Pd$: C, 43.16; H, 4.75; N, 9.44; Cl, 7.96. Found: C, 42.98; H, 4.81; N, 7.59; Cl, 7.38; HRMS-ESI (*m*/*z*) [M + H$^+$] calcd for $C_{16}H_{22}ClN_3O_3Pd$ 445.0385, found 445.0371.

Representative Procedure for the Synthesis of 13a. To a mixture of **2** (3 mol %), sodium sulfate (100 mg, 0.7 mmol), benzaldehyde (0.020 mL, 0.2 mmol), and aniline (0.018 mL, 0.2 mmol) in 1 mL of CH_2Cl_2 in a pressure tube was added dropwise TMSCN (0.053 mL, 0.4 mmol). The pressure tube was closed and stirred for 24 h at 23 °C. The mixture was then filtered, and the residue was washed with CH_2Cl_2 (10 mL). The filtrate was collected, and the solvent was removed under reduced pressure to obtain 2-phenyl-2-(phenylamino)acetonitrile **13a** (33 mg, 79% yield) as a light yellow solid: mp 76−79 °C; ^{1}H NMR (250 MHz) δ 4.67 (br s, 1H), 5.36 (s,

1H), 6.72 (d, $J = 7.8$ Hz, 2H), 6.84 (t, $J = 7.4$ Hz, 1H), 7.22 (t, $J = 8.0$ Hz, 2 H), 7.37−7.44 (m, 3H), 7.52−7.55 (m, 2H); ^{13}C NMR (63 MHz) δ 50.1, 114.1, 118.1, 120.2, 127.2, 128.4, 129.2, 129.4, 134.0, 144.7.

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Supporting Information Available: Experimental procedures, compound characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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