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Cyano-borrowing: titanium-catalyzed direct amination of cyanohydrins with amines and enantioselective examples†

Tang-Lin Liu, *[a] Zhao-Feng Li,[a] Jing Tao,[a] Qing-Hua Li,[a] Wan-Fang Li,[b] Qian Li,[b] Li-Qing Ren[a] and Yun-Gui Peng*[a]

The direct amination of cyanohydrins with amines *via* a catalytic cyano-borrowing reaction was developed. The transformation features broad substrate scope, excellent functional group compatibility, and very mild and simple operations. Moreover, a titanium catalyst supported by quinine and (*S*)-BINOL ligands enabled an asymmetric cyano-borrowing reaction with moderate to high enantioselectivity.

α-Aminonitriles serve as conventional precursors for α-amino acids, which constitute the fundamental building blocks for peptides and proteins.[1] α-Aminonitriles are basic structures for the preparation of pharmaceuticals and agrochemicals and drugs.[2] In many organic transformations, α-aminonitriles also exhibit dual reactivity.[3] The Strecker reaction – the hydrocyanation of imines – represents one of the most direct and efficient routes to access α-aminonitriles (Scheme 1a).[4] However, the usage of extremely toxic hydrogen cyanide (HCN) is a major obstacle in traditional Strecker reactions. Owing to their lower explosion hazard and easier handling, cyanohydrins have evolved into an increasingly safe and versatile cyano source for organic synthesis.[5] When cyanohydrins are used as the HCN source, carbonyl compounds (such as ketones or aldehydes) are generally released as the side products, which decreases the atom-economy of the process. Therefore, it would be a very valuable catalytic transformation if both the cyano group and the carbonyl side products could be utilized. As hypothesized in Scheme 1b, the C–CN bond of the cyanohydrin was cleaved in the presence of titanium and the metal-cyano (**A**) and corresponding carbonyl compounds were delivered (**B**), followed by imine formation *via* the condensation of carbonyl compounds with amines, and then the cyano group was transferred from the intermediate (**A**) to the imine (**C**) to give the α-aminonitriles. Overall, water was the sole byproduct and all the other functionalities ended up in the target products. Recently, we have developed a direct amination of cyanohydrins with the partner of ammonia to produce N-unprotected α-aminonitriles.[6] In view of the importance of α-aminonitriles[1–3] and our continued interest in cyano-borrowing reactions,[6,7] herein, we explored the direct amination of cyanohydrins with amines *via* the titanium-catalyzed cyano-borrowing reaction. Various types of aromatic amines, aliphatic amines and sulfonyl amide were tolerated. The titanium-catalyzed enantioselectivity cyano-borrowing reaction was also developed (Table 3).

We started our investigation by the amination of commercially available mandelonitrile **1a** with *p*-methoxybenzyl amine ($PMPNH_2$) **2a** to provide the desired α-aminonitrile **3**, which could be synthesized by the Strecker reaction. After careful studies on the reaction conditions, we discovered that the best results were obtained by using $Ti(Oi\text{-}Pr)_4$ as the catalyst in toluene at 40 °C (see ESI† for more detailed screening).

The control experiments show that titanium was essential for the envisioned transformation. We then focused on the scope of the direct amination of cyanohydrins in a non-enantioselective version. As shown in Table 1, various commercially available aldehyde cyanohydrins were tolerated in this titanium-catalyzed amination procedure. Aldehyde cyanohydrins bearing various electron-withdrawing substituents, including halogens (**4–6**), ester (**10**), trifluoromethyl (**11**) and electron-donating groups (Table 1, **7** and **8**) at the *para*-position of the phenyl ring reacted with amine **2** to deliver the corresponding α-aminonitrile in good to excellent yields (41–92%). Noticeably, a cyano group on the phenyl ring was also tolerated and afforded the desired product (**9**) smoothly with a moderate yield. The substrates containing an *ortho* or *meta* substitute were still compatible in this transformation (Table 1, **12–14** and **17–18**). Substrates with naphthyl (**15** and **16**) or heteroaryl (**19** and **20**) underwent successful amination to deliver a range of α-aminonitriles with isolated yields ranging from 56% to 92%. A good chemical yield was achieved when cinnamaldehyde cyanohydrin (**21**) was introduced to this transformation. Alkyl substitutes, such as *n*-pentyl (**22**), cyclohexyl (**23**) and methyl (**24**), were tested and the desired alkyl substituted cyano amines

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[a] *School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China. E-mail: liuschop@swu.edu.cn, pyg@swu.edu.cn*
[b] *College of Science, University of Shanghai for Science and Technology, Shanghai 200093, China*

