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ARTICLE TYPE

Efficient and selective nitrile hydration reaction in water catalyzed by unexpected dimethylsulfinyl anion generated *in situ* from CsOH and DMSO†‡

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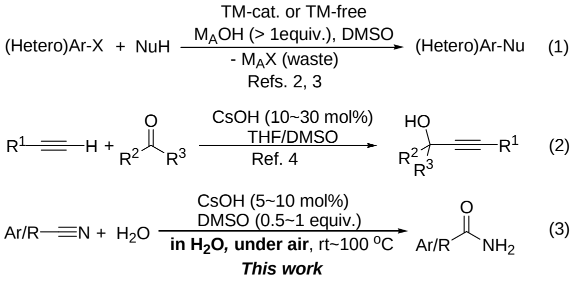
The unexpected dimethylsulfinyl anion (I), generated *in situ* from superbase system CsOH/DMSO, was found to be a highly active catalyst for controllable nitrile hydration reaction in water, which selectively afforded the versatile amides *via* interesting Cs-activated I-catalyzed direct and indirect hydration mechanisms involving an O-transfer process from DMSO onto nitriles.

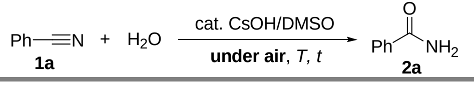
Akali hydroxides M_AOH (M_A = Na, K, Cs, etc.) are without doubt the most common and the most frequently used bases in all fields of chemistry; while dimethylsulfoxide (DMSO) is one of the most widely used aprotic polar solvent in synthesis. Due to exceptionally strong basicity attributed to synergetic effect of M_AOH and DMSO, M_AOH/DMSO are generally known as the superbasic media.[1-3] Initiated by Trofimov and coworkers,[1] M_AOH/DMSO were also widely employed by many groups in recent years, especially in transition metal (TM)-catalyzed[2] or TM-free[3] couplings of (hetero)aryl halides and nucleophiles (eq. 1). In all cases, both M_AOH and DMSO were used in large amounts as base and solvent. In contrast, M_AOH/DMSO-catalyzed reactions were extremely rare. To the best of our knowledge, only Knochel and co-workers reported a CsOH-catalyzed alkynylation of carbonyl compounds using DMSO as a co-solvent (eq. 2).[4] Herein we report an efficient and controllable nitrile hydration reaction catalyzed by an unexpected CsOH/DMSO system (eq. 3), which can successfully avoid undesired over hydrolysis of the nitriles in water under mild conditions, and provide a mild, efficient, practical, green, and scalable method for selective synthesis of the versatile amides from the readily available nitriles.



During our previous studies in M_AOH-mediated or -catalyzed synthetic methods[5] for cinnamonitrile[5a] and (hetero)aryl ether[3d-e] synthesis, we accidentally observed that the unexpected amides could be selectively obtained from corresponding nitriles by using M_AOH as the bases. Amides are important functional groups and versatile synthons in organic and pharmaceutical synthesis, biochemistry, natural products, and materials science.[6,7] Although various new methodologies have been developed,[7] nitrile hydration is still an effective, atom economic, straightforward, and thus an attractive way to obtain the target amides.[8-13] Since conventional nitrile hydration reactions under strong basic or strong acidic conditions have severe limitations,[6,8] and the modified methods still have drawbacks such as requiring large amounts of mixed acids[9] or peroxides,[10] or harsh conditions like high temperature and microwave irradiation,[11] TM-catalyzed reactions[8,12] and nitrile hydratase (NHase)-catalyzed enzymatic methods[13] have also become useful alternatives. However, except few examples, expensive and air-sensitive rare metal complexes comprising caprious ligands, high catalyst loadings, harsh conditions such as high temperature (>100 °C), inert atmosphere protection, and long reaction time, as well as metal contaminant in products are associated problems in TM-catalyzed methods. Some methods even require organic solvents instead of the greener water.[8,12] On the other hand, although enzymatic methods are usually mild, selective, efficient, and enviromentally-benign,[13] they also have problems such as narrow scope of the substrates, sensitive nature of NHase emzymes that requires special storage, handling, and treatment, as well as difficulties in catalyst/product separation. Therefore, efficient and practical methods that can employ easily available, water-soluble, even TM-free catalysts under milder conditions using water as the green solvent are still highly desirable. Above interesting findings in our laboratories[3d-e,5a] intrigued us to investigate the reaction in detail.

