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An efficient hydration of nitriles promoted by gallic acid derived from renewable bio-resources

Tao Deng,[a,b] and Cheng-Zhang Wang*[a,b]

Dedication ((optional))

Abstract: An efficient gallic acid promoted nitriles hydration at room temperature with ethanol/water as solvent has been developed. The present protocol offers a wide range of amides in moderate to good yields. Moreover, galla chinensis extract can serve as the promoter to perform the hydration, which also shows the potential utilization of natural feedstocks.

Introduction

Amide is a useful and prevalent key group in nature due to its ubiquitous in proteins, pharmaceuticals, biomolecules, constitute excellent intermediates, and other raw materials for synthetic organic chemistry (Figure 1).[1] Typical conventional reactions for amide formation have been extensively investigated in the past decades.[2] Among them, the hydration of nitriles seems to provide a direct and efficient approach, as it offers the most atom-economical access to valuable amide molecules.[3] However, traditional procedures requires strong acids and bases which results in high cost and by-products along with large amount of chemical waste (Scheme 1a).[4] Meanwhile, numerous metal catalysts such as Ru,[5] Au,[6] Rh,[7] Pd,[8] Pt,[9] Cu,[10] Mn[11] have been proven to achieve this transformation, along with one or more drawbacks, such as high temperatures, long reaction times, large excess of reagents and sometimes extra steps preparing catalyst (Scheme 1b). Hence, challenges still remain, but it is still highly desirable to develop more efficient, environmentally-benign and sustainable methods to obtain amides from nitriles.

With the growing emphasis on the applications of green principles in organic synthesis, significant effort has been dedicated to develop some green reaction media, catalysts, and reaction conditions.[12] An increasing number of chemists are drawing significant awareness to utilize natural feedstocks as catalyst or promoter in organic synthesis not only because of the abundance and benign nature of the renewable source which are the cause for the majority of waste and pollution but also because of the lower cost and lesser energy.[13] Among them, gallic acid is a widespread natural polyphenolic compound with strong antioxidant activity,[14-16] and it can be extracted from vegetal sources such as fruits, nuts, and flowers. Free radicals can be effectively scavenged by the phenolic hydroxyl group, by which can also act as a hydrogen donor.[17]

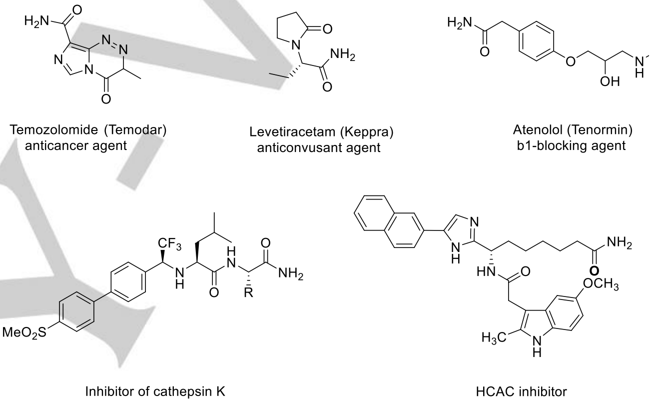

Figure 1. Representative pharmaceuticals and biomolecules containing a primary amide functionality

On the other hand, the employment of reactive oxygen species (ROS) is commonly used in numerous fields.[18] The photoirradiation of gallic acid was demonstrated for augmentation of the antimicrobial activity along with formation of reactive oxygen species.[19] In fact, the auto-oxidation process can be achieved through both the thermal and the photochemical routes. Although well-documented procedures on bactericidal activity are available in the literature, the auto-oxidation issues associated with the generation of H_2O_2 still remains as one of the main bottlenecks current methodology, and there is little information available about the organic reaction with H_2O_2 generated from gallic acid as catalyst. Inspired by the above work, we envisioned that gallic acid would be oxidized with O_2 in air under mild conditions to form hydrogen peroxide (H_2O_2), which would participate in the next nitrile hydration.

