PAPER

Copper(II)-catalyzed C–H (sp^3) oxidation and C–N cleavage: synthesis of methylene-bridged compounds using TMEDA as a carbon source in water†

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A green, simple, and efficient protocol for the selective methylenation *via* CuCl$_2$/oxygen-mediated C–H (sp^3) oxidation and C–N cleavage using tetramethylethylenediamine (TMEDA) as a carbon source has been developed. The reactions were achieved in green solvent water under atmospheric conditions. The protocol exhibited a broad substrate scope including indoles, anilines, pyrroles and 1,3-dicarbonyls. Furthermore, two key intermediates of the reaction were successfully identified and the mechanism was explored.

Introduction

With the concern about environmental impact, transition metal-catalyzed C–H bond activation and subsequent C–C bond formation without pre-functionalization of the substrates and undesired byproducts have been a fascinating hot-topic in organic synthesis.[1] Recently, transition metal-catalyzed oxidation of an sp^3 C–H bond adjacent to a nitrogen atom in a tertiary amine, followed through C–N bond cleavage has emerged as a useful strategy for C–C bond construction.[2] However, these protocols commonly required diethyl azodicarboxylate (DEAD) or *tert*-butyl hydrogen peroxide (TBHP) as an oxidant and were also conducted in organic solvents. Considering an environmentally benign and effective methodology for oxidative transformation of amines, atmospheric oxygen as a highly abundant and cheap resource[3] in place of DEAD or TBHP is still one of the most reasonable options. As a unique solvent, water is a green, low cost, non-flammable, non-toxic liquid with a wide temperature range. It also possesses a high heat capacity making it inherently safe.[4] Besides, transition metal catalysts can be separated from the reaction mixture by simple phase separation because many organic substrates are hydrophobic and insoluble in water.[5]

C–C bond formation through catalytic C–H bond activation in water is one of the hotspots in organic synthesis.[6] The selective reaction of less reactive C–H bonds in the presence of various functional groups and the stability of intermediates to water make this subject highly challenging.[7] The first C–C coupling by the reaction of sp^3 C–H bond *via* cross-dehydrogenative-coupling (CDC) reaction in water was reported in 2007 by Li.[8]

Indoles are important synthetic blocks in organic synthesis and the chemical industry, and have been widely used in medicinal chemistry.[9] Alkylated indoles are usually synthesized with strong acid- or base-mediated alkylation reactions, in which highly air- and water-sensitive organometallic reagents are essential.[10] Thus, there still is a need to develop a green method for the efficient synthesis of these compounds under mild and green conditions.

Recently, we have reported a novel method for the synthesis of 3,3′-bisindolylmethane and 4,4′-diaminodiphenylmethane using TMEDA as methylene source catalyzed by CuCl$_2$ in the presence of atmospheric oxygen as an oxidant in acetonitrile.[11] Encouraged by these results, we expect to broaden the scope of functional group tolerance and decrease operating cost *via* developing a milder and more environmentally friendly procedure.