An initial test on hydration of benzonitrile (**1a**) showed that, different to known basic methods,[6,8,10,11] CsOH exhibited an extraordinary catalytic activity and afforded a moderate yield of benzamide (**2a**) in water at 100 °C (Table 1, run 1); whereas, over hydrolysis of **1a** to PhCOOH was inevitable in the reaction, because amide hydrolysis is a difficult-to-control reaction kinetically faster than the nitrile hydration step.[8] Solvent screening showed again DMSO was the best one[14] as in our previous findings,[3d-e,5a] as over hydrolysis of **1a** could be inhibited in DMSO to give a high yield of **2a** (run 2).[15] The reaction was very efficient at 100 °C and the reaction time could be shortened to only 1 h (run 3), indicating that CsOH/DMSO was a highly active system. We also found H_2O/DMSO ratio was flexible so that DMSO could be used in catalytic amounts. Thus, a reaction in water using 10 mol% of CsOH and 0.5 equiv. of DMSO afforded a high 92% yield of **2a** (run 4). Another simple sulfoxide $PhS(O)CH_3$ was also tested, but it was not effective under the same condition (run 5). Moreover, CsOH could be used in a lower amount (5 mol%) and the reaction was still very efficient at a lower temperature of 60 °C (runs 6-8). Thus, the best result was obtained by running the reaction in water at 60 °C by using 5 mol% of CsOH and 1 equiv. of DMSO, giving a high 94% yield of **2a** (run 8). In contrast, lower amounts of either CsOH or DMSO or both led to obvious decrease in product yields.[14] By employing the M_AOH/DMSO protocol, other bases also exhibited certain catalytic activities,[14] which are also surprising results in comparison with the known basic methods,[6,8] but CsOH was still the best one for being much more effective than others.[16] Moreover, CsOH/DMSO system was so active that the reaction was still efficient at room temperature, giving high yields of **2a** in prolonged times (runs 9-10). In contrast, no obvious product was detected in the reaction without adding DMSO under the same condition (run 11). All above results clearly revealed that CsOH is the best base precatalyst and DMSO the best sulfoxide, as well as their crucial roles and obvious synergetic effect in the reaction. Finally, inert atmosphere protection is not necessary at all by employing the CsOH/DMSO method. Thus, all reactions could be readily performed in air, greatly simplifying the condition and operation of the reactions.

Table 1. Optimization of the reaction conditions.[a,14]



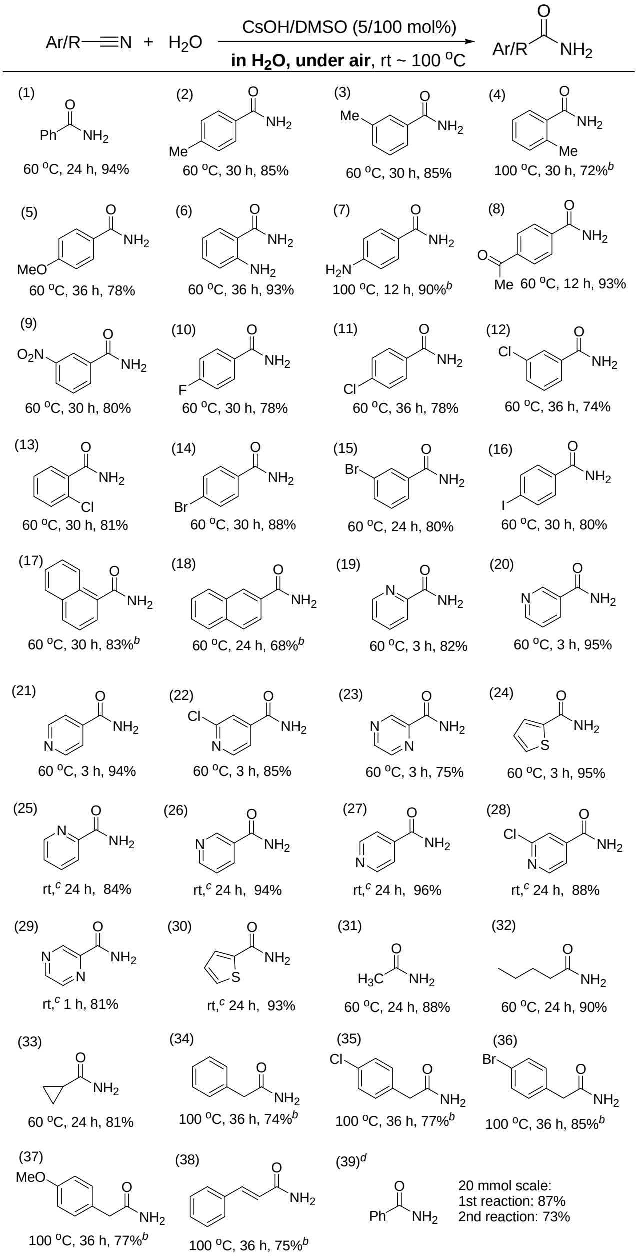
run	$Cs_{mol\%}$	DMSO	H_2O	*T, t*	**2a**%[b]
1	10	-	0.5 mL	100 °C, 24 h	65[c]
2	10	0.5 mL	1.1 equiv.	100 °C, 24 h	85[d]
3	10	0.5 mL	1.1 equiv.	100 °C, 1 h	88
4	10	0.5 equiv.	0.5 mL	100 °C, 1.5 h	92
5[e]	10	0.5 equiv.	0.5 mL	100 °C, 2 h	trace
6	5	0.5 equiv.	0.5 mL	100 °C, 1.5 h	89
7	5	1 equiv.	0.5 mL	100 °C, 1.5 h	94
8	5	1 equiv.	0.5 mL	60 °C, 24 h	94
9	5	1 equiv.	0.5 mL	rt,[f] 132 h	85[d]
10	5	0.25 mL	0.25 mL	rt,[f] 84 h	90
11	5	-	0.5 mL	rt,[f] 84 h	trace

