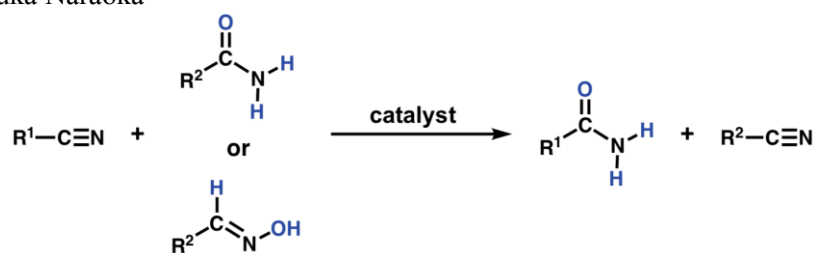# Graphical Abstract

Recent advances in transfer hydration of nitriles with amides or aldoximes

Hiroshi Naka and Asuka Naraoka

$$R^1\!-\!C\!\equiv\!N \;+\; \underset{\text{or}}{\overset{\displaystyle \underset{R^2}{\overset{O}{\|}}\!C\!-\!N\!\overset{H}{\underset{H}{}}}{}} \;\xrightarrow{\text{catalyst}}\; \underset{R^1}{\overset{O}{\|}}\!C\!-\!N\!\overset{H}{\underset{H}{}} \;+\; R^2\!-\!C\!\equiv\!N$$

Digest Paper

Recent advances in transfer hydration of nitriles with amides or aldoximes

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ABSTRACT

This digest paper focuses on recent developments in metal-catalyzed transfer hydration of nitriles to afford amides, using amides or aldoximes as water donors. Recent examples of applications in synthetic chemistry are also described.

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Introduction

The catalytic hydration of nitriles (R^1CN) to afford primary amides (R^1CONH_2) is one of the most important chemical transformations in synthetic chemistry (Scheme 1A).[1,2] Numerous catalytic methods for direct nitrile hydration have been developed to date, but further improvements in the substrate scope, catalytic activity, and selectivity are still needed. Two drawbacks unique to hydration catalysis are: 1) the low nucleophilicity of water towards cyano groups under neutral conditions, and 2) the low miscibility of water with oily nitrile substrates. An emerging approach for simultaneously solving these issues is to use amides (R^2CONH_2) or aldoximes ($R^2CH=NOH$)[3] as charge-neutral water surrogates (Scheme 1B). In this reaction scheme, an H_2O molecule is formally transferred from the water donor to the product and the remaining nitrile fragment (R^2CN) is released. By analogy to well-established transfer hydrogenation catalysis,[4] this hydration scheme can be called transfer hydration. Other similar reactions involving molecular transfer catalysis have also been recently reported.[5,6] Despite its lower atom economy as compared with direct hydration, metal-catalyzed transfer hydration using amides and aldoximes is becoming widely used for the challenging conversion of nitriles to amides. In this digest paper, we review recent developments in metal-catalyzed transfer hydration of nitriles to afford amides, using amides or aldoximes as H_2O donors. Some synthetic applications are also described.
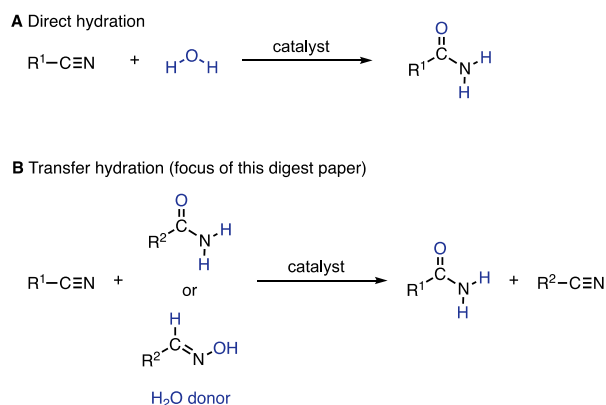

Scheme 1. (A) Direct catalytic nitrile hydration. (B) Transfer hydration catalysis, using amides or aldoximes as water donors.
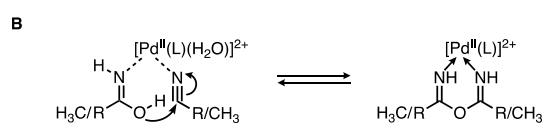
Amide-mediated transfer hydration of nitriles

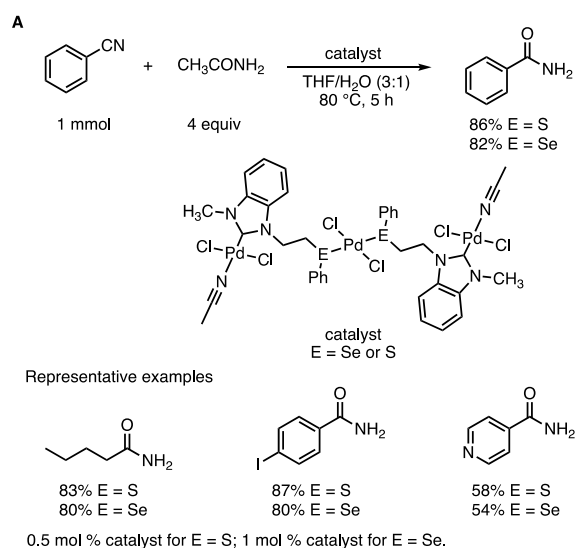Amide-mediated transfer hydration of nitriles was first reported by Maffioli and coworkers in 2005.[7] They described palladium-catalyzed transfer dehydration of amides to afford nitriles, using acetonitrile as a water acceptor.[7–9] To demonstrate

the reversible nature of this catalytic dehydration, they tested PdCl$_2$-catalyzed hydration of three nitriles with acetamide (Scheme 2A).[7] The transfer dehydration of benzonitrile was completed in 6 h under the reported conditions (10 mol % PdCl$_2$, 4 equiv acetamide, THF/H$_2$O = 3:1, rt). Aliphatic nitriles are less reactive (90% conversion of 1-naphthylacetonitrile in 22 h; 53% conversion of 4-phenylbutyronitrile in 22 h). Yields for the amide products were not reported. The authors proposed a mechanism involving the formation of an imidic anhydride intermediate (Scheme 2B).
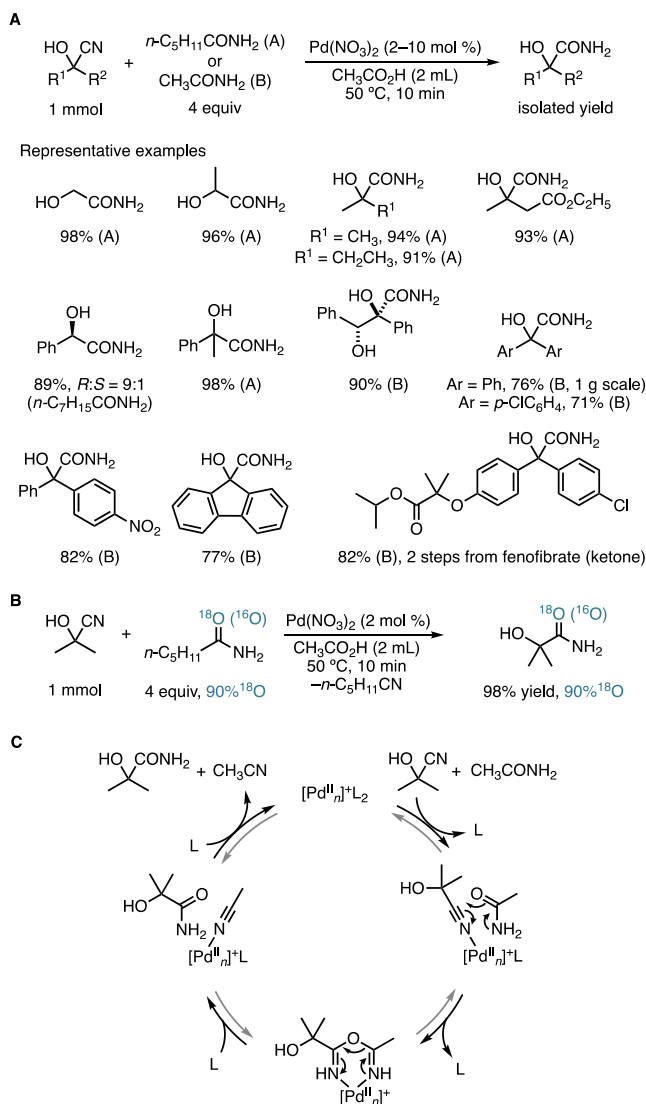
A