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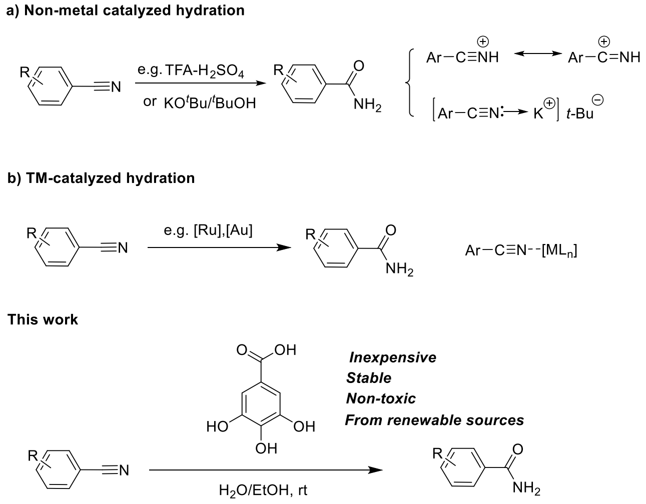


Scheme 1. Comparison of previous work and this work

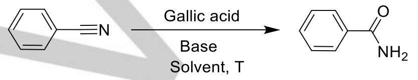
Results and Discussion

In order to examine this design, benzonitrile **1a** was treated with $NaHCO_3$ in the absence of gallic acid in $EtOH/H_2O$ at 70 ºC under air atmosphere. Only with $NaHCO_3$ as the additive cannot produce any product (Table 1, entry 1). To our delight, performing the reaction using 1.0 equiv. of gallic acid afforded benzamide **2a** in 15% yield (Table 1, entry 2). Subsequently we discovered that increases in amount of gallic acid have an accountable effect on the yield. Among them, the employment of gallic acid (2.0 equiv.) as the promoter led to a proportionate increase in yield (Table 1, entry 4).

We then screened the reaction in the presence of various additives including inorganic and organic bases. The reaction proceeded smoothly with inorganic base tested in each case (Table 1, entries 6-11) whereas the reaction failed when organic base (e.g. Et_3N, DBU and DMAP) was used as the additive (Table 1, entries 12-14). Inorganic bases such as Na_2CO_3, K_2CO_3 and NaOH only generate the product in very low to moderate yields (Table 1, entries 6-11). When choosing KOH, yield of the product was among the best (Table 1, entry 10). Notably, the additive also played a key role in the present reaction, and no reaction took place when no suitable additive were used (Table 1, entry 15). Further, the experimental outcome showed that other mixed solvent such as acetone/H_2O and THF/H_2O were not all efficient (Table 1, entries 16 and 17). Lower yields (53% and 29%) of the product were observed, while single solvent H_2O could not product any hydration product (Table 1, entry 18).

In particular, the catalytic system afforded the desired product in 72% yield at 50 ºC (Table 1, entry 19). Performing the reaction at room temperature afforded **2a** in 67% yield while extending the reaction time to 24 h further improved the yield of **2a** to 89% (Table 1, entries 20 and 21). It is known that for the production of H_2O_2 from catechol moiety, both thermodynamic and kinetic challenging processes can be effected in the presence of light. [19] And therefore we next performed the reaction with gallic acid and KOH under light at room temperature. When, to our delight, the reaction was completed in 15 h to afforded **2a** in 93% yield (Table 1, entry 22). Additionally, similar results were obtained with open air and O_2 (Table 1, entries 20 and 23). The reaction failed when under the rigorous exclusion of oxygen (Table 1, entry 24). Considering that yields were not significantly different whether the reaction was conducted under light (Table 1, entries 21 and 22), thus the optimal conditions were identified as nitrile (1.0 equiv.), gallic acid (2.0 equiv.), KOH (5% in H_2O) in $EtOH/H_2O$ at room temperature for 24 hours.

