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Nitrile Synthesis by Aerobic Oxidation of Primary Amines and *in situ* Generated Imines from Aldehydes and Ammonium Salt with Grubbs Catalyst

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Abstract. Herein, a Grubbs-catalyzed route for the synthesis of nitriles via the aerobic oxidation of primary amines is reported. This reaction accommodates a variety of substrates, including simple primary amines, sterically hindered β,β-disubstituted amines, allylamine, benzylamines, and α-amino esters. Reaction compatibility with various functionalities is also noted, particularly with alkenes, alkynes, halogens, ester silyl ethers, and free hydroxyl groups. The nitriles were also synthesized via the oxidation of imines generated from aldehydes and NH_4OAc *in situ*.

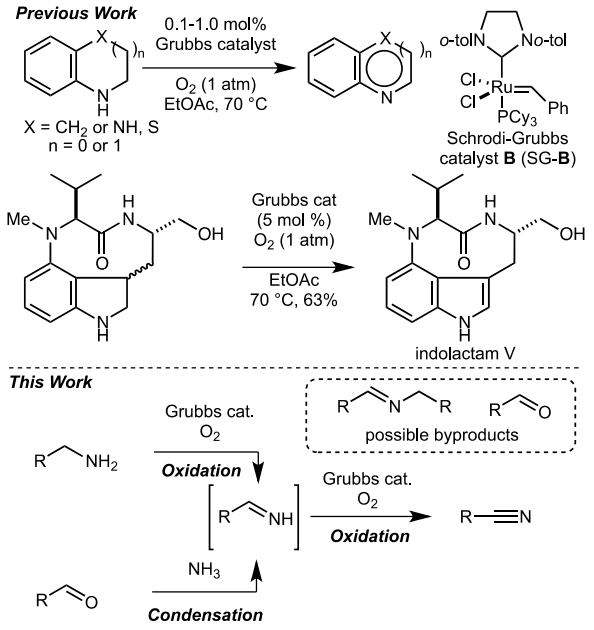
Keywords: nitrile; aerobic oxidation; Grubbs catalyst; amine; aldehyde

Nitriles are fundamental functional groups, which are often used as an important electron-deficient group to tune the chemical properties of organic compounds such as pharmaceuticals, agrochemicals, and polymers.[1] Since nitriles serve as a versatile synthetic precursor for a variety of functional groups,[2] numerous methodologies for their formation have been developed.[3-9] The oxidation of primary amines or imines via catalytic dehydrogenation in an oxygen atmosphere is one of the most efficient and environmentally friendly methods to date, particularly for green chemistry applications.[5-9]

For nitrile synthesis by catalytic dehydrogenation of primary amines, numerous aerobic conditions using homogeneous and heterogeneous transition metal catalysts including Ru, Fe, and Co catalysts have so far been reported.[5–7] Taking advantage of the high catalytic activity, heterogeneous catalysts[7] are generally advantageous in terms of low catalyst loading, reusability, and scalability. However, conditions using highly active catalyst occasionally cause a problem of functional group compatibility due to undesired oxidation or decomposition of sensitive functional groups such as alcohols.[10] In particular, during the oxidation of primary amines to nitriles, the problematic issue should be generation of aldehydes via hydrolysis of the transient imine intermediate or generation of complex mixture by decomposition during imine-enamine equilibrium if there is β-proton in the substrate. Therefore, some of the conventional methods are usually limited to synthesis of benzonitrile derivatives and are not applicable to synthesis of aliphatic nitriles.[6a, 6b] Under these backgrounds, we considered that there would be room to develop a mild and chemoselective condition for nitrile synthesis being applicable to a wide range of substrates.

