Catalytic Transfer Hydration of Cyanohydrins to α-Hydroxyamides

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Supporting Information Placeholder

ABSTRACT: We report the palladium(II)-catalyzed transfer hydration of cyanohydrins to α-hydroxyamides by using carboxamides as water donors. This method enables selective hydration of various aldehyde- and ketone-derived cyanohydrins to afford α-mono- and α,α-disubstituted-α-hydroxyamides, respectively, under mild conditions (50 °C, 10 min). The direct conversion of fenofibrate, a drug bearing a benzophenone moiety, into a functionalized α,α-diaryl-α-hydroxyamide was achieved by means of a hydrocyanation−transfer hydration sequence. Preliminary kinetic studies and the synthesis of a site-specifically ^{18}O-labeled α-hydroxyamide demonstrated the carbonyl oxygen transfer from the carboxamide reagent into the α-hydroxyamide product.

The catalytic, chemoselective hydration of nitriles is one of the most important issues in both laboratory and industrial synthetic chemistry. Hydration of cyanohydrins (**1**) to α-hydroxycarboxamides (**2**) represents a primary target in this field (Figure 1A, (i)).[1] Cyanohydrins are readily available through (asymmetric) cyanation of aldehydes or ketones.[2] Further, α-hydroxyamide substructures are found in various bioactive compounds, and are easily convertible to α-hydroxyl esters, α-hydroxycarboxylic acids, and acrylic analogs.[3,4] The hydration of acetone cyanohydrin by manganese oxide catalyst is used in the industrial production of methyl methacrylates.[5] Despite the utility of recently developed transition-metal catalysts for nitrile hydration,[6] however, hydration of cyanohydrins by homogeneous catalysts is not straightforward, firstly because cyanohydrins often decompose into carbonyl compounds and hydrogen cyanide (HCN), especially at high temperature or under basic conditions, and secondly, because HCN often deactivates the metal catalysts (Figure 1A, (i)).[1] The hydration of aldehyde-derived cyanohydrins could be effectively catalyzed by borates.[7] Tyler *et al*. introduced a series of elegant methods using Pt,[8] Mo,[8] and Ru[9] complexes as well as Pt and Ag nanoparticle catalysts.[10] Very recently, Virgil, Grubbs, *et al.* developed improved Pt complexes for catalytic cyanohydrin hydration.[11] Enzymatic methods have been also developed.[12] These catalytic methods are more atom-economical than the conventional methods using stoichiometric acid- or base-reagents. However, most of the existing catalysts are far less effective in the hydration of ketone-derived cyanohydrins than aldehyde-derived cyanohydrins due to the lower stability of α,α-disubstituted cyanohydrins.[13] Beauchemin *et al.* recently introduced an efficient carbohydrate/base-promoted hydration of α-aminonitriles, amino-analogs of cyanohydrins, but the applicability of this method to base-sensitive cyanohydrins remains unclear.[14] In particular, selective hydration of diarylcyanohydrins has been hardly achieved (Figure 1A, (ii)). Thus, a universal method for catalytic nitrile hydration that is capable of hydrating these challenging substrates remains to be developed.

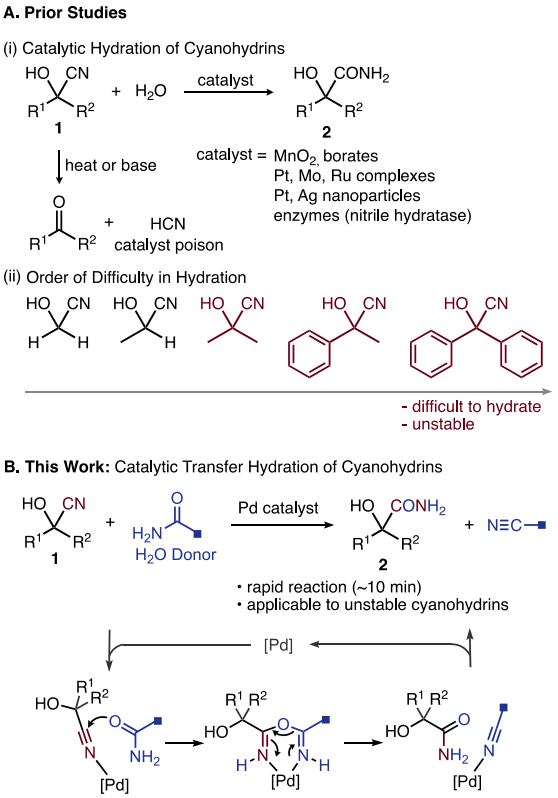


Figure 1. (A) Previous approaches, order of difficulty in nitrile hydration, and (B) working hypothesis of this work.

