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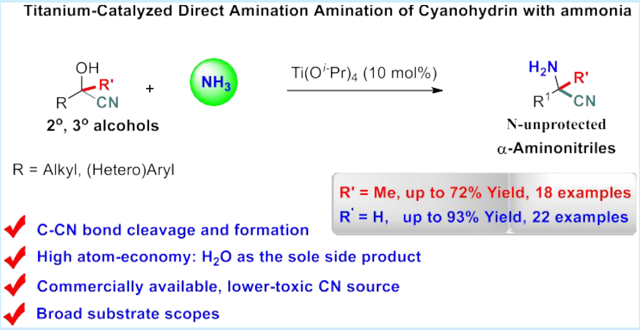
Titanium-Catalyzed Cyano-Borrowing Reaction for the Direct Amination of Cyanohydrins with Ammonia

Qing-Hua Li,*,† Zhao-Feng Li,† Jing Tao,† Wan-Fang Li,‡ Li-Qing Ren,† Qian Li,† Yun-Gui Peng,† and Tang-Lin Liu*,†

†School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China
‡College of Science, University of Shanghai for Science and Technology, Shanghai 200093, China

Supporting Information

ABSTRACT: α-Aminonitrile was an important building block in natural products and key intermedia in organic chemistry. Herein, the direct amination of cyanohydrins with the partner of ammonia to synthesis N-unprotected α-aminonitriles is developed. The reaction proceeds via titanium-catalyzed cyano-borrowing reaction, which features high atom economy and simple operation. A broad range of ketone or aldehyde cyanohydrins was tolerated with ammonia, and the N-unprotected α-aminonitriles were synthesis with moderate to high yields under mild reaction conditions.



As an atom-economic nitrogen source in organic synthesis, ammonia is the simplest and useful molecule.[1] Amination of alcohols with the partner of ammonia represents an important direct procedure to synthesis primary amines.[2] Conventional procedure to transfer alcohols to amines involves oxidation, imine formation, and reduction or reductive amination, which need an excess amount of oxidants and reductants, and meanwhile, a large amount of wastes could be formed (Scheme 1a).[3] A direct and atom-economical process is transition-metal catalyzed hydrogen borrowing reaction; in this transformation, water is the sole byproduct.[4] In 2008, Milstein reported the first amination of primary alcohols with the partner of ammonia catalyzed by Ru/PNP pincer complex.[5] The pioneering work of amination of secondary alcohols with ammonia was developed by Vogt[6] and Beller[7] using ruthenium[8] as the catalysts, respectively. Other procedures on the amination of alcohols with the partner of ammonia via hydrogen borrowing were also explored.[9] The major challenge of the amination of alcohols with ammonia is the lack of selectivity. However, we notice that the hydrogen borrowing reaction just aminates the primary and secondary alcohols with ammonia, and we wonder whether the tertiary alcohols with a cyano group could be aminated by ammonia with the analogous mechanism of hydrogen borrowing to produce the primary amines with a quaternary carbon center.

α-Aminonitriles are important structural building blocks of pharmacy and drugs.[10] The Strecker reaction, the hydrocyanation of imines, was the most efficiently procedure to access the N-protected α-aminonitriles.[11] Deprotection is necessary to prepare the N-unprotected α-aminonitriles containing free pri-mary amines, which could produce lots of byproducts and lower the atom-economy of the transformation. However, the Strecker reaction of NH-imine to synthesis of N-unprotected α-aminonitriles is rare.[12] Other procedures to deliver N-protected α-aminonitriles were also developed: (a) α−C-H cyanation of primary amines[13] and (b) electrophilc amination of stabilized carbanions.[14] Herein, we developed the first amination of ketone cyanohydrins (3° alcohols) with the partner of ammonia[15] via titanium-catalyzed cyano-borrowing reaction. Additionally, the aldehyde cyanohydrins (2° alcohols) could be aminated by ammonia under mild reaction conditions as well.