We report herein a CuCl$_2$/oxygen-mediated, mild and efficient transformation for the synthesis of methylene-bridged indole derivatives in water using tetramethylethylenediamine (TMEDA) as methylene donor. To the best of our knowledge, this is the first example of C–C bond formation *via* C–H and C–N bonds cleavage in water. The success of indoles methylenation inspired us to further extend the substrate scope beyond indoles. Very meaningfully, the optimized reaction conditions were also available in the transformation of anilines, pyrroles, and even 1,3-dicarbonyl derivatives.
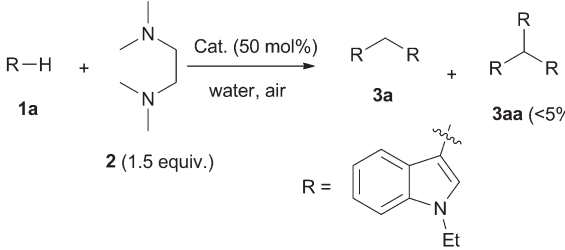
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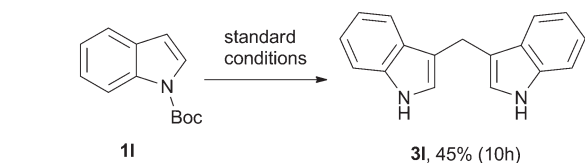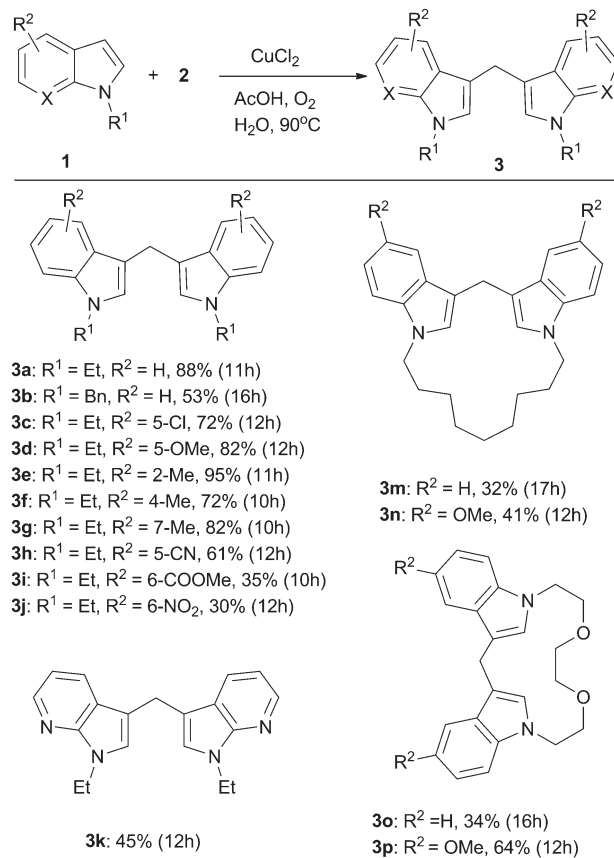
Results and discussion

With continuous interest in developing environmentally benign and efficient reaction conditions for C(aryl)–C(aryl)

Table 1 Optimization of reaction conditions[a]

Entry	Cat.	T (°C)	t (h)	Additive (equiv.)	Yield (%)[b]
1	CuCl$_2$	90	5	—	20
2	CuCl$_2$	90	12	—	42
3	FeCl$_3$	90	12	—	0
4	Cu(OAc)$_2$	90	12	—	23
5	ZnCl$_2$	90	12	—	10
6	NiCl$_2$	90	12	—	17
7	CuCl$_2$	20	12	—	Trace
8	CuCl$_2$	50	12	—	15
9[c]	CuCl$_2$	90	12	—	8
10	CuCl$_2$	90	5	CH$_3$CO$_2$H (1.0)	55
11	CuCl$_2$	90	5	CF$_3$CO$_2$H (1.0)	35
12	CuCl$_2$	90	5	C$_6$H$_5$CO$_2$H (1.0)	51
13	CuCl$_2$	90	5	HCO$_2$H (1.0)	33
14	CuCl$_2$	90	5	HO$_2$CCH$_2$CH$_2$CO$_2$H (1.0)	45
15	CuCl$_2$	90	12	CH$_3$CO$_2$H (1.0)	88
16	CuCl$_2$	90	12	CH$_3$CO$_2$H (3.0)	76

[a] Reaction conditions: **1a** (1.0 mmol) was added to a mixture of catalyst, **2**, and water (10 mL), then heated to indicated temperature and time under air conditions. [b] Isolated yield. [c] Catalyst (10 mol%).

