Acceptor-Controlled Transfer Dehydration of Amides to Nitriles

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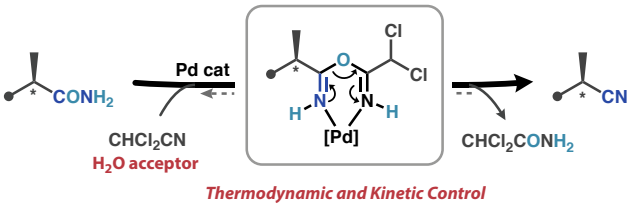
Supporting Information Placeholder

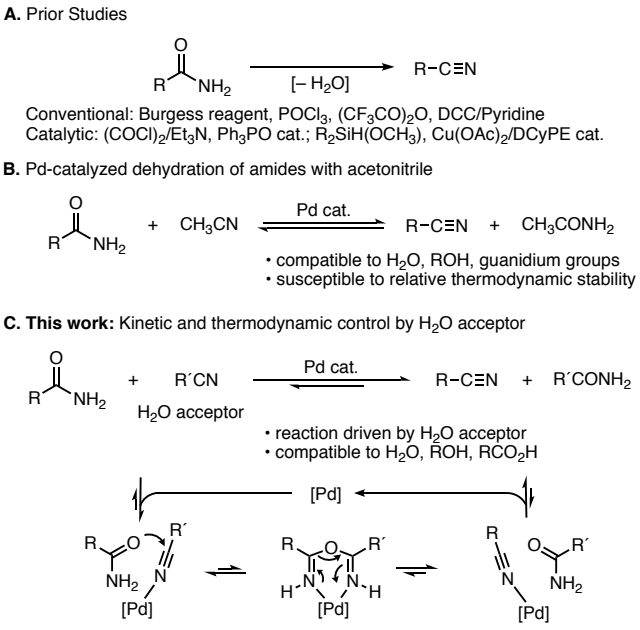
ABSTRACT: Palladium-catalyzed dehydration of primary amides to nitriles efficiently proceeds under mild, aqueous conditions via the use of dichloroacetonitrile as a water acceptor. A key to the design of this transfer dehydration catalysis is the identification of an efficient water acceptor, dichloroacetonitrile, that preferentially reacts with amides over other polar functional groups with the aid of the Pd catalyst and makes the desired scheme exergonic, thereby driving the dehydration.



The cyano group is a privileged functionality that is widely found in natural products and pharmaceuticals.[1] Accordingly, selective introduction of cyano groups into (bio)molecules is of great interest to the synthetic community.[2] One of the most popular approaches has been the dehydration of primary amides to nitriles by using dehydrating agents (Scheme 1A).[2,3] Recent major advances in this approach include the development of phosphine oxide and copper catalytic systems.[4,5] Nevertheless, developing a general methodology for the dehydration of amides that is compatible with other nucleophilic or protic functionalities (*e.g.,* carboxylic acids and water) has remained a significant challenge.

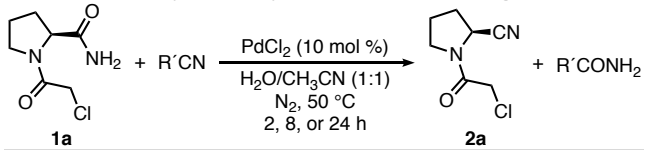
Palladium-catalyzed dehydration of amides using acetonitrile as a dehydrating agent is an exceptionally chemoselective reaction that overcomes this limitation (Scheme 1B).[6] This method was first reported by Maffioli and co-workers for dehydrating aromatic and aliphatic amides in aqueous acetonitrile,[6a] and could be used for dehydration of an amide group in pseudouridimycin where the presence of hydroxyl and guanidinium groups is tolerated.[6c] Because this reaction is reversible in equilibrium, however, the product distribution is susceptible to the relative thermodynamic stability and therefore the dehydration of electron-deficient amides with acetonitrile is energetically unfavorable.[7] On the basis of these reports and our recent investigations of catalytic hydration reactions,[8] we reasoned that the scope of the Pd-catalyzed dehydration of amides with nitriles can be greatly expanded by designing a more efficient water acceptor as compared with acetonitrile. The water acceptor should (1) be kinetically reactive for the Pd-catalyzed dehydration of amides and (2) give a thermodynamically stable co-product, thereby making the desired dehydration scheme exergonic enough to produce the nitrile products in high yields. We here report an improved Pd-catalyzed transfer dehydration of amides by controlling the thermodynamic properties of the water acceptor (Scheme 1C). We found that the use of electron-deficient nitriles as water acceptors enabled the selective dehydration of variously functionalized primary amides with retention of the chirality at the α-carbons.