On the basis of our ongoing research on the cyano-borrowing reaction,[16] we selected acetophenone cyanohydrin **1a** as the starting material with the partner of ammonia (7 M in methanol). In the presence of $Ti(O^iPr)_4$, the amination was carried out in the media of toluene, and the corresponding **2a** was obtained with 25% yield (Table 1, entry 1). We used TBME instead and delivered the product with 41% yield (Table 1, entry 2), and other solvents, such as THF, CH_3CN, DCM, CPME, and MeOH, did not improve the reactivity of this transformation (Table 1, entries 3−7 vs 2). Benzoic acid was added as the additive, and 64% of **2a** was obtained. Other carbonyl acids, such as *p*-nitrobenzoic acid, *p*-methoxylbenzoic acid, and acetic acid, gave moderate yields (40−54%) (Table 1, entries 9−11). When the reaction temperature was increased to 80 °C, the reactivity of this cyano-borrowing reaction was almost the same as at 60 °C (Table 1, entry 12), and a lower yield was obtained while the reaction was carried out at 40 °C (Table 1, entry 13). The optimized condition was the ketone

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Scheme 1. Amination of Alcohols Using Ammonia

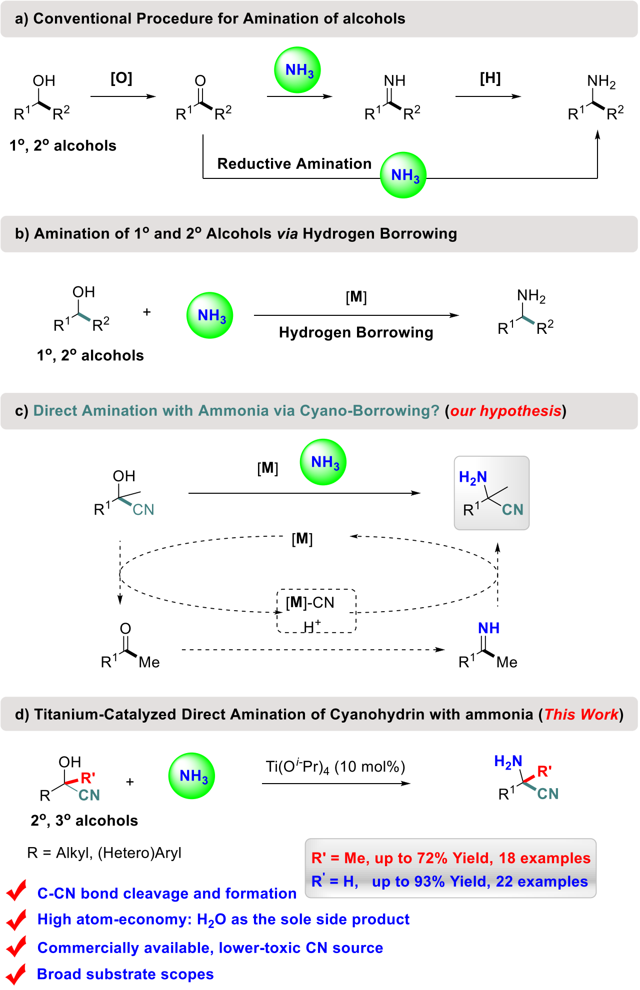
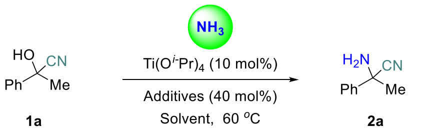


Table 1. Optimization of Reaction Conditions[a]



