Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 1589

www.rsc.org/greenchem

COMMUNICATION

Cu(0) nanoparticle catalyzed efficient reductive cleavage of isoxazoline, carbonyl azide and domino cyclization in water medium†

Krishnanka S. Gayen,[a] Tista Sengupta,[a] Yasmin Saima,[a] Adita Das,[a] Dilip K. Maiti*[a] and Atanu Mitra*[b]

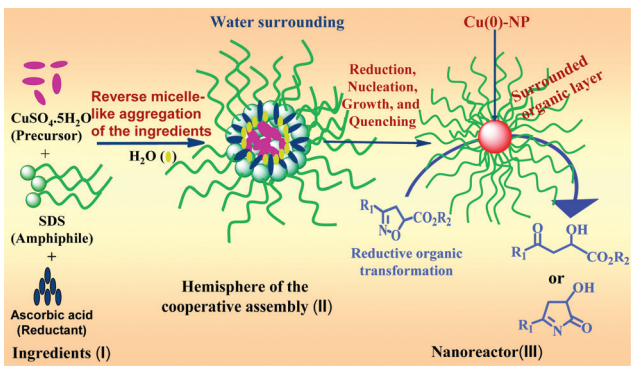
Received 20th February 2012, Accepted 30th March 2012
DOI: 10.1039/c2gc35252d

Small Cu(0)-nanoparticles (NPs) are fabricated utilizing $CuSO_4{\cdot}5H_2O$, surfactant (SDS) and ascorbic acid in aqueous medium. Its outstanding catalytic activity under low catalyst loading is developed toward reductive cleavage of isoxazoline, carbonyl azide and domino cyclization to furnish valuable 2-hydroxy-4-keto esters, primary amides and a new class of heterocycle, 4-hydroxy-2-pyrroline-5-one.

Water is the solvent of a magnificent array of reactions taking place in our body for keeping it healthy and functioning. Water is inevitable for selective formation of new bonds during biosynthesis of small molecules and multistep synthesis of macromolecules.[1] These outstanding properties of water are due to its unique structure, both acidic (H_3O^+) and basic (HO^-) nature, strong hydrogen bonding, high polarity, dielectric constant, surface tension and heat capacity. Although, Wohler's use of water as a medium for the synthesis of urea has been known for many years, scientists of academic and industrial settings are now exploring the possibility of replacing large volumes of toxic organic solvents by water as the reaction medium toward the development of cleaner and green processes.[2] To avoid toxic organic solvents, highly reactive metal-NPs[3,4] can be employed as efficient catalysts for organic synthesis in a water medium. Although, it is very difficult for a chemist to use water as a medium for the fabrication of small metal-NPs and the simultaneous development of their outstanding catalytic activity toward fundamental organic transformation.

Nitrile oxide cycloaddition[5–8] derived Δ^2-isoxazoline represents a responsive heterocyclic scaffold for the total synthesis of natural products and valuable synthons.[6] On treatment of the appropriate reagents, the cycloadduct provides easy access to 3-amino alcohols, allyl alcohols, 1,3-diols, hydroxy ketones, 1,3-diketones, enones, 1,6-diketones, 1,3-dienes and other diversely functionalized synthons.[6a,7,8] In addition to existing methods, in this communication we report another frontier for its synthetic application by devising a simple catalytic reduction strategy in a water medium involving *in situ* fabricated Cu(0)-NPs. In our experiment, a cooperative assembly[3a] (**II**, Scheme 1) is constructed in a water medium by utilizing inexpensive $CuSO_4{\cdot}5H_2O$, SDS and ascorbic acid. Cu(0)-NPs are fabricated (**III**) inside the cooperative assembly by reduction of $CuSO_4$, nucleation, growth and quenching at 60 °C. For clarity, surfactants are removed from the top portion of the NPs (**III**, Scheme 1). The major problem of the insolubility of the hydrophobic phase organic precursor in the water medium is solved by the construction of a surfactant surrounded lipophilic environment (**III**). Small Cu(0)-NPs are fabricated by reducing $Cu(AOT)_2$ with $NaBH_4$ (or N_2H_4) in AOT reverse micelle (size: ~20 nm)[9b] and also using nanoporous SBA-15 (3 nm).[9d] We have avoided using strong reducing agents which are harmful to most reduction prone organic functionalities. In this context, the reflux synthesis of Cu(0)-NPs is encouraging.[9c] The morphology of the nanoreactor is determined by SEM imaging (dimension: 90–110 nm, panel a, Fig. 1). Routine characterization of the Cu(0)-NPs is performed by means of UV-vis studies [plasmone peak: 586 nm, panel b), DLS study (7.8 nm, panel c), TEM imaging (histogram: 2–7 nm, panel d) and comparing the literature X-ray diffraction pattern [peaks at (2θ): 43.4°, 50.4°, 73.9°, 90.0° and 95.7°, panel e].[10]