Our preliminary studies on the synthesis of monoterpene indole alkaloids have revealed that Grubbs catalyst promoted aerobic oxidation of tertiary amines.[11] Based on these findings, we recently established the catalytic aerobic dehydrogenation of *N*-heterocycles using sub-mol% quantities of Grubbs catalyst (Scheme 1).[12] The extensive mechanistic study using in situ IR spectroscopy indicated that the active catalytic species is a CO-Ru complex generated from Grubbs catalyst under oxygen atmosphere.[12] The reported reaction conditions tolerated a variety of functional groups; these conditions were even applicable for the oxidation of an indoline analog of indolactam V[13] that possessed a tertiary amine, an amide, and a free hydroxyl group, the synthesis of which was difficult under conventional oxidation conditions[14] (Scheme 1). Given that Grubbs catalyst was also capable of oxidizing the imine functionality to a nitrile group, we theorized that a novel route for nitrile synthesis via one-pot sequential oxidation of primary amines through the corresponding imine intermediate was also possible (Scheme 1). Herein, a novel nitrile synthesis via the catalytic aerobic oxidation of primary amines with Grubbs catalyst is described. Furthermore, the chemistry of the reaction was expanded for nitrile synthesis from an aldehyde starting material via the one-pot formation of an

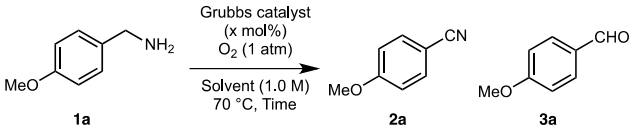
imine through condensation with the NH_3 equivalent (Scheme 1).



Scheme 1. Outline of This Work.

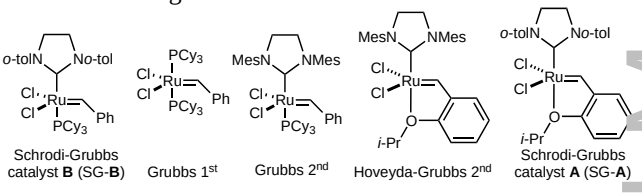
At the outset, the working hypothesis was tested using 4-methoxybenzylamine (**1a**) as the model substrate (Table 1). The initial trial was conducted under the optimal conditions established by the previous dehydrogenation project (Entry 1). Briefly, the EtOAc solution of **1a** was treated with 5 mol% Schrodi–Grubbs catalyst **B** (SG-**B**) in an oxygen atmosphere (1 atm, balloon) at 70 °C. The expected two-step oxidation reaction[15] proceeded to the nitrile product, and **2a** was isolated in 76% yield along with a small amount of aldehyde **3a**.[16] Screening various Grubbs catalysts revealed that other Grubbs catalysts resulted in decreased yields of **2a** and lengthened the reaction time (Entries 2–5). In the absence of the catalyst, no desired nitrile product **2a** was obtained, and the recovery of 96% of the starting compound (**1a**) (Entry 6) indicated that no background oxidation had occurred. Of the solvents tested, toluene was determined to be optimal for the prevailing reaction (Entries 7–10). When the reaction was conducted in refluxing toluene, substantial acceleration of reaction rate and an improvement in the product yield were observed (Entry 11). The catalyst loading could be reduced to 2 mol% without any loss in product yield (Entry 13). In a gram-scale reaction, **2a** was obtained in satisfactory yield after a prolonged reaction time (Entry 14).

Table 1. Optimization of the Reaction Conditions.



