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Transfer Hydration of Dinitriles to Dicarboxamides

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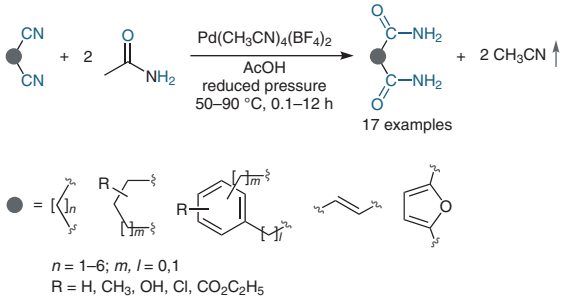

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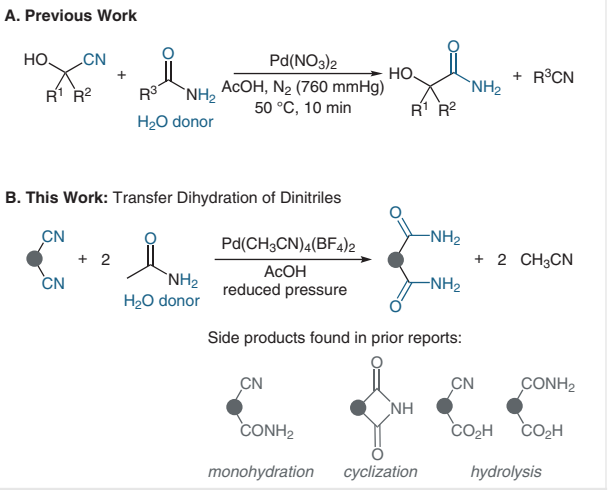
Abstract We present a robust method for double transfer hydration of dinitriles to afford diamides. The transfer hydration of 1,*n*-dinitriles (*n* = 1–6) proceeds smoothly in the presence of a palladium(II) catalyst with acetamide as a water donor, affording the corresponding diamides in moderate to high yields, without involving significant side reactions such as monohydration or cyclization. The equilibrium was shifted in the forward direction by removing coproduced acetonitrile under reduced pressure.

Keywords hydration, nitriles, palladium, amides, diamides

Dicarboxamides are important synthetic intermediates for fine chemicals and show interesting physical properties due to their hydrogen-bonding ability.[1,2] The double hydration of 1,*n*-dinitriles is a powerful method for producing 1,*n*-diamides.[3] While this simple approach has been successful using typical homogeneous[4] and heterogeneous[5] catalysts, the substrate scope for 1,2- and 1,3-dinitriles remains limited due to incomplete conversions and the occurrence of side reactions. In the course of our study on the catalytic selective hydration of unsaturated compounds,[6] we recently found that palladium(II)-catalyzed transfer hydration of cyanohydrins proceeds efficiently with carboxamides as a water donor (Scheme 1, A).[7] We expected that the double hydration of dinitriles to diamides could be achieved by extending this Pd-catalyzed transfer (de)hydration catalysis.[8,9] Here we show that the double transfer hydration of dinitriles to diamides proceeds well in the presence of a Pd catalyst with acetamide as a water donor under reduced pressure (Scheme 1, B). Unlike previous methods, the present protocol does not suffer from incomplete reaction (monohydration to afford cyanoamides) or side reactions such as cyclization to form carbocyclic imides and hydrolysis to cyano- or aminocarbonyl-carboxylic acids.