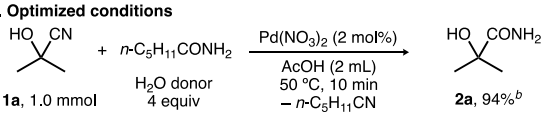
In order to solve this problem, we report here the palladium(II)-catalyzed transfer hydration of cyanohydrins to α-hydroxyamides using carboxamides as a water donor (Figure 1B). We postulate this reaction as catalytic transfer hydration, in which H_2O is formally transferred from the H_2O donor to cyanohydrin through the activation of nitrile and amide by cationic Pd^{II} catalysts, as inspired by the concept of transfer

hydrogenation, in which H_2 is formally transferred from hydrogen donors to acceptors.[15]

During the course of our recent study seeking efficient methods for catalytic hydration of unsaturated organic compounds,[16] we found that the use of palladium chloride and carboxamide[17–19] allows the hydration of acetone cyanohydrin (**1a**). The conversion of nitriles to amides by palladium chloride and acetamide was initially described by Maffioli *et al.* as a reverse reaction of the dehydration of amides to nitriles.[17a] After a thorough examination of this transfer hydration of **1a**, the optimum reaction conditions were identified. The catalytic transfer hydration of **1a** (1.0 mmol) at 50 °C for 10 min using *n*-hexanamide (4 equiv), $Pd(NO_3)_2$ (2 mol %), and acetic acid (2 mL) gave **2a** in an excellent isolated yield (Table 1A). The reaction was stopped by adding a metal scavenger (R-cat-Sil-AP, 50 mg). The rapid and efficient catalytic conversion of **1a** to **2a** (94% yield in 10 min) was unprecedented, and the calculated turnover frequency (TOF) of 280 h^{-1} is at least 15 times larger as compared with those reported for the hydration of **1a** [Pt complexes (TOF (h^{-1}) of 0.02 and 18);[8,11] a Mo complex (0.07);[8] Ru complexes (1.3);[9] Pt nanoparticles (0.51);[10a] Ag nanoparticles (0.70)].[10b]

Table 1. Catalytic Transfer Hydration of 1a[a]

A. Optimized conditions



B. Pd catalyst (with CH_3CONH_2)

Pd catalyst	yield (%)[c]
$Pd(NO_3)_2$	94
$Pd(CH_3CN)_2(BF_4)_2$	88
$Pd(CH_3CN)_2(OTf)_2$	64
$Pd(OAc)_2$	47
$Pd(O_2CCF_3)_2$	68
$Pd(acac)_2$	15
$Pd(hfacac)_2$	57
$PdCl_2$	1
$PdBr_2$	< 1
PdI_2	< 1
$Pd(CN)_2$	< 1
$Pd(dba)_2$	< 1
none	< 1

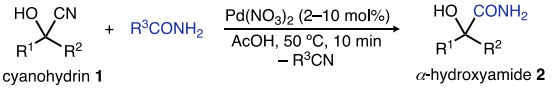
C. H_2O donor (with 1 mol % $Pd[NO_3]_2$)

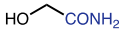
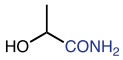
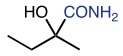
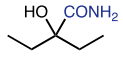
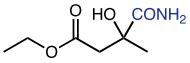
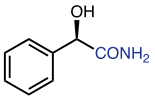
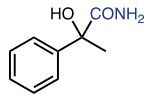
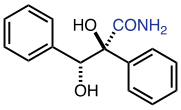
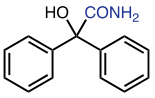
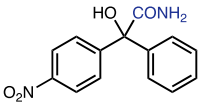
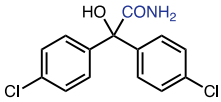
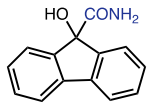
H_2O donor	yield (%)[c]
none	< 1
CH_3CONH_2	42
$C_2H_5CONH_2$	55
n-$C_3H_7CONH_2$	73
n-$C_5H_{11}CONH_2$	75[b]
n-$C_7H_{15}CONH_2$	65[b]
n-$C_{11}H_{23}CONH_2$	< 1
t-$C_4H_9CONH_2$	1
CF_3CONH_2	< 1
$C_6H_5CONH_2$	1
$HCONH_2$	1
H_2O	< 1
$CH_3CH{=}NOH$	< 1