[a] Unless otherwise noted, the mixture of **1a** (2 mmol) and $CsOH·H_2O$ (99% purity) in H_2O/DMSO was directly sealed under air in a Schlenk tube and then stirred and monitored by TLC. [b] Isolated yields based on **1a**. [c] Reaction incomplete and over hydrolysis of **1a** giving PhCOOH was observed. [d] Slight over hydrolysis of **1a** was observed. [e] $PhS(O)CH_3$ was used. [f] Ca. 30 °C.

The optimized conditions were then applied to various nitriles to extend the scope of the method (Table 2). Firstly, most electron-rich and -deficient aromatic nitriles reacted slightly slower than **1a** (run 1), but they could still afford generally good to high yields of the amides at 60 °C (runs 2-18). The reaction of *o*-methyl benzonitrile was much slower than its *p*- and *m*-isomers (runs 2-3). Thus, more amounts of CsOH and a higher temperature of 100 °C were required (run 4). This should be attributed to the steric effect of the *o*-methyl group. Similarly, reactions of naphthonitriles also required 10 mol% of CsOH (runs 17-18). Contrarily, *o*-amino benzonitrile was readily hydrated under the standard condition (run 6), but the *p*-isomer required a harsher condition to obtain a good result (run 7). The reason for this difference is not clear yet. What worth noting is that, in addition to nitriles with inert substituents (runs 2-5, 17-18), those bearing reactive groups such as NH_2, acetyl, NO_2, F, Cl, Br, and I could also be tolerated in the present method to give good to high yields of the target amides (runs 6-16), which may provide more synthetic possibilities if these reactive groups can be utilized in further transformations. As to nitriles bearing heteroarenes like pyridine, pyrazine, and thiophene, we initially run the reactions at 60 °C and found they were much faster than the aromatic nitriles, giving good to high yields of the amides in only 3 h (run 19-24), with tolerance of a reactive 2-chloropyridyl block (run 22). We later found the reactions of these substrates could even be very efficient at room temperature (runs 25-30). Cyanopyrazine is an exceptional example, because a strong exothermic reaction quickly occurred at room temperature to give a good yield of pyrazinamide in only 1 h (run 29). This comparatively higher reactivity of the heteroaryl nitriles may be attributed to the activation of CN group by the adjacent heteroarenes. By employing this new method, reactions of the usually less reactive aliphatic nitriles were also highly efficient. Thus, acetonitrile, valeronitrile, and cyclopropyl nitrile afforded corresponding amides in good to high yields under the standard conditions (runs 31-33). In contrast, 2-arylacetonitriles were less reactive and required 100 °C and 10 mol% CsOH to obtain good results (runs 34-37). This may be due to the presence of the adjacent aryl groups, which led to certain steric hindrance as in the case of *o*-methyl benzonitrile (run 4). Moreover, an alkenyl nitrile, cinnamonitrile, was also suitable substrates for the reaction, affording cinnamamide in good yields (runs 38). It should also be mentioned that, in all the above reactions, similar to the reactions of **1a** (Table 1), formation of byproduct acids due to over hydrolysis of the nitriles could be well controlled by employing the CsOH/DMSO system, and thus, no acid byproducts were observed in most cases.