Scheme 1. Dehydration of Amides to Nitriles



We focused on the selective introduction of cyano groups into amino acid derivatives **1** because this issue is considerably important in synthetic chemistry.[2a,3,9] Peptides bearing a cyano group at the C-terminus are widely used as covalent drugs[1b,10] as well as synthetic intermediates.[11] Functionalization of proteins with a cyano group in the side chain is a powerful strategy for characterizing microscopic environments in proteins with infrared or Raman spectroscopy.[12] Thus, we initially studied the reactivity of water acceptors for the efficient dehydration of *N*-chloroacetyl-L-prolinamide (**1a**) to nitrile **2a**, a synthetic intermediate for vildagriptin.[1b,3c,10] Guided by preliminary density functional theory (DFT) calculations of the Gibbs energy changes in the dehydration of amide **1a** to nitrile **2a** using various nitriles as water acceptors (Table S1), we screened nitriles bearing an electron-deficient group, expecting that the introduction of electron-deficient groups into nitriles would effectively shift the equilibrium point from the left (**1a** + R´CN) to the right (**2a** + R´$CONH_2$). As a result, we found that dichloroacetonitrile serves as an excellent water acceptor (Table 1).

Table 1. Catalytic Dehydration of 1a Using Nitriles[a]



		yield of **2a** (%)[b]		
entry	R´CN	2 h	8 h	24 h
1	CH_3CN	56	55	56
2	CH_2ClCN	93	95	>98
3	$CHCl_2CN$	>98	>98	–[c]
4	CCl_3CN	65	86	94
5	$CH_3SO_2CH_2CN$	51	79	92
6	$CH_2[OCH_3]CN$	88	88	–[c]
7	2-furylCN	61	94	96
8	C_6H_5CN	63	62	60
9	$CH_2[CO_2H]CN$	41	55	61
10	$CH_2[CO_2CH_3]CN$	32	49	56
11	$CH_2[CN]_2$	19	25	26
12	CH_2=CHCN	<1	<1	<1
13	$[CH_3]_2NCH_2CN$	<1	<1	<1
14	$[(CH_3)_3NCH_2CN]Cl$	<1	<1	<1
15[d]	$CHCl_2CN$	95[e]	–[c]	–[c]