Scheme 1 Transfer hydration of nitriles

Building on our previous work,[7] we initially focused on the selective transfer hydration of 1,3-dinitriles to afford 1,3-diamides, for which no practical method currently exists. Using glutaronitrile (**1a**) as a model substrate for 1,3-dinitriles, we optimized the reaction conditions for hydration of **1a** to 1,3-diamide **2a** (Table 1). Table 1, entry 1 shows the conditions and results optimized for a closed reaction vessel containing air (760 mmHg). The transfer hydration of **1a** with acetamide ($AcNH_2$) in the presence of $Pd(CH_3CN)_4(BF_4)_2$ (Pd/**1a**/$AcNH_2$ = 0.01:1:10) in acetic acid (2 mL) proceeded smoothly at 50 °C. ^1H NMR analysis of the reaction mixture indicated the complete consumption of **1a** and the formation of the desired diamide **2a** (73%) and monohydrated **3a** (25%). The reaction with a smaller amount of acetamide (**1a**/$AcNH_2$ = 1:2) resulted in incomplete conversion of **1a** and lower yields of **2a** (29%) and **3a** (58%, Table 1, entry 2). Diamide **2a** was hardly obtained without acetamide or when water was used in place of ac-

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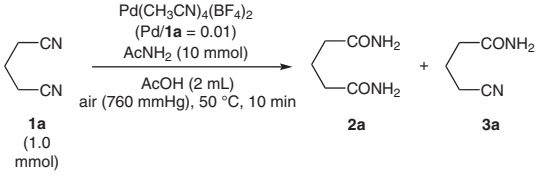
etamide (Table 1, entries 3 and 4). A Pd catalyst was prerequisite (Table 1, entry 5). $Pd(NO_3)_2$[7] was as reactive as $Pd(CH_3CN)_4(BF_4)_2$ (Table 1, entry 6) but $PdCl_2$ was totally unreactive (Table 1, entry 7). The reaction in methanol was much slower than that in acetic acid (Table 1, entry 8).

Table 1 Reaction Development[a]



Entry	Changes from the above scheme	Yield of **2a** (%)[b]	Yield of **3a** (%)[b]
1	none	73	25
2	**1a**/$AcNH_2$ = 1:2	29	58
3	without $AcNH_2$	<1	<1
4	H_2O instead of $AcNH_2$, **1a**/H_2O = 1:10	<1	15
5	without $Pd(CH_3CN)_4(BF_4)_2$	<1	<1
6	$Pd(NO_3)_2$ instead of $Pd(CH_3CN)_4(BF_4)_2$	70	28
7	$PdCl_2$ instead of $Pd(CH_3CN)_4(BF_4)_2$	<1	<1
8	CH_3OH instead of AcOH	3	41
9	under N_2 (760 mmHg)	72	28
10	reduced pressure (0.8–1.2 mmHg)[c]	81	17
11	**1a** (10 mmol), reduced pressure, 1 h[c,d]	>99	<1
12	**1a** (10 mmol),Pd/**1a** = 0.001, reduced pressure, 1 h[c,d]	99	1

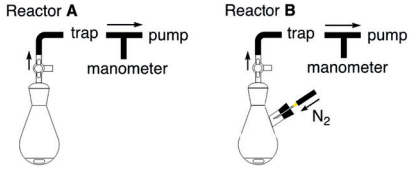
[a] Pd/**1a**/$AcNH_2$ = 0.01:1:10, in a closed reaction vessel.
[b] Determined by ^1H NMR spectroscopy using mesitylene as an internal standard.
[c] Reduced pressure by continuous evacuation (see reactor A in Table 2 graphic).
[d] AcOH (20 mL), 0.8–1.2 mmHg.

While reaction under a nitrogen atmosphere was as effective as that in air (Table 1, entry 9 vs entry 1), the product yield much increased when the pressure was reduced (Table 1, entry 10). Under reduced pressure, acetic acid and coproduced acetonitrile (byproduct) were removed from the reaction medium, leaving a solid crude mixture that contained **2a** in 81% yield. This protocol is more effective when all the volatile components were removed by continuous evacuation for 1 h (10 mmol scale, Table 1, entry 11). Under such conditions, the catalyst loading was successfully reduced (Pd/**1a** = 0.001:1, Table 1, entry 12). No obvious side reactions were observed throughout the experiments in Table 1 (entries 1–12).