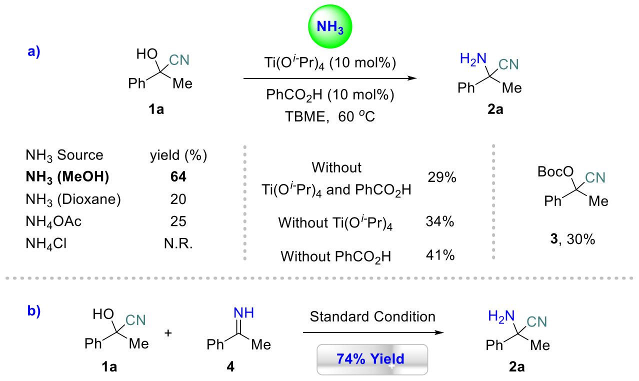
entry	solvent	additives	yield (%)
1	toluene		25
2	TBME		41
3	THF		trace
4	CH_3CN		30
5	DCM		21
6	CPME		trace
7	MeOH		trace
8	**TBME**	**$PhCO_2H$**	**64**
9	TBME	p-$NO_2C_6H_4CO_2H$	54
10	TBME	p-$MeOC_6H_4CO_2H$	51
11	TBME	AcOH	40
12[b]	TBME	$PhCO_2H$	63
13[c]	TBME	$PhCO_2H$	42

[a] Reaction was carried out with 0.4 mmol of **1**, 0.2 mL of ammonia (7 M in methol), and 10 mol % Ti(O^{i}Pr)$_4$, in 0.8 mL of solvent at 60 °C for 18 h. The yields are isolated yields. [b] Reaction was carried out at 80 °C. [c] Reaction was carried out at 40 °C.

cyanohydrins reacted with 3.5 equipment of ammonia in methanol in the presence of 10 mol % of Ti(O^{i}Pr)$_4$ and 40 mol % of benzoic acid with TBME as the reaction media at 60 °C.

Then we turned our attention to other ammonia sources, such as ammonia in dioxane and ammonium acetate, and found that these ammonias were also compatible in this cyano-borrowing reaction but delivered the target compound with low isolated yields (20% and 25%) (Scheme 2a). The inorganic salt, ammonium chloride, was found not suitable for this transformation. When this reaction was carried out without titanium catalyst and benzoic acid, the design product was obtained with 29% yield, which indicated that the catalyst was indispensable to improve reactivity. Meanwhile, the result suggested that this transformation may undergo nucleophilic substitution pathway; however, as Boc (*tert*-Butyloxy carbonyl) protected acetophenone cyanohydrin **3**, the more reactivity substrate in nucleophilic substitution reaction did not improve the reactivity. The free imine **4** was subjected to reaction with acetophenone cyanohydrin **1a** under standard reaction condition, and **2a** was obtained with 74% yield (Scheme 2b), indicating cleavage of the C−CN bond instead of the C−O bond of ketone cyanohydrins in this titanium-catalyzed transformation.

Scheme 2. Control Experiments

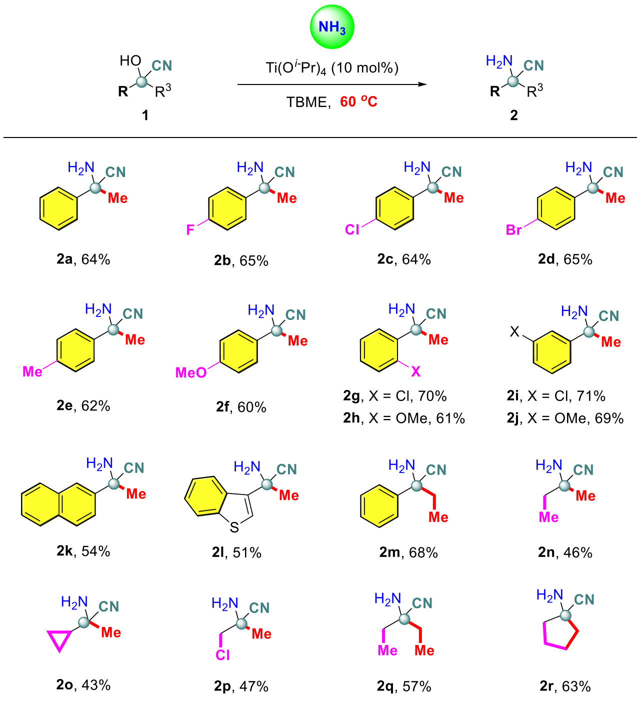


NH_3 Source	yield (%)
NH_3 (MeOH)	**64**
NH_3 (Dioxane)	20
NH_4OAc	25
NH_4Cl	N.R.