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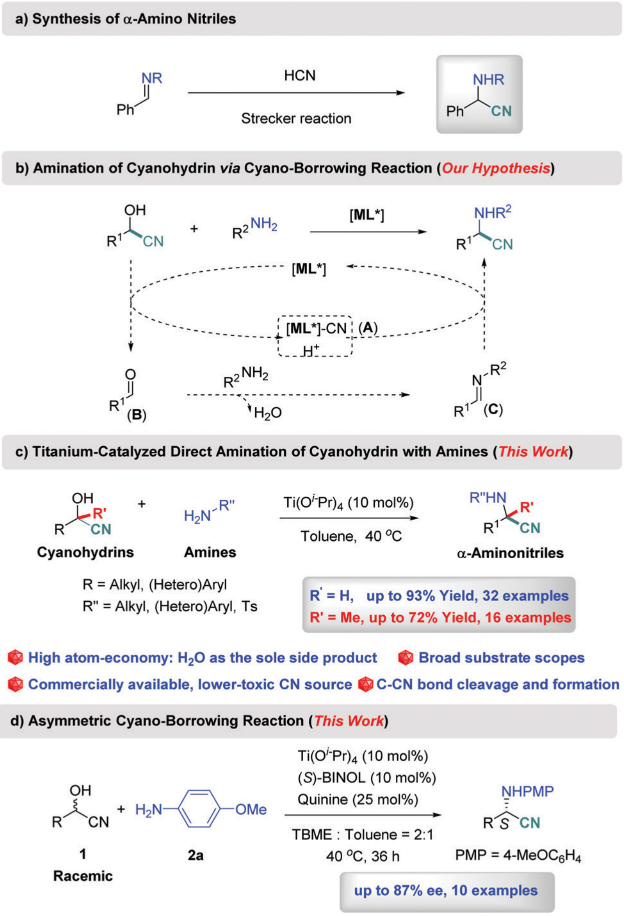
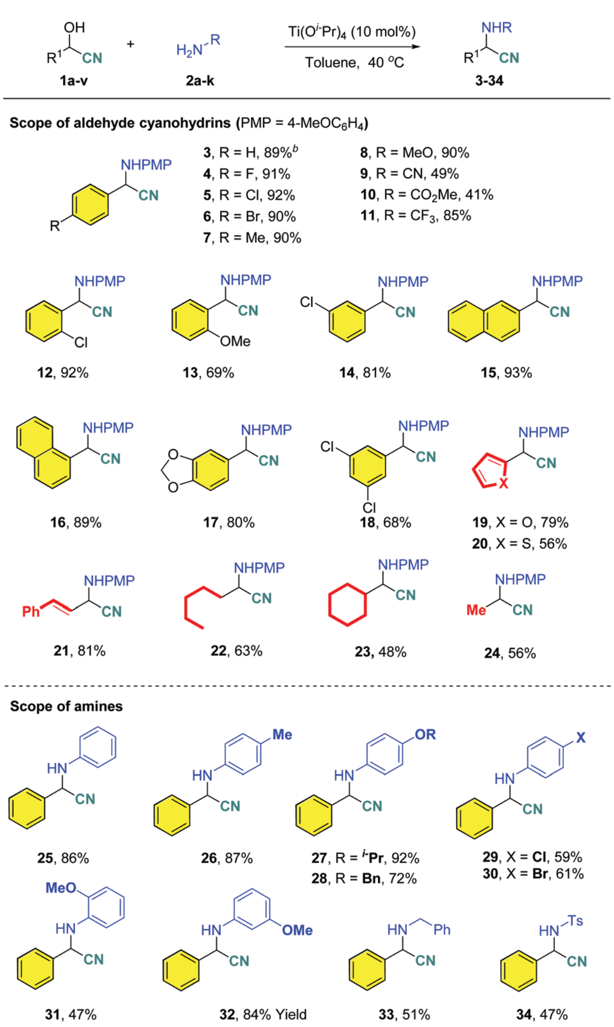


Scheme 1 Amination of cyanohydrins *via* the cyano-borrowing reaction.

Table 1 Substrate scope with respect to the aldehyde cyanohydrins and amines[a]