B
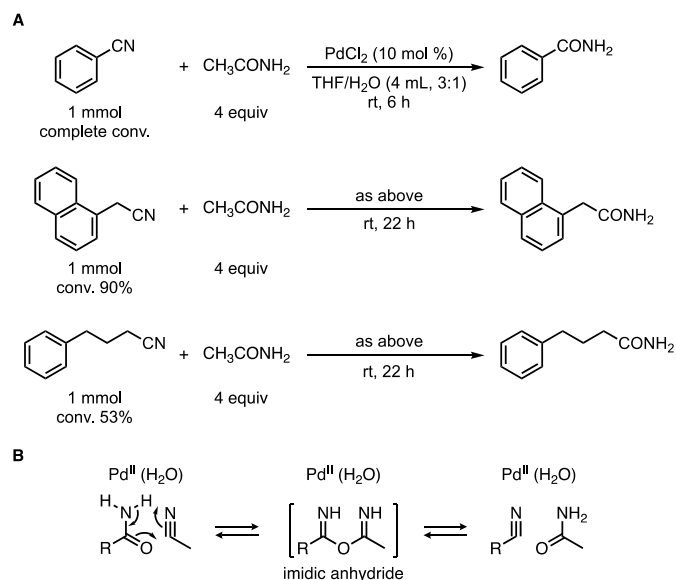
Scheme 2. Transfer hydration of nitriles with acetamide catalyzed by palladium(II) dichloride.

In 2017, Singh and coworkers found that trinuclear complexes with chalcogenated N-heterocyclic carbene ligands catalyze transfer hydration of nitriles to amides in the presence of acetamide as an H$_2$O donor (Scheme 3A).[10] Sulfur- or selenium-based trinuclear palladium structures were identified by X-ray crystallographic analysis. The conditions were optimized for the hydration of benzonitrile (0.5 mol % sulfur-based precatalyst, THF/H$_2$O = 3:1, 80 °C, 5 h, 95% NMR yield). Hydration of aliphatic, aromatic, and heteroaromatic nitriles proceeds at 80 °C, where the sulfur-based precatalyst is slightly more reactive than the selenium analogue. The same complexes catalyze reverse dehydration of amides with acetonitrile and Sonogashira coupling. Based on ESI-MS studies, the authors proposed a mechanism involving hydroamidation of nitriles to form the imidic anhydride for the reversible transfer hydration process, in which the hydrogen atoms in the product predominantly originate from the amide reagent, not H$_2$O in the reaction mixture (Scheme 3B).

A

Representative examples

0.5 mol % catalyst for E = S; 1 mol % catalyst for E = Se.
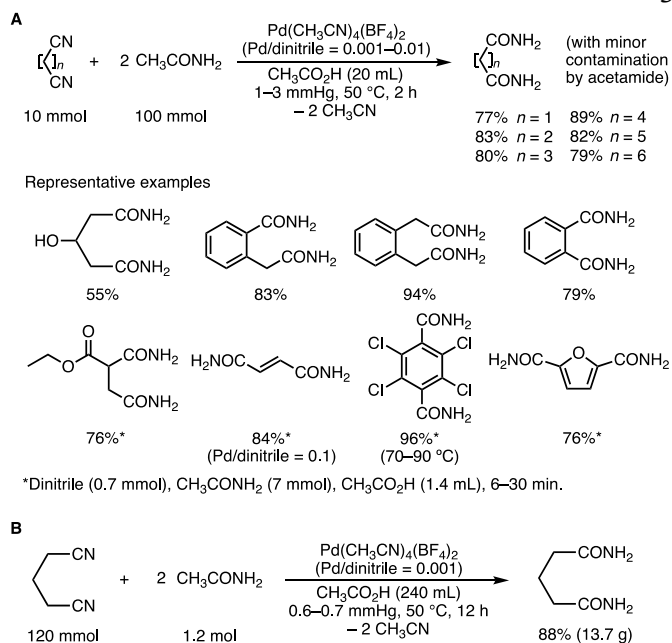
B

Scheme 3. Transfer hydration of nitriles by trinuclear palladium complexes with sulfur- or selenium-linked N-heterocyclic carbene ligands.

In 2019, Naka and coworkers reported palladium-catalyzed transfer hydration of cyanohydrins using amides (Scheme 4A).[11] Acetone cyanohydrin was effectively converted to the corresponding amide in less than 10 min at 50 °C by using palladium(II) nitrate, aliphatic amide (*e.g.* acetamide, *n*-hexanamide), and acetic acid as catalyst, H$_2$O donor, and solvent, respectively. The transfer hydration reaction is also efficient in a water-acetonitrile mixture. Both aldehyde- and ketone-derived cyanohydrins bearing alkyl/aromatic substituents could be hydrated using hexanamide or acetamide, affording the corresponding α-hydroxyamides in 71–98% yield with retention of the α-carbon stereochemistry. Unlike prior metal-catalyzed methods for hydrating cyanohydrins, this method is applicable to the hydration of α,α-diaryl-substituted cyanohydrins. Transfer of the oxygen atom in the amide reagent to the α-hydroxyamide product was indicated based on an experiment using an ^{18}O-labeled amide reagent (Scheme 4B). The results of this isotope-labeling study and kinetic studies led the authors to propose a catalytic cycle involving the formation of imidic anhydride (Scheme 4C). A similar system (catalyst/water acceptor/solvent) effects efficient transfer dehydration of amides to nitriles, allowing installation of a cyano group on the side chains of amino acids, or at the carbon-terminus of peptides.[9e]

A

Pd(NO₃)₂ (2–10 mol %)

HO CN + n-C₅H₁₁CONH₂ (A) or CH₃CONH₂ (B) → HO CONH₂

R¹ R²   CH₃CO₂H (2 mL) 50 °C, 10 min   R¹ R²

1 mmol   4 equiv   isolated yield

Representative examples

HO─CONH₂ 98% (A)

HO─CONH₂ (with CH₃) 96% (A)

HO CONH₂ R¹ = CH₃, 94% (A); R¹ = CH₂CH₃, 91% (A)

HO CONH₂ CO₂C₂H₅ 93% (A)

OH Ph─CONH₂ 89%, R:S = 9:1 (n-C₇H₁₅CONH₂)

OH Ph─CONH₂ 98% (A)

HO CONH₂ Ph Ph OH 90% (B)

HO CONH₂ Ar Ar; Ar = Ph, 76% (B, 1 g scale); Ar = p-ClC₆H₄, 71% (B)

HO CONH₂ Ph ─NO₂ 82% (B)

HO CONH₂ (fluorene) 77% (B)

HO CONH₂ (fenofibrate derivative) Cl 82% (B), 2 steps from fenofibrate (ketone)