We also tested the scalability of the method and recoverability of the CsOH/DMSO/H_2O reaction media. Thus, as shown in run 39 of Table 2, by simple filtration, the first 20 mmol reaction of **1a** afforded 87% yield of **2a** and a CsOH/DMSO/H_2O filtrate. The latter was then recovered and directly reused in another 20 mmol reaction of **1a**, which afforded 73% yield of **2a**. This result revealed the practicality and potential of the new nitrile hydration method in synthesis.

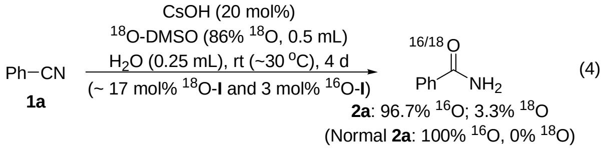
Table 2. Substrate extension of the new nitrile hydration reaction.[a]



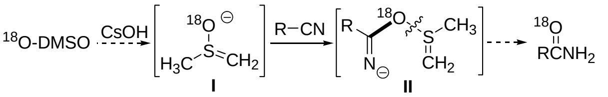
[a] Unless otherwise noted, nitrile (2 mmol), DMSO (2 mmol, 1 equiv.), and CsOH·H_2O (5 mol%) in H_2O (0.5 mL) were directly sealed under air in a Schlenk tube and then stirred and monitored by TLC. Isolated yields based on nitrile. [b] 10 mol% CsOH·H_2O. [c] Ca. 30 °C. [d] CsOH/DMSO/H_2O filtrate recovered from the 1st reaction was directly reused in the 2nd reaction.

Above results revealed that this new nitrile hydration reaction is a mild and efficient, general and practical, green and scalable method for selective synthesis of amides that is also highly tolerant with reactive functional groups, suitable for a wide range of nitriles and large scale preparations, and thus should be a more advantageous method than many of the known ones.[6,8-13] In addition, successful inhibition of nitriles' over hydrolysis in water, synergetic effect of CsOH and DMSO, and contrary results in the reactions used or used not DMSO (Table 1, runs 9-11) indicated that a more active new species generated *in situ* from CsOH and DMSO other than the free hydroxide anion OH^- should be responsible to catalyze the reaction, and mechanism of the reaction should thus be interesting. Indeed, it has been known that DMSO can be easily deprotonated by bases to form ambident dimethylsulfinyl anion (**I**) even at room temperature;[17] we thus deduced that **I** might be the active catalyst for the reaction.

To prove this hypothesis, ^{18}O-DMSO (containing 86% ^{18}O) was prepared and tested.[14,18] As shown in eq. 4, in contrast to a normal sample of **2a** that contains no ^{18}O-**2a** at all, secondary mass analysis of the product obtained from the reaction of ^{18}O-DMSO showed that it contains 3.3% ^{18}O-**2a** (addition of 20 mol% CsOH equals to generation of at best ~17 mol% ^{18}O-**I** and ~3 mol% ^{16}O-**I**), which should correspond to an ^{18}O-DMSO-participated ^{18}O-transfer process.[14,19] Indeed, O-attack at various electrophiles and O-transfer reactions are common transformations among sulfoxides like DMSO,[19] and one of us had previously reported O-transfer reactions of DMSO.[19d,g] Above contrastive results may imply that an intimate interaction between **I** and the nitrile most likely took place to fulfill the O-attack of **I** at CN moiety to form new C-O bond and intermediate **II**, followed by S-O bond cleavage to give O-transferred amides (eq. 5). These results and the findings in condition screening[14] also indicated that **I** should be the true catalyst and the reaction a TM-free process.