bond formation,[12] a reaction of 1-ethyl-1*H*-indole (**1a**) and TMEDA (**2**) was selected as a model one. In the reaction, the bisindole was synthesized through direct arylation catalyzed by some abundant and cheap metal salts.[13] As shown in Table 1, when water was chosen as a solvent, treatment of **1a** and **2** with CuCl$_2$ at 90 °C for 5 h afforded the desired product **3a** in only 20% yield (entry 1). As usual, we prolonged the reaction time, the yield was increased, but just to 42% (entry 2). Next, a series of other transition metal catalysts including FeCl$_3$, Cu(OAc)$_2$, ZnCl$_2$ and NiCl$_2$ were tested (entries 3–6), unfortunately, all were inferior to CuCl$_2$. When CuCl$_2$ was reduced to 10 mol%, product yield was lowered to 8% (entry 9). Further screening of the reaction temperature revealed that the reaction at 90 °C gave the best results (entries 2, 7 and 8), but the yields were still dissatisfied. To our delight, when the same starting materials of entry 1 were treated with 1.0 equiv of acetic acid, **3a** was provided in 55% yield (entry 10) within 5 h. Excitedly, **3a** was obtained in 88% yield (entry 15) when reaction time prolonged to 12 h. However, as acetic acid was increased to 3.0 equiv the yield declined to 76% (entry 16). Other carboxylic acids such as benzoic acid, formic acid, succinic acid were also evaluated. Although each yield was different, all of the tested acids showed promotive activity (entries 11–14). It was noticed that *tris*(1-ethyl-1*H*-indol-3-yl)methane **3aa** (<5%) was isolated as a byproduct in the reactions (Table 1). For the methylene donor, another tertiary


3a: R^1 = Et, R^2 = H, 88% (11h)
3b: R^1 = Bn, R^2 = H, 53% (16h)
3c: R^1 = Et, R^2 = 5-Cl, 72% (12h)
3d: R^1 = Et, R^2 = 5-OMe, 82% (12h)
3e: R^1 = Et, R^2 = 2-Me, 95% (11h)
3f: R^1 = Et, R^2 = 4-Me, 72% (10h)
3g: R^1 = Et, R^2 = 7-Me, 82% (10h)
3h: R^1 = Et, R^2 = 5-CN, 61% (12h)
3i: R^1 = Et, R^2 = 6-COOMe, 35% (10h)
3j: R^1 = Et, R^2 = 6-NO$_2$, 30% (12h)

3m: R^2 = H, 32% (17h)
3n: R^2 = OMe, 41% (12h)

3k: 45% (12h)

3o: R^2 = H, 34% (16h)
3p: R^2 = OMe, 64% (12h)

standard conditions

1l

3l, 45% (10h)

[a] Reaction conditions: for **1a**–**k** (1.0 mmol) was added to a mixture of CuCl$_2$ (0.5 mmol), **2** (1.5 mmol), AcOH (1.0 mmol) and water (10 mL), then heated to indicated temperature (90 °C) and time under air conditions; for **1m**–**p**, the same conditions as **1a**–**k** except using 80% acetonitrile aqueous solution (30 mL) as a solvent in place of water; isolated yield.

Scheme 1 Scope of synthesis of bisindolylmethane using TMEDA as methylene donor.[a]

amine *N,N′*-dimethylpiperazine was also available and afforded the desired product in 61% yield under the same reaction conditions as entry 15.