[a]Typical conditions: **1a** (1.0 mmol), acetamide (4.0 mmol), $Pd(NO_3)_2$ [2 mol % for (B); 1 mol % for (C)], AcOH (2 mL), mesitylene (0.34 mmol, internal standard for ^1H NMR analysis), 50 °C, 10 min, N_2; metal scavenger (R-cat-Sil-AP, 50 mg). [b]Isolated yield. [c]NMR yield.

The catalyst effects are summarized in Table 1B. Cationic palladium(II) catalysts effectively promoted the hydration of **1a**.[20] In contrast, catalysts bearing (pseudo)halogen ligands (Cl, Br, I, and CN) were ineffective. The transfer hydration of **1a** scarcely proceeded with $Pd^0(dba)_2$ or in the absence of a Pd catalyst. The reactivity of H_2O donors was studied in the presence of a decreased amount (1 mol %) of $Pd(NO_3)_2$ (Table 1C). The use of the amide reagent was found to be prerequisite: the transfer hydration of cyanohydrin **1a** did not proceed at all in its absence. Carboxamide bearing a linear alkyl chain afforded **2a** in better yield (65−75%) than acetamide (42%). An amide reagent bearing a longer alkyl chain (n-$C_{11}H_{23}$) was poorly soluble in the reaction mixture and remained unreacted. Amides bearing a sterically more demanding substituent and electron-deficient substituents were significantly less reactive, as compared with linear alkyl substituents. The use of water[21,22] and aldoxime[23] as a H_2O donor was ineffective under otherwise identical conditions. Further details on the influences by reaction parameters are shown in Tables S1−5 in Supporting Information (SI). Acetic acid proved to be the best solvent for the efficient transfer hydration of **1a**, yet the reaction proceeded in other carboxylic acids, alcoholic solvents, and mixed solvent systems of water with THF, acetonitrile, or acetone albeit with decreased yields (Table S3).

Table 2. Scope of the Catalytic Transfer Hydration[a]



1	product (2)		R³	Pd (mol%)	yield (%)[b]
1b		**2b**	n-C_5H_{11}	2	98
1c		**2c**	n-C_5H_{11}	2	96
1d		**2d**	n-C_5H_{11}	2	91
1e		**2e**	n-C_5H_{11}	3	92
1f		**2f**	n-C_5H_{11}	3	93
(*R*)-**1g**		(*R*)-**2g**	n-C_7H_{15}	4	89[c]
1h		**2h**	n-C_5H_{11}	4	98
1i		**2i**	CH_3	5	90
1j		**2j**	CH_3	5	75
1k		**2k**	CH_3	10	82
1l		**2l**	CH_3	10	71
1m		**2m**	CH_3	10	77

[a]Conditions analogous to Table 1A. [b]Isolated yield. [c]The *R*:*S* ratio of (*R*)-**2g** = 91:9, as determined by chiral GC after acetylation of the hydroxyl group. The *R*:*S* ratio of (*R*)-**1g** = 81:19.

The substrate scope of the Pd-catalyzed transfer hydration was investigated under the optimized conditions (Table 2).[24] The current transfer hydration of cyanohydrins proved to be effective for the conversion of various cyanohydrins bearing hydrogen or alkyl substituents. Glycolonitrile (**1b**) and

lactonitrile (**1c**) underwent complete conversion in 10 min to the corresponding hydroxyamides. Analogously to **1a**, the transfer hydration of dialkyl-substituted cyanohydrins **1d** and **1e** proceeded smoothly. Cyanohydrin **1f** derived from ethyl acetoacetate was hydrated to amide **2f** without loss of the ester functionality. In all these cases, products **2** were obtained in excellent isolated yields (91−98%).

