Electrochemistry
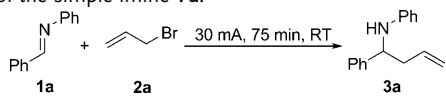
Electrochemical Allylation Reactions of Simple Imines in Aqueous Solution Mediated by Nanoscale Zinc Architectures**

Jing-Mei Huang,* Xu-Xiao Wang, and Yi Dong

Addition of allylmetal reagents to C=N double bonds is one of the most important and straightforward methods to afford homoallylic amines, which are useful building blocks for many biologically active compounds and nitrogen-containing natural products.[1] In recent years, organic reactions that can be performed in aqueous media have attracted great interest because of significant environmental and economical advantages,[2] especially for the Barbier-type reactions in aqueous media.[3] However, owing to the lower electrophilicity of simple imines and their instability in water, most of the previously reported metal-mediated aqueous allylation reactions were focused on the use of special imines, such as sulfonimines, tosyl or aryl hydrazones, and glyoxylic oxime ethers.[4] The limited scope of these reported systems encourages us to search for methods to achieve the allylation reactions of simple imines in aqueous media. Electrochemical methods are another approach to efficient organic transformations and sustainable chemistry,[5,6] and we have also been interested in developing new electrochemical process in aqueous solution.[7] Herein, we reported a zinc-mediated electrochemical allylation reaction of simple imines in a mixture of saturated aqueous NH$_4$Br and tetrahydrofuran (9:1) at room temperature; this method is also suitable for the alkylation and benzylation of simple imines.

Initial studies were performed at room temperature under neutral aqueous conditions of 0.1M LiClO$_4$/tetrahydrofuran (9:1; Table 1, entry 1) in a one-compartment cell under a constant current (30 mA), and zinc foils (1.5 cm^2 each) were chosen as both the anode and cathode. After electrolysis for 75 minutes, none of the desired product was obtained. The same result was observed in 0.1M NaOH solution (Table 1, entry 2), whilst in an acidic 0.1M HCl solution (Table 1, entry 3), only a trace amount of the desired product was detected. In 0.1M HOAc solution and ammonia solution (4.5M)[7a], the desired homoallylic amine was obtained with yields of <5% and <15%, respectively (Table 1, entries 4 and 5). When ammonium salts were employed, the results were more promising (Table 1, entries 6–8), and NH$_4$Br was

[*] Prof. Dr. J.-M. Huang, X.-X. Wang, Y. Dong
School of Chemistry and Chemical Engineering, South China University of Technology
Guangzhou, Guangdong, 510640 (P. R. China)
Fax: (+86) 20-8711-0622
E-mail: chehjm@scut.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004852.

Table 1: Optimization of the reaction conditions for the electrochemical allylation of the simple imine **1a**.[a]

Entry	Anode–cathode	Electrolyte	Yield [%][b]
1	Zn–Zn	LiClO$_4$ (0.1 M)/THF (9:1)	0
2	Zn–Zn	NaOH (0.1 M)/THF (9:1)	0
3	Zn–Zn	HCl (0.1 M)/THF (9:1)	trace
4	Zn–Zn	HOAc (0.1 M)/THF (9:1)	<5
5	Zn–Zn	NH$_3$·H$_2$O (4.5 M)/THF (9:1)	15
6	Zn–Zn	NH$_4$Cl (0.1 M)/THF (9:1)	20
7	Zn–Zn	sat. aq NH$_4$Cl/THF (9:1)	60
8	Zn–Zn	sat. aq NH$_4$Br/THF (9:1)	92
9	Zn–Zn	sat. aq NH$_4$Br/THF (95:1)	70
10	Zn–Zn	sat. aq NH$_4$Br/MeOH (9:1)	35
11[c]	Zn–Zn	sat. aq NH$_4$Br/THF (9:1)	72
12[d]	Zn–Zn	sat. aq NH$_4$Br/THF (9:1)	74
13	Pt–Pt	sat. aq NH$_4$Br/THF (9:1)	0
14	Al–Al	sat. aq NH$_4$Br/THF (9:1)	10
15	Sn–Sn	sat. aq NH$_4$Br/THF (9:1)	15