With the optimized conditions in hand, a series of 3,3′-bisindolylmethane (**3a**–**p**) were generated by this novel protocol (Scheme 1). The Cu-catalyzed C3-selective transformation of indoles was compatible with a range of substituents in all positions of the indole ring, and generated the corresponding products in reasonable to excellent yields. For *N*-protecting groups, the *N*–Et group delivered a good result (**3a**), while *N*–Bn group gave moderate yield (**3b**). In indole ring, substituents such as Me, CN, and MeO were well tolerated, and the positions of substituents did not appear to exert much appreciable influence on the efficiency (**3d**–**h**).
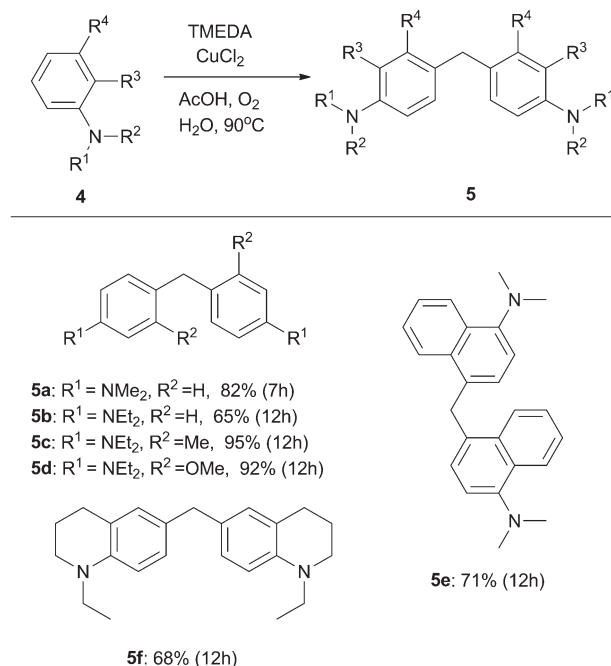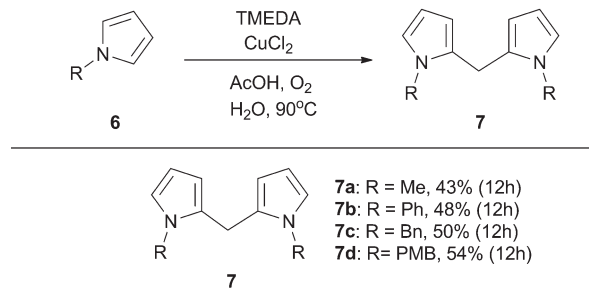
Scheme 2 Scope of synthesis of 4,4′-diaminodiphenylmethane using TMEDA as methylene donor.[a]

[a] Reaction conditions: pyrrole (**6**) (1.0 mmol) was added to a mixture of CuCl$_2$ (0.5 mmol), **2** (1.5 mmol), AcOH (1.0 mmol) and water (10 mL), then heated to indicated temperature (90 °C) and time under air conditions; isolated yield.

Scheme 3 Scope of synthesis of bispyrrolylmethane using TMEDA as methylene donor.[a]

Notably, C–Cl bond remained intact during the reaction (**3c**), which provided an additional handle for further elaboration of product. For electron-withdrawing groups such as COOMe and NO$_2$ in indole ring and azaindole, the reactions were still practical although the yields were low (**3i–k**), however, they were unavailable in our previous works.[11] Moreover, four aza-macrocyclic compounds were successfully constructed in the reaction system when 80% acetonitrile aqueous solution was used as a solvent (**3m–p**). Very interestingly, when conducted in pure water, those reactions mainly provided intermolecular methylene-bridged compounds. While in pure acetonitrile, the main products were C3-formylation indoles. The reason might be presumably due to the concentration inequality caused by bad solubility of substrates in water. It is worth mentioning that *tert*-butyl carbonate (Boc)-protected indole reacted with TMEDA affording the *N*-free compound (**3l**) that was unavailable to be obtained with other *N*–Et protected or non-protected indoles. The result makes this protocol more useful for the introduction of new *N*-functional groups. As a summary, the electronic nature of the substituents in the indole ring affected this transformation, the reactivity of electron-donating groups was superior to that of the electron-withdrawing groups, which might be due to the higher nucleophilicity of electron rich indoles.