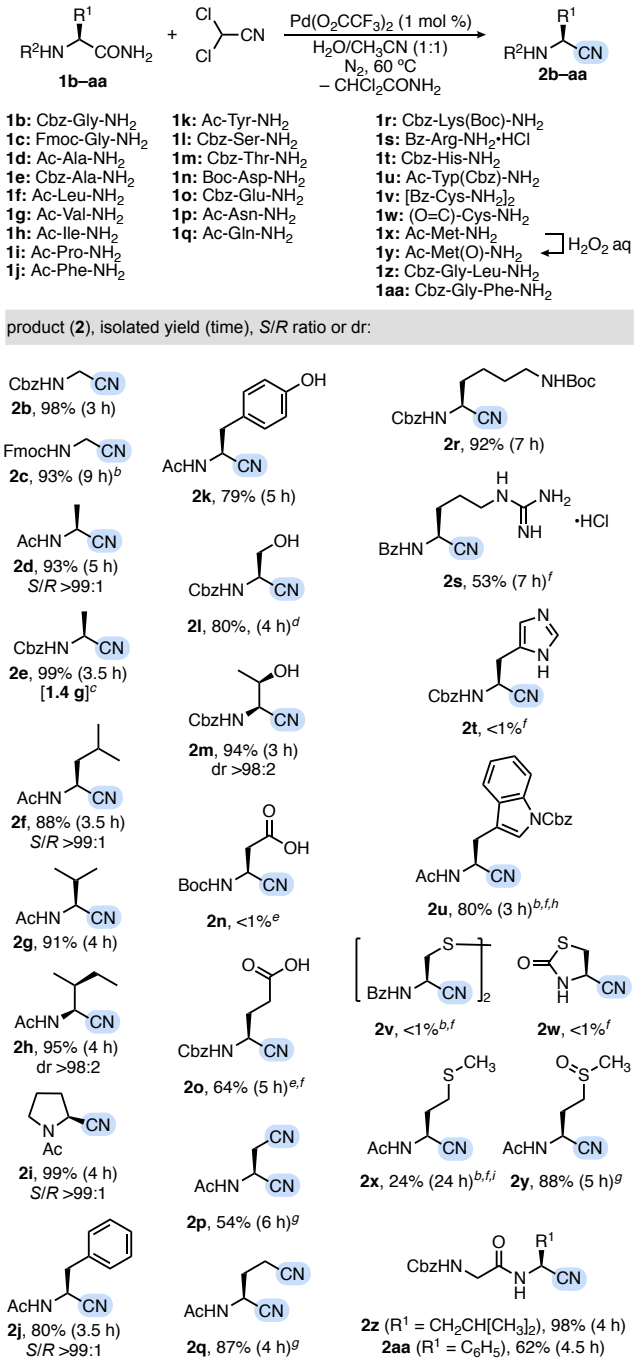
[a]**1a** (0.50 mmol), R´CN (10 equiv), $PdCl_2$ (10 mol %), H_2O/CH_3CN (6 mL, 1:1), 50 °C. A part of the reaction mixture (90 μL) was quenched with R-Cat-Sil-AP (Pd scavenger, 10 mg) at 2, 8, or 24 h. [b]Determined by GC/MS using anisole as an internal standard. [c]Not measured. [d]**1a** (2.6 mmol), $CHCl_2CN$ (10 equiv), $Pd(O_2CCF_3)_2$ (1 mol %), H_2O/CH_3CN (5.4 mL, 1:1), 60 °C, 2 h; R-Cat-Sil-AP (0.5 g), rt, 2 h. [e]Isolated yield.

Whereas the conditions including 120 equiv of acetonitrile in the presence of additional 10 equiv of acetonitrile afforded **2a** in no more than 57% yield (Table 1, entry 1), the presence of chlorinated nitriles significantly increased the product yield (from 94 to >98%, Table 1, entries 2−4). Among these, dichloroacetonitrile proved to be the most efficient water acceptor, leading to the desired **2a** in excellent yields (entry 3). In accordance with the prediction based on the DFT calculations, other electron-deficient nitriles provided high product yields in comparison to that of acetonitrile (entries 5−8). However, electron-deficient, potentially bidentate nitriles retarded or silenced the dehydration (entries 9−14). Under slightly modified reaction conditions, the dehydration of **1a** using dichloroacetonitrile in the presence of palladium trifluoroacetate (1 mol %) at 60 °C gave **2a** in 95% yield on a sub-gram scale (Table 1, entry 15, see also Tables S2–S4 for the effect of the reaction parameters). The complete retention of chirality at the α-carbon of **2a** under typical reaction conditions was confirmed by chiral GC/MS analysis (see the SI for details).

Two main reasons for the high reactivity of dichloroacetonitrile in the transfer dehydration of **1a** as compared with that of acetonitrile are (1) the transfer dehydration of **1a** with dichloroacetonitrile is thermodynamically more favorable than that with acetonitrile (by 40.1 kJ mol^{-1} at the M06-2X/6-311++G** level, Table S1, entry 12 vs 1), and (2) dichloroacetonitrile is sufficiently stable to undesired hydration with water. Such thermodynamic and kinetic considerations in the molecular design of reagents for reversible catalysis are known to be important, as exemplified by transfer (de)hydrogenation,[13] olefin metathesis,[14] and (de)hydrocyanation.[15]