Table 1. Optimization of the reaction conditions for transformation nitriles to amides[a]



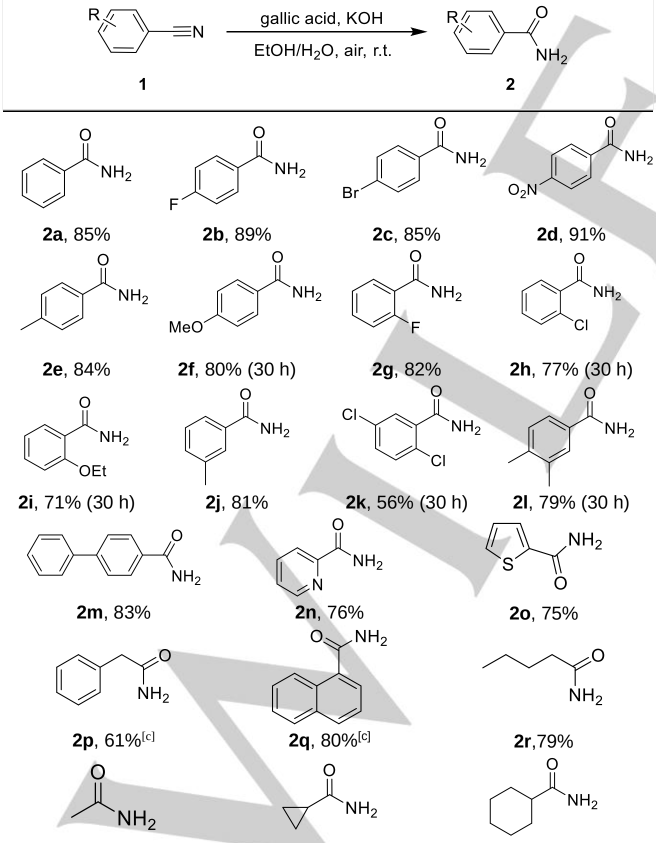
1a **2a**

Entry	Gallic acid (equiv.)	Base	Solvent	T (ºC)	Yield[b] (%)
1	--	$NaHCO_3$	$EtOH/H_2O$	70	NR
2	1.0	$NaHCO_3$	$EtOH/H_2O$	70	15
3	1.5	$NaHCO_3$	$EtOH/H_2O$	70	16
4	2.0	$NaHCO_3$	$EtOH/H_2O$	70	22
5	2.5	$NaHCO_3$	$EtOH/H_2O$	70	20
6	2.0	Na_2CO_3	$EtOH/H_2O$	70	37
7	2.0	K_2CO_3	$EtOH/H_2O$	70	39
8	2.0	KH_2PO_4	$EtOH/H_2O$	70	22
9	2.0	KF	$EtOH/H_2O$	70	19
10	2.0	KOH	$EtOH/H_2O$	70	88
11	2.0	NaOH	$EtOH/H_2O$	70	73
12	2.0	Et_3N	$EtOH/H_2O$	70	NR
13	2.0	DBU	$EtOH/H_2O$	70	NR
14	2.0	DMAP	$EtOH/H_2O$	70	NR
15	2.0	--	$EtOH/H_2O$	70	NR
16	2.0	KOH	Acetone/H_2O	70	53
17	2.0	KOH	THF/H_2O	70	29
18	2.0	KOH	H_2O	70	NR
19	2.0	KOH	$EtOH/H_2O$	50	72
20	2.0	KOH	$EtOH/H_2O$	r.t.	67
21[c]	2.0	KOH	$EtOH/H_2O$	r.t.	89(85)[d]
22	2.0	KOH	$EtOH/H_2O$	light (r.t.)	93
23[e]	2.0	KOH	$EtOH/H_2O$	r.t.	70
24[f]	2.0	KOH	$EtOH/H_2O$	r.t.	NR

[a] Reactions were carried out with benzonitrile (**1a**, 0.5 mmol), gallic acid, additive (if any, 5% in H_2O), 1.5 mL of solvent (v/v=1:2) in air under the corresponding temperature for 15 h. [b] Yields were determined by GC using naphthalene as an internal standard. [c] Reaction time: 24 h. [d] Isolated yield. [e] Under O_2. [f] Under N_2.