(4)



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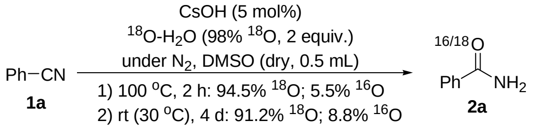
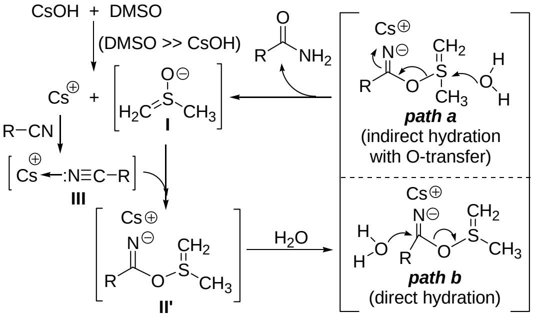


(6)

On the other hand, partial selectivity of the O-transferred product (eqs. 4-5) also indicated that other hydration processes should also exist in the reaction. Thus, controlled parallel hydration reactions of **1a** were investigated by using ^{18}O-H_2O as the water source in dry DMSO. As shown in eq. 6, ^{18}O-**2a** was obtained in high selectivities,[14] indicating that direct hydration of **1a** with ^{18}O-H_2O is the dominant way. The results also showed that selectivity of ^{16}O-**2a** derived from usual ^{16}O-DMSO increased by 17~60% from the reaction at 100 °C to the one at room temperature (eq. 6). Lower temperature should correspond to lower reactivity of ^{18}O-H_2O as well as stronger interaction between **I** and **1a**. Thus, selectivity of ^{16}O-DMSO-participated process to give ^{16}O-**2a** should be higher in the reaction at room temperature than the one at 100 °C. Clearly, this hypothesis consists well with the above findings (eq. 6), supporting the existence of DMSO-participated O-transfer process (eq. 5).

Since CsOH also exhibited a much higher catalytic activity than other M_AOH,[14] we propose Cs^+ may hold certain cesium effect[16] in the reactions, possibly through a strong coordination with and activation of the strong ligating CN group analogous to the cases in TM-catalyzed reactions,[8,12] and consequently enhance the reactivity of the CN group in hydration steps.

A possible mechanism was then proposed (Scheme 1). Thus, CsOH readily reacts with DMSO to give dimethylsulfinyl anion **I** and Cs^+;[17] meanwhile, coordination of Cs^+ with nitriles may form Cs-activated complex **III**.[8,12,16] To avoid existence of free OH^- that can lead to over hydrolysis of nitriles to byproduct acids, more DMSO than CsOH must be added to ensure complete consumption of OH^-. Then, O-addition of **I** at the carbon of CN moiety of **III** may take place to give **II'**, a more reactive intermediate than free **II** (eq. 5) due to activation by coordinating with Cs^+.[16] Next, H_2O may attack the S centre of DMSO moiety to afford amides and regenerate **I** and Cs^+ *via* an old S-O bond cleavage and a new S-O bond formation (*path a*), which can be described as a DMSO-participated indirect hydration process involving O-transfer from DMSO onto nitriles to give O-transferred amides; otherwise, H_2O may also directly attack the carbon of CN moiety of **II'** *via path b* to afford amides and regenerate Cs^+ and **I**. Although direct hydration of nitirles by free OH^- can not be excluded completely, it should be a less possible process, because the preceding contrastive results have clearly showed that **I** is a much more active catalyst than free OH^- (Table 1, runs 9-11), even not to mention that free OH^- has already been controlled in very low levels by using much more amounts of DMSO than CsOH.



Scheme 1. Proposed mechanism for Cs-activated dimethylsulfinyl anion-catalyzed controllable and selective nitrile hydration reaction in water

In summary, we developed a mild and efficient, general and practical, green and scalable method for selective synthesis of the versatile amides from the readily available nitriles in water by using a simple, water soluble, and recoverable CsOH/DMSO catalyst system. Mechanistic studies showed that the reaction may proceed *via* novel and unexpected Cs-activated processes including a DMSO-participated indirect hydration reaction involving O-transfer from DMSO onto nitriles to give O-transferred amides or a dimethylsulfinyl anion-catalyzed direct hydration reaction of the nitriles with water.[20] Further extensions of the hydration method and deeper mechanistic insights are underway.

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† Dedicated to the memory of Professor Xian Huang on the occasion of his 80th birthday.

‡ Electronic Supplementary Information (ESI) available: experimental details, condition screening tables, product characterization, secondary mass analysis, and ^1H and ^{13}C NMR copies of all products. See DOI: 10.1039/b000000x/

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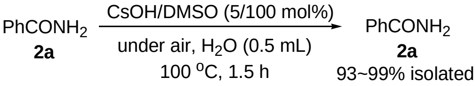
14 See Electronic Supplementary Information for detail.

