Cite this: *Chem. Commun.*, 2011, **47**, 10148–10150

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Metal-free aerobic oxidative coupling of amines to imines†

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Received 31st May 2011, Accepted 27th July 2011
DOI: 10.1039/c1cc13202d

Oxidative coupling of primary amines to imines is achieved with high to moderate yields by refluxing suspensions of amines and water under one atmosphere dioxygen without any additives. Tandem acid-free aza Diels–Alder reactions for synthesis of *N*-alkyl-4-pyridones are also accomplished.

Highly efficient, selective and metal-free oxidation of organic substrates that utilize dioxygen as the terminal oxidant is one of the most important current challenges for synthetic organic chemistry.[1] Oxidation of amines provides an alternative strategy to prepare imines which are versatile synthetic intermediates in a variety of organic transformations.[2] Great progress has been made in recent years in developing mild and practical methods for oxidation of secondary amines to imines.[3] But oxidation of primary amines utilizing green oxidants (dioxygen and peroxide) to imines is much less developed.[4] Notable examples include vanadium-,[4i,5] gold-,[6] ruthenium-,[7] copper-,[8] tyrosine-derived quinone-,[9] and polyaniline-catalyzed[10] aerobic oxidation of amines, and photo-induced aerobic oxidative coupling of amines by TiO_2,[11] carbon nitride,[12] and uracil-annulated heteroazulene derivatives.[13] Metal-free catalytic systems are quite rare.[9,10,12,13] Landge *et al.* reported a microwave-assisted solvent-free system catalyzed by K-10 montmorillonite requiring a very high temperature (150 °C).[14] Chu and Li first achieved oxidative coupling of amines to imines in water using V_2O_5 as catalyst at room temperature. However, excessive H_2O_2 was used as the terminal oxidant and the scope of the substrates was limited to benzylamines with electron withdrawing groups.[15] This article reports on an unprecedented metal-free aerobic oxidative coupling of amines to imines using dioxygen as the sole oxidant and water as the reaction medium.

Heating the homogeneous solution of 4-methylbenzylamine (0.60 mmol) in organic solvents such as acetonitrile, toluene or xylene (0.6 ml) under one atmosphere dioxygen results in trace amounts of the product (Table 1, entries 1–3). There is no imine observed when 0.6 ml of water and one atmosphere of nitrogen are used (Table 1, entry 4). However, a notable amount of *N*-(4-methylbenzylidene)-*p*-methylbenzylamine is formed after refluxing the biphasic water and amine suspension under one atmosphere dioxygen for two days. The highest yield is obtained when the ratio of the volume of water to the amine is 8 (Table 1, entry 5). When the ratio of water to amine increases, the yield of imine decreases dramatically (Table 1, entries 6–8). The yield of imine is effectively unchanged by use of a Teflon-reactor to avoid contact with light and glass surfaces. These observations exclude the possibility of light-induced or glass-catalyzed processes, and indicate that the presence of water and dioxygen is essential.

Prolonging the refluxing time results in higher yield (up to 83%, Table 2, entry 1) although the selectivity declines due to the overoxidation of imine to oxime, amide and carboxylate salt, which are detected by GC-MS and ^1H NMR. A variety of substituted benzylamine derivatives are also observed to form imines in moderate to high yields (Table 2). Electronic effects associated with electron donating and electron withdrawing substituents on the phenyl ring have little effect on the efficiency of the oxidation reaction (Table 2, entries 3–7). The thiophen-2-ylmethanamine is effectively coupled to form imine **P8** indicating good tolerance of heteroatoms (Table 2, entry 8). A noteworthy feature of our method is the formation of imine **P9** (Table 2, entry 9) which is a significant improvement over previously reported methods for the preparation of sterically hindered imines.[16] Aliphatic amines, allylic- or propargylic-amines do not produce measurable quantities of imine products under the same reaction conditions and the yields for secondary amines are very low. Oxidative coupling of aliphatic amines usually gives relatively low yield,[5b,6e,f,8] and reports on the oxidative coupling of allylic- and propargylic-amines are very rare.

The imine products are observed in equilibrium with free amines and aldehydes in water. Heating the mixture of **P2** and **P4** leads to immediate formation of two new species *N*-benzylidene-*p*-methoxylbenzylamine and *N*-(4-methoxylbenzylidene)-benzylamine.