The higher efficiency under reduced pressure (Table 1, entry 10) as compared with that at 760 mmHg (Table 1, entries 1 and 9) is likely to be due to two factors: (1) The equilibrium of the reversible transfer hydration reaction would be shifted to the right by the removal of the coproduced acetonitrile under reduced pressure;[10] (2) the reaction rate at the late stage of the reaction would be increased because of the higher concentration of the Pd catalyst (and **1a** or **3a**) resulting from removal of the solvent (acetic acid). Unlike the cyanohydrin transfer hydration,[7] the removal of acetonitrile is necessary for achieving high product yield of **2a** because the transfer hydration of **1a** to **2a** is energetically almost neutral. Analysis of the pressure dependence indicated that the solvent removal is critical (Table 2). Whereas transfer hydration of **1a** at 124 mmHg (continuous evacuation with a diaphragm pump, Table 2, entry 1) gave a similar result with that at 760 mmHg (1 atm, closed, *t* = 10 min, Table 1, entry 1), product yields were higher under lower-pressure conditions (56 and 0.8–1.2 mmHg) where the reaction mixtures were concentrated to form solidified residues (Table 2, entries 2 and 3). As compared with these experiments using a typical reaction setup (reactor A, Table 2, entries 1–3), the solvent removal was more efficient and the product yields were even higher at 80–120 and 54–58 mmHg when N_2 was continuously blown to the reaction mixture through a needle during the evacuation (reactor B, Table 2, entries 4 and 5).[11]

Table 2 Pressure Dependence in the Transfer Hydration of **1a**[a]

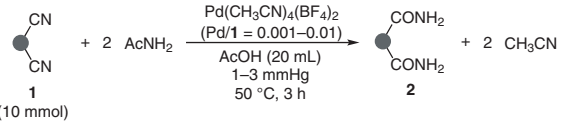
Entry	Reactor	Pressure (mmHg)	Yield of **2a** (%)[b] *t* = 10 min	*t* = 15 min
1	A	124	71	74
2	A	56	80	80
3	A	0.8–1.2	81	>99
4	B	80–120	>99	>99
5	B	54–58	97	>99



[a] Conditions are analogous to those in Table 1, entry 1 unless otherwise noted.
[b] Determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

The scope of this method is summarized in Table 3.[12,13] The transfer hydration of **1a** at 10 mmol scale under the optimized conditions for 2 h (sufficient time to completely remove volatile components), followed by washing the crude mixture with acetonitrile and drying under reduced pressure, afforded the desired diamide **2a** in 80% yield (1.04 g) with minor contamination with acetamide (27 mg, as determined by ^1H NMR spectroscopy). Recrystallization from methanol gave pure **2a** in 69% overall yield. The decreased yield as compared with that in Table 1, entry 12 is due to the loss of product during the purification.

Table 3 Substrate Scope[a]