The success of indoles methylenation encouraged us to further extend the substrate scope beyond indoles. Anilines and pyrroles are structurally unique and possess a variety of

interesting chemical properties.[14] As shown in Schemes 2 and 3, 4,4′-diaminodiphenylmethane were prepared in good to excellent yields. 2,2′-Bispyrrolylmethanes were also synthesized although the yields were relatively low. It should be indicated that regioselectivity of these transformations for diaminodiphenylmethane was excellent. Only 4,4′-diaminodiphenylmethane was isolated in the reactions, no 4,2′- or 4,3′-diaminodiphenylmethane was observed. Notably, *N*-protecting groups also showed an influence on reactivity of substrates (**5a** and **5b**). Besides, the same as indoles, the electronic nature of the substituents affected the transformation. For example, *m*-Me- and *m*-OMe-substituted aniline reacted smoothly to furnish desired products (**5c** and **5d**) in better yields than that of **5b**. Gratifyingly, naphthylamine and cyclic amine selectively underwent the target coupling reaction in moderate yields (**5e** and **5f**). As bispyrrolylmethane have been synthesized using a variety of procedures in organic solvents,[15] with the optimized reaction conditions, a series of 2,2′-bispyrrolylmethanes (**7a–d**) were also prepared (Scheme 3). However, pyrroles with *N*-protecting groups, *e.g.*, Me, Ph, Bn and 4-methylbenzyl (PMB), gave relatively low yields.

The results above mainly focused on sp^2 C–H and sp^3 C–H cross-coupling reactions. To address the even more challenging reactions under current conditions, we expanded our substrates to sp^3 C–H and sp^3 C–H cross-couplings to generate methylene-bridged compounds. An iron-catalyzed protocol for the synthesis of methylene-bridged bis-1,3-dicarbonyls was initially reported by Li *et al.*,[2b] and further several synthetic procedures have been created.[16] Considering the valuableness, 1,3-dicarbonyl compounds were used to investigate the availability of our protocol (Scheme 4). Very interestingly, the desired products were successfully obtained although the yields were low. To improve the yields, a different catalytic system might be desired, and further effort is essential.

Further experiments have been performed to obtain the insight into the mechanism. Based on our previous research and reported data, we speculated formaldehyde might be the key intermediate of the reaction. Therefore, a reaction of **1a**

Scheme 4 Scope of synthesis of bis-1,3-dicarbonylmethane using TMEDA as methylene donor.[a]
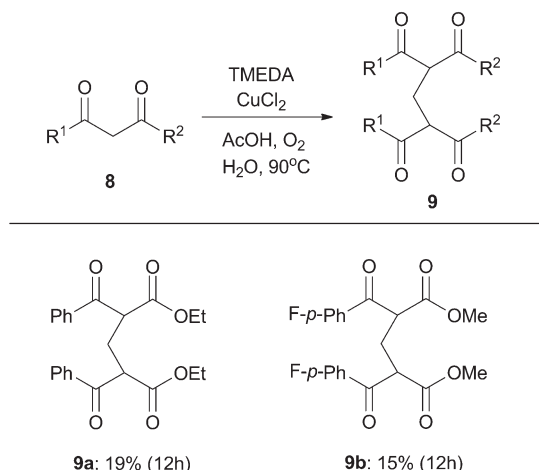
[a] Reaction conditions: 1,3-dicarbonyl derivatives (8) (1.0 mmol) was added to a mixture of CuCl$_2$ (0.5 mmol), 2 (1.5 mmol), AcOH (1.0 mmol) and water (10 mL), then heated to indicated temperature (90 °C) and time under air conditions; isolated yield.