Next, we turned our attention to the development and optimization of the catalytic reduction property of the metal Cu(0)-NPs. After extensive studies, reductive cleavage (Table 1) of ethyl 3-naphthylisoxazoline-5-carboxylate (**1a**) to ethyl 2-hydroxy-4-keto-4-naphthylbutyrate (**2a**, entry 1, Table 1) is optimized with very low catalyst loading (0.6 mol%) and good yield (84%, entry 1, Table 2). Product **2a** is not detected if the



Scheme 1 Fabrication of Cu(0)-NPs and their catalytic activity.

[a]*Department of Chemistry, University of Calcutta, University College of Science, 92, A. P. C. Road, Kolkata-700009, India*
[b]*Sree Chaitanya College, Habra-743268, India. E-mail: dkmchem@caluniv.ac.in, mitatanu@gmail.com; Fax: +91-33-2351-9755; Tel: +91-33-2350-9937*

†Electronic supplementary information (ESI) available: procedures, characterization data, spectra. See DOI: 10.1039/c2gc35252d

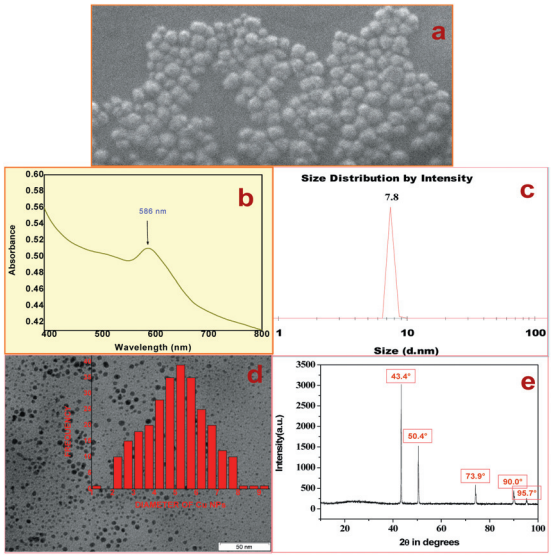


Fig. 1 (a) SEM image of the cooperative assembly. (b) UV-vis spectrum. (c) DLS data. (d) TEM image. (e) Powder XRD data.

Table 1 Development and optimization of the reaction

Entry	Catalyst (mol%)	Reagents and reaction conditions[a,b]	Conversion (%)	Yield (%)
1	$CuSO_4$ (0.6)	**1a**, AA, SDS, 60 °C, 4 h	100	**2a**, 84
2	$CuSO_4$ (0.6)	**1a**, AA, SDS, rt, 24 h	0	**2a**, nd[c]
3	$CuSO_4$ (0.6)	**1a**, AA, 60 °C, 12 h	0	**2a**, nd
4	—	**1a**, AA, SDS, 60 °C, 12 h	0	**2a**, nd
5	Cu dust (200)[d]	**1a**, AA, 60 °C, 12 h	0	**2a**, nd
6	CuOTf (10)	**1a**, AA, 60 °C, 12 h	0	**2a**, nd
7	Cu $(OTf)_2$(10)	**1a**, AA, 60 °C, 12 h	0	**2a**, nd
8	$CuSO_4$ (0.6)	**1a**, AA, SDS, EDC[e], 60 °C, 12 h	0	**2a**, nd
9	$CuSO_4$ (0.6)	**1a**, AA, SDS, 80 °C, 4.0 h	100	**3a**, 89

[a] Ascorbic acid (1 mmol). [b] Sodium dodecylsulfonate (20 mol%). [c] Not detected. [d] Bulk copper powder. [e] Ethylenedichloride.

reaction is conducted at ambient temperature, without surfactant SDS or $CuSO_4{\cdot}5H_2O$ (entries 2–4, Table 1). The results in Table 1 reveal that the *in situ* fabricated Cu(0)-NPs (entry 1, Table 1) are efficient compared to bulk Cu(0), Cu(I) and Cu(II) (entries 5–7, Table 1). Due to the absence of the hydrated form of Cu(0)-NPs, the reaction is unsuccessful in organic solvent (entry 8, Table 1). On enhancement of the temperature to 80 °C, a new class of heterocycle, 4-hydroxy-5-keto-2-pyrroline (**3a**) is furnished (entry 9, Table 1).