[a] Standard condition: imine (0.5 mmol), allyl bromide (1 mmol) in electrolyte was electrolyzed at a constant current of 30 mA in a round-bottomed-flask cell equipped with a pair of zinc electrodes (1.5 cm^2) at RT. [b] Yield of isolated product. [c] 15 mA. [d] 45 mA. THF = tetrahydrofuran.

found to be superior (92% yield) to NH$_4$Cl as an electrolyte salt. Reducing the amount of the tetrahydrofuran or using methanol instead resulted in lower yields (Table 1, entries 9 and 10). Studies on the effect of current density (Table 1, entries 11 and 12) showed that an increase or decrease of the current resulted in a decrease in the yield. No allylation occurred when the electrolysis was carried out with platinum electrodes (Table 1, entry 13). Other electrodes (aluminium and tin) showed low yields (10% and 15%, respectively, Table 1, entries 14 and 15). Therefore, our optimized reaction conditions were found to be those given in Table 1, entry 8.

Next, a wide variety of simple imines were investigated, and the results are summarized in Table 2. Imines derived from aromatic, heteroaromatic, aliphatic aldehydes, and aromatic or aliphatic amines were all suitable substrates and produced the corresponding homoallylic amines in good yields. The functionalities including methoxyl, chloro, bromo, hydroxy, and cyano[8] were tolerated by this mild method.

Encouraged by the above results, we applied this reaction system to chiral imines to explore a new method for the synthesis of enantiomerically enriched homoallylic amines in aqueous solution. By using the imines derived from L-valine methyl ester, L-phenylalanine methyl ester, and L-phenylglycinol, it was found that the reaction worked well in the

Table 2: Zinc-mediated electrochemical allylation of imines in an aqueous solution.[a]

R1=aryl, alkyl
R2=aryl, alkyl
R3=H, CH3

Entry	R1	R2	R3	3	Yield [%][b]
1	Ph	Ph	H	3a	92
2	2-OH-C6H4	Ph	H	3b	96
3	4-MeO-C6H4	Ph	H	3c	95
4	4-Cl-C6H4	Ph	H	3d	90
5	4-CN-C6H4	Ph	H	3e	88
6	2-furyl	Ph	H	3f	86
7[c]	C6H4CH2CH2	Ph	H	3g	67
8[c]	nPr	Ph	H	3h	61
9	Ph	CH2=CHCH2	H	3i	79
10	Ph	PhCH2	H	3j	75
11	Ph	n-C4H9	H	3k	62
12[d]	Ph	Ph	CH3	3l	97[e]
13	Ph	(iPr, CO2Me)	H	3m	88 (98:2[f])
14	Ph	(Ph, OH)	H	3n	90 (>99:1[f])
15	Ph	(CO2Me)	H	3o	91 (>99:1[f])

[a] Imine (0.5 mmol), allyl bromide (1 mmol), electrolyte (sat. aq NH4Br/ THF (9:1), 6 mL), constant current (30 mA), zinc electrodes (1.5 cm²), RT. [b] Yield of isolated product, d.r. in parentheses. [c] One-pot reaction of aliphatic aldehyde (0.5 mmol), amine (0.5 mmol), and allyl bromide (1 mmol); see the Supporting Information. [d] Allyl bromide was replaced with crotyl bromide. [e] Anti/syn = 44:56 (determined by ¹H NMR analysis). [f] d.r. was determined by ¹H NMR spectroscopic analysis of crude product.