15 High yields of **2a** could be recovered by treatment with CsOH/DMSO, indicating that amide hydrolysis could be inhibited by adding DMSO.



$$\underset{\mathbf{2a}}{PhCONH_2} \xrightarrow[\text{under air, } H_2O \text{ (0.5 mL)},\ 100\ ^{o}C,\ 1.5\ h]{\text{CsOH/DMSO (5/100 mol\%)}} \underset{\mathbf{2a}\ \text{93\textasciitilde 99\% isolated}}{PhCONH_2}$$

16 This may tentatively be attributed to cesium effect: (*a*) G. Dijkstra, W. H. Kruizinga and R. M. Kellogg, *J. Org. Chem.,* 1987, **52**, 4230; (*b*) E. J. Corey, Y. Bo and J. Busch-Petersen, *J. Am. Chem. Soc.,* 1998, **120,** 13000; (*c*) R. N. Salvatore, A. S. Nagle and K. W. Jung, *J. Org. Chem.,* 2002, **67**, 674; (*d*) F. Siopa, *Synlett*, 2009, 2048; (*e*) Ref. 4.

17 Dimethylsulfinyl anion (**I**) has been known for decades, but its catalytic activity was not known yet: (*a*) E. Buncel, E. A. Symons and A. W. Zabel, *Chem. Commun*., 1965, 173; (*b*) A. Rauk, E. Buncel, R. Y. Moir and S. Wolfe, *J. Am. Chem. Soc*., 1965, **87**, 5498; (*c*) E. Buncel, K.-T. Park, J. M. Dust and R. A. Manderville, *J. Am. Chem. Soc.,* 2003, **125**, 5388; (*d*) P. Haiss and K.-P. Zeller, *Org. Biomol. Chem.,* 2011, **9**, 7748.

18 A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.,* 1966, **88**, 1762.

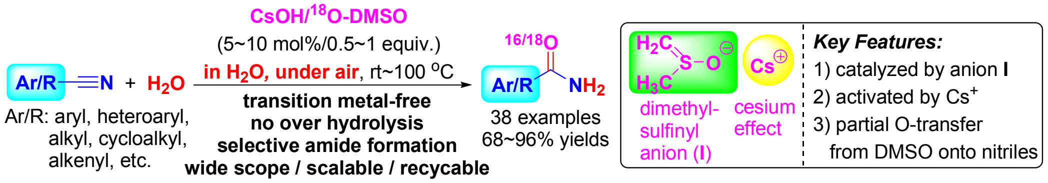
19 (*a*) S. Ma, H. Ren and Q. Wei, *J. Am. Chem. Soc.,* 2003, **125**, 4817; (*b*) C. Fu, X. Huang and S. Ma, *Tetrahedron Lett.,* 2004, **45**, 6063; (*c*) W. Li, J. Li, M. Lin, S. Wacharasindhu, K. Tabei and T. S. Mansour, *J. Org. Chem.,* 2007, **72**, 6016; (*d*) R. Xu, J.-P. Wan, H. Mao and Y. Pan, *J. Am. Chem. Soc.,* 2010, **132**, 15531; (*e*) Y. Ashikari, T. Nokami and J.-I. Yoshida, *J. Am. Chem. Soc.,* 2011, **133**, 11840; (*f*) Y. Ashikari, T. Nokami and J.-I. Yoshida, *Org. Lett.,* 2012, **14**, 938; (*g*) R. Xu, L. Yue and Y. Pan, *Tetrahedron,* 2012, **68**, 5046.

20 After submission of this work, we noticed that Bortolini and co-workers just reported a dimethylsulfinyl anion-catalyzed cross-benzoin reaction using *t*-BuOK as the base precatalyst and DMSO as the solvent: O. Bortolini, G. Fantin, V. Ferretti, M. Fogagnolo, P. Giovannini, A. Massi, S. Pacifico and Daniele Ragno, *Adv. Synth. Catal.,* 2013, **355**, 3244.

Table of Contents

Efficient and selective nitrile hydration reaction in water catalyzed by unexpected dimethylsulfinyl anion generated *in situ* from CsOH and DMSO

Haonan Chen, Wujie Dai, Yi Chen, Qing Xu,* Jianhui Chen, Lei Yu, Yajuan Zhao, Mingde Ye and Yuanjiang Pan*



Dimethylsulfinyl anion derived from CsOH/DMSO readily catalyzed nitrile hydration reaction in water to give selectively the versatile amides *via* interesting DMSO-participated mechanisms.