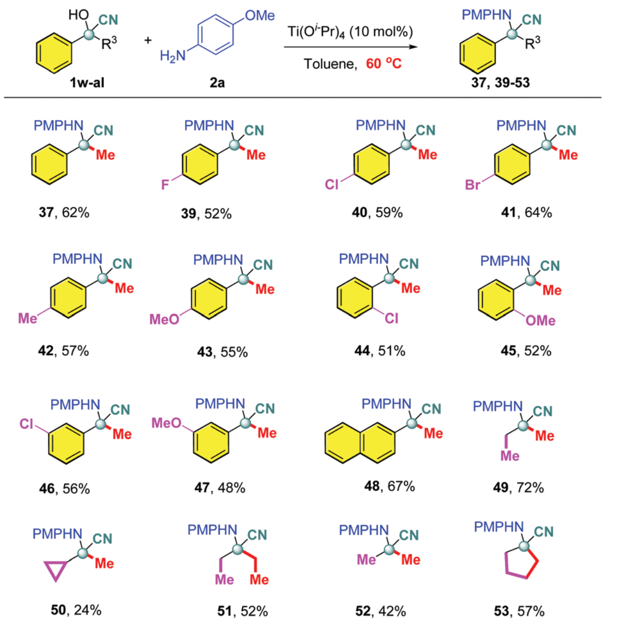


[a] The reaction was carried out with 0.4 mmol of cyanohydrins, 0.2 mmol of amines and 10 mol% Ti(Oi-Pr)$_4$, in 1.0 mL of toluene at 40 °C for 18 h. The yields are isolated yields. [b] <10% yield was obtained in the absence of Ti(Oi-Pr)$_4$.

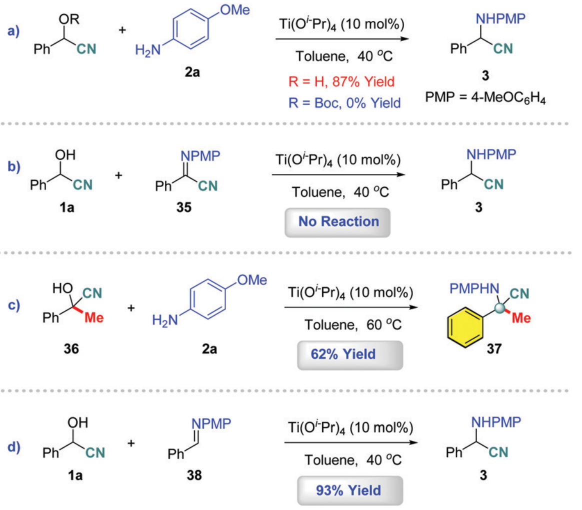
were obtained in moderate yields. Encouraged by the results achieved with aldehyde cyanohydrins, we next expanded the scope of the amine. Table 2 summarizes the amination of mandelonitrile **1** with various amines. Aromatic amines bearing electron-rich and electron-deficient substitutions at the *para*, *ortho* and *meta*-positions were all well tolerated in this titanium-catalyzed cyano-borrowing procedure with yields ranging from 47% to 92% (**25–32**). Additionally, an aliphatic amine, *e.g.*, benzylic amine was also tested in the transformation and the corresponding α-aminonitrile **33** was obtained in 51% yield. On the other hand, a moderate yield could be achieved when the sulfonyl amide was tested in the titanium-catalytic transformation (compound **34** in Table 1).

Based on the previous reports from others and ourselves, there could be three plausible mechanisms for this transformation: (1) nucleophilic substitution;[8] (2) a catalytic hydrogen-borrowing mechanism;[9] and (3) a catalytic cyano-borrowing mechanism.[6,7] To shed some light on the reaction pathway, a series of studies were carried out under the standard reaction conditions (Scheme 2). Firstly, we found that the Boc (*tert*-butyloxy carbonyl) protected mandelonitrile which contained a more reactive leaving group, did not react with amine **2a**. Secondly, in order to know whether this transformation goes through the hydrogen-borrowing pathway, we introduced the imine **35** under the standard reaction condition whereas the desired α-aminonitrile **3** was not observed. On the other hand, with the acetophenone cyanohydrin **36** which has no α-hydrogen to 'borrow', the corresponding quaternary α-aminonitrile **37** was obtained in 62% yield.[10] These results rule out the nucleophilic substitution and hydrogen-borrowing pathways. Additionally, the crossover reaction between mandelonitrile and N-PMP benzaldehyde imine (**38**) delivered the corresponding α-aminonitrile **3** with 93% yield. On the other hand, based on the control experiments, we found that a titanium catalyst improves the step of imine intermediate formation, and the titanium catalyst was indispensable for the cleavage of the C–CN bond in cyanohydrins and the formation of C–CN in the Strecker reaction under the optimal reaction conditions. And the fragment of Ti–CN was detected by HIMS (see ESI† for more details and the proposed catalytic cycle). Taken together, these experimental results are in good accordance with our initial

Table 2 Scope of ketone cyanohydrins with partner amine **2a**[a]

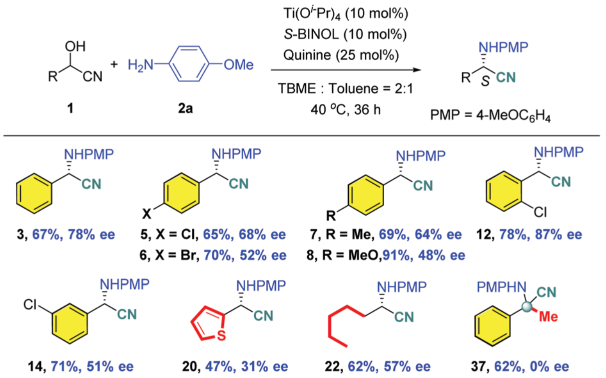


[a] The reaction was carried out with 0.4 mmol of cyanohydrins, 0.2 mmol of PMPNH$_2$ and 10 mol% Ti(Oi-Pr)$_4$, in 1.0 mL of toluene at 60 °C for 18 h. The yields are isolated yields.