Table 3: Zinc-mediated electrochemical benzylation and alkylation of imines in aqueous solution.[a]

Entry	R1	R2	R4	X	5	Yield [%][b]
1	Ph	Ph	PhCH2	Br	5a	95
2	4-MeO-C6H4	Ph	PhCH2	Br	5b	96
3	2-furyl	Ph	PhCH2	Br	5c	92
4	Ph	n-C4H9	PhCH2	Br	5d	76
5	Ph	Ph	c-C6H11	I	5e	86
6	Ph	Ph	i-C3H7	I	5f	90
7	Ph	Ph	n-C4H9	I	5g	68
8	Ph	PhCH2	i-C3H7	I	5h	76

[a] Imine (0.5 mmol), benzyl bromide (1 mmol) or alkyl iodide (2 mmol), electrolyte (sat. aq NH4Br/THF (9:1), 6 mL), constant current (60 mA for benzylation and 15 mA for alkylation), zinc electrodes (1.5 cm²), RT. [b] Yield of isolated product.

a three-dimensional (3D) *Tremella fuciformis*-like hierarchitecture (with pore diameters in the range of 150–400 nm, and wall thicknesses at about 50 nm).

Figure 1. SEM image of deposits (Zn-1) from the reaction mixture.

system to afford the desired products in both good yields (88–91%) and good diastereoselectivities of up to greater than 99:1 d.r. (Table 2, entries 13–15).

Furthermore, this electrochemical method was also effective for the benzylation and alkylation of simple imines in aqueous solution,[9] which have received much less attention compared with the allylation of imines. After a brief screening of reaction conditions, it was found that benzylation and alkylation reactions proceeded smoothly under similar conditions, with only a minor adjustment in the applied current necessary. A substrate screen showed that both aromatic and heteroaromatic imines were good substrates for the benzylation and alkylation reactions (Table 3). It was notable that a primary iodide (Table 3, entry 7) could also be used for the alkylation reaction.
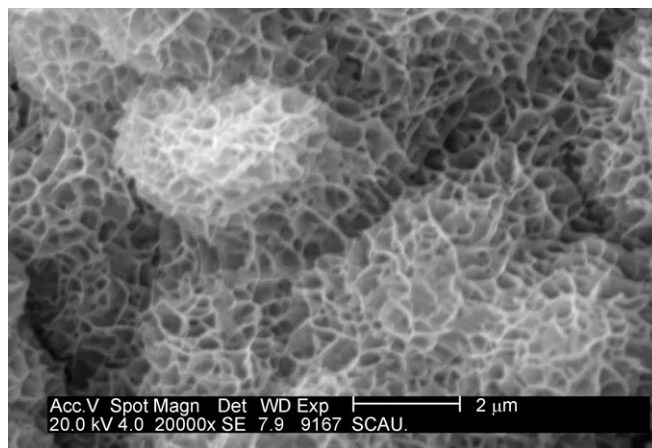
During the electroallylation process, we observed that the zinc deposited on the cathode was of a metallic luster, instead of a dark-gray color as for the commercial zinc powder. Further investigations using X-ray diffraction (XRD) analysis showed that the deposits (represented as Zn-1) consisted of pure zinc(0) with a good crystalline structure. Scanning electron microscopy (SEM; Figure 1) showed that Zn-1 had

Attempts to obtain the Zn-1 by deposition of zinc in the electrolyte (sat. aq NH4Br/THF, 9:1) without the imine or allyl bromide failed, and instead Zn-2 was obtained,[10] which indicated that the morphology of the deposited zinc was controlled by the organic composition in the electrolyte. Therefore, the effects of imine and allyl bromide on the controlling of morphology were investigated by SEM. It was found that with only allyl bromide in the electrolyte, Zn-3 was obtained,[10] whilst with only imine in the electrolyte, Zn-4 was obtained;[10] zinc with nano-hierarchitectures could not be obtained in both cases. Finally, the deposition of Zn-1 was reproduced in the real reaction mixture (in the presence of imine and allyl bromide), and 36 mg of Zn-1 was obtained after 75 minutes.