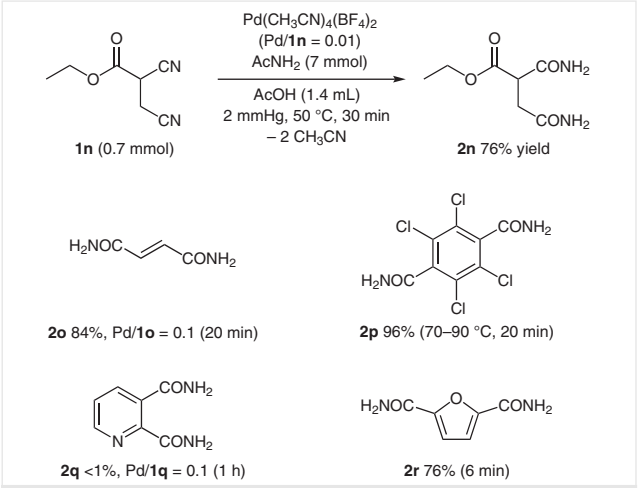


1	Product 2		Pd/1	Yield (%)[b]
1a[c]		2a	0.001	80 (69)
1b	H_2NOC $CONH_2$	2b	0.01	77 (43)
1c	H_2NOC $CONH_2$	2c	0.001	83 (61)
1d	$CONH_2$ $CONH_2$	2d	0.001	68 (63)
1e[d]	HO $CONH_2$ $CONH_2$	2e	0.003	55 (32)
1f	$CONH_2$ $CONH_2$	2f	0.003	83 (54)
1g	$CONH_2$ $CONH_2$	2g	0.001	89 (84)
1h	$CONH_2$ $CONH_2$	2h	0.003	94 (79)
1i	$CONH_2$ $CONH_2$	2i	0.001	82 (74)
1j	$CONH_2$ $CONH_2$	2j	0.003	79 (66)
1k	$CONH_2$ $CONH_2$	2k	0.01	79
1l[c]	H_2NOC $CONH_2$	2l	0.001	91
1m[e]	$CONH_2$ H_2NOC	2m	0.001	91

[a] Conditions: Pd/**1**/$AcNH_2$ = 0.001:1:10.[12]
[b] Yields of products with minor contamination by acetamide as determined by NMR spectroscopy. Overall yields after recrystallization are given in parenthesis.
[c] 2 h.
[d] 3.67 mmol scale.
[e] 70 °C, 1.5 h.

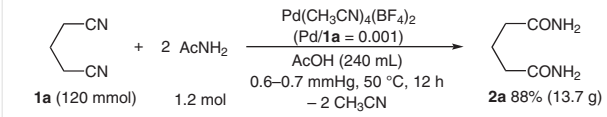
This protocol proved effective for the transfer hydration of commercially available aliphatic dinitriles with a C1 (**1b**), C2 (**1c**), C3 (**1d–f**), C4 (**1g**, **h**), C5 (**1i**), or C6 (**1j**) linkage, as well as aromatic dinitriles **1k–m** (Table 3). As the diamides are less soluble than acetamide in typical solvents (e.g. acetonitrile, THF, and water), washing of the crude mixture with these solvents and drying under reduced pressure yielded diamides **2a–m** with only minor contamination with acetamide. They were further purified by recrystallization to give analytically pure products. Most of these dinitriles uniformly underwent the transfer hydration within 2–3 h to give the corresponding diamides **2** under optimized conditions (Pd/**1** = 0.001–0.003). 1,3-Dinitrile **1e** bearing a hydroxyl group could be hydrated to diamide **2e**. The transfer hydration reactions of dinitriles **1b** and **1k** were conducted with higher Pd loadings (Pd/**1** = 0.01) because the hydration of **1b** was slower and that of **1k** involved side reactions under the optimized conditions (Pd/**1** = 0.001). In order to ensure dissolution of poorly soluble **1m** in AcOH, transfer hydration of **1m** was conducted at 70 °C.

Further studies on the functional group compatibility were conducted on smaller scales (Scheme 2). The presence of ethyl ester (**1n**), substituted olefin (**1o**), aryl chloride (**1p**), and furyl (**1r**) moieties were found to be well tolerated whereas a pyridine functionality in **1q** significantly inhibited the transfer hydration.



Scheme 2 Functional group compatibility

Furthermore, the transfer hydration protocol was scalable to 10 gram scale (Scheme 3): The reaction of 120 mmol **1a** followed by recrystallization from methanol gave **2a** in 88% yield (13.7 g). The reaction mixture was evacuated for a longer time (12 h) to remove the solvent and coproduced acetonitrile completely.



Scheme 3 10 gram-scale synthesis

In summary, we have developed a robust, scalable method for double transfer hydration of dinitriles. The transfer hydration of 1,*n*-dinitriles (*n* = 1–6) proceeds

smoothly in the presence of a palladium(II) catalyst with acetamide as a water donor, affording the corresponding diamides in high yields. Notably, the current protocol is the first to achieve efficient conversion of 1,3-dinitriles into 1,3-diamides without significant side reactions.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690026.

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(11) Reactor A was used throughout the experiments unless otherwise noted.

