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An efficient transformation of primary halides into nitriles through palladium-catalyzed hydrogen transfer reaction[†]

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Two-step one-pot transformation of primary halides into corresponding nitriles is successfully achieved. Nucleophilic substitution of primary halides with sodium azide and subsequent palladium-catalyzed hydrogen transfer proceed smoothly in the ¹⁰ presence of the sterically bulky ligand dicyclohexyl(2',4',6'triisopropylbiphenyl-2-yl)phosphine (XPhos) in acetone to produce nitriles in satisfactory to good yields.

Nitrile groups can be easily converted into other functional groups, such as amines, amides, and acids.¹ Therefore, nitriles are ¹⁵ frequently utilized as versatile and key synthetic intermediates to prepare several natural products, bioactive compounds, and polymers.² Over the past few decades, three main synthetic methods have been developed for nitrile synthesis. The first method involves direct cyanation of aryl diazonium salts,³ aryl ²⁰ halides,^{4.5} and some appropriate substrates via C–H bond functionalization.⁶ The second method involves aldoxime⁷ and

- functionalization.⁶ The second method involves aldoxime' and amide⁸ dehydration. The third method involves oxidation⁹ or dehydrogenation¹⁰ of primary azides¹¹. Among these methods, the third method has recently emerged as an extremely powerful ²⁵ tool for nitrile synthesis. However, oxidation of primary azides usually requires the use of stoichiometric amounts of strong oxidants, such as bromine trifluoride (BrF₃), 2,3-dichloro-5,6dicyano-1,4-benzoquinone (DDQ), and *tert*-butyl hydroperoxide (TBHP). Dehydrogenation of primary azides must employ a
- ³⁰ valuable hydrogen acceptor, such as diphenylethyne or styrene (Scheme 1).

Previous work

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Scheme 1. Transformation of primary azides to nitriles.

Over the course of our continuous research on the development of efficient methods for nitrile synthesis,⁵ⁿ we determined that nitriles can be readily obtained from palladium-catalyzed hydrogen transfer of primary azides in the presence of acetone as a solvent and hydrogen acceptor (Scheme 2). However, we failed to obtain the desired nitrile products from one-pot reaction of ⁴⁰ primary halides with sodium azide (NaN₃) under identical reaction conditions, and the nucleophilic substitution reaction products were collected in nearly quantitative yields. These results indicate that the azido anion (N₃ [¬]), similar to the cyano anion (CN [¬]),¹² also poisons the palladium-catalyzed hydrogen transfer.



Scheme 2. Palladium-catalyzed hydrogen transfer reaction of 1-(azidomethyl)naphthalene.

- ⁵⁰ Organic azides are generally unstable toward heating, and, in particular, organic azides with low molecular weights are dangerous and difficult to handle.¹³ Therefore, generation of organic azides in situ for one-pot synthesis of nitriles is an important requirement.
- Palladium-catalyzed cyanation of aryl bromides with $K_4[Fe(CN)_6]$ was found to proceed smoothly in the presence of a sterically bulky phosphine ligand in previous studies.⁵ⁿ Based on previous findings, several sterically bulky phosphine ligands were during palladium-catalyzed one-pot initially examined 60 transformation of 1-(chloromethyl)naphthalene (1a) into the corresponding nitrile by using acetone as a solvent and hydrogen acceptor, the results of which are shown in Table 1. Pd(OAc)₂ was first used as a precatalyst for ligand screening. As expected, the desired nitrile product could not be obtained without the 65 phosphine ligand. Only the nucleophilic substitution reaction product, 1-(azidomethyl)naphthalene (3), was collected in 86% yield (entry 1). The desired product, 1-naphthonitrile (2a), was obtained in 12% and 31% yields when sterically bulky phosphine ligands L1 and L2 were respectively utilized (entries 2 and 3).¹⁴

Although the yields obtained were unsatisfactory, these results suggest that using an appropriate sterically bulky phosphine ligand may successfully achieve nitrile product in satisfactory yield. The commercially available sterically bulky phosphine s ligands **L3–L6** were then examined to improve the yield of nitrile product **2a** (entries 4–7). Among ligands **L3–L6 L6** (XPhos)

- product **2a** (entries 4–7). Among ligands **L3–L6**, **L6** (XPhos) proved to be the most effective ligand for this type of palladiumcatalyzed transformation. The yield of **2a** increased to 72% by using ligand **L6**. A decrease in yield was observed when PdCl₂ 10 was used as the precatalyst instead of Pd(OAc)₂ in the presence
- of **L6** (entry 8, 66% yield). The effects of catalyst loading and reaction temperature on the yield of **2a** were investigated with Pd(OAc)₂ as the precatalyst in the presence of **L6**, and results showed that the target reaction can proceed smoothly with 2 ¹⁵ mol% of Pd(OAc)₂ at 80 °C to furnish product **2a** in higher yields (entry 7 vs. entries 9 and 10; entry 7 vs. entries 11 and 12). Only the azide product was isolated in 88% yield in the absence of the palladium catalyst (entry 13). Therefore, subsequent two-step one-pot transformation reactions of primary halides into the ²⁰ corresponding nitriles were performed in the presence of Pd(OAc)₂ as the precatalyst using **L6** as the ligand in acetone (3 mL) at 80 °C under a N₂ atmosphere.