With the optimized reaction conditions in hand, we next examined the scope of the method with different nitriles. As presented in Table 2, various functional groups commonly utilized in organic synthesis were fully compatible with the simple hydration method. Substrates bearing electron-withdrawing groups, irrespective of their positions of attachment, underwent the hydration to give the corresponding amides **2b**, **2c**, **2d**, **2g** and **2h** in good yields. Note that benzonitriles bearing electron-donating functional groups such as methyl (**1e** and **1j**), methoxyl (**1f**) and ethyoxyl (**1i**) at different positions were also suitable substrates for this process to provide corresponding products. Accordingly, steric effects of substituents on the phenyl ring were evaluated. In comparison to benzonitrile (**1a**), the presence of either a *meta*- or a *para*-group, did not show any significant effect on the product yields ranging from 80–91%. Likewise, comparable yields of the products (**2g**) and (**2h**) were obtained when the phenyl ring is substituted at the *ortho*-position. However, the presence of two groups in the ring resulted in an obvious decrease in the product yield (**2k** and **2l**), along with the requirement of longer reaction time.

Table 2. Substrate Scope[a]



1 **2**

2a, 85% **2b**, 89% **2c**, 85% **2d**, 91%

2e, 84% **2f**, 80% (30 h) **2g**, 82% **2h**, 77% (30 h)

2i, 71% (30 h) **2j**, 81% **2k**, 56% (30 h) **2l**, 79% (30 h)

2m, 83% **2n**, 76% **2o**, 75%

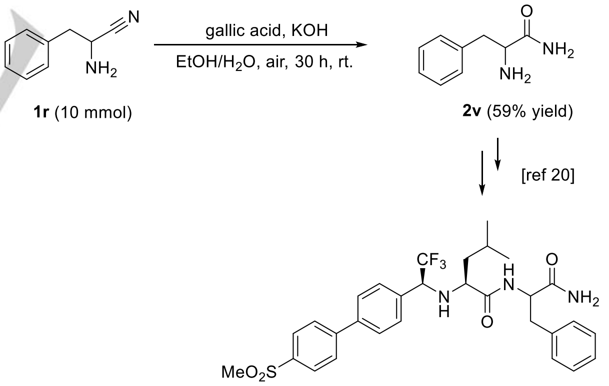
2p, 61%[c] **2q**, 80%[c] **2r**,79%

2s, 77% (30 h) **2t**, 68% **2u**, 71%

[a] Reaction conditions: nitrile **1** (1 mmol), gallic acid (2 eq), KOH (5% in H_2O), 3 mL of EtOH/H_2O (v/v=1:2), room temperature, corresponding time in air. [b] Isolated yield. [c] At 50 ^{o}C.

Furthermore, a variety of nitriles having heterocycle, biphenyl as well as other aryl groups was explored (Table 2, **2m**-**2q**). The biphenyl derivative (**1m**) had similar activity on the product yield relative to the electron-neutral substrate (**1a**). Nitriles bearing heterocycle substituent, cyanopyridine (**1n**) and sulphur-containing heterocycle (**1o**) gave their desired products respectively, in relatively lower yields to that of the phenyl analogue (**2m**). Moreover, 2-arylacetonitrile was less reactive and required 50 ^{o}C to obtain good results (**2p**, 61%). This may be due to the presence of the adjacent aryl group, which led to certain steric hindrance as in the case of *ortho*-sustituted benzonitrile. Similarly, reaction of naphthonitrile also required 50 ^{o}C (**2q**). Gratifyingly, four aliphatic nitriles also worked well, allowing easy access to the corresponding products **2r**-**2u** in moderate yields.

On the basis that many biomolecules possess primary amide substituents, we set out to improve the potential practicality of the reaction conditions to enable this methodology to be used in the pharmaceutical industry. The hydration of 2-amino-3-phenylpropanamide was tested in a gram scale (Scheme 2). In this instance, the reaction was still very efficient under the standard conditions, albeit with extended reaction time to 30 h, and produced good yield of the product **2r** (59% yield). Product **2r** can be further transformed to a cathepsin K inhibitor 3 through known procedures,[20] which also showed excellent selectivity against the cathepsins B, L, and S. The result showed that this protocol was applicable to the late-stage hydration of medicinally relevant compounds.