Monoaryl-substituted cyanohydrins (*R*)-**1g**−**1i** were less reactive and thermally less stable than the aliphatic analogs, but could be successfully hydrated in 10 min to the corresponding amides in good to excellent yields with 4 or 5 mol % Pd catalyst (Table 2). A chiral cyanohydrin (*R*)-**1g** underwent the same reaction to furnish the corresponding (*R*)-**2g** in 89% yield with retention of the chirality around the α-carbon center. A congested α,ß-dihydroxyamide **2i** was produced from benzoin-derived **1i**, an intermediate of the benzoin condensation of benzaldehyde with cyanide. The stereochemistry at the α- and ß-carbons was completely retained to give the amide bearing an *anti*-diol moiety exclusively (see SI).

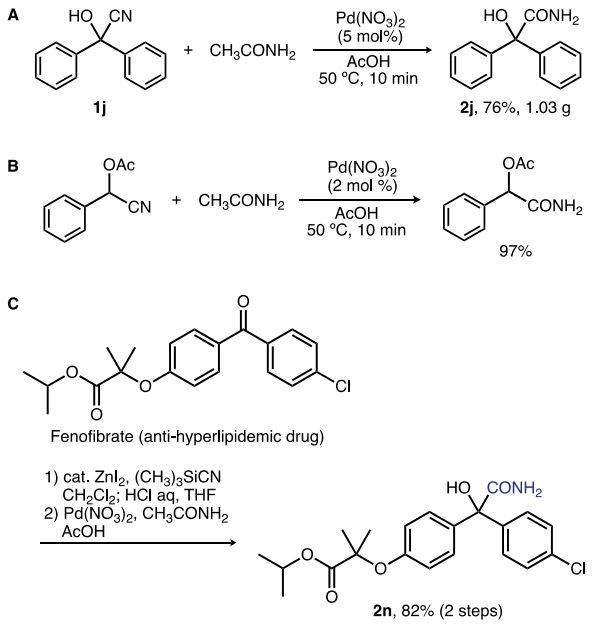


Figure 2. (A) Gram-scale catalytic transfer hydration of **1j**. (B) Transfer hydration of *O*-acetylated cyanohydrin. (C) Direct drug derivatization via hydrocyanation−transfer hydration sequence.

α,α-Diaryl-substituted cyanohydrins were highly unstable and readily decomposed into the benzophenones upon storage at room temperature. Nevertheless, these substrates were hydrated quickly to afford **2j**−**m** in 71−82% yields, without the loss of the nitro (in **1k**) or chlorine (in **2l**) functionality (Table 2). Because aryl substituted products **2j**−**m** were poorly soluble to water, they could be purified without involving any chromatographic procedures: the products were isolated by the precipitation upon addition of water or recrystallization. Furthermore, the current protocol was found to be gram-scalable, as exemplified by the transfer hydration of cyanohydrin **1j** to **2j** (Figure 2A). In addition, the presence of the hydroxyl group in cyanohydrins is not prerequisite: hydration of acetylated mandelonitrile smoothly proceeded to give the corresponding amide in 97% yield (Figure 2B). Overall, this transfer hydration strategy appears to offer general and practical access to this class of products from the benzophenone analogs.

With the transfer hydration protocol on cyanohydrins in hand, we next explored the direct derivatization of ketone (Figure 2C). As a representative example, we chose fenofibrate (an anti-hyperlipidemic drug), bearing a benzophenone moiety with ester, ether, and chlorine functionalities. This ketone was directly converted to the corresponding α,α-diaryl-α-hydroxyamide **2n** in 82% isolated yield for 2 steps by sequential hydrocyanation and Pd-catalyzed transfer hydration.

The transfer hydration protocol was also effective in the synthesis of hydroxyamides regio-specifically ^{18}O-labeled at the carbonyl moiety. When ^{18}O-labeled *n*-hexanamide[25] was used for the transfer hydration of cyanohydrin **1a**, the labeled α-hydroxyamide [^{18}O]**2a** was obtained in 98% yield (Figure 3A). The degree of ^{18}O labeling (90% ^{18}O) was confirmed by ESI-MS analysis (Figure 3B). The ratio of intensities for [(^{18}O)**2a** + Na]$^+$ and [**2a** + Na]$^+$ (90:10, Figure 3B (ii)) was nearly identical to that for the ^{18}O-labeled amide reagent. The ^{13}C{^{1}H} NMR and IR analyses confirmed that the ^{18}O atom is incorporated at the carbonyl group (see SI). Thus, this method offers new opportunities for site-specific ^{18}O-labeling of carboxamide derivatives. At the same time, the result proved that the oxygen atom in the amide reagent is unambiguously transferred to the nitrile substrate without any oxygen-exchange with water or acetic acid in the Pd-catalyzed transfer hydration of nitriles. This reaction pattern is in marked contrast to the Pd-catalyzed nitrile hydration using water[21,22] and is similar to the conversion of nitriles to amides using aldoximes.[23]