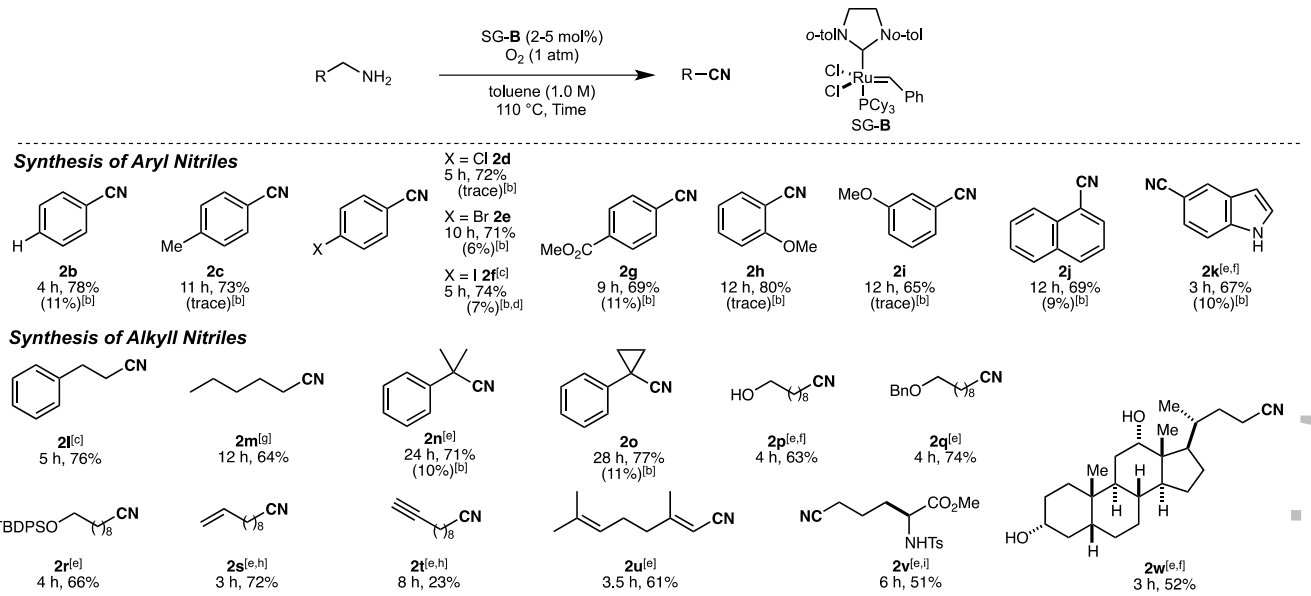
Entry[a]	Catalysts	x	Solvent	Time (h)	Yield (%) 2a	3a
1	SG-**B**	5	EtOAc	5	76	3
2	Grubbs 1st	5	EtOAc	9	67	4
3	Grubbs 2nd	5	EtOAc	5	73	5
4	Hoveyda-Grubbs 2nd	5	EtOAc	23	55	10
5	Schrodi-Grubbs **A**	5	EtOAc	5	59	2
6[b]	-	-	EtOAc	48	0	0
7	SG-**B**	5	dioxane	4	61	3
8	SG-**B**	5	DCE	6	57	10
9	SG-**B**	5	EtOH	9	59	11
10	SG-**B**	5	toluene	4	69	4
11[c]	SG-**B**	5	toluene	0.67	82	4
12[c]	SG-**B**	3	toluene	2.5	85	3
13[c]	SG-**B**	2	toluene	6	84	10
14[c,d]	SG-**B**	2	toluene	24	81	10

[a]All reactions proceeded in 100% conversion of the starting materials [b]**1a** was recovered in 96% yield. [c]This reaction temperature was 110 °C. [d]The reaction was conducted on a gram scale.



Next, the substrate scope was investigated (Table 2). Reactions of benzylamines possessing various substituents at the *para*-position, such as methyl, chloro, bromo, iodo, or methoxy carbonyl groups, uneventfully gave nitriles **2b**–**2g**. Benzylamines with an *ortho*- or a *meta*-methoxy phenyl group also provided the corresponding nitriles **2h** and **2i** in high yields. This reaction was also compatible with 1-naphtyl amine (**1j**) and 5-indolylmethylene amine (**1k**). In addition to this series of benzylamines, simple primary amines and sterically hindered primary amines subjected to these reaction conditions afforded the corresponding nitriles **2l**–**2o** in high yields. Under these reaction conditions, the synthesis of cyclopropyl nitrile **2o** circumvented the formation of the radical intermediate species. This reaction was extremely compatible with a variety of functional groups, including free hydroxy, benzyl ethers, and siloxy moieties **2p**–**2r**. In the presence of a terminal alkene **1s** or alkyne **1t**, prior treatment of the Grubbs catalyst with molecular oxygen was required. The unexpected low yield of **2t** would be possibly due to, side reaction associated with activation of alkyne moiety with Ru complex such as polymerization or

Table 2. Substrate Scope of Nitrile Synthesis by Aerobic Oxidation of Primary Amines.[a]