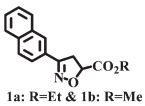
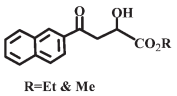
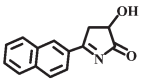
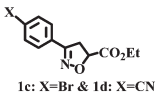
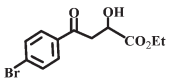
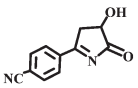
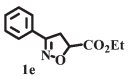
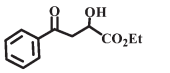
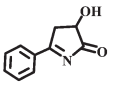
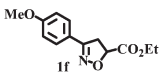
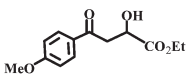
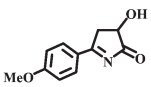
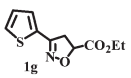
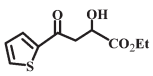
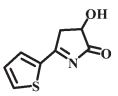
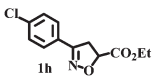
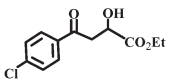
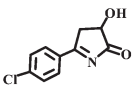
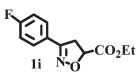
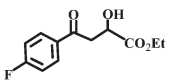
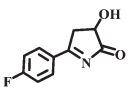
Selective activation of N–O bond and its reductive cleavage are important process for both biochemical and chemical synthesis of valuable compounds.[11] RANEY Ni–H_2 in aqueous acetic acid,[12] SmI_2/$B(OH)_3$/0 °C[7a] and Fe(10 equiv.)/NH_4Cl/EtOH–H_2O(1 : 1)/80 °C[7b] are employed for the reduction of Δ^2-isoxazoline to achieve valuable β-hydroxy ketone synthons. Our fabricated Cu(0)-NPs in a water medium chemoselectively reduced functionalized Δ^2-isoxazolines (**1a–i**) possessing an ester functionality to afford valuable 2-hydroxy-4-keto ester synthons (**2a–h**, Table 2) with fast reaction convergence (3.5–5.0 h) and good yields (79–89%). In the presence of water, the reduction property of the surface electrons[13] is significantly enhanced because water is used as the electron carrier for the reduction of the N–O bond of the cycloadduct. Expectantly, a very low catalyst loading (0.6 mol%) of Cu(0)-NPs is found to be active due to the formation of an ideal reaction system of Cu(0)-NPs possessing highly active surfaces with surrounding water molecules as an electron carrier. Dehalogenation is one of the major concerns of reduction processes, involving hydride and metal catalyzed hydrogenation reactions. Herein, the mild Cu(0)-NPs catalyzed process does not remove the halogens (F, Cl or Br, entries 3, 7, 8, Table 2). Activated phenyl, naphthyl and heterocyclic aromatic nuclei are also tolerated in this chemoselective reduction process.

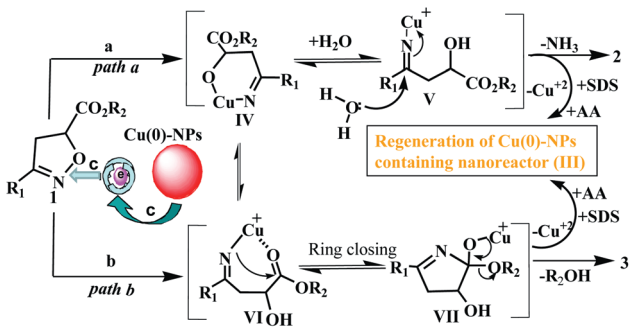
Metal catalyzed ring opening and domino or sequential cyclization strategies are becoming important tools for the synthesis of difficult to access hetero- and carbocyclic frameworks.[14] Herein, we disclose our novel studies on the domino cyclization process by the Cu(0)-NPs (path b, Scheme 2). Interestingly, on treatment of Δ^2-isoxazoline-5-esters (**1a**) at an elevated temperature (80 °C), the reductive process has furnished 4-hydroxy-2-pyrroline-5-one (**3a**) along with traces of the corresponding β-hydroxy ketone (**2a**). Pyrrolinone compounds are found to be peptidomimetics and anti-HIV agents.[15] Only 0.6 mol% of $CuSO_4{\cdot}5H_2O$ is required for rapid (3.5–4.0 h) ring opening and domino cyclization to afford the new class of γ-hydroxy pyrrolinones (**3a–g**, Table 2) in high yields (80–89%). Involvement of the ester group in the catalytic domino cyclization process is verified by using two isoxazoline precursors possessing different ester groups (methyl and ethyl, **1a** and **1b**, entries 1 and 2, Table 2) which has furnished the same heterocycle **3a**.