Table 1 Reaction condition screening

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	CI + NaN ₃	cat. Pd (2 m ligand (4 mo acetone, 80 °	ol%) CN C, 6 h	+ N ₃
1a			2a	3
Entry	Catalyst	Ligand	2a : Yield (%) ^b	3 : Yield $(\%)^{b}$
1	$Pd(OAc)_2$	none	0	86
2	$Pd(OAc)_2$	L1	12	62
3	$Pd(OAc)_2$	L2	31	38
4	$Pd(OAc)_2$	L3	61	<5
5	$Pd(OAc)_2$	L4	60	<5
6	$Pd(OAc)_2$	L5	65	0
7	$Pd(OAc)_2$	L6	72	0
8	PdCl ₂	L6	66	0
9^c	$Pd(OAc)_2$	L6	52	23
10^d	$Pd(OAc)_2$	L6	71	0
11^e	$Pd(OAc)_2$	L6	70	0
12^{f}	$Pd(OAc)_2$	L6	64	0
13	none	L6	0	88
a				

²⁵ ^a Reaction conditions: 1-(chloromethyl)naphthalene (**1a**, 0.5 mmol, 88.3 mg), NaN₃ (0.55 mmol, 35.8 mg), Pd(OAc)₂ (2 mol%, 2.2 mg), PdCl₂ (2 mol%, 1.8 mg) and ligand (4 mol%) in acetone (3 mL) under a N₂ atmosphere for 6 h. ^b Isolated yield. ^c 1 mol% Pd(OAc)₂ and 2 mol% **L6** were used. ^d 3 mol% Pd(OAc)₂ and 6 mol% **L6** were used. ^e The reaction ³⁰ was performed at 70 °C. ^f The reaction was performed at 90 °C.



The scope of benzyl chloride substrates was then determined under optimized reaction conditions, and the results are **Table 2** One-pot transformation of benzyl chlorides into nitriles through35 palladium-catalyzed hydrogen transfer reaction^a

		aN ₃	Pd(OAc ligannd I	$R = \frac{1}{1}$	CN	
	1b-1s		acetone, 80 °C 2b-2s		s	
Entry	Chloride 1		t (h)	Nitrile 2		Yield
1	CI	1b	6	CN	2b	80 ^c
2	Me	1c	6	CN	2c	84
3	MeO	1d	6	MeO	2d	83
4	MeO	1e	6	MeO	2e	81
5	MeO OMe	1f	12		2f	75
6	BnO	1g	6	BnO	2g	88
7	F	1h	6	F	2h	82
8	CI	1i	6	CI	2i	79
9	CI CI	1j	12	CI CI	2j	60
10	O ₂ N CI	1k	24	O ₂ N CN	2k	65
11	онс	11	12	OHC	21	38 ^{<i>d</i>}
12	Ph	1m	6	Ph	2m	82
13	CI	1n	6	CN	2n	70
14	CI	10	6	CN	20	76
15	CI	1p	6		2p	78
16	CI	1q	12	CN N	2q	70
17	CI S	1r	12	CN	2r	72
18	CI	1s	12	CN	2s	70

^{*a*} Reaction conditions: benzyl chlorides (**1b–1s**, 0.5 mmol), NaN₃ (0.55 mmol, 35.8 mg), Pd(OAc)₂ (2 mol%, 2.2 mg) and **L6** (4 mol%, 9.5 mg) in acetone (3 mL) at 80 °C under a N₂ atmosphere. ^{*b*} Isolated yield. ^{*c*} GC ⁴⁰ yield due to product volatility; *n*-dodecane was used as an internal standard. ^{*d*} The aldol condensation reaction of **2l** with acetone was took place to produce (*E*)-4-(3-oxobut-1-en-1-yl)benzonitrile (**4**) in 20 % yield.

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summarized in Table 2. Transformation of benzyl chloride (1b), which is the simplest benzyl chloride substrate, also proceeded smoothly and was completed within 6 h. Benzonitrile (2b) was obtained in 80% yield (entry 1). The reactions of benzyl chloride 5 substrates 1c-1e and 1g-1i bearing an electron-donating group (Me, MeO, and BnO) or an electron-withdrawing group (F and Cl) at the para- or meta-positions, respectively, could also be completed within 6 h to obtain the desired nitrile products in good yields (entries 2-4 and entries 6-8; 79%-88%). Benzyl 10 chloride substrates 1f and 1j exhibited relatively low reactivity as a result of the steric effect of ortho-substituents (MeO or Cl); the reactions of these substrates were completed under prolonged reaction times (12 h). Nitrile products 2f and 2j were obtained in relatively low yields (entries 5 and 9; 75% and 60%, respectively). 15 The Cl atom linked to the aromatic ring was notably maintained in the structures of products 2i and 2j under the reaction conditions; this observation suggests that further manipulation may produce useful compounds. A moderate yield (65%) of para-nitrobenzonitrile (2k) was observed in the reaction of para-20 nitrobenzyl chloride (1k) with NaN₃ (entry 10). The desired product, para-formylbenzonitrile (21), was isolated in 38% yield along with an aldol condensation product 4 in 20% yield from the reaction of para-formylbenzyl chloride (11) with NaN₃ (entry 11). These results indicate that the electronic properties of substituents 25 linked to the benzene ring, except those of NO₂ and CHO, do not influence the reactivity of benzyl chloride substrates. Interestingly, the succeeding investigation showed that benzyl chloride substrates 1m and 1n derived from 1,2-diphenylethyne and styrene, which were employed as hydrogen acceptors in 30 previous literatures,¹⁰ could be utilized in this type of