1r (10 mmol) **2v** (59% yield) **3**

Scheme 2. Gram-scale synthesis of cathepsin K inhibitor precursor

On the basis of the experiment results and previous reports, a plausible mechanism for this hydration was proposed in Scheme 3. H_2O_2 can be produced through both thermal and photochemical routes. For the thermal process, gallic acid can be oxidized in couple with the intermediate **I** formation. Intermediate **I** was followed by reoxidation, releasing quinone product **II** and regenerating O_2^- from O_2. After gallic acid oxidation was complete, HO_2^-, O_2^- and H+ can easily react to form H_2O_2. For minor part, it has been shown earlier that, as expected, both two hydrogen

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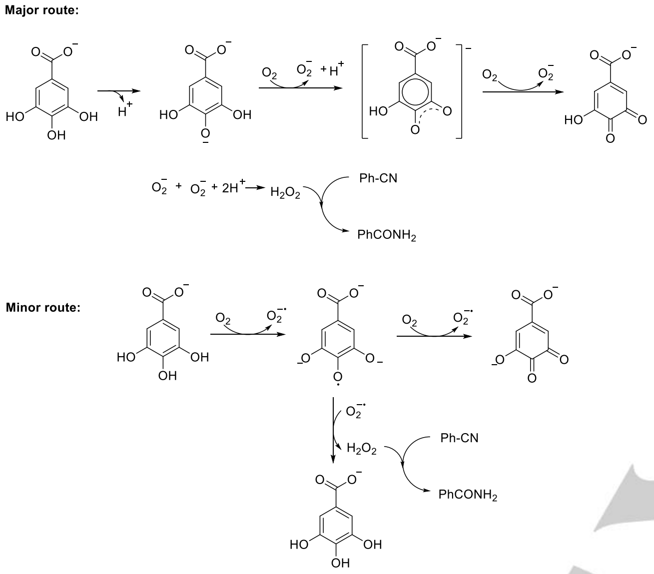
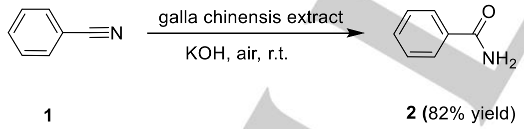
bond interactions and captodative effect can effectively stabilize the radical at 4OH in galloyl radical.[13c, 21] The initiation step would be the photo-oxidation of gallic acid by O_2 under light to generate a superoxide anion ($O_2^{-\bullet}$) and a semiquinone radical. The semiquinone radical is more susceptible to be oxidized by O_2 than gallic acid itself. In consideration of $O_2^{-\bullet}$ as a stronger one-electron oxidant than O_2, it can be easily reduced to H_2O_2. Consequently, H_2O_2 can be readily catalyze the hydration of nitrile to afford the desired amide.



Scheme 3. Proposed reaction mechanism

Subsequently, experiment directly with galla chinensis extract was performed to get a better understanding on the reaction, as shown in Scheme 4. The dry galla chinensis was purchased from the local Chinese market, and other detailed procedure can be seen in the SI. The reaction proceeded smoothly under the optimized condition, which thereby indicated that other complex compounds in the extract had no influence on this process.



Scheme 4. Hydration of benzonitrile by galla chinensis extract

Conclusions

Taken together, we have developed a general and efficient transformation of nitriles to primary amides. The methodology is clearly advantageous not only because of the use of inexpensive renewable promoter and metal-free mild conditions but also because it employs ethanol/water as solvent. Gram-scale reactions can be easily performed. The broad substrates scope applicability together with the wide range of functional groups tolerance make this protocol flexible and particularly suitable for preparing primary amides. Gallic acid is the simplest prototype of tannin. In terms of the abundant renewable source, this protocol also shows the potential utilization of natural feedstocks.

Experimental Section

General Information

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer and tetramethylsilane (TMS) was used as a reference. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, quin = quintuplet, sex = sextet and br = broad), coupling constant (J values) in Hz and integration. The visible light irradiation upon the tube reactor was provided by a 300W xenon lamp (PLS-SXE300C, Beijing Perfect Light Co.) equipped with a 360-580 nm filter. Gallic acid from ALDRICH were used. Galla chinensis was purchased from the local Chinese market. All of the products were known compounds and were identified by comparison of their physical and spectra data with those of authentic samples.