with an aqueous solution of formaldehyde was carried out using the CuCl$_2$/AcOH/H$_2$O system [eqn (1)]. As expected, the desired product **3a** was generated in 89% yield, which suggested that formaldehyde was most likely a possible intermediate for the present transformation. To confirm the presence of formaldehyde, Nash reagent as a capturing tool was applied.[17] Fortunately, formaldehyde was successfully identified in the CuCl$_2$/AcOH/H$_2$O system (see ESI†). For the byproduct **3aa**, a reaction of **1a** and 3-formylindole (**1q**) gave **3aa** in 18% yield [eqn (2)], suggesting that **1q** should be important in the formation of the byproduct generated from three-component couplings (Table 1). Expectedly, **1q** was exactly detected *via* ^{1}H NMR in the reaction system (see ESI†).
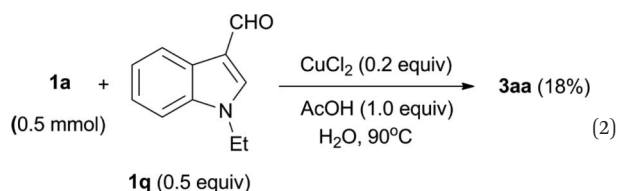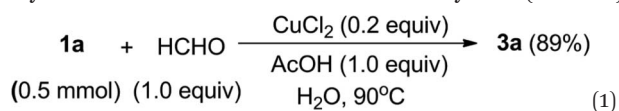
With above evidences and reported information in hand, we proposed a tentative mechanism as shown in Scheme 5. Initially, TMEDA coordinated with CuCl$_2$ affording Cu(II)–TMEDA complex **A**. Iminium ion **B** is generated in the reaction system *via* the general accepted mechanism as follows:[18] one-electron oxidation of nitrogen, deprotonation of C–H adjacent to a nitrogen atom, and second one-electron oxidation. Following this, the formation of formaldehyde could be
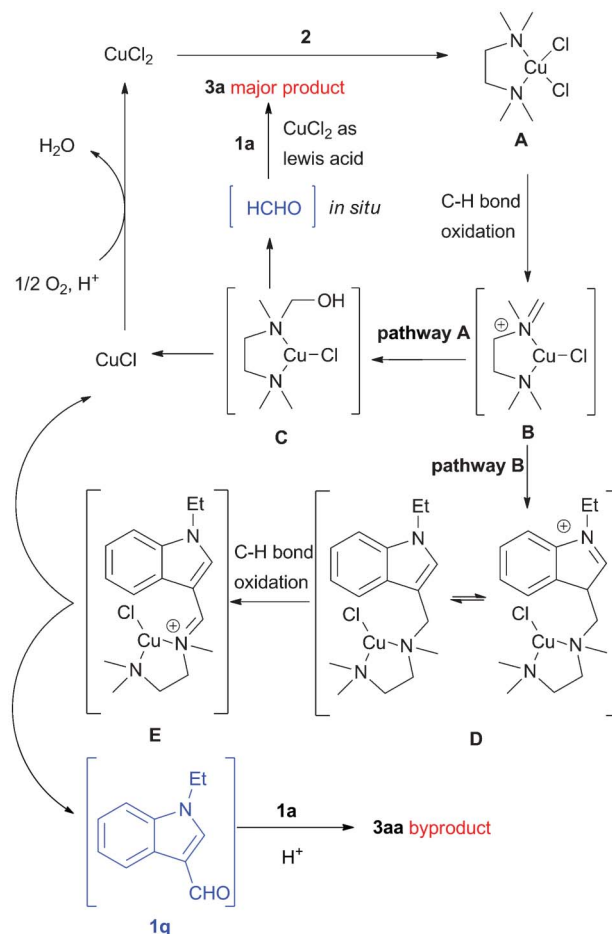
Scheme 5 Proposed reaction mechanism.

ascribed to trapping of intermediate **B** by coordinated OH or by water, to give α-hydroxylated amine **C**, which subsequently decomposes to give formaldehyde and *N*-demethylation product.[19] In the presence of Lewis acid, two molecules of indoles react with one molecule of formaldehyde to afford bisindolylmethane (pathway **A**).[20] In view of pathway **B**, nucleophilic addition of indole affords the oxidative Mannich-type product **D**,[21] which undergoes further oxidation to the second iminium ion **E**, followed by hydrolysis to generate 3-formylindole (**1q**).[2f] Next, nucleophilic substitution of **1q** with two molecules of indoles afforded byproduct *via* protonation and elimination of one molecule of H$_2$O.[22] The final step of the catalytic cycle is oxidation of Cu(I) to Cu(II), using O$_2$ as terminal oxidant in presence of H$^+$,[23] which might be the reason why acetic acid elevated reaction yields. Notably, relatively strong acid such as CF$_3$COOH was not conducive to methylenation as shown in Table 1 (entries 11–14). We postulated that this is attributed to the formation of an ion pair consisting of TMEDA cation and strong acid anion, which weakens the coordination of TMEDA and the catalyst.