B

HO CN + n-C₅H₁₁ ¹⁸O (¹⁶O) NH₂ → Pd(NO₃)₂ (2 mol %) CH₃CO₂H (2 mL) 50 °C, 10 min −n-C₅H₁₁CN → HO ¹⁸O (¹⁶O) NH₂

1 mmol   4 equiv, 90%¹⁸O   98% yield, 90%¹⁸O

C

HO CONH₂ + CH₃CN / HO CN + CH₃CONH₂ [Pdⁿₙ]⁺L₂ ... [Pdⁿₙ]⁺L ... [Pdⁿₙ]⁺
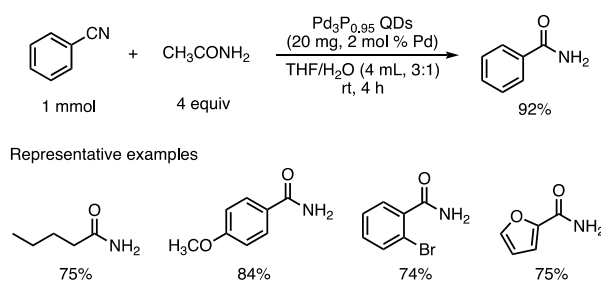
Scheme 4. Transfer hydration of cyanohydrins catalyzed by palladium(II) nitrate.

In the same year, Naraoka and Naka developed a method for hydrating dinitriles to diamides using acetamide as an H₂O donor (Scheme 5A).[12] The transfer hydration of 1,1- through 1,6-dinitriles smoothly proceeds in the presence of a Pd(CH₃CN)₄(BF₄)₂ catalyst and acetamide in acetic acid under reduced pressure, affording the diamides in 55–96% yields with minor contamination by acetamide (32–84% overall yields after recrystallization). Many of the existing methods for nitrile hydration are unsuitable for the hydration of 1,3-dinitriles because of competing cyclization and over-hydrolysis, but the Pd/acetamide/acetic acid catalytic system allows the selective hydration of 1,3-dinitriles to 1,3-diamides on a gram scale. Decagram-scale transfer hydration of glutaronitrile is also feasible (Scheme 5B). Reaction under reduced pressure is the key to the successful hydration, enabling coproduced acetonitrile to be removed to shift the equilibrium towards the desired products.

A

CN [( )ₙ] CN + 2 CH₃CONH₂ → Pd(CH₃CN)₄(BF₄)₂ (Pd/dinitrile = 0.001–0.01) CH₃CO₂H (20 mL) 1–3 mmHg, 50 °C, 2 h − 2 CH₃CN → CONH₂ [( )ₙ] CONH₂ (with minor contamination by acetamide)

10 mmol   100 mmol

77% n = 1; 89% n = 4; 83% n = 2; 82% n = 5; 80% n = 3; 79% n = 6

Representative examples

HO─CONH₂ / CONH₂ 55%

(benzene di-CONH₂) 83%

(benzene di-CH₂CONH₂) 94%

(benzene o-di-CONH₂) 79%

ethyl ester CONH₂ CONH₂ 76%*

H₂NOC─CONH₂ 84%* (Pd/dinitrile = 0.1)

Cl₄ tetra-CONH₂ 96%* (70–90 °C)

H₂NOC─O─CONH₂ (furan) 76%*

*Dinitrile (0.7 mmol), CH₃CONH₂ (7 mmol), CH₃CO₂H (1.4 mL), 6–30 min.

B

CN ( ) CN + 2 CH₃CONH₂ → Pd(CH₃CN)₄(BF₄)₂ (Pd/dinitrile = 0.001) CH₃CO₂H (240 mL) 0.6–0.7 mmHg, 50 °C, 12 h − 2 CH₃CN → CONH₂ CONH₂

120 mmol   1.2 mol   88% (13.7 g)

Scheme 5. Pd-catalyzed transfer hydration of dinitriles to diamides.

In the same year, Singh and coworkers reported that palladium-based quantum dots (Pd₃P₀.₉₅ QDs) promote transfer hydration of nitriles to amides in the presence of acetamide as an H₂O donor (Scheme 6).[13] The quantum dots (QDs) were synthesized through thermolysis of Pd(PPh₃)₂Cl₂ in the presence of oleylamine and octadecane. Transfer hydration of aliphatic, aromatic, and heteroaromatic nitriles using acetamide proceeds at room temperature in the presence of the Pd₃P₀.₉₅ QDs (2 mol % Pd) to give the amides in good yields. The mechanism was considered to be similar to that previously reported.[7] The reverse dehydration of amides with aqueous acetonitrile (at rt), direct hydration of nitriles (at 90 °C) and transfer hydrogenation of ketones with 2-propanol were demonstrated using the same Pd₃P₀.₉₅ QDs. The QDs were recyclable with retention of moderate reactivity.

CN + CH₃CONH₂ → Pd₃P₀.₉₅ QDs (20 mg, 2 mol % Pd) THF/H₂O (4 mL, 3:1) rt, 4 h → CONH₂ 92%

1 mmol   4 equiv

Representative examples

(pentanamide) 75% / H₃CO─CONH₂ 84% / Br─CONH₂ 74% / (furan CONH₂) 75%

Scheme 6. Transfer hydration of nitriles to amides catalyzed by Pd₃P₀.₉₅ quantum dots.
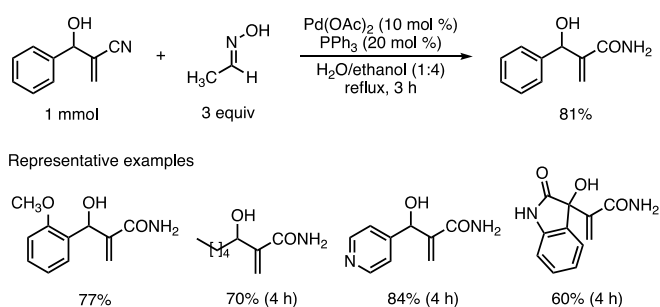
Aldoxime-mediated transfer hydration of nitriles

In 2009, Kim and coworkers reported palladium-catalyzed hydration of nitriles using aldoximes as H₂O donors (Scheme 7A).[14] Building on their work on palladium-catalyzed transfer dehydration of aldoximes to afford nitriles,[15] the authors designed a catalytic system for hydrating nitriles to give amides in the presence of palladium(II) acetate and triphenylphosphine. Both aromatic and aliphatic nitriles undergo the transfer hydration

under typical reaction conditions [2 mmol nitrile, 2 equiv acetaldoxime, 10 mol % Pd(OAc)$_2$, 20 mol % PPh$_3$, H$_2$O/ethanol (1:4), reflux, 3 h], affording the corresponding amides in 77–94% yields. This method is also applicable to the hydration of congested nitriles (*e.g.* 2,6-dichlorobenzonitrile) and base-sensitive acrylonitrile. The selective hydration of cyanoacetophenone proceeds without loss of the aromatic ketone moiety to give the corresponding ketoamide in 77% yield. The catalytic cycle was proposed to involve the addition of aldoxime to nitrile activated by the Pd catalyst (Scheme 7B). N–O bond cleavage gives the desired amide and acetonitrile (by-product) and regenerates the Pd catalyst.
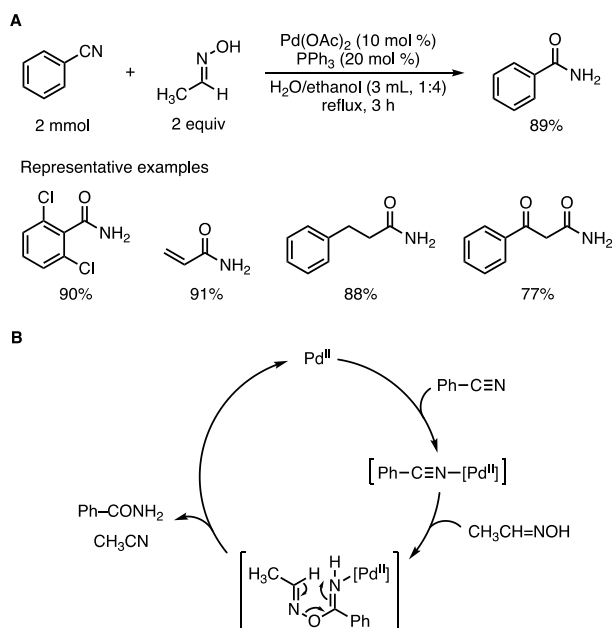
Scheme 7. Pd-catalyzed transfer hydration of nitriles to amides using acetaldoxime as a water donor.