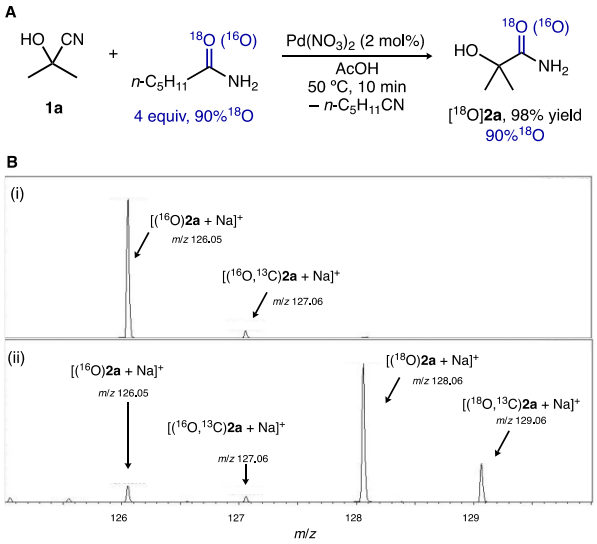


Figure 3. (A) Transfer hydration of **1a** using *n*-[^{18}O]hexanamide (90 atom % ^{18}O). (B) ESI-MS spectra of (i) **2a** and (ii) [^{18}O]**2a**.

To better understand the catalytic profile, preliminary kinetic studies were conducted (Figure 4). Monitoring of the Pd-catalyzed transfer hydration of **1a** with acetamide showed the smooth reaction progress with 2 mol % of $Pd(NO_3)_2$ catalyst at 40 °C (Figure 4A). The pseudo-first-order plot indicated the presence of two mechanistic periods (0−1 min and 1−10 min) in the catalytic profile (Figure 4B). The reaction exhibited a first-order dependence on [**1a**] in both periods, indicating the participation of one molecule of **1a** in the catalytic cycle. This profile was observed in results with different catalyst

concentrations ([Pd]$_0$ = 5−25 mM). The reaction showed first and second orders in [Pd]$_0$ during t = 0−1 min (Figure 4C) and 1−10 min (Figure 4D), respectively. This result implies the involvement of reactive mononuclear and less reactive binuclear Pd species in these periods.[26] Further mechanistic studies are currently underway.

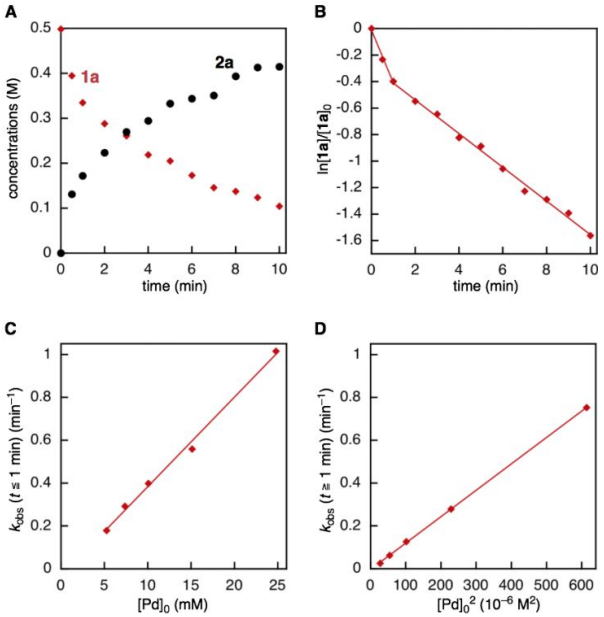


Figure 4. (A) Reaction time course and (B) Pseudo-first-order plot of the transfer hydration of **1a** using $Pd(NO_3)_2$ (2 mol %, 10 mM). Dependence of the rate constant on [Pd]$_0$ during (C) t = 0−1 min and (D) 1−10 min. Conditions: [**1a**]$_0$ = 0.50 M, [CH_3CONH_2]$_0$ = 2.0 M, [$Pd(NO_3)_2$]$_0$ = 5−25 mM, AcOH (2 mL), 40 °C.