General procedure for the photocatalytic nitriles hydration reactions

A mixture of gallic acid (2 mmol) and 2.0 mL of 5% KOH was stirred open-flask at room temperature for 15 min. Then, 1 mmol of benzonitrile in EtOH (1 mL) was added. The progress of the reaction was monitored by TLC, until the starting material disappeared. The mixture was poured into saturated aqueous NH_4Cl (10 mL, saturated solution) and extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was chromatographed by silica gel to obtain the desired product 2a as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J = 7.3 Hz*, 2H), 7.55-7.52 (m, 1H), 7.47-7.44 (m, 2H), 6.20 (s, 2H).

Procedure with galla chinense extract

The dry galla chinensis was purchased from the local Chinese market, and ground to powder with a mini electric grinder. Of this raw powder, 5 g was extracted with 50 mL of the mixture of ethanol/water/HCl (37%) (1:1.9:0.1) at 70 ºC for 5 h. The resulting solution was filtered to remove the solid residue. To 3 mL of such extract, KOH (268 mg) was added. The reaction vessel was stirred open-flask at room temperature for 15 min. Then, benzonitrile (0.1 mmol) was added. The resulting mixture was stirred for 15 h and the precipitate was poured into saturated aqueous NH_4Cl (10 mL, saturated solution) and extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was chromatographed by silica gel to obtain the desired product.

Acknowledgements

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Keywords: hydration • gallic acid • bio-resources • oxidation • amides

[1] a) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev*. **1997**, *6*, 2243-2266; b) C. M. Breneman, J. F. Liebman, The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science (ed.: A. Greenberg), John Wiley & Sons, New York, **2000**; c) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem. Int. Ed*. **2006**, *45*, 1248-1252; d) B. L. Bray, *Nat. Rev. Drug Discovery*. **2003**, ***2***, 587; e) B. Attenni, J. M. Ontoria, P. Jones, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3081-3084.

[2] R. C. Larock, Comprehensive Organic Transformation, 2nd ed, Wiley, **1999**, 1623.

[3] a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev*. **2011**, *40*, 3405-3415; b) V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta.* **2005**, *358*, 1-21; c) T. Tu, Z. Wang, Z. Liu, X. Feng, Q. Wang, *Green Chem*. **2012**, *14*, 921-924; d) S. Das, B. Wendt, K. Moller, K. Junge, M. Beller, *Angew. Chem*. **2012**, *124*, 1694-1698; *Angew. Chem. Int. Ed*. **2012**, *51*, 1662-1666; e) C. Zhu, R. Wang, J. R. Falck, *Chem. Asian. J*. **2012**, *7*, 1502-1514; f) J. S. Carey, D. Laffan, C. Thomson , M. T. Williams, *Org. Biomol. Chem*. **2006**, *4*, 2337-2347.

[4] a) J. N. Moorthy, N. Singhal, *J. Org. Chem*. **2005**, *70*, 1926-1929; b) G. C. Midya, A. Kapat, S. Maiti, J. Dash, *J. Org. Chem*. **2015**, *80*, 4148-4151.

[5] a) A. Cavarzan, A. Scarso, G. Strukul, *Green Chem*. **2010**, *12*, 790-794; b) V. Cadierno, J. Deiz, J. Francos, J. Gimeno, *Chem. Eur. J*. **2010**, *16*, 9808-9817; c) R. García-Álvarez, M. Zablocka, P. Crochet, C. Duhayon, J-P. Majoral, V Cadierno, *Green Chem*. **2013**, *15*, 2447-2456; d) E. Tomás- Mendivil, F. J. Suárez, J. Díez, V. Cadierno, *Chem. Commun*. **2014**, *50*, 9661-9664; e) R. García-Álvarez, J. Diez, P. Crochet, V. Cadierno, *Organometallics*. **2010**, *29*, 3955-3965.

[6] R. S. Ramón, N. Marion, S. P. Nolan, *Chem. Eur. J*. **2009**, *15*, 8695-8697.

[7] a) A. Goto, K. Endo, S. Saito, *Angew. Chem. Int. Ed*. **2008**, *47*, 3607-3609; b) M. C. K-B. Djoman, A. N. Ajjou, *Tetrahedron Lett*. **2000**, *41*, 4845-4849.