Based on their successful selective 1,2-hydration of acrylonitrile to acrylamide,[14] in the same year Kim and coworkers applied their Pd(OAc)$_2$−PPh$_3$ system to the transfer hydration of Morita–Baylis–Hillman adducts of acrylonitrile, using acetaldoxime as a water surrogate (Scheme 8).[16] This protocol allows formal synthesis of Morita–Baylis–Hillman adducts of acrylamide, which are otherwise difficult to access. Similarly, their Pd(OAc)$_2$−PPh$_3$ catalytic system is effective in synthesizing *N*-tosyl/mesyl/phthalyl *aza*-Morita-Baylis-Hillman adducts of acrylamide from the acrylonitrile analogues [Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), acetaldoxime (2 equiv), aq ethanol, reflux, 3 h, 81–91% yields, 9 examples].[17] However, the mechanism of the transfer hydration was not discussed.

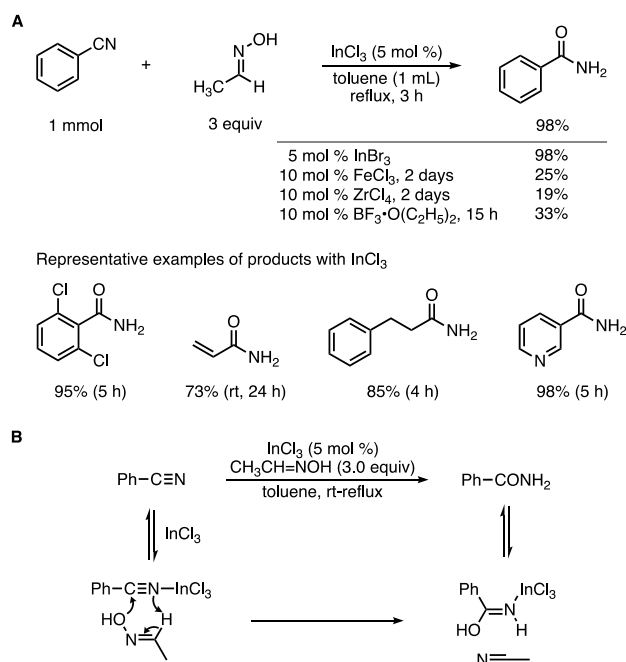**Scheme 8.** Pd-catalyzed transfer hydration of Morita-Baylis-Hillman adducts of acrylonitrile.

In 2009, Chang, Lee, and coworkers reported hydration of nitriles using aldoximes as H$_2$O donors (Scheme 9A).[18] Based on their preceding study on the rhodium-catalyzed rearrangement of aldoximes to amides,[19] they demonstrated that the conversion of nitriles to amides proceeds smoothly in the presence of aldoximes (5 equiv; *e.g.* acetaldoxime, pivalaldoxime) and Wilkinson's catalyst [RhCl(PPh$_3$)$_3$, 1 mol %] in toluene at 110 °C. This method is applicable to both aromatic and primary aliphatic nitriles. The presence of base-sensitive ester functionalities and acid-sensitive ether groups was well tolerated under the catalytic conditions. The desired nitrile hydration with acetaldoxime involves the co-production of acetonitrile as a byproduct. The proposed mechanism of the transfer hydration of benzonitrile with benzaldoxime by Rh(IMes) complex is shown in Scheme 9B.
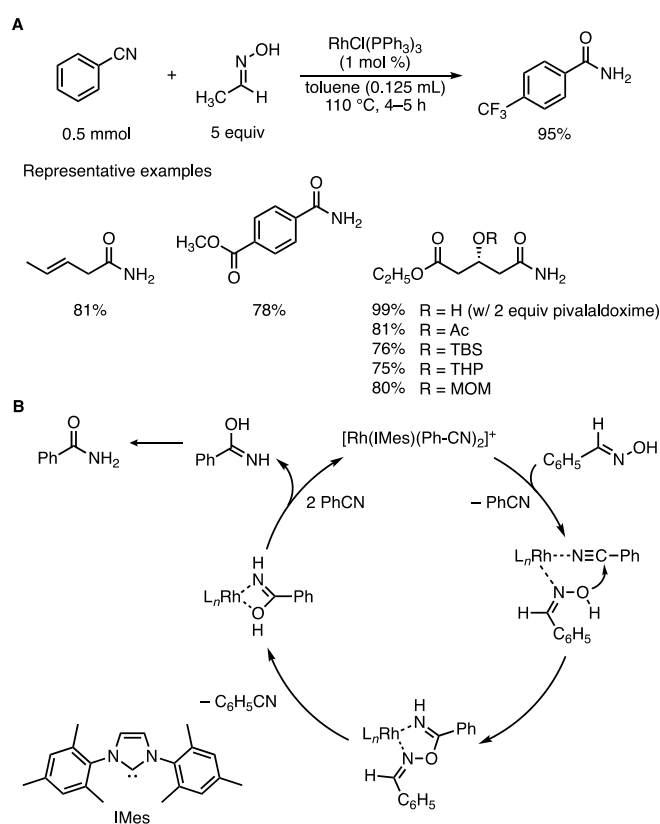
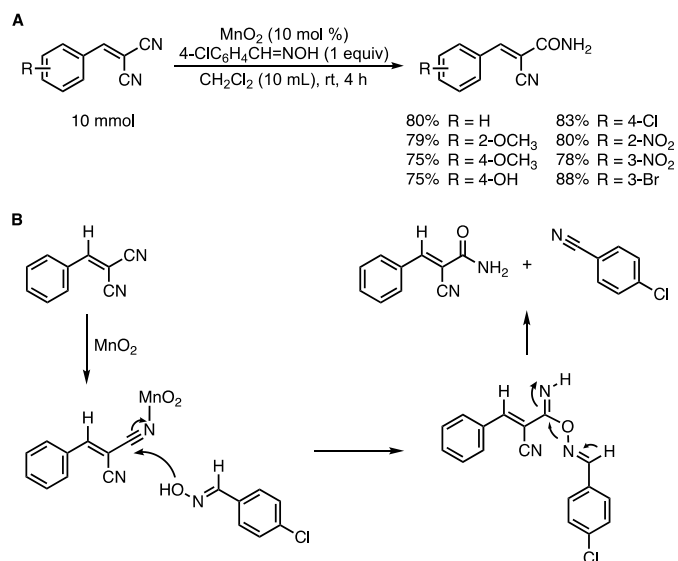**Scheme 9.** Rh-catalyzed transfer hydration of nitriles to amides using aldoximes as water donors.