Without Ti(O^{i}Pr)$_4$ and $PhCO_2H$	29%
Without Ti(O^{i}Pr)$_4$	34%
Without $PhCO_2H$	41%

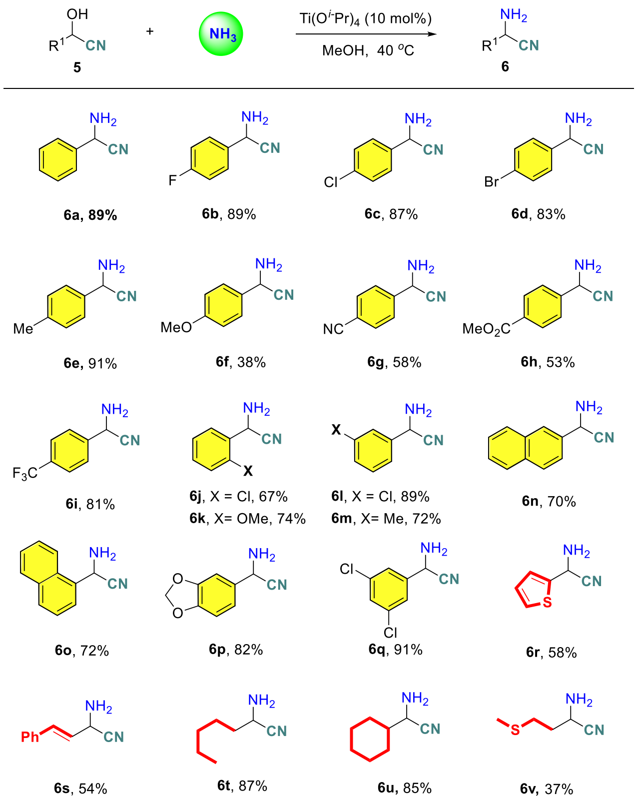
Having identified optimal conditions, we then evaluated the substrate scope of ketone cyanohydrins with the partner of ammonia in methanol on 0.4 mmol scale, and the results are listed in Scheme 3. Ketone cyanohydrins bearing both electron-donating, electron-deficient and electron-neutral groups on the aromatic moiety were well tolerated and delivered the corresponding unprotected α-aminonitriles with moderate to good isolated yields (**2b**−**2k**). Substitution on the phenyl ring did not affect the reaction of titanium-catalyzed cyano-borrowing (**2g**−**2j** vs **2a**−**2f**). Nevertheless, heterocycle-containing such as benzo[*b*]thiophen-3-yl underwent direct amination to furnish the corresponding α-aminonitrile (**2l**) in synthetically useful yield. The reaction of propiophenone cyanohydrin gave the desired product **2m** bearing ethyl substituent in 68% yield. In general, aliphatic substituted cyanohydrins also proved suitable substrates (**2n**−**2r**). The methyl ketone cyanohydrins bearing ethyl, cyclopropyl, and chloromethyl (**2p**) were applicable in this cyano-borrowing reaction (**2n**−**2p**). Even the cyanohydrins derived from the symmetric ketone, such as 3-pentanone (**2q**) and cyclopentanone (**2r**), performed well to deliver the corresponding

Scheme 3. Scope of Ketone Cyanohydrins for Cyano-Borrowing Reaction[a]



[a] Reaction was carried out with 0.4 mmol of 1, 0.2 mL of ammonia (7M in methanol), 40 mol % $PhCO_2H$, and 10 mol % $Ti(O^iPr)_4$, in 0.8 mL of TBME at 40 °C for 18 h. The yields are isolated yields.