At present, it is still not clear why Zn-1 could only be obtained under the actual reaction conditions. It was tentatively suggested that the nitrogen atom of the imine coordinated with zinc(II) in the solution to form a complex, which

might account for the unique deposition of Zn-1 with nanoscale hierarchitectures. However, the allyl bromide turned out to be another determining factor for producing such hierarchitectures: in the presence of allyl bromide, the deposition potential was lowered.[11]

We propose that the distinct activity of Zn-1 towards the allylation of simple imines might be attributed to its special nanoscale hierarchitectures. Different from low dimensional nanomaterials, materials with nanoscale hierarchitectures showed the features of both micrometer-scaled (e.g. highly stabilized, easily operated) and nanometer-scaled (e.g. highly activated) building blocks.[12] A preliminary study on the relationship between reaction activity and surface morphology was carried out using the zinc(0) powders under non-electrochemical processes (Table 4). Here, Zn-1 to Zn-6

Table 4: Studies on the relationship of reaction activity and surface morphology.[a]

| Entry	Zinc powders[b]	Composition of product mixture		
		product **3a** [%]	aniline [%]	unreacted Imine **1a** [%]
1	Zn-1	78	5	<10
2	Zn-2	18	13	62
3	Zn-3	42	10	43
4	Zn-4	44	10	41
5	Zn-5	55	<10	30
6	Zn-6	<10	15	70
7[c]	Zn-1	92	0	0

[a] Standard conditions: Zn (1 mmol), sat. aq NH$_4$Br-THF (9:1) (1.0 mL), **1a** (0.5 mmol), **2** (1 mmol), RT, 75 min, non-electrochemical process. [b] Zn-1: zinc with 3D nano-hierarchitectures; Zn-2: zinc deposited from sat. aq NH$_4$Br/THF (9:1); Zn-3: zinc deposited from sat. aq NH$_4$Br/THF (9:1) with only allyl bromide; Zn-4: zinc deposited from sat. aq NH$_4$Br/THF (9:1) with only imine; Zn-5: zinc deposited from 4.5 M aqueous ammonia solution. Zn-6: commercial zinc. [c] Standard electrochemical process listed under Table 2.

represented zinc(0) powders[13] with different surface morphologies (for their SEM images, see the Supporting Information). As we can see from Table 4, the activity of zinc towards the allylation reaction is strongly dependent on its morphology. Zn-1, which has a nanoscale hierarchitecture (Figure 1), showed the highest reactivity towards the allylation of simple imine **1a** in water (78%, Table 4, entry 1). Zn-5,[7a] with a porous network structure (Figure 2a), was the second most effective (55%, Table 4, entry 5). Commercial zinc (Zn-6),[14] which contained irregular and relatively larger-sized particles (Figure 2b), showed very low activity (yield <10%, Table 4, entry 6).