(12) **Typical Procedure for Double Transfer Hydration**
To a 500 mL round-bottom flask equipped with a stirring bar and a 2-necked Teflon stopcock were added glutaronitrile (**1a**, 942.1 mg, 10.0 mmol), acetamide (5900.5 mg, 99.9 mmol), and acetic acid (20 mL). The mixture was stirred at 50 °C for 30 min under open air (760 mmHg). $Pd(CH_3CN)_4(BF_4)_2$ (4.52 mg, 0.0102 mmol) was added to start the reaction, and the mixture was stirred at 50 °C for 2 h under reduced pressure (1–3 mmHg). The internal pressure was continuously reduced by means of a belt drive rotary vane vacuum pump (SATO VAC INC. USW-50) equipped with a 450 mL liq. nitrogen trap (for acetonitrile and acetic acid). The resulting pale-yellow crude mixture was washed with acetonitrile (50 mL) with sonication for 1 h to remove acetamide. The precipitate was collected by filtration on a membrane filter (Merck Millipore JHWP04700 0.45 μm pore size, hydrophilic PTFE membrane, 47 mm diameter) and dried in vacuo at 120 °C overnight to afford glutaramide (**2a**, 1043.3 mg, 80% yield) with minor contamination with acetamide (27.0 mg, as determined by ^{1}H NMR spectroscopy). The product (499.7 mg) was recrystallized from methanol to give analytically pure **2a** (418.9 mg, 69% overall yield).

(13) **Analytical Data of Selected Products**
Compound **2a**: white solid; mp 181–182 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.67 (quin, *J* = 7.6 Hz, 2 H), 2.03 (t, *J* = 7.6 Hz, 4 H), 6.69 (br s, 2 H), 7.24 (br s, 2 H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 21.3, 34.6, 174.5. IR (KBr): 3381 (NH), 3190 (NH), 1650 (CO) cm^{-1}. HRMS (FAB): *m/z* calcd for $[C_5H_{10}N_2O_2Na^+]$ [M + Na$^+$]: 153.0640; found: 153.0633.
Compound **2d**: white solid; mp 153–154 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.98 (d, *J* = 6.9 Hz, 3 H), 1.45–1.51 (m, 1 H), 1.62–1.69 (m, 1 H), 1.95–2.09 (m, 2 H), 2.19 (sext, *J* = 6.9 Hz, 1 H), 6.69 (br s, 2 H), 7.23 (br s, 2 H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 17.8, 29.3, 32.9, 39.0, 174.0, 177.5. IR (KBr): 3396 (NH), 3210 (NH), 1660 (CO) cm^{-1}. HRMS (FAB): *m/z* calcd for $[C_6H_{12}N_2O_2Na^+]$ [M + Na$^+$]: 167.0796; found: 167.0796.
Compound **2e**: white solid; mp 157–159 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.16–2.17 (m, 4 H), 4.15 (dquin, *J* = 6.1, 4.8 Hz, 1 H), 4.87 (d, *J* = 4.8 Hz, 1 H), 6.81 (br s, 2 H), 7.28 (br s, 2 H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 42.8, 65.1, 172.8. IR (KBr): 3411 (NH), 3184 (NH), 1651 (CO) cm^{-1}. HRMS (FAB): *m/z* calcd for $[C_5H_{10}N_2O_3Na^+]$ [M + Na$^+$]: 169.0589; found: 169.0581.
Compound **2f**: white solid; mp decomp. >150 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.59 (s, 2 H), 6.99 (br s, 1 H), 7.27–7.30 (m, 2 H), 7.38 (dt, *J* = 7.6, 1.4 Hz, 1 H), 7.43 (br s, 1 H), 7.47 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.68 (br s, 1 H), 8.22 (br s, 1 H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 39 (overlapped with DMSO-d_6), 126.4, 128.0, 129.6, 130.4, 134.0, 136.8, 170.7, 172.8. IR (KBr): 3394 (NH), 3195 (NH), 1650 (CO) cm^{-1}. HRMS (FAB): *m/z* calcd for $[C_9H_{10}N_2O_2Na^+]$ [M + Na$^+$]: 201.0640; found: 201.0632.