Although anilines could not undergo homo-coupling reaction due to lack of the α-carbon hydrogen, it is feasible to obtain cross-coupling products with benzylamines through the tandem reaction of homo-coupling of benzylamines to form imines, hydrolysis to form aldehydes, and condensation with excess anilines to give cross-coupling products (Scheme S1, ESI†). Their cross-coupling products *N*-aryl imines are thermodynamically more stable than *N*-benzylidene–benzylamine which drives the coupling of benzylamines with anilines

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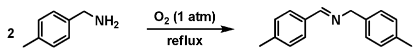
† Electronic supplementary information (ESI) available: The general procedure of the reactions, the preparation of imines and their spectral data. See DOI: 10.1039/c1cc13202d

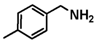
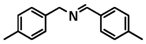
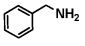
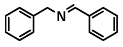
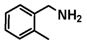
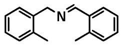
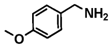
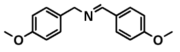
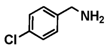
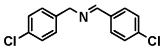
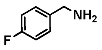
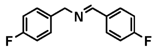
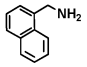
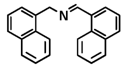
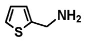
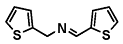
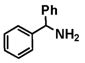
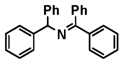
Table 1 Optimization of the oxidation conditions[a]



Entry	Sol. (vol./ml)	System status	Yield[b] (%)	Selectivity[b] (%)
1	CH_3CN (0.6)	Homogeneous	<1	—
2	Toluene (0.6)	Homogeneous	4	>95
3[c]	Xylene (0.6)	Homogeneous	5	>95
4[d]	H_2O (0.6)	Biphase	<1	—
5	H_2O (0.6)	Biphase	49	>95
6	H_2O (5)	Oil-in-water	36	>95
7	H_2O (10)	Oil-in-water	18	>95
8[e]	H_2O (20)	Homogeneous	4	>95

[a] Reaction conditions: 4-methylbenzylamine 0.60 mmol, 1 atm of O_2, reflux for 48 hours. [b] GC results. [c] 120 °C. [d] 1 atm of N_2. [e] 150 ml flask.

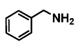
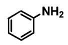
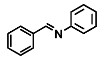
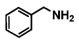
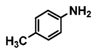
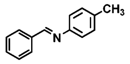
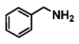
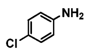
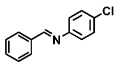
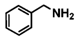
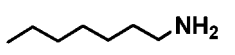
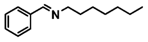
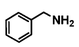
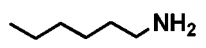
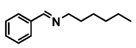
Table 2 Aerobic oxidation of various amines[a]

Entry	Substrate	Product	(P)	Time/h	Yield[b] (%)
1			**(P1)**	64	83
2			**(P2)**	28	75
3			**(P3)**	48	83
4			**(P4)**	28	64
5			**(P5)**	28	79
6			**(P6)**	32	71
7			**(P7)**	12	85
8			**(P8)**	28	65
9			**(P9)**	48	51[c]

[a] Reaction conditions: 0.6 mmol of amine, 0.6 ml of water, and 1 atm of O_2. [b] GC yield, the conversions >95%. [c] 15% benzophenone was formed; selectivity = 77%.

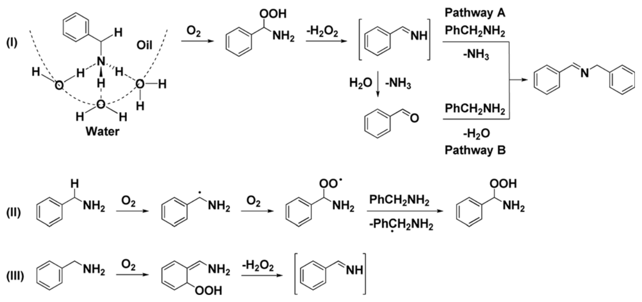
(Table 3, entries 1–3). On the other hand, aliphatic amines have low activity toward oxidative coupling reaction, but the cross-coupling of aliphatic amines with benzylamines is viable with the presence of excess aliphatic amines (Table 3, entries 4 and 5). The real-time monitoring of the reaction between benzylamine and hexamine indicates that initially *N*-benzylidene–benzylamine is the main product which gradually turns to *N*-benzylidene–hexamine along with the proceeding of the reaction (Fig. S2, ESI†).