However, under non-electrochemical conditions, the allylation reaction mediated by preformed Zn-1 was not as active as in the electrochemical process (78% vs 92%; Table 4, entries 1 and 7). Thus, the pH value was carefully monitored under electrochemical and non-electrochemical (Figure 3) reaction conditions. It was found that under the electrochemical process, the pH value of the reaction solution increased to pH 6.7 from pH 5.4 very fast (less than 10 min) and maintained at pH 6.7 during the remaining reaction time,[15] whilst in the non-electrochemical process, the pattern
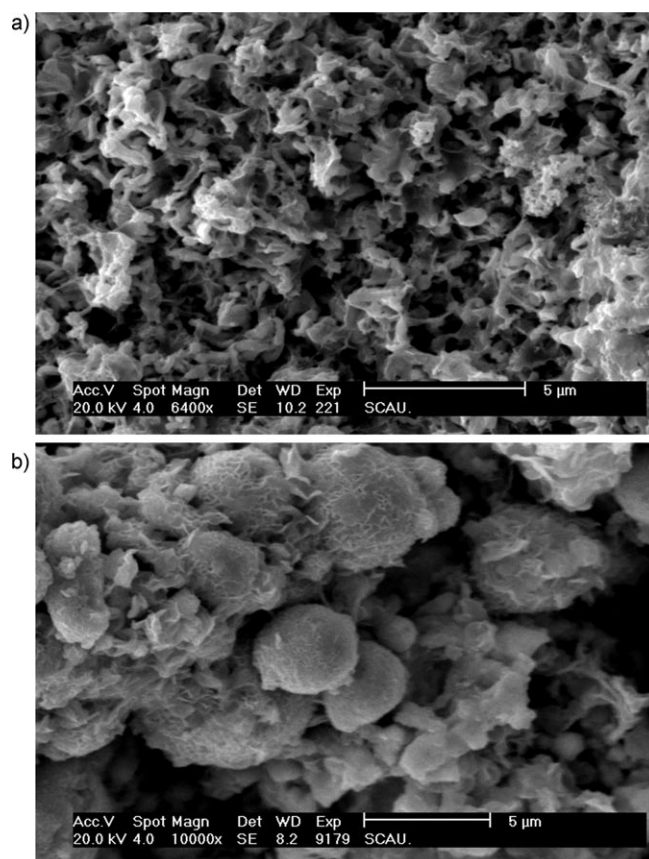
Figure 2. a) SEM image of Zn-5 and b) SEM image of Zn-6.
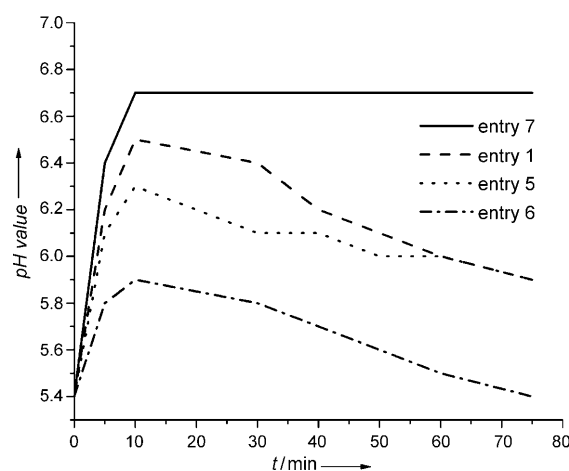
Figure 3. pH values for solutions of the reaction mixtures from Table 4.

of the pH curves was different, and decomposition of the imine was observed. These results suggested that at lower pH values, the imines were prone to hydrolysis to produce aniline and benzaldehyde (see Table 4), which is one of the reasons for the lower yield under non-electrochemical reaction conditions. Furthermore, during the electrochemical process, direct electroreduction of the imine and the halides at the cathode to produce active intermediates may also assist the desired reactions of simple imines.[16] Therefore, it can be concluded that, besides the promotion of active Zn-1 with 3D

nano-hierarchitectures, the electrochemical process is another factor for the excellent yield of allylation of simple imines in water.

In conclusion, an efficient electrosynthesis of amines from simple imines with allylic bromides, benzyl bromides, and alkyl iodides in aqueous solution has been developed. This preliminary study showed that the deposited zinc(0) powder with nanoscale hierarchitectures played an important role in the reaction of simple imines in aqueous media. High efficiencies and environmental friendliness rendered this methodology as an attractive alternative synthetic route to amines. Further investigation to determine the mechanism of this reaction and to expand its scope is underway in our laboratory.

Experimental Section

General procedure for the allylation of imines: A mixture of **1a** (0.5 mmol) in THF (0.6 mL) and allyl bromide (1.0 mmol) was added to a saturated aqueous NH_4Br solution (5.4 mL). The stirring mixture was then electrolyzed at a constant current of 30 mA in a round-bottom-flask cell equipped with a pair of zinc electrodes (1.5 cm^2) at RT. The electrolysis was stopped when the imine had been completely consumed (monitored by TLC, 75 min, 2.6 F mol^{-1}). After the electrolysis, THF was removed on a rotary evaporator. The residue was extracted with ethyl acetate (2×10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2CO_3, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) and the product was obtained as a colorless oil (**3a**, 103 mg, 92%).