- transformation. C–C triple and double bonds were not changed under the reaction conditions (entries 12 and 13; 82% and 70% yields). To explore the reaction scope further, fused aromatic ring-containing substrates were then examined under optimized ³⁵ reaction conditions. The reactions of 2-
- (chloromethyl)naphthalene (10) and 9-(chloromethyl)phenanthrene (1p) proceeded smoothly to obtain the corresponding products 20 and 2p in 76% and 78% yields, respectively (entries 14 and 15). *N*- or *S*-containing heterocycleacentaining substates such as 2 (chloromethyl)puriding (1c) and
- ⁴⁰ containing substrates such as 3-(chloromethyl)pyridine (**1q**) and 3-(chloromethyl)thiophene (**1r**) were also successfully used in this type of transformation. The corresponding products **2q** and **2r** were obtained in 70% and 72% yields, respectively (entries 16 and 17). Finally, cinnamyl chloride (**1s**) was tested, and the
- ⁴⁵ corresponding nitrile product **2s** was isolated in 70% yield (entry 18).

The scope of this type of transformation was further demonstrated by using aliphatic primary halides. Aliphatic primary bromides were employed instead of chlorides to expand 50 the substrate scope because chloride substrates exhibit low

- reactivity in the first step of nucleophilic substitution. The results are shown in Table 3. One-pot transformations of aliphatic primary bromides, namely, (2-bromoethyl)benzene (1t), (4bromobutoxy)benzene (1u), (6-bromohexyloxy)benzene (1v), and
- ⁵⁵ 2-(4-bromobutyl)isoindoline-1,3-dione (1w), into the corresponding nitriles were also successfully achieved under optimized reaction conditions. Nitriles 2t-2w were isolated in 65%-84% yields.

 Table 3 One-pot transformation of aliphatic primary bromides into

 60 nitriles through palladium-catalyzed hydrogen transfer reaction^{a,b}



^{*a*} Reaction conditions: aliphatic bromides (**1t–1w**, 0.5 mmol), NaN₃ (0.55 mmol, 35.8 mg), Pd(OAc)₂ (2 mol%, 2.2 mg) and **L6** (4 mol%, 9.5 mg) in acetone (3 mL) at 80 °C under a N₂ atmosphere. ^{*b*} Isolated yield.

To prove the practicality of the present method in nitrile synthesis, gram-scale synthesis of nitrile **2a** was performed, and the result is shown in Scheme 3. When 1.06 g of **1a** and 1.1 equivalents of NaN₃ were utilized, 0.65 g of the nitrile product **2a**⁷⁰ was obtained in 71% yield. This yield is comparable with that obtained in small-scale experiments.



Scheme 3. Gram-scale synthesis of 1-naphthonitrile (2a).

A plausible mechanism for primary halide transformation into ⁷⁵ the corresponding nitriles is shown in Scheme 4. The Pd(II) species would react with the benzyl azide derived from the nucleophilic substitution reaction of benzyl chloride (**1b**) with NaN₃ to produce palladium benzylideneamide intermediate A along with nitrogen and acetic acid (HOAc).¹⁵ β –H elimination ⁸⁰ would then occur to produce the desired product, benzonitrile (**2b**), and palladium hydride intermediate B. Hydropalladation of acetone with intermediate B would occur to produce palladium alkoxide intermediate C, which subsequently undergoes hydrolysis with the HOAc generated in the initial step of ⁸⁵ intermediate A formation to produce isopropyl alcohol¹⁶ and regenerate the Pd(II) species.



Scheme 4. Proposed mechanism for the one-pot transformation of primary halides into nitriles.

In summary, an efficient method for one-pot nitrile synthesis has been developed under mild conditions with affordable and simple starting materials. In this novel protocol, inexpensive and widely available acetone functions both as a solvent and a

- ⁵ hydrogen acceptor. The poisoning of palladdium catalyst by the azido anion (N3⁻) was observed in mentioned results. The wide availability of the starting materials, mild reaction conditions, and experimental simplicity demonstrate that the present methodology is highly useful in organic chemistry.
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- † Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for isolated compounds. See DOI: 10.1039/b000000x/
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