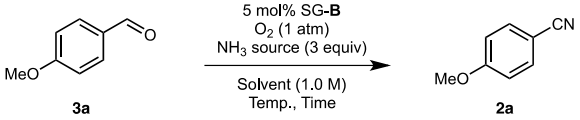


[a]The reaction was conducted with amines (0.50 mmol), SG-**B** (2.0 mol%) in toluene (1.0 M) at 110 °C. All reactions proceeded in 100% conversion of the starting materials. [b]The yield was the corresponding aldehyde. [c]The catalyst loading was 3 mol%. [d]NMR yield. [e]The catalyst loading was 5 mol%. [f]The reaction was conducted in DMF (1.0 M) at 120 °C. [g]GC yield. [h]Before the addition of the substrate, the reaction mixture was stirred for 30 min. The catalyst loading was 3 mol%. [i]Toluene (0.5 M) was used as the solvent.

decomposition. Finally, this reaction was compatible with multifunctionality compounds such as geranylamine, lysine, and deoxycholic acid derivatives, resulting in nitriles **2u**[6c, 6e, 7a, 7b], **2v**[3f] and **2w** in good yields. No corresponding isomerized product was detected in addition to **2u**. In these substrate scope, a small amount of the corresponding aldehyde of the primary amine substrate possessing a proton at the β position was obtained.

After establishing the versatile synthesis of nitriles via the catalytic aerobic and sequential oxidation of primary amines under mild conditions, our attention was focused on developing an alternative method. We theorized that taking advantage of the high catalytic activity and the functional group compatibility of SG-**B** would result in the desired nitrile products, which could be accomplished via a one-pot imine synthesis protocol through the condensation of aldehyde and an ammonia equivalent, followed by an oxidation reaction. This theory was tested by treating *p*-anisaldehyde (**3a**) with 5 mol% SG-**B** and ammonium acetate (3 equiv.) in refluxing toluene in an oxygen atmosphere (Table 2). The expected reaction proceeded smoothly to afford the desired nitrile **2a** in 85% yield (Entry 1). The yield was slightly improved to 90% when the reaction was conducted in xylene at 130 °C (Entry 3). Other ammonium sources significantly decreased the yield of **2a** (Entries 4–7). The amount of ammonium acetate could be reduced to two equivalents without any loss in product yield (Entry 8).

Table 3. Optimization of the Reaction Conditions.