[1] a) C. Agami, F. Coutyand, G. Evano, *Tetrahedron: Asymmetry* **2000**, *11*, 4639; b) H. Ding, G. K. Friestad, *Synthesis* **2005**, 2815; c) A. M. Schmidt, P. Eilbracht, *J. Org. Chem.* **2005**, *70*, 5528; d) J. E. Kropf, I. C. Meigh, M. W. P. Bebbington, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 2046; e) C. Denhez, J.-L. Vasse, D. Harakat, J. Szymoniak, *Tetrahedron: Asymmetry* **2007**, *18*, 424.

[2] For recent leading reviews, see: a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095; b) C.-J. Li, *Acc. Chem. Res.* **2002**, *35*, 533; c) C.-J. Li, *Chem. Rev.* **1999**, *99*, 2023; d) C.-J. Li, *Tetrahedron* **1996**, *52*, 5643.

[3] a) C. C. K. Keh, C.-M. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 4062; b) W.-C. Zhang, C.-J. Li, *J. Org. Chem.* **1999**, *64*, 3230; c) T. H. Chan, M. B. Isaac, *Pure Appl. Chem.* **1996**, *68*, 919; d) Z.-L. Shen, T.-P. Loh, *Org. Lett.* **2007**, *9*, 5413; e) Z.-L. Shen, H.-L. Cheong, T.-P. Loh, *Chem. Eur. J.* **2008**, *14*, 1875; f) Z.-L. Shen, Y.-L. Yeo, T.-P. Loh, *J. Org. Chem.* **2008**, *73*, 3922; g) H. Miyabe, T. Naito, *Org. Biomol. Chem.* **2004**, *2*, 1267; h) F. F. Fleming, S. Gudipati, *Org. Lett.* **2006**, *8*, 1557; i) F. F. Fleming, S. Gudipati, J. A. Aitken, *J. Org. Chem.* **2007**, *72*, 6961; j) Z.-L. Shen, H.-L. Cheong, T. P. Loh, *Tetrahedron Lett.* **2009**, *50*, 1051.

[4] For examples, see: a) X. Piao, J. K. Jung, H. Y. Knag, *Bull. Korean Chem. Soc.* **2007**, *28*, 139, and references therein; b) T. H. Chan, W. Lu, *Tetrahedron Lett.* **1998**, *39*, 8605; c) W. Lu, T. H. Chan, *J. Org. Chem.* **2000**, *65*, 8589; d) W. Lu, T. H. Chan, *J. Org. Chem.* **2001**, *66*, 3467; e) H. M. S. Kumur, S. Anjaneyulu, E. J. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2000**, *41*, 9311; f) D. J. Ritson, R. J. Cox, J. Berge, *Org. Biomol. Chem.* **2004**, *2*, 1921; g) L. Bernardi, V. Cere, C. Fermoni, S. Pollicino, A. Ricci, *J. Org. Chem.* **2003**, *68*, 3348; h) H. Miyabe, Y. Yamaoka, T. Naito, Y. Takemoto, *J. Org. Chem.* **2003**, *68*, 6745; i) H. Miyabe, Y. Yamaoka, T. Naito, Y. Takemoto, *J. Org. Chem.* **2004**, *69*, 1415; j) G.-Q. Lin, X.-W. Sun, M. H. Xu, *Org. Lett.* **2008**, *10*, 1259; k) I. H. S. Estevam, L. W. bieber, *Tetrahedron Lett.* **2003**, *44*, 667; l) S. Kumar, P. Kaur, *Tetrahedron Lett.* **2004**, *45*, 3413.