[8] T. Hirano, K. Uehara, K. Kamata, N. Mizuno, *J. Am. Chem. Soc*. **2012**, *134*, 6425-6433.

[9] X. B. Jiang, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Org. Chem*. **2004**, *69*, 2327-2331.

[10] P. Marcé, J. Lynch, A. J Blacker, J. M. J. Williams, *Chem. Comm*. **2016**, *52*, 1436-1438.

[11] a) C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett*. **2014**, *16***,** 1060-1063; b) H. J. Young, L. R. Haefele, *Ing. Eng. Chem. Prod. Res. Develop*. **1972**, *11*, 365-369.

[12] a) V. K. Sharma, J. Filip, R. Zborilb, R. S. Varma, *Chem. Soc. Rev*. **2015**, *44*, 8410-8412; b) B. Nasir Baig, R. S. Varma, *Chem. Commun*. **2013**, *49*, 752-770; c) M. B. Gawande, P. S. Brancoa, R. S. Varma, *Chem. Soc. Rev*. **2013**, *42*, 3371-3393 and references therein.

[13] a) P. R. Boruah, A. A. Ali, B. Saikia, D. Sarma, *Green Chemistry*. **2015**, *17*, 1442-1445; b) B. Saikia, P. Borah, *RSC Adv*. **2015**, *5*, 105583-105586; c) M. D. Perretti, D. M. Monzón, F. P. Crisóstomo, R. Carrillo, *Chem. Commun*. **2016**. *52*, 9036-9039.

[14] K. Kondo, M. Kurihara, N. Miyata, T. Suzuki, M. Toyoda, *Free. Radical. Biol. Med*. **1999**, *27*, 855-863.

[15] Z. Liu, L. Ma, B. Zhou, L. Yang, Z. Liu, *Chem. Phys. Lipids*. **2000**, *106*, 53-63.

[16] Y. Yilmaz, R. T. Toledo, *J. Agric. Food. Chem*. **2004**, *52*, 255-260.

[17] K. Heim, A. Tagliaferro, D. J. Bobilya, *Nutr. Biochem*. **2002**, *13,* 572-582.

[18] a) J. A. Imlay, *Nat. Rev. Microbiol*. **2013**, *11*, 443-454; b) M. P. Brynildsen, J. A. Winkler, C. S. Spina, I. C. MacDonald, J. J. Collins, *Nat. Biotechnol*. **2013**, *31*, 160-165; c) J. J. Foti, B. Devadoss, J. A. Winkler, J. J. Collins, G. C. Walker, *Science*. **2012**, *336*, 315-319; d) M. A. Kohanski, D. J. Dwyer, B. Hayete, C. A. Lawrence, J. J. Collins, *Cell*. **2007**, *130*, 797-810; e) A. T. Dharmaraja, M. Alvala, H. Chakrapani, *Chem. Commun*. **2012**, *48*, 10325-10327.

[19] K. Nakamura, Y. Yamada, H Ikai, T. Kanno, K. Sasaki, Y. Niwano, *J. Agric. Food Chem*. **2012**, *60*, 10048−10054.

[20] S Léger, C I. Bayly, J-F. Truchon, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4328-4332.

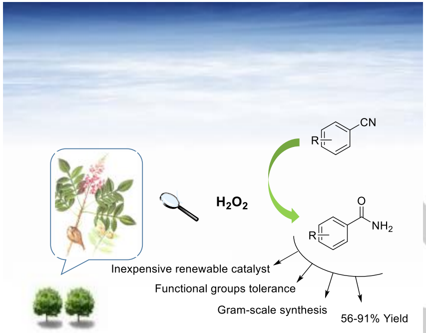
[21] a) M. Leopoldini, T. Marino, N. Russo, M. Toscano, *J. Phys. Chem. A*. **2004**, *108*, 4916-4922; b) R. Sustmann, H.-G. Korth, *Adv. Phys. Org. Chem*. **1990**, *26*, 131-134.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

An efficient gallic acid promoted nitriles hydration under mild conditions in ethanol/water is developed for the formation of amines. The use of renewable bio-resources (gallic acid and galla chinensis extract) makes the reaction environmentally friendly, which also offers an alternative method of reutilization of natural feedstocks.



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