In 2010, Kim and coworkers developed indium-catalyzed transfer hydration of nitriles using acetaldoxime (Scheme 10A).[20] The nitrile hydration with indium(III) trichloride or tribromide proceeds in refluxing toluene to give the corresponding amides in high yields. These indium salts are more reactive than typical Lewis acids such as FeCl$_3$, ZrCl$_4$, and BF$_3$•O(C$_2$H$_5$)$_2$. The substrate scope is reasonably broad. The InCl$_3$-catalyzed transfer hydration of acrylonitrile to acrylamide proceeds at room temperature (73% yield, 24 h), but polymerization takes place competitively at 80 °C (45% acrylamide, 4 h). A reaction mechanism involving H$_2$O transfer from aldoxime to nitrile coordinated by InCl$_3$ was proposed (Scheme 10B). The acetaldoxime/InCl$_3$ catalytic system is also applicable to the

transfer hydration of cyanamides (RHN-CN) to ureas [RHN-CONH$_2$, 88–96% yields (3 mol % InCl$_3$, toluene, rt–40 °C, 30 min), 9 examples].[21] The mechanism was considered to be similar to that shown in Scheme 10B.
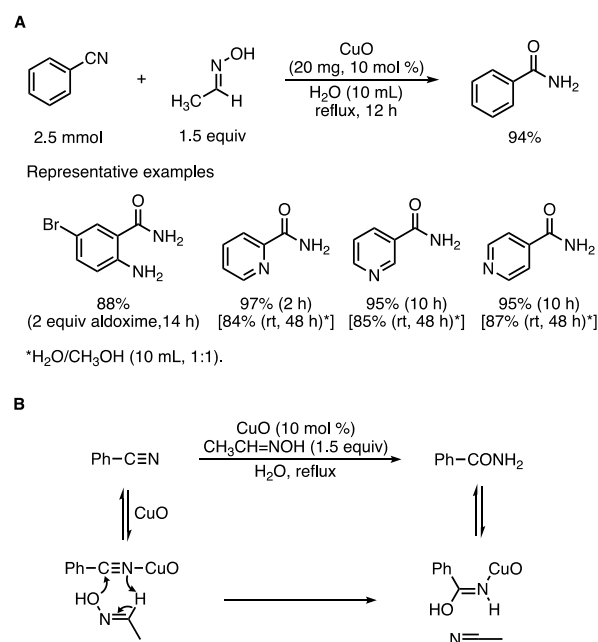
A

Representative examples of products with InCl$_3$

95% (5 h)   73% (rt, 24 h)   85% (4 h)   98% (5 h)

B

Scheme 10. In-catalyzed transfer hydration of nitriles to amides using acetaldoxime as a water donor.

In 2012, Qureshi and coworkers reported aldoxime-mediated hydration of benzalmalononitriles catalyzed by manganese oxide (Scheme 11A).[22] The hydration of benzalmalononitrile takes place exclusively at a cyano group *anti* to the phenyl group. This MnO$_2$-mediated transfer hydration is compatible with the presence of typical functional groups such as methoxy, hydroxy, halogen, and nitro functionalities on the substrate aromatic rings. The proposed mechanism involves addition of aldoxime to nitrile activated by MnO$_2$ (Scheme 11B).

A

80% R = H   83% R = 4-Cl
79% R = 2-OCH$_3$ 80% R = 2-NO$_2$
75% R = 4-OCH$_3$ 78% R = 3-NO$_2$
75% R = 4-OH   88% R = 3-Br

B

Scheme 11. MnO$_2$-catalyzed transfer hydration of benzalmalononitriles to amides, using 4-chlorophenylaldoxime as a water donor.

In 2012, Lu and coworkers reported acetaldoxime-mediated, copper-oxide-catalyzed hydration of nitriles (Scheme 12A).[23] CuO and CuCl$_2$•2H$_2$O efficiently catalyze the transfer hydration of benzonitrile in water. Other copper salts such as CuBr$_2$, CuSO$_4$•5H$_2$O, and Cu(OAc)$_2$ were slightly less reactive. The substrate scope was investigated using 2.5 mmol nitrile substrate, 1.5 equiv acetaldoxime, 10 mol % CuO, and 10 mL H$_2$O (reflux). Successful examples using the CuO catalyst include primary aliphatic, aromatic, and heteroaromatic nitriles (typical reaction time: 10−14 h). The reaction of 2-cyanopyridine derivatives is significantly faster (2 h) than those of other regioisomers (10 h). The transfer hydration of aromatic and pyridyl nitriles can be carried out at room temperature by using a methanol/water 1:1 mixture as a solvent (48 h, 75−88% yields). The proposed mechanism involves H$_2$O transfer from aldoxime to nitrile activated by CuO (Scheme 12B).

A

Representative examples

88%   97% (2 h)   95% (10 h)   95% (10 h)
(2 equiv aldoxime,14 h) [84% (rt, 48 h)*] [85% (rt, 48 h)*] [87% (rt, 48 h)*]
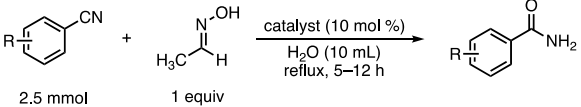
*H$_2$O/CH$_3$OH (10 mL, 1:1).

B

Scheme 12. Transfer hydration of nitriles using acetaldoxime catalyzed by copper oxide.

In the same year, Lu and coworkers reported a systematic evaluation of the catalytic activity of zinc, nickel, cobalt, iron, and manganese salts for transfer hydration of benzonitriles with acetaldoxime.[24] Whereas chloride salts of Ni, Zn, Co, and Mn display catalytic activity for the transfer hydration of benzonitrile, their activity is substrate-dependent (Table 1). The authors selected nickel chloride hexahydrate as the most reactive catalyst for their examination of the substrate. The nickel-catalyzed transfer hydration of aromatic, heteroaromatic, and aliphatic nitriles to the corresponding amides was demonstrated. 2/4-Pyridyl, 2-furyl, and 2-thienyl nitriles are reactive enough to undergo the aldoxime-mediated Ni-catalyzed transfer hydration at room temperature in water or a methanol/water 1:1 mixture (12−24 h, 85−96% yields). The authors also noted that background, direct hydration of 2-pyridyl (75−90%), 2-furyl (25%), and 2-thienyl nitriles (10%) is promoted by NiCl$_2$•6H$_2$O in the absence of acetaldoxime in refluxing water (24 h). The

high reactivity of the nickel–2-heteroaryl system was considered to originate from the formation of a five-membered nickel complex in which nickel effectively activates the cyano group (Scheme 13).
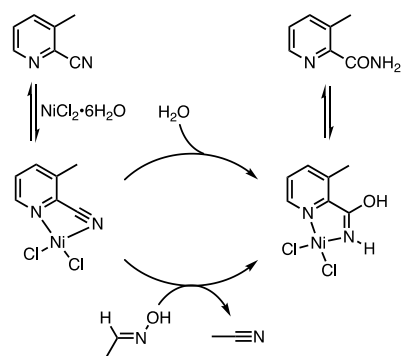
Table 1. Product yields in catalyst screening for transfer hydration of benzonitriles with acetaldoxime.

catalyst \ R, time	H, 12 h	4-OCH$_3$, 10 h[a]	2-Cl, 5 h[a]
NiCl$_2$•6H$_2$O	89%	92%	95%
ZnCl$_2$	88%	90%	87%
CoCl$_2$•6H$_2$O	80%	65%	0%
MnCl$_2$•4H$_2$O	75%	40%	0%
FeCl$_2$•4H$_2$O	5%	—[b]	—[b]
none	5%	—[b]	—[b]

[a]2 equiv acetaldoxime.

[b]Not available.