[5] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and, Practice*, Oxford University Press, New York, **1997**; b) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686.

[6] a) K. Uneyama, H. Matsuda, S. Torii, *Tetrahedron Lett.* **1984**, *25*, 6017; b) R. Grigg, B. Putnikovic, C. J. Urch, *Tetrahedron Lett.* **1997**, *38*, 6307; c) S. Seka, O. Burize, J. Y. Nédélec, J. Périchon, *Chem. Eur. J.* **2002**, *8*, 2534; d) G. Hilt, K. I. Smolko, *Angew. Chem.* **2001**, *113*, 3514; *Angew. Chem. Int. Ed.* **2001**, *40*, 3399; e) G. Hilt, *Angew. Chem.* **2002**, *114*, 3737; *Angew. Chem. Int. Ed.* **2002**, *41*, 3586; f) D. Nematollahi, R. A. Rahchamani, *J. Electroanal. Chem.* **2002**, *520*, 145; g) G. Hilt, *Angew. Chem.* **2003**, *115*, 1760; *Angew. Chem. Int. Ed.* **2003**, *42*, 1720; h) P. Gomes, C. Gosmini, J. Périchon, *J. Org. Chem.* **2003**, *68*, 1142; i) Z. Zha, A. Hui, Y. Zhou, Q. Miao, Z. Wang, H. Zhang, *Org. Lett.* **2005**, *7*, 1903; j) G. Hilt, K. I. Smolko, C. Waloch, *Tetrahedron Lett.* **2002**, *43*, 1437; k) Z. Li, Z. Zha, Z. Zhang, Y. Li, Z. Wang, *Chem. Commun.* **2010**, *46*, 7196; l) L. Zhang, Z. Zha, Z. Wang, *Synlett* **2010**, 1915.

[7] a) J.-M. Huang, Y. Dong, *Chem. Commun.* **2009**, 3943; b) J.-M. Huang, H. R. Ren, *Chem. Commun.* **2010**, *46*, 2286.

[8] For the reduction of the CN group in an electrochemical process, see Ref. [6j].

[9] To the best of our knowledge, it is the first report of the benylation of simple imines in aqueous media. The alkylation of simple imines in aqueous media has only recently been reported; see: T.-S. Huang, C. K. K. Keh, C.-J. Li, *Chem. Commun.* **2002**, 2440, and Ref. [3d].

[10] For the SEM images of the depositions from different electrolyte solutions, see the Supporting Information.

[11] In the absence of allyl bromide, the deposition potential was 0.6 V, whilst in the presence of allyl bromide, the potential was 0.2 V. It has been reported that the deposition potential was critical for controlling the morphology of deposited particles. See: L. Xiao, L. Zhuang, Y. Liu, J. Lu, H. D. Abrunda, *J. Am. Chem. Soc.* **2009**, *131*, 602.

[12] a) Z. L. Sun, S. C. Liufu, X. H. Chen, L. D. Chen, *Chem. Commun.* **2010**, *46*, 3101; b) B. F. Lu, W. P. Cai, Y. G. Zhang, *Adv. Funct. Mater.* **2008**, *18*, 1047, and references therein.

[13] XRD analysis has shown that all of the powders contain zinc in its zero valence state, with good crystalline forms. XRD patterns demonstrated that these crystals are in different shapes; for further information, see the Supporting Information.

[14] The commercial zinc powder was activated before used for allylation and SEM studies. For the procedure of activating zinc, see: C. L. K. Lee, H.-Y. Ling, T.-P. Loh, *J. Org. Chem.* **2004**, *69*, 7787.

[15] It is believed that the electrolysis process helped to maintain a suitable proton concentration.

[16] Reductive waves were observed for imine **1a**, allylic bromide, benzyl bromide, and cyclohexane iodide by cyclic-voltammetry studies. For further details, see the Supporting Information.