The Pd-catalyzed transfer dehydration of amides **1** to nitriles **2** proved to be effective for various aminoamides derived from naturally abundant amino acids (Table 2). The transfer dehydration proceeded smoothly with aminoamides **1** and afforded nitriles **2** in good to excellent yields. The reaction could be carried out under air and gave a result (with **1b**, 95% yield of **2b**) comparable with that under N_2 (98%). The scalability of the transfer dehydration protocol was verified with **1e**, giving **2e** on a gram scale (1.4 g). No epimerization was observed at the α-carbons of products **2d−y** obtained from natural amino acids as judged from the $[\alpha]_D$ values and chiral GC/MS analysis. The catalytic system was compatible with the presence of various functional groups, such as carbamates (*e.g.,* Cbz in **2b** and Fmoc in **2c**), hydroxyl groups in **2k−2m**; carboxylic acid in **2o**; Boc-protected amine in **2r**; a guanidinium moiety in **2s**; a Cbz-protected indole in **2u**; and a sulfoxide in **2y**. Amino(bis)amides **1p** (Asn) and **1q** (Gln) were doubly dehydrated to give bisnitriles **2p** and **2q**, respectively, in acceptable yields. The presence of a neighboring carboxylic acid in **1n** or a heteroatom in **1t**, **1v**, and **1w** was detrimental to the dehydration. A methionine derivative **1x** was less reactive than its sulfoxide analogue **1y** but slowly underwent dehydration in the presence of zinc acetate.

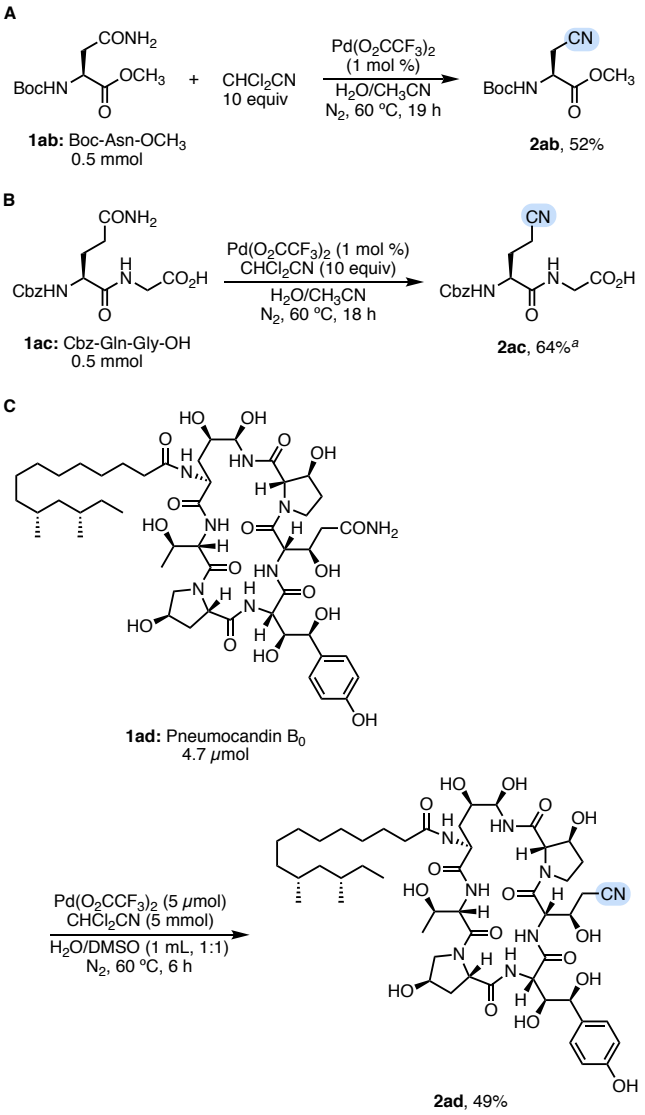
Table 2. Dehydration of α-Aminoamides[a]