Scheme 13. Proposed mechanism for nickel-catalyzed transfer hydration of 2-heteroarylnitriles using acetaldoxime.

In 2013, Lu and coworkers also showed that Na$_2$MoO$_4$•2H$_2$O serves as a catalyst for the transfer hydration of nitriles with acetaldoxime (Scheme 14).[25] The Mo-catalyzed transfer hydration of aromatic, heteroaromatic, and aliphatic nitriles gives the corresponding amides in refluxing water.
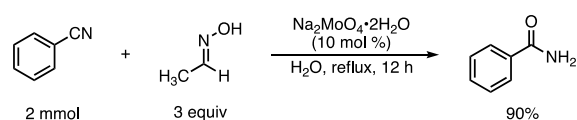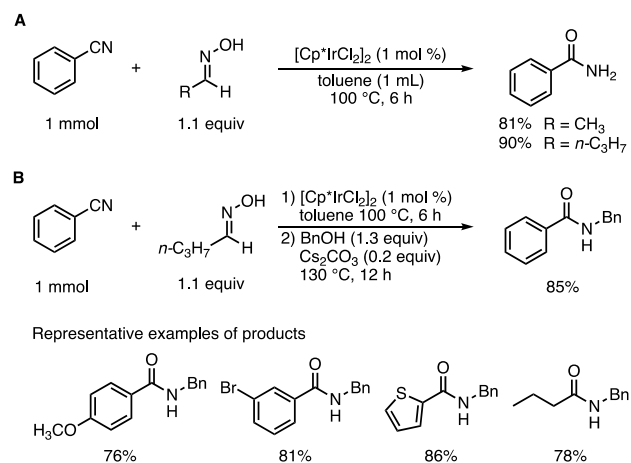

Scheme 14. Mo-catalyzed transfer hydration of nitriles using acetaldoxime.

In the same year, Sajadi and coworkers reported transfer hydration of cyanamides to ureas with acetaldoxime catalyzed by cerium oxide nanoparticles.[26] Hydration of aromatic and

benzylic cyanamides under optimized conditions (refluxing ethanol) gives the ureas in 83–91% yield. The reaction mechanism was proposed to involve H$_2$O transfer from aldoxime to nitrile activated by CeO$_2$.

In 2014, Li and coworkers reported a tandem reaction involving transfer hydration of nitriles using aldoximes and N-alkylation of the resulting amides with alcohols, both of which are catalyzed by a [Cp*IrCl$_2$]$_2$ complex.[27] The transfer hydration of benzonitrile with acetaldoxime (or n-butylaldoxime) proceeds at 100 °C in the presence of 1 mol % [Cp*IrCl$_2$]$_2$ complex to give benzamide in 81% (or 90%) yield (Scheme 15A). Iridium-catalyzed N-benzylation of the resulting benzamide occurs upon heating the reaction mixture after the addition of benzyl alcohol and cesium carbonate (Scheme 15B). This sequential protocol can be used with other aromatic and heteroaromatic nitriles. Aliphatic nitriles undergo the desired reaction under slightly modified conditions. The scope of the alcohols was also discussed. The reaction mechanism for the Ir-catalyzed transfer hydration was considered analogous to that proposed for the Rh-catalyzed transfer hydration (Scheme 9B).[17]
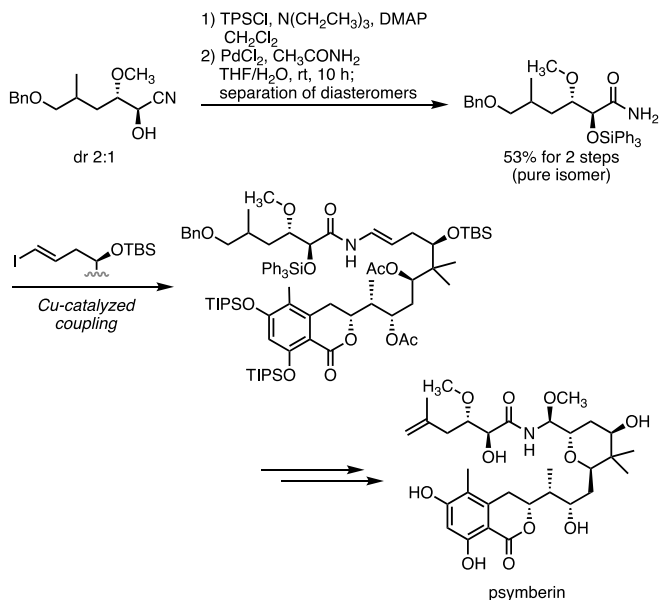

Scheme 15. Ir-catalyzed transfer hydration−N-alkylation sequence for producing N-alkylated amides from nitriles, aldoximes, and alcohols.

In 2015, Nasrollahzadeh and coworkers showed that CuO nanoparticles catalyze transfer hydration of cyanamides to ureas in refluxing ethanol in the presence of acetaldoxime as a water donor.[28] A mechanism similar to that in Lu's report on CuO-catalyzed transfer hydration was proposed.

Applications of amide-mediated transfer hydration in synthetic chemistry

In 2007, Huang and coworkers employed the PdCl$_2$/acetamide/THF–H$_2$O catalytic system[7] for hydrating a silyl-protected cyanohydrin as part of a total synthesis of psymberin (Scheme 16).[29] The isolated product yield (53%) for the desired diastereomer is reasonably high, considering the diastereomeric ratio of the starting cyanohydrin (dr = 2:1). The presence of benzyl ether, methyl ether, and triphenylsilyl ether is well tolerated under the hydration conditions. Copper-catalyzed cross-coupling of the amide product with a vinyl iodide gives an alkenyl enamide, which is further transformed to psymberin via oxidative cyclization as a key step.

Scheme 16. Pd-catalyzed transfer hydration of protected cyanohydrin in the total synthesis of psymberin.

In 2013, Rodrigo, Assoud, and coworkers reported the synthesis of indolinocodeine through a route involving a Pd-catalyzed transfer hydration–amidation sequence (Scheme 17).[30] They initially aimed at preparing the primary amides from homoallyl nitriles (R = CH$_3$ or Ac) through transfer hydration, but 5-membered lactams were directly obtained instead in the presence of stoichiometric quantities of palladium(II) acetate after reaction for 3 days. The use of catalytic amounts of palladium species resulted in incomplete conversion. Based on these results the authors proposed a reaction pathway involving palladium(II)-catalyzed transfer hydration and the consumption of the homoallyl amide intermediate by a stoichiometric amount of palladium(II) species.
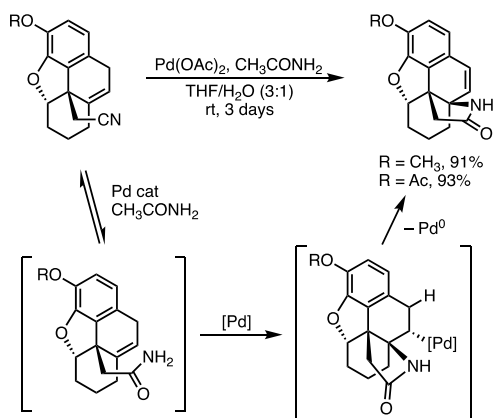
Scheme 17. Pd-catalyzed transfer hydration of homoallyl nitriles to amides followed by Pd-mediated cyclization.