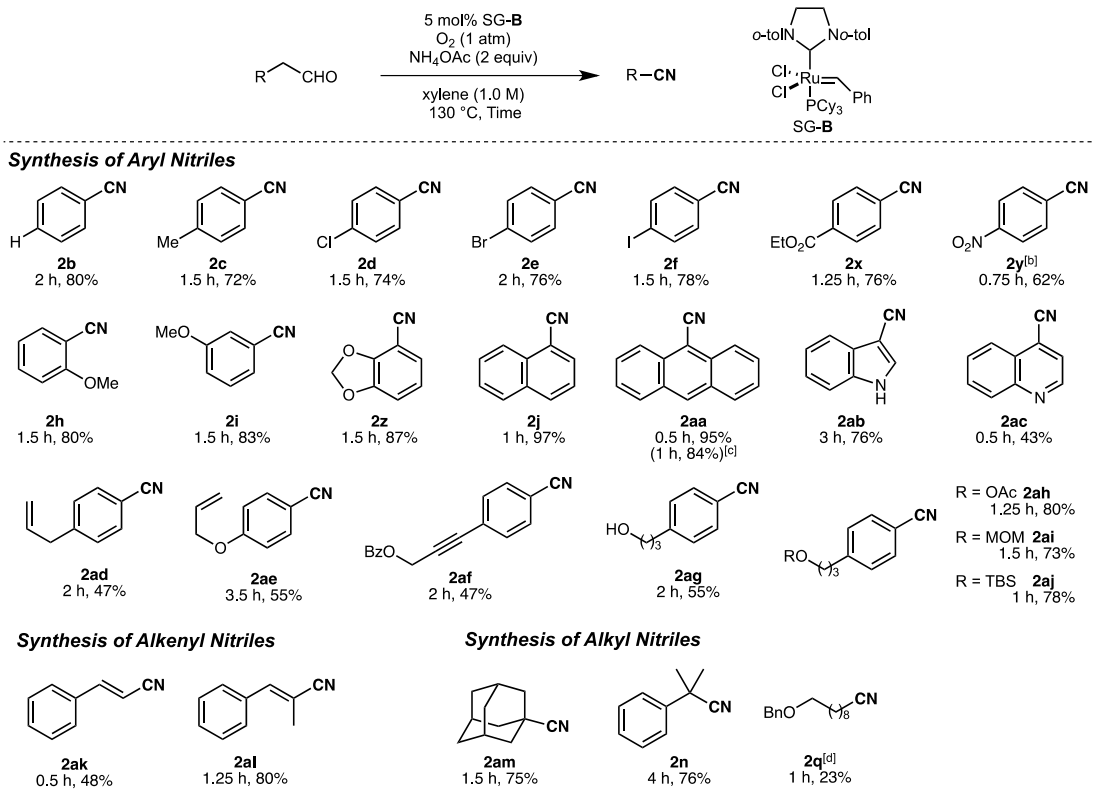


Entry	NH_3 source	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	NH_4OAc	toluene	110	2	85
2	NH_4OAc	xylene	110	3	78
3	NH_4OAc	xylene	130	1.5	90
4	NH_4Cl	xylene	130	24	15
5	NH_4HCO_2	xylene	130	24	32
6	$NH_4H_2PO_4$	xylene	130	24	10
7	aq. NH_3	xylene	130	24	12
8 [a]	NH_4OAc	xylene	130	1.25	90

[a] 2 equivalent NH_4OAc was used.

Encouraged by these results, we then focused on establishing the substrate scope of the aldehyde starting material (Figure 2). *Para*-substituted benzaldehydes bearing both electron-donating and withdrawing groups such as methyl, chloro, bromo, and iodo moieties as well as ethoxycarbonyl and nitro groups, resulted in the corresponding nitriles **2b**–**2f**, **2x**, and **2y** in good to high yields. Reactions using other aromatic aldehydes, including *ortho*- and *meta*-disubstituted benzaldehyde, 1-naphthylaldehyde, 9-anthraldehyde, 3-formylindole, and 4-formylquinoline, proceeded uneventfully to afford **2h**

Table 4. Substrate Scope of Nitrile Synthesis from Aldehydes and Ammonium Salt.[a]



[a]The reaction was conducted using aldehydes (0.50 mmol), Grubbs catalyst (5.0 mol%), NH_4OAc (2 equiv.) in xylene (1.0 M) at 130 °C. All reactions proceeded in 100% conversion of the starting materials. [b]The reaction temperature was 110 °C. [c]A gram-scale reaction. [d] The catalyst loading was 10 mol%.

2i, **2z**, **2j**, **2aa**, **2ab and 2ac** respectively. The scalability of the reaction was determined by conducting a gram-scale reaction using 9-anthraldehyde to obtain **2aa** in comparable yields. Reactions that would usually be impaired under conventional transition metal-catalyzed conditions due to the presence of functional groups such as allyl, allyl ether, and propargyl alcohol derivatives were well tolerated; here, the corresponding nitriles, **2ad**, **2ae**, and **2af**, were obtained in good yields without isomerization. Furthermore, nucleophile-, acid-, or oxidant-sensitive functional groups, such as hydroxyl, acetoxy, methoxymethyl, and siloxy groups, were compatible with the optimized conditions. The expected nitriles, **2ag**–**2aj**, were obtained with these functional groups remaining untouched. In addition to aromatic aldehydes, alkenyl aldehydes proved to be suitable substrates. Cinnamaldehyde and α-methyl *trans*-cinnamaldehyde gave the α,β-unsaturated nitriles **2ak** and **2al** in good to high yields. Regarding aliphatic aldehydes, sterically hindered α,α-disubstituted aldehydes gave the desired products **2am** and **2n** in high yields. However, synthesis using a simple linear aldehyde produced **2q** in low yields, possibly due to imine–enamine tautomerization, ultimately resulting in the decomposition of the imine intermediate.