[a]Conditions: **1** (0.50 mmol), $CHCl_2CN$ (10 equiv), $Pd(O_2CCF_3)_2$ (1 mol %), H_2O/CH_3CN (1 mL, 1:1), N_2, 60 °C; R-Cat-Sil-AP (Pd scavenger, 100 mg), CH_3OH (5 mL), rt, 2 h. Enantiomeric (*S*/*R*) and diastereomeric ratios (dr) were determined by chiral GC/MS and ^1H NMR, respectively; $[\alpha]_D$ values for products are shown in the SI. [b]**1** (0.10 mmol). [c]**1e** (6.75 mmol), $CHCl_2CN$ (4 equiv), H_2O/CH_3CN (13 mL, 1:1). [d]Yield of the methyl ester produced by treating the crude product with $(CH_3)_3SiCHN_2$ in toluene/CH_3OH. [e]CCl_3CN was used in place of $CHCl_2CN$. [f]With 10 mol % Pd. [g]With 2 mol % Pd. [h]H_2O/DMSO (1:1). [i]$Zn(OAc)_2$ (0.1 mmol).

Primary amide groups at the C-terminus of dipeptides are easily available in standard peptide synthesis.[16] Under the standard conditions, dipeptides **1z** and **1aa** were successfully converted to nitriles **2z** and **2aa**, respectively, that bear a key motif of peptidase inhibitors with covalent drug properties (Table 2, right bottom).[1b,10]

Scheme 2. Dehydration of Primary Amides at the Side Chain: (A) Boc-Asn-OCH_3, (B) Cbz-Gln-Gly-OH, and (C) Pneumocandin B_0.



[a]Isolated yield after methylation with $(CH_3)_3SiCHN_2$ in toluene/CH_3OH.

The current dehydration protocol could also be applied to an asparagine derivative **1ab** and a glutamine-based dipeptide **1ac**, each having a carboxamide in the side chain (Schemes 2A, B). Furthermore, pneumocandin B_0 (**1ad**, a natural product with antifungal activity)[17] underwent the selective transfer dehydration to give **2ad** (49%), a synthetic intermediate for caspofungin acetate (Scheme 2C).[18] **2ad** was characterized by MALDI-MS and NMR after isolation by preparative HPLC (Figure 1). MS signals for **1ad** and **2ad** indicated the loss of H_2O (m/z −18) after the catalytic reaction (Figure 1A). The ^1H NMR signal of a proton adjacent to the primary amide (δ ~2.5

ppm) in **1ad** shifted to a higher frequency (δ ~2.7 ppm) in **2ad** while other signals remained almost the same (Figure 1B). Changes in ^{13}C NMR signals were also consistent (CN carbon in **2ad**, δ 119.6 ppm; see the SI for full characterization).

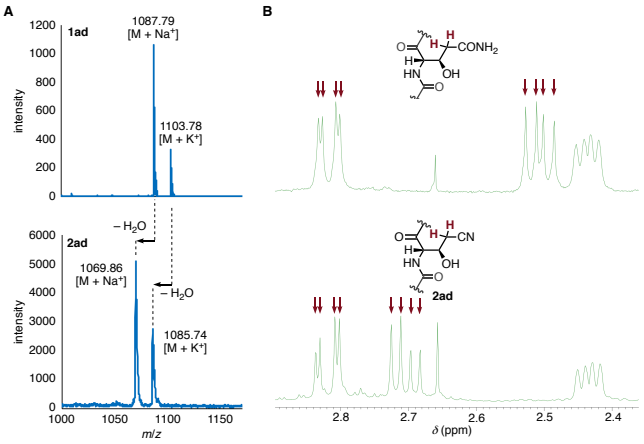


Figure 1. (A) MALDI-MS and (B) ^{1}H NMR charts of **1ad** and **2ad**.

In summary, an efficient catalytic system for the palladium-catalyzed transfer dehydration of primary amides to nitriles under aqueous conditions was established using an electron-deficient nitrile as a water acceptor, by considering the thermodynamic and kinetic nature of the reversible catalysis. Further applications of this method for the direct functionalization of complex natural products, pharmaceuticals, and biomolecules are envisaged.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxxxxx.
Supplementary Tables, experimental procedures, and spectral data (PDF)
^{1}H and ^{13}C NMR spectra; Chromatographic charts (PDF)

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Notes

The authors declare no competing financial interest.

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