In 2016, Lindhagen and coworkers used the acetamide/PdCl$_2$-mediated transfer hydration[7] to convert a 1,1-dinitrile to a diamide.[31] Their aim was to establish a synthetic route to (R)-allyl-(3-amino-2-(2-methylbenzyl)propyl) carbamate, a target product in their internal drug discovery program, on a kilogram scale (Scheme 18). Transfer hydration of o-

methylbenzylmalononitrile using acetamide as an H$_2$O donor gives the corresponding dehydrated product in 85% yield. This diamide is further reduced with BH$_3$•THF to a 1,3-diamine. This route is more efficient than the direct reduction of the dinitrile with BH$_3$•THF (30% yield), or other typical reduction methods. While the hydration-reduction sequence was evaluated as a good route, the authors chose another route starting from dimethylmalonate for the kilogram scale synthesis because the malonate route was operationally simpler and more effective in producing the diamine.
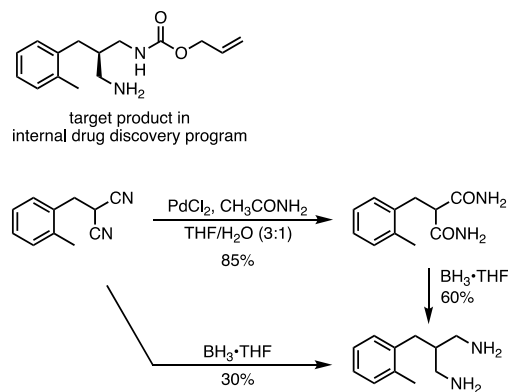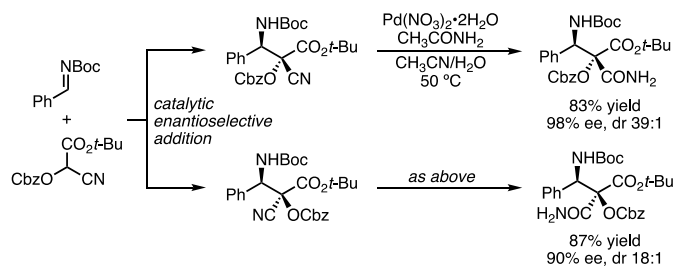
Scheme 18. Pd-catalyzed transfer hydration of dinitrile to diamide.

In 2018, Grugel and Breit employed acetamide/PdCl$_2$-mediated transfer hydration to derivatize a chiral malononitrile obtained via their Rh-catalyzed allylation (Scheme 19).[32] One of the two cyano groups is hydrated with retention of the chirality at the ß-carbon to give the cyanamide as a 1:1 diastereomeric mixture.
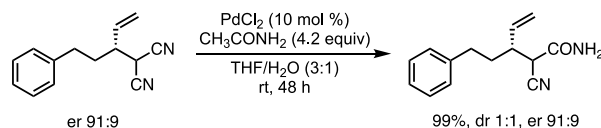
Scheme 19. Pd-catalyzed transfer hydration of malononitrile derivative to cyanamide.

In 2019, Takemoto and coworkers utilized acetamide/Pd(NO$_3$)$_2$-mediated transfer hydration[11] to derivatize highly functionalized, O-protected cyanohydrins (Scheme 20).[33] Enantio- and diastereoselective catalytic addition of O-protected cyanohydrins to imines gave cis- and trans-adducts, both of which were selectively hydrated with acetamide/Pd(NO$_3$)$_2$ in a water and acetonitrile mixture to give the corresponding amides in good yield.
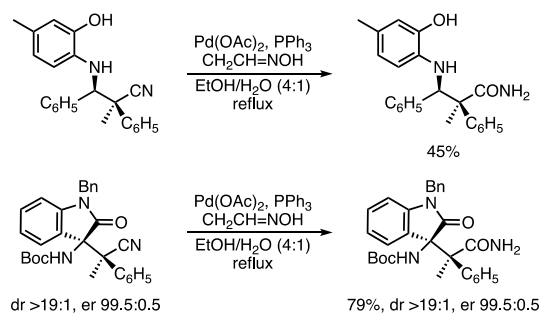
Scheme 20. Pd-catalyzed transfer hydration of highly functionalized, *O*-protected cyanohydrins.

Applications of oxime-mediated transfer hydration in synthetic chemistry

In 2012, Hyodo, Nakamura, and Shibata hydrated a chiral *aza*-Morita-Baylis-Hillman adduct of acrylonitrile to obtain an acrylamide analogue under Kim's conditions[14] [Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), acetaldoxime (2 equiv), aq ethanol, reflux, 1 h, 90% yield].[34] The chirality at the carbon alpha to the NHTs group is well retained during the transfer hydration.

In 2013 and 2015, Feng and coworkers used Pd(OAc)$_2$/PPh$_3$/aldoxime-mediated transfer hydration to derivatize ß-aminonitriles to ß-aminoamides (Scheme 21).[35,36] This formed a part of their study on the utility of ß-aminonitrile products obtainable through their asymmetric Mannich reaction of silyl ketene imines with aldimines[35] or isatine-derived ketimines.[36] Each reaction gave the amide products with retention of the stereochemistry.
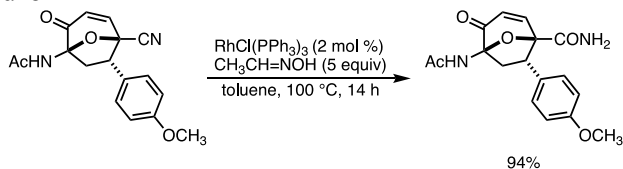

Scheme 21. Pd-catalyzed transfer hydration of ß-aminonitriles.

In 2015, Waser and coworkers developed Pd-catalyzed asymmetric decarboxylative allylation of cyanoketoesters and derivatized one of their chiral cyanoketone products by means of Pd-catalyzed transfer hydration using acetaldoxime as an H$_2$O donor (Scheme 22).[37]
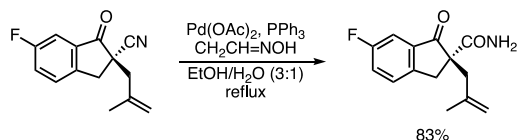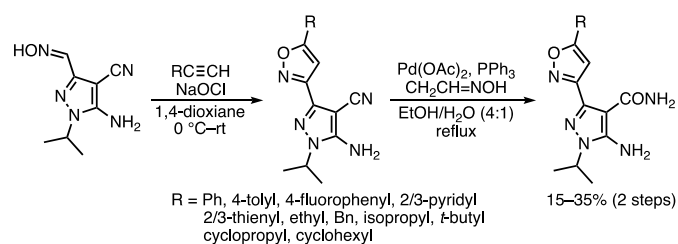

Scheme 22. Pd-catalyzed transfer hydration of cyanoketone.

In 2016, Sarpong and coworkers employed Rh-catalyzed transfer hydration using acetaldoxime[18] to derivatize a cyano-functionalized [3,2,1]oxabicyclooctenone to an amide analogue (Scheme 23).[38] The hydration proceeds efficiently with retention of the oxabicyclooctenone skeleton.
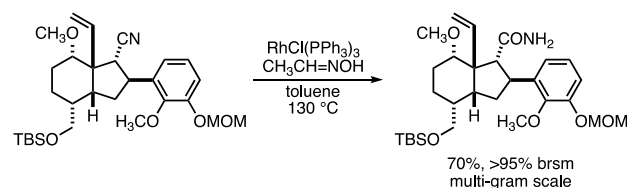

Scheme 23. Rh-catalyzed transfer hydration of cyano group on [3,2,1]oxabicyclooctenone.

In 2017, Sim and coworkers used acetaldoxime-mediated, palladium-catalyzed transfer nitrile hydration to prepare 5-amino-3-(5-functionalized-oxazol-3-yl)-1-isopropyl-1*H*-pyrazole-4-carboxamides as specific RET kinase inhibitors (Scheme 24).[39] Oxazole formation through [2+3] cycloaddition of aldoxime and various alkynes is followed by transfer hydration with the Pd(OAc)$_2$−PPh$_3$ catalytic system, affording the corresponding primary amides in 15–35% yields in 2 steps. One of the products (R = cyclopropyl) is a potent inhibitor of RET kinase.