Table 3 Oxidative cross-coupling of amines[a]

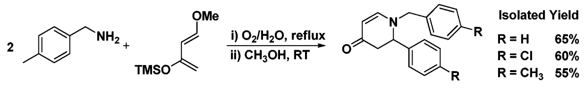
Entry	Amine 1	Amine 2	Product	Time/h	Yield[b] (%)
1				36	77
2				36	73
3				36	66
4				48	53
5				56	45

[a] Reaction conditions: 0.6 mmol of amine **1**, 1.8 mmol of amine **2**, 0.6 ml of water, and 1 atm of O_2. [b] GC yield, the conversions of benzylamine are over 95%.

Landge *et al.* proposed that a dehydrogenation pathway occurs after the amine coordinates to the acid center in the solvent-free system catalyzed by a solid acid.[14] Chu and Li proposed that a benzylic anion intermediate is generated by deprotonation of benzylaminium when V_2O_5 is used as the catalyst in aqueous solution.[15] Since Sharpless and co-workers reported that water insoluble reactants stirred vigorously in pure water gave a faster reaction rate compared to that in an organic solution or in neat conditions in 2005,[17] performing organic reactions "on water" has received intense attention due to the high efficiency, low pollution, low economic costs, facile separation processes, and safety considerations.[18] Recently, Aubry and co-workers developed two or three-liquid-phase microemulsion systems for the oxidation with singlet oxygen generated *in situ*;[19] Shapiro and co-workers successfully developed a metal-free system accomplishing aerobic oxidation of aldehydes on water.[20] Beattie *et al.* observed a rate accelerated reaction when performed on water and proposed that strong adsorption of the hydroxide ion at the oil–water interface facilitated the acid-catalysis process.[21] We observe that reduction of the yield of imine with increase of the ratio of water to amine (Table 1, entries 5–8) most probably results from switching from "on water" to "in water" conditions where addition of 20 ml of water to the biphasic water (0.6 ml) and amine (0.6 mmol) suspension gives a homogeneous solution. Based on our observations and those mechanisms reported in the literature, we propose that the amino group may form hydrogen bonds with water; amines react with oxygen to form peroxide complexes which subsequently release hydrogen peroxide which can also act as the oxidant to form imine intermediates; the imines react with free amines to give the coupling products or with water to form benzaldehydes which are then converted to coupling products through condensation with free amines (Scheme 1–I). Refluxing benzophenone and diphenylmethamine on water under nitrogen atmosphere results in less than 1% imine product which indicates that **P9** is probably formed from deamination condensation reaction of diphenylmethimine and diphenylmethamine (Scheme 1–I, pathway A). The fact that the substrates are limited to aromatic methylamines and the substitution on the phenyl ring has small influence suggests that the oxygen insertion may undergo a radical pathway: oxygen grabs the α-H of benzylamine to form a benzyl radical, which reacts with oxygen to form a peroxide complex (Scheme 1–II). An alternative mechanism has been suggested by one of the reviewers: the first step is an ene-reaction with the singlet oxygen to form a hydroperoxide complex, which



Scheme 1 Possible mechanisms for oxidative coupling of amines.



Scheme 2 Tandem oxidative aza Diels–Alder reaction.

eliminates a hydrogen peroxide with the recovery of aromaticity as the driving force (Scheme 1–III).

Encouraged by high yields of the coupling of benzylamines and the ease of separation of the imines from water, an effort was initiated to explore the feasibility of integrating such reactions in transformations of more practical interest such as aza Diels–Alder reactions. The imine product generated from amine oxidative coupling is extracted by diethyl ether. After removal of the solvent, it is mixed with a methanol solution of Danishefsky's diene to form an aza Diels–Alder product (Scheme 2). *N*-Aryl imines are previously found to undergo efficient acid-free aza Diels–Alder reaction in methanol.[22] Observation of an acid-free aza Diels–Alder reaction of *N*-alkyl imines substantially expands the scope of the synthesis of *N*-alkyl-4-pyridones.