Conclusions

In summary, we have successfully developed a carboxylic acid-promoted $CuCl_2$/oxygen-mediated method for the synthesis of methylene-bridged compounds using TMEDA as methylene source in water. The electronic properties of the *N*-protecting groups and substituents impacted the reactivity of the methylenation. The current protocol showed a broad substrate scope, not only indoles, but also anilines, pyrroles and 1,3-dicarbonyls. Notably, two key intermediates of the reaction were identified and a mechanism was proposed. Moreover, green solvent might decrease operation cost for large scale preparation of the regioselective synthesis of methylene-bridged compounds. Further study on TMEDA reacting with other nucleophiles is currently underway in our laboratory.

Acknowledgements

References

1 (*a*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633–639; (*b*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731–1770; (*c*) B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050–8057.

2 (*a*) X. Xu, X. Li, L. Ma, N. Ye and B. Weng, *J. Am. Chem. Soc.*, 2008, **130**, 14048–14049; (*b*) H. Li, Z. He, X. Guo, W. Li, X. Zhao and Z. Li, *Org. Lett.*, 2009, **11**, 4176–4179; (*c*) M.-Z. Wang, C.-Y. Zhou, M.-K. Wong and C.-M. Che, *Chem.–Eur. J.*, 2010, **16**, 5723–5735; (*d*) K. Ramachandiran, D. Muralidharan and P. T. Perumal, *Tetrahedron Lett.*, 2011, **52**, 3579–3583; (*e*) W. Liu, J. Liu, D. Ogawa, Y. Nishihara, X. Guo and Z. Li, *Org. Lett.*, 2011, **13**, 6272–6275; (*f*) W. Wu and W. Su, *J. Am. Chem. Soc.*, 2011, **133**, 11924–11927.

3 (*a*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062–11087; (*b*) K. M. Gligorich and M. S. Sigman, *Chem. Commun.*, 2009, 3854–3867; (*c*) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329–2364; (*d*) J.-S. Tian and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2010, **49**, 8417–8420; (*e*) S. Li and J. Wu, *Org. Lett.*, 2011, **13**, 712–715.

4 (*a*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998; (*b*) P. Norcott, C. Spielman and C. S. P. McErlean, *Green Chem.*, 2012, **14**, 605–609; (*c*) Y.-X. Su, Y.-H. Deng, T.-T. Ma, Y.-Y. Li and L.-P. Sun, *Green Chem.*, 2012, **14**, 1979–1981; (*d*) N. Liu, C. Liu and Z. Jin, *Green Chem.*, 2012, **14**, 592–597.

5 C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82.

6 (*a*) L. Ackermann, J. Pospech and H. K. Potukuchi, *Org. Lett.*, 2012, **14**, 2146–2149; (*b*) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, *Org. Lett.*, 2012, **14**, 728–731.

7 (*a*) C.-M. Wei and C.-J. Li, *Green Chem.*, 2002, **4**, 39–41; (*b*) C.-M. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2003, **125**, 9584–9585; (*c*) C. I. Herrerias, X.-Q. Yao, Z.-P. Li and C.-J. Li, *Chem. Rev.*, 2007, **107**, 2546–2562; (*d*) C.-J. Li, *Sci. China: Chem.*, 2011, **54**, 1815–1830.