Scheme 4. Scope of Aldehyde Cyanohydrins for Cyano-Borrowing Reaction[a]



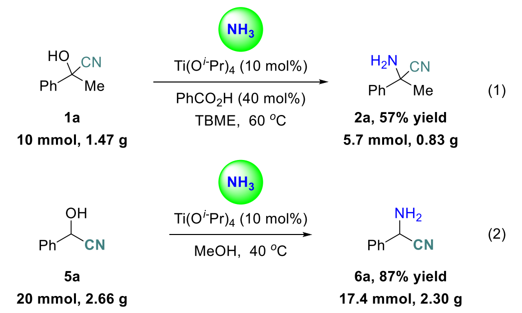
[a] Reaction was carried out with 0.4 mmol of 1, 0.2 mL of ammonia (7M in methol), and 10 mol % $Ti(O^iPr)_4$, in 0.8 mL of MeOH at 40 °C for 18 h. The yields are isolated yields.

quaternary center-containing α-aminonirtiles in moderate yield (57% and 63%).

Subsequently, this titanium-catalyzed cyano-borrowing reaction was also applicable to aldehyde cyanohydrins with the partner of ammonia in methanol. To our surprise, the aldehyde cyanohydrins could be transferred to the corresponding α-aminonitriles at the absence of benzoic acid in methanol, and the reaction temperature could be lower to 40 °C without any loss of reactivity. As is shown in Scheme 4, aromatic aldehyde cyanohydrins bearing various functional groups, such as halogen, methyl, methoxyl, nitride, ester, and trifluoromethyl on the phenyl rings, were well-tolerated to deliver the corresponding products **6a**−**6m** in moderate to high yields. Naphthalenyl was tolerated in this cayno-borrowing reaction and gave the desired product with synthetically useful isolated yields (70% for **6n** and 72% for **6o**). Notably, the disubstituted cyanohydrins were also effective in the transformation (**6p** and **6q**). The amination product **6r**, containing a furanyl group, was formed with 58% yield. To our satisfaction, several synthetically useful alkyl groups were tolerated in this transformation. α,β-Unsaturated cyanohydrin proved to be a viable substrate, providing the desired product with 54% yield. Aliphatic aldehyde cyanohydrins derived from hexanal and cyclohexanecarbaldehyde worked well in this cyano-borrowing reaction and gave the corresponding α-aminonitriles (**6t** and **6u**) with 87% and 85% yield, respectively. Cyanohydrin **5v**, an aliphatic substrate containing a sulfur atom, reacted smoothly with the partner of ammonia and provided product **6v** in 37% yield.

To demonstrate the applicability of this direct amination of cyanohydrins with ammonia, the reaction also proceeded on gram-scale; the reaction of acetophenone cyanohydrin **1a** (10 mmol, 1.47 g) with ammonia afforded 0.83 g (5.7 mmol) of the product **2a**. A gram-scale synthesis of α-aminonitrile **6a** was conducted, and high yield (87%) was retained (Scheme 5).

Scheme 5. Gram Scale Reaction



In conclusion, we have presented a new and scalable procedure for the direct amination of cyanohydrins with the partner of ammonia via titanium-catalyzed cyano-borrowing reaction. Under the optimized conditions, a wide range of cyanohydrins were tolerated in this transformation and afforded the unprotected α-aminonitriles in good to high yields under mild reaction conditions. Additionally, α-aminonitriles containing a quaternary center were obtained via this cyano-borrowing process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03194.

> General information; procedures for titanium-catalyzed cyano-borrowing reaction and gram scale reaction; analytical and spectral characterization data; NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: liqinghua@swu.edu.cn.
*E-mail: liuschop@swu.edu.cn.

ORCID

Wan-Fang Li: 0000-0002-2544-1756
Tang-Lin Liu: 0000-0002-7318-4520

Notes

The authors declare no competing financial interest.

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