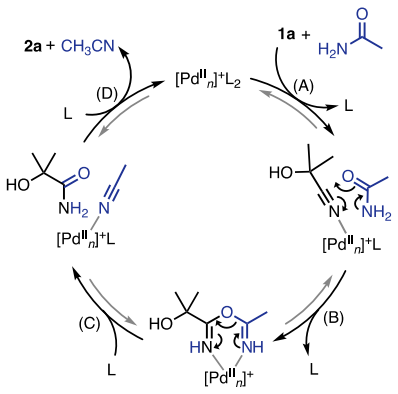


Figure 5. Proposed mechanism for catalytic transfer hydration of **1a** with acetamide to give **2a** and acetonitrile. n = 1 or 2; L = AcOH, CH_3CONH_2, **1a**, **2a**, or CH_3CN.

A plausible catalytic cycle is shown in Figure 5. The proposed catalytic cycle involves (A) formation of mononuclear or binuclear cationic palladium(II) species coordinated by cyanohydrin **1a**; (B) hydroamidation of acetamide to **1a**; (C) its reverse reaction (dehydroamidation) leading to cationic palladium(II) species coordinated by acetonitrile; (D) liberation of acetonitrile and amide **2a** from the catalytic center. This catalytic cycle is based on the postulated mechanism by Maffioli *et al.* for their dehydration of primary amides with $PdCl_2$ in aqueous acetonitrile.[17a] Coproduction of acetonitrile was confirmed by ^{1}H NMR analysis (Figure S1). The incorporation of ^{18}O atom to **2a** from ^{18}O-labeled *n*-hexanamide in Figure 3 is in line with the proposed catalytic cycle in Figure 5. High reactivity of electron-rich aliphatic amides as H_2O donors implies that the product yields are affected by the equilibrium point depending on the relative stability of starting materials and products. For example, the transfer hydration of **1b** with acetamide to **2b** and acetonitrile is exothermic by −29.4 kJ mol^{-1} in ΔH and −26.2 kJ mol^{-1} in ΔG as estimated by DFT calculations (M06-2X/6-311++G**, T = 25 °C). This reaction pattern is also closely related to the shuttle catalysis stated by Morandi *et al.*[27]

In summary, we have developed a Pd-catalyzed transfer hydration of cyanohydrins to afford α-hydroxyamides by using carboxamides. This is the first example of a cyanohydrin hydration reaction with a reasonably broad substrate scope, including aromatic ketone-derived cyanohydrins. This catalytic transfer hydration strategy should present a new approach for inventing methods for challenging chemical transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Tables S1−5, Figure S1, experimental procedures, and spectral data (PDF); ^{1}H and ^{13}C NMR spectra (PDF).

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Funding Sources

H.N. is grateful for financial support from JSPS (KAKENHI Grant Numbers JP15KT0141 and JP17K05859), IQCE, and Toyota Physical and Chemical Research Institute (Toyota Riken).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Dr. J. Shimokawa (Kyoto U.) for his valuable suggestions. We are grateful to Dr. K. Oyama (Nagoya U.) for his technical support in MS and IR analyses. Generous support from Profs. R. Noyori and S. Saito (Nagoya U.) is acknowledged.

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(25) ^{18}O-labeled hexanamide was prepared by the reaction of hexanenitrile with $H_2{}^{18}O$ and trimethylsilyl chloride. The degree of ^{18}O labeling (90%) was determined by ESI-MS analysis and showed good agreement with the $^{13}C\{^1H\}$ NMR and IR data (see SI). See: Basu, M. K.; Luo, F.-T. Efficient transformation of nitrile into amide under mild condition. *Tetrahedron Lett.* **1998**, *39,* 3005−3006.

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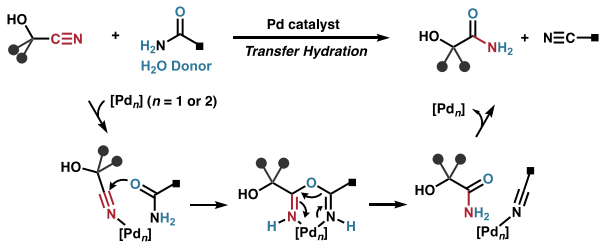
HO
C≡N
+
O
H2N
H2O Donor
Pd catalyst
Transfer Hydration
HO
O
NH2
+
N≡C
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