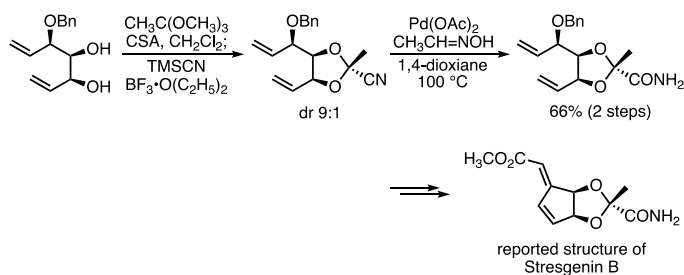**Scheme 24.** Oxazole formation and Pd-catalyzed transfer hydration.

In 2017, Sarpong and coworkers used Rh-catalyzed transfer hydration with acetaldoxime in their total synthesis of diterpenoid alkaloids (Scheme 25).[40] The chemoselectivity is so high that recycling the unreacted nitrile results in >95% overall yield based on the recovered starting material. The amide product could be produced on a multi-gram scale and served as a common synthetic intermediate for a series of diterpenoid alkaloids (weisaconitine D, liljestrandinine, cochlearenine, paniculamine, and *N*-ethyl-1α-hydroxy-17-veratoyldictyzine).

Scheme 25. Rh-catalyzed transfer hydration of highly functionalized nitrile for the synthesis of diterpenoid alkaloids.

In 2018, Chan and Koide used Pd-catalyzed transfer hydration with acetaldoxime in their total synthesis of a reported structure of stresgenin B (Scheme 26).[41] The authors found that orthoester formation from a diol followed by cyanation gives a cyanoketal, and this cyanoketal undergoes Pd(OAc)$_2$-catalyzed transfer hydration using acetaldoxime to afford an amide in 66% yield from the diol. The development of this hydration protocol was initiated on the basis of their observation that the transfer

hydration using RhCl(PPh₃)₃ gives trace amounts of the desired amide. Typical direct hydration conditions such as alkaline H_2O_2 and Parkins' Pt catalyst are not suitable for the conversion of this cyanoketal to the amide, because ring-opening of the dioxolane proceeds competitively.

Scheme 26. Pd-catalyzed transfer hydration of a cyanoketal in the total synthesis of a reported structure of stresgenin B.

In 2019, Sarpong and coworkers elegantly employed Rh-catalyzed transfer hydration using acetaldoxime in their total synthesis of ambiguine P (Scheme 27).[42] Hydration of a highly congested, functionalized nitrile gives a mixture of the corresponding amide and its synthetically equivalent lactam. Treatment of this mixture with methyl formate under basic conditions followed by reduction of the ketone group and ring-opening of hemiaminal ether provides a formylated product. The amide group serves as a directing group for regioselective formylation of a highly functionalized ketone.
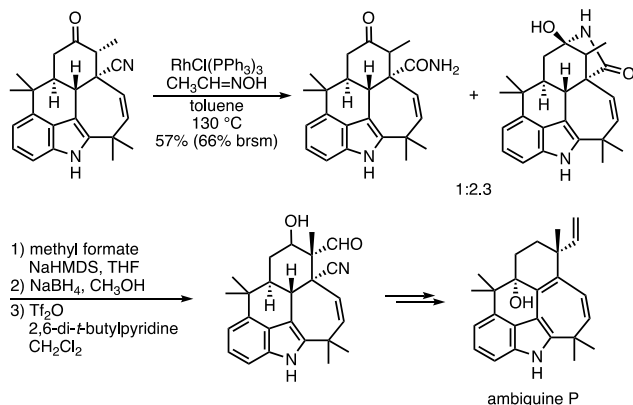
Scheme 27. Rh-catalyzed transfer nitrile hydration in the total synthesis of ambiguine P.

Conclusion

This digest paper has focused on recent developments in the metal-catalyzed transfer hydration of nitriles to afford amides, with aldoximes or amides as H_2O donors.

The amide-mediated transfer hydration of nitriles began with the identification of palladium-catalyzed interconversion between nitriles and amides by Maffioli in 2005. Since Huang demonstrated that this protocol is effective in hydrating a structurally complex nitrile under mild conditions, Pd-catalyzed transfer hydration has been widely used in various synthetic scenarios. Naka's systematic design of catalyst/amide reagent/solvent systems expanded the scope of this catalysis to nitriles that are otherwise difficult to selectively hydrate. Examples include hydration of 1,3-dinitriles and diarylated

cyanohydrins in acetic acid or an H_2O/CH_3CN mixture. Singh demonstrated that the amide-mediated transfer hydration of nitriles can be catalyzed by metal nanoparticles.

The development of aldoxime-mediated transfer hydration was led by two key discoveries in 2009: Kim's $Pd(OAc)_2$-PPh_3 catalytic system and Chang and Lee's method using a $RhCl(PPh_3)_3$ catalyst. Aldoxime-mediated nitrile hydration can be catalyzed by various homogeneous and heterogeneous metallic species (e.g. Cu, Zn, In, Ir). In particular, Rh and Pd catalytic systems have been utilized in the synthesis of natural products and bioactive molecules. These methods have also been used to derivatize representative chiral nitrile products in methodology studies.

Whereas aldoxime-mediated nitrile hydration is exothermic, the amide-mediated nitrile hydration is thermodynamically almost neutral. Therefore, when the overall scheme is not sufficiently exothermic, the use of excess amounts of amide reagents or non-equilibrium conditions (e.g. reactions under continuous evacuation) is desirable in order to overcome incomplete conversion and to achieve high product yields.

Although numerous methods have been developed to hydrate nitriles with water, it remains a challenge to selectively hydrate nitriles with retention of other acid-/base-sensitive functional groups. A common advantage of the amide- and aldoxime-mediated transfer hydration is the high level of chemoselectivity for nitrile hydration over other hydrolysable functional groups (e.g. esters, methoxymethyl ethers). Such selectivity has been best demonstrated with catalytic systems involving $Pd(NO_3)_2$ or $Pd(CH_3CN)_4(BF_4)_2$/acetamide/acetic acid, $RhCl(PPh_3)_3$/acetaldoxime/toluene, and $Pd(OAc)_2$/acetaldoxime/1,4-dioxane. In some cases, the catalytic activity for the transfer hydration is higher than that of existing catalysts for the direct hydration, allowing rapid formation of the amide products under mild conditions. In particular, the hydration of oily substrates can be performed under milder conditions with the transfer hydration methodology because it can be run in dehydrated organic solvents. Thus, synthetic applications of these transfer hydration under dehydrated conditions are becoming more common. However, further development of improved catalytic systems is still needed. For example, selective hydration of the cyano group in (R)-3-hydroxy-3-methyl-5-hexenenitrile can hardly be achieved by metal-catalyzed direct hydration, and the palladium-catalyzed transfer hydration using acetamide is inefficient (Scheme 28).[43,44] In addition, efficient methods for removal and recycling of the coproduced nitriles and excess water donors (amides and aldoximes) remain to be developed.
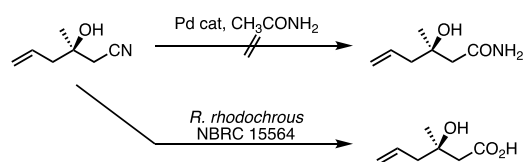
Scheme 28. A challenging nitrile hydration.

Acknowledgments

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