As shown in the above experiments, the nitrile synthesis by aerobic oxidation with Grubbs catalyst demonstrated a wide range of substrate scope. The established conditions tolerate a number of functional groups that are sometimes difficult to apply under other the conventional conditions. For examples, a free hydroxyl group competes for amine oxidation and propargyl benzoate is easily formed π-complex with transition metal catalysts. Moreover, advantage of this oxidation conditions is compatibility of pharmaceutically important and easily oxidizable π-excessive and π-deficient *N*-containing heterocycles such as indole and quinoline.

In summary, two different routes for the synthesis of nitrile were developed based on catalytic aerobic oxidation with Grubbs catalyst. These reaction conditions were exceptionally mild, environmentally benign, and generally tolerated a variety of functional groups. Since this research has highlighted a new function of Grubbs catalyst, further development of the catalyst is expected in the future.

Experimental Section

General Procedure of Nitrile Synthesis with Primary Amines

A 10-mL screw cap test tube equipped with a Teflon-coated magnetic stirring bar containing primary amine **1a** (75.8 mg, 0.553 mmol), which was obtained from commercial supplier and used with purification by distillation under reduced pressure, toluene (0.55 mL), and

SG-**B** (8.8 mg, 11 µmol) was charged with oxygen gas (1 atm) at room temperature and sealed with a Teflon liner screw cap. The resulting mixture was stirred at 110 °C and then the color of solution turned black. After stirring for 6 hours, the reaction mixture was cooled to room temperature and purified by silica gel column chromatography (pentanes/CH_2Cl_2 = 1:1) to afford nitrile **2a** (61.6 mg, 0.463 mmol, 84%) as a white solid and aldehyde **3a** (7.4 mg, 54 µmol, 10%) as a color less oil. Nitrile **2a**; Mp = 59–60 °C (hexanes); R_f = 0.23 (hexanes/CH_2Cl_2 = 1:1); IR (ATR, cm^{-1}): 2224, 1605, 1508, 1258, 1172, 1023, 843; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* = 8.4 Hz), 6.95 (2H, d, *J* = 8.4 Hz), 3.86 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.4, 133.4, 118.7, 114.3, 103.2, 55.1; HRMS (ESI) calcd. for C_8H_8NO $[M+H]^+$, 134.0600, found 134.0594.

General Procedure of Nitrile Synthesis with Aldehydes
A sealed tube equipped with a magnetic stirring bar containing 4-methoxybenzaldehyde (**3a**) (66.0 mg, 0.485 mmol), which was obtained from commercial supplier and used with purification by distillation under reduced pressure, ammonium acetate (74.6 mg, 0.968 mmol), xylene (0.49 mL) and SG-**B** (19.1 mg, 24.1 µmol) was charged with oxygen gas (1 atm) at room temperature and sealed with a screw cap. The resulting mixture was heated at 130 °C and then the color of solution turned black. After stirring for 2 hours, the reaction mixture was cooled to room temperature and purified by silica gel column chromatography (hexanes/CH_2Cl_2 = 1:1) to afford **2a** (56.5 mg, 0.424 mmol, 88%) as a pale yellow solid; Mp = 56–58 °C (CH_2Cl_2); R_f = 0.63 (CH_2Cl_2 only); IR (neat, cm^{-1}): 2936, 2917, 2846, 2224, 1603, 1498, 1172, 1024, 835, 683; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (2H, d, *J* = 8.8 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 133.9, 119.2, 114.7, 103.9, 55.5; HRMS (ESI) calcd. for C_8H_8NO $[M+H]^+$, 134.0600, found 134.0606.

Acknowledgements

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[15] The proposed reaction mechanism of this nitrile synthesis with Grubbs catalyst is considered to be similar to the mechanism proposed by Mizuno *et al*.[7b] According to our recently reported research,[12] the CO-Ru complex derived from SG-B under oxygen would work as the activate species. The generation of CO-Ru complex was confirmed by the IR measurement of the crude products after the reaction.

[16] Aldehyde was possibly generated via a direct hydrolysis of the generated imine intermediate or aqueous treatment of the imine byproduct derived from condensation between the oxidized imine intermediate and the primary amine.

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