8 O. Basle and C.-J. Li, *Green Chem.*, 2007, **9**, 1047–1050.

9 D. J. Faulkner, *Nat. Prod. Rep.*, 2001, **18**, 1–49.

10 (*a*) F. Andreani, R. Andrisano, C. D. Casa and M. Tramontini, *J. Chem. Soc. C*, 1970, 1157–1161; (*b*) D. Dolman and M. Sainsbury, *Tetrahedron Lett.*, 1981, **22**, 2119–2120.

11 L. Zhang, C. Peng, D. Zhao, Y. Wang, H.-J. Fu, Q. Shen and J.-X. Li, *Chem. Commun.*, 2012, **48**, 5928–5930.

12 (*a*) L. Zhang, M. Geng, P. Teng, D. Zhao, X. Lu and J.-X. Li, *Ultrason. Sonochem.*, 2012, **19**, 250–256; (*b*) J. Jin, M.-M. Cai and J.-X. Li, *Synlett*, 2009, 2534–2538.

13 (*a*) Y. Kuninobu, M. Nishi and K. Takai, *Chem. Commun.*, 2010, **46**, 8860–8862; (*b*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672–3673; (*c*) F. Yang, J. Li, J. Xie and Z.-Z. Huang, *Org. Lett.*, 2010, **12**, 5214–5217.

14 (*a*) M. R. V. Finlay, D. G. Acton, D. M. Andrews, A. J. Barker, M. Dennis, E. Fisher, M. A. Graham, C. P. Green, D. W. Heaton, G. Karoutchi, S. A. Loddick, R. Morgentin, A. Roberts, J. A. Tucker and H. M. Weir, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4442–4446; (*b*) K. Papireddy, M. Smilkstein, J. X. Kelly, Shweta, S. M. Salem, M. Alhamadsheh, S. W. Haynes, G. L. Challis and K. A. Reynolds, *J. Med. Chem.*, 2011, **54**, 5296–5306.

15 (*a*) M. J. Plater, S. Aiken and G. Bourhill, *Tetrahedron*, 2002, **58**, 2405–2413; (*b*) J. L. Sessler, M. R. Johnson, S. E. Creager, J. C. Fettinger and J. A. Ibers, *J. Am. Chem. Soc.*, 1990, **112**, 9310–9329; (*c*) P. D. Rao, S. Dhanalekshmi, B. J. Littler and J. S. Lindsey, *J. Org. Chem.*, 2000, **65**, 7323–7344.

16 (*a*) W.-J. Yoo, A. Tanoue and S. Kobayashi, *Chem.–Asian J.*, 2012, **7**, 2764–2767; (*b*) R. Balamurugan and S. Manojveer, *Chem. Commun.*, 2011, **47**, 11143–11145.

17 T. Nash, *Biochem. J.*, 1953, **55**, 416–421.

18 (*a*) Z. Li and C.-J. Li, *Org. Lett.*, 2004, **6**, 4997–4999; (*b*) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810–11811; (*c*) K. McCamley, J. A. Ripper, R. D. Singer and P. J. Scammells, *J. Org. Chem.*, 2003, **68**, 9847–9850.

19 D. C. Heimbrook, R. I. Murray, K. D. Egeberg, S. G. Sligar, M. W. Nee and T. C. Bruice, *J. Am. Chem. Soc.*, 1984, **106**, 1514–1515.

20 (*a*) C. Pal, S. Dey, S. K. Mahato, J. Vinayagam, P. K. Pradhan, V. S. Giri, P. Jaisankar, T. Hossain, S. Baruri, D. Ray and S. M. Biswas, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4924–4928; (*b*) A. Kumar, S. Sharma and R. A. Maurya, *Tetrahedron Lett.*, 2009, **50**, 5937–5940.

21 (*a*) Z. Li, D. S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928–8933; (*b*) S. I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312–15313.

22 R. Nagarajan and P. T. Perumal, *Tetrahedron*, 2002, **58**, 1229–1232.

23 J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie and J.-H. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 3453–3457.