In summary, we have developed a green protocol for oxidative coupling of benzylamines to imines by simply refluxing aerated suspensions of water and benzylamines. This simple metal-free system which uses dioxygen as the sole oxidant may find a wide range of applications in green oxidation chemistry. Mechanistic studies accessible for this "on water" reaction are on the way to obtain a deeper understanding of the origins of high efficiency and high selectivity of these aerobic oxidative coupling reactions.

We are grateful for support by the starter grant from Peking University, NSFC (Grants 20841002 and 20801002).

Notes and references

1 For examples of alcohol oxidation: (*a*) S. Wertz and A. Studer, *Adv. Synth. Catal.*, 2011, **353**, 69; (*b*) F. Su, S. C. Mathew, G. Lipner, X. Fu, M. Antonietti, S. Blechert and X. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 16299; (*c*) R. Mu, Z. Liu, Z. Yang, Z. Liu, L. Wu and Z. Liu, *Adv. Synth. Catal.*, 2005, **347**, 1333. Hydrocarbon oxidation: (*d*) Y. Wang, H. Li, J. Yao, X. Wang and M. Antonietti, *Chem. Sci.*, 2011, **2**, 446; (*e*) G. Zheng, C. Liu, Q. Wang, M. Wang and G. Yang, *Adv. Synth. Catal.*, 2009, **351**, 2638; (*f*) H. Miao, X. Tong and J. Xu, *Adv. Synth. Catal.*, 2005, **347**, 1953.

2 For reviews on the formation of imines and typical reactions: (*a*) S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2443; (*b*) J. P. Adams, *J. Chem. Soc., Perkin Trans. 1*, 2000, 125; (*c*) J. S. M. Samec, A. H. Éll and J.-E. Bäckvall, *Chem.–Eur. J.*, 2005, **11**, 2327.

3 G. Jiang, J. Chen, J.-S. Huang and C.-M. Che, *Org. Lett.*, 2009, **11**, 4568, and references cited therein.

4 For examples to nitriles: (*a*) Y. Zhang, K. Xu, X. Chen, T. Hu, Y. Yu, J. Zhang and J. Huang, *Catal. Commun.*, 2010, **11**, 951; (*b*) M. Kotani, T. Koike, K. Yamaguchi and N. Mizuno, *Green Chem.*, 2006, **8**, 735; (*c*) K. Yamaguchi and N. Mizuno, *Chem.–Eur. J.*, 2003, **9**, 4353; (*d*) Y. Maeda, T. Nishimura and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2399; (*e*) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, **42**, 1480; (*f*) K. Mori, Y. Yamaguchi, T. Mizugaki, K. Ebitani and K. Kaneda, *Chem. Commun.*, 2001, 461. To amide: (*g*) J. W. Kim, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2008, **47**, 9249; (*h*) S. K. Klitgaard, K. Egablad, U. V. Mentzel, A. Popov, T. Jensen, E. Taarning, I. S. Nielsen and C. H. Christensen, *Green Chem.*, 2008, **10**, 419. To acids: (*i*) R. Neumann and M. Levin, *J. Org. Chem.*, 1991, **56**, 5707. To aldehydes or ketones: (*j*) J. Srogl and S. Voltrova, *Org. Lett.*, 2009, **11**, 843. To oximes: (*k*) K. Suzuki, T. Watanabe and S.-I. Murahashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 2079. To oxaziridines: (*l*) Y.-M. Lin and J. Muller, *J. Org. Chem.*, 2001, **66**, 8282. To *N*-monoalkylhydroxylamines: (*m*) A. Heydari and S. Aslanzadeh, *Adv. Synth. Catal.*, 2005, **347**, 1223. To mixtures: (*n*) S. Kamiguchi, A. Nakamura, A. Suzuki, M. Kodomari, M. Nomura, Y. Iwasawa and T. Chihara, *J. Catal.*, 2005, **230**, 204; (*o*) S. Minakata, Y. Ohshima, A. Takemiya, I. Ryu, M. Komatsu and Y. Ohshiro, *Chem. Lett.*, 1997, 311; (*p*) A. J. Bailey and B. R. James, *Chem. Commun.*, 1996, 2343.