Scheme 2 Mechanism studies.

Table 3 Scope of the asymmetric cyano-borrowing reaction[a]



[a] The reaction was carried out with 0.4 mmol of **1**, 0.2 mmol of **2a**, 10 mol% of Ti(Oi-Pr)$_4$, 10 mol% of (*S*)-BINOL and 25 mol% of quinine in 1.0 mL of toluene at 40 °C for 36 h. The yields are isolated yields. Ee was determined by chiral HPLC.

hypothesis on the direct amination of cyanohydrins with amines *via* a cyano-borrowing process (Scheme 1b).

Since the acetophenone cyanohydrin **37** reacted with the amine **2a** smoothly and gave the corresponding product **37** in 62% yield, we found that commercially available ketone cyanohydrins are also suitable substrates for this titanium-catalyzed cyano-borrowing reaction. We then examined the scope of ketone cyanohydrins to the cyano-borrowing reaction with the partner of *p*-methoxyphenyl amine **2a**, as shown in Table 2. We also found a broad scope of ketone cyanohydrins for this transformation. The other ketone cyanohydrins were subjected to the titanium-catalyzed cyano-borrowing procedure at 60 °C. Under these conditions, acetophenone cyanohydrins with either electron-deficient, electron-neutral or electron-rich groups at all kinds of positions of the phenyl rings gave moderate isolated yields (48–67%) (**39–48**). It is noteworthy that the cyanohydrins derived from dialkyl ketones were also compatible. The cyanohydrin from methyl ethyl ketone was well tolerated and delivered **49** in 72% yield, and the cyclopropyl containing α-aminonitrile **50** was obtained in 24% yield. Moderate yields were obtained when the symmetric cyanohydrins, such as acetone cyanohydrin, 3-pentanone cyanohydrin and cyclopentanone cyanohydrin, were subjected to the titanium-catalyzed cyano-borrowing reaction under the optimized conditions (Table 2, **51–53**).

We next concentrated our attention on the development of an asymmetric variant of the cyano-borrowing reaction. The combination of titanium, dinaphthols and quinines was chosen as the catalytic system for the asymmetric cyano-borrowing reaction.[11] After the screening of the reaction parameters, we found that Ti(Oi-Pr)$_4$ (10 mol%), (*S*)-BINOL (10 mol%) and quinine (25 mol%) was the best combination as the catalyst, and the optimal conditions were using mixed toluene/TBME (v/v = 1 : 2) (TBME = *tert*-butyl methyl ether) and setting the reaction temperature at 40 °C for 36 h (see ESI† for more details). The absolute configurations were determined to be *S* by comparison with known compounds. Then the scope of asymmetric cyano-borrowing was tested, which is listed in Table 3. The aromatic cyanohydrins with electron-deficient or electron-rich substitutes on the phenyl rings were tolerated and delivered the corresponding chiral α-aminonitriles in moderate yields and moderate to good enantioselectivity excess (49–78% ee). To our delight, the *ortho*-chloride substituted product **12** was obtained with 87% ee. Additionally, the heteroarenes, *e.g.*, thiophenyl containing product **20**, could be successfully obtained albeit with moderate yields and 31% ee. The cyanohydrin from caproaldehyde was tolerated in the titanium-catalyzed asymmetric cyano-borrowing reaction, and the alkyl substituted product was formed with 57% ee. An attempt with acetophenone cyanohydrin **36** was less efficient in the asymmetric version of the cyano-borrowing reaction and only the racemic product **37** was obtained.

In conclusion, we have developed a titanium-catalyzed direct amination of commercially available cyanohydrins *via* a novel cyano-borrowing strategy. Various types of aromatic amines, aliphatic amines and sulfonyl amide were tolerated in this cyano-borrowing reaction. This titanium-catalyzed cyano-borrowing features broad substrate scope, excellent functional group tolerance, and mild and convenient operational advantages for the high-yielding synthesis of various valuable α-aminonitriles. Quaternary centers containing amines could be obtained by the amination of tertiary alcohols (ketone cyanohydrins). Moreover, a titanium catalyst of quinine and (*S*)-BINOL was used for an enantioselective amination of racemic cyanohydrins with amines and moderate to high ee's were obtained. Further studies on the cyano-borrowing reaction are in progress in our research lab and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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