5 (*a*) S. Kodama, J. Yoshida, A. Nomoto, Y. Ueta, S. Yano, M. Ueshima and A. Ogawa, *Tetrahedron Lett.*, 2010, **51**, 2450; (*b*) K. Nakayama, M. Hamamoto, Y. Nishiyama and Y. Ishii, *Chem. Lett.*, 1993, 1699.

6 (*a*) M.-H. So, Y. Liu, C.-M. Ho and C.-M. Che, *Chem.–Asian J.*, 2009, **4**, 1551; (*b*) A. Grirrane, A. Corma and H. Garcia, *J. Catal.*, 2009, **264**, 138; (*c*) L. Aschwanden, T. Mallat, F. Krumeich and A. Baiker, *J. Mol. Catal. A: Chem.*, 2009, **309**, 57; (*d*) L. Aschwanden, B. Panella, P. Rossbach, B. Keller and A. Baiker, *ChemCatChem*, 2009, **1**, 111; (*e*) B. Zhu, M. Lazar, B. G. Trewyn and R. J. Angelici, *J. Catal.*, 2008, **260**, 1; (*f*) B. Zhu and R. J. Angelici, *Chem. Commun.*, 2007, 2157.

7 A. Prades, E. Peris and M. Albrecht, *Organometallics*, 2011, **30**, 1162.

8 R. D. Patil and S. Adimurthy, *Adv. Synth. Catal.*, 2011, **353**, 1695–1700.

9 M. Mure, *Acc. Chem. Res.*, 2004, **37**, 131.

10 (*a*) K. Chi, H. Y. Hwang, J. Y. Park and C. W. Lee, *Synth. Met.*, 2009, **159**, 26; (*b*) T. Hirao and S. Fukuhara, *J. Org. Chem.*, 1998, **63**, 7534; (*c*) M. Higuchi, I. Ikeda and T. Hirao, *J. Org. Chem.*, 1997, **62**, 1072; (*d*) T. Hirao, M. Higuchi, Y. Ohshiro and I. Ikeda, *Chem. Lett.*, 1993, 1889.

11 X. Lang, H. Ji, C. Chen, W. Ma and J. Zhao, *Angew. Chem., Int. Ed.*, 2011, **50**, 3934.

12 F. Su, S. C. Mathew, L. Möhlmann, M. Antonietti, X. Wang and S. Blechert, *Angew. Chem., Int. Ed.*, 2011, **50**, 657.

13 (*a*) S.-I. Naya, Y. Yamaguchi and M. Nitta, *Tetrahedron*, 2005, **61**, 7384; (*b*) M. Nitta, D. Ohtsuki, Y. Mitsumoto and S.-I. Naya, *Tetrahedron*, 2005, **61**, 6073; (*c*) S.-I. Naya and M. Nitta, *Tetrahedron*, 2004, **60**, 9139; (*d*) Y. Mitsumoto and M. Nitta, *J. Org. Chem.*, 2004, **69**, 1256.

14 S. M. Landge, V. Atanassova, M. Thimmaiah and B. Török, *Tetrahedron Lett.*, 2007, **48**, 5161.

15 G. Chu and C. Li, *Org. Biomol. Chem.*, 2010, **8**, 4716.

16 B. E. Love and J. Ren, *J. Org. Chem.*, 1993, **58**, 5556.

17 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.

18 R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302.

19 (*a*) V. Nardello-Rataj, L. Caron, C. Borde and J. Aubry, *J. Am. Chem. Soc.*, 2008, **130**, 14914; (*b*) C. Borde, V. Nardello, L. Wattebled, A. Laschewsky and J. Aubry, *J. Phys. Org. Chem.*, 2008, **21**, 652, and references cited therein.

20 (*a*) N. Shapiro, M. Kramer, I. Goldberg and A. Vigalok, *Green Chem.*, 2010, **12**, 582; (*b*) N. Shapiro and A. Vigalok, *Angew. Chem., Int. Ed.*, 2008, **47**, 2849.

21 J. K. Beattie, C. S. P. McErlean and C. B. W. Phippen, *Chem.–Eur. J.*, 2010, **16**, 8972.

22 Y. Yuan, X. Li and K. Ding, *Org. Lett.*, 2002, **4**, 3309.