The reaction is presumed to proceed *via* the predominant activation and reductive cleavage of the heteroatomic N–O bond by electron transfer[16] from the highly active surface of the Cu(0)-NPs involving water clusters to form a stable Cu^{+2}-chelated six membered intermediate **IV**. It, on protonation and subsequent Cu^{+2}-assisted removal of ammonia (**V**), provides **2** (*path a*, Scheme 2). On the other hand, intermediate **IV** at a higher temperature (80 °C) is expected to undergo domino cyclization involving the C═O group of the ester functionality to form a seven-membered intermediate, **VI**, which is subsequently transformed into γ-hydroxy pyrrolinone (**3**, *path b*) *via* the formation of a putative five-membered cyclic intermediate **VII**. The Cu(0)-NPs are regenerated from Cu^{+2}, which involves the construction of the nanoreactor (**III**, Scheme 1).

Many natural products and functional molecules possess a primary amide as a crucial functionality and have found a broad spectrum of applications in energetically viable aggregated materials, construction of cell surface-active *N*-glycosyl peptides, novel functionalities and valuable heterocycles.[17] Application of the robust catalytic system is extended for the homoatomic reductive-cleavage of the N–N bond (**VIII** and **IX**) in carbonyl-azide (**4**) to afford valuable primary amides (**5a–j**, Scheme 3) with fast reaction rates (1.5–2.0 h) and high yields (79–95%). The performance of our benign method is evaluated by the

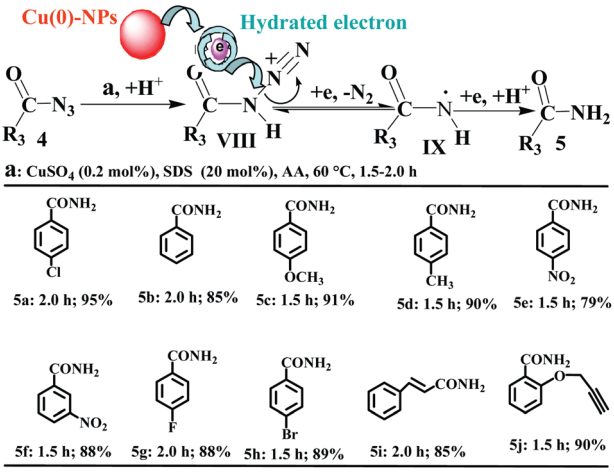
Table 2 Synthesized β-hydroxyketone and γ-hydroxypyrrolinone

Entry	Isoxazoline (**1**)	Time (h)	**2**, yield (%)	β-Hydroxy ketone (**2**)	Time (h)	**3**, yield (%)	γ-Hydroxy pyrrolinone (**3**)
1	 1a: R=Et & 1b: R=Me	3.5	**2a**, 84	 R=Et & Me	3.5	**3a**, 89	
2		3.5	**2b**, 89		3.5	**3a**, 88	
3	 1c: X=Br & 1d: X=CN	4.0	**2c**, 88		4.0	**3b**, 88	
4	 1e	4.0	**2d**, 79		4.0	**3c**, 85	
5	 1f	4.0	**2e**, 83		4.0	**3d**, 83	
6	 1g	4.5	**2f**, 82		4.5	**3e**, 85	
7	 1h	4.0	**2g**, 81		3.5	**3f**, 81	
8	 1i	5.0	**2h**, 83		3.5	**3g**, 80	



a: $CuSO_4$ (0.6 mol%), AA, SDS (20 mol%), H_2O, 60 °C, 3.5-5.0 h; **b**: $CuSO_4$ (0.6 mol%), AA, SDS (20 mol%), H_2O, 80 °C, 3.5-4.5 h; **c**: Surface electron transfer by water cluster.

Scheme 2 Possible reaction paths.



Scheme 3 Reduction of carbonyl azides to primary amides.

reduction of carbonyl azides bearing electron donating, electron withdrawing, halogens and π-bonds to afford functionalized amides with an extremely low catalyst loading (0.2 mol%). We have recovered SDS (82%) from the concentrated aqueous solution by crystallization. Recovered Cu(0)-NPs are less efficient because a higher catalytic loading (3%) is required for the reduction process.

In conclusion, we have developed robust catalytic reduction properties of *in situ* fabricated small Cu(0)-NPs in water medium toward the heteroatomic cleavage of N–O bonds, homoatomic N–N bonds and domino cyclizations to afford 2-hydroxy-4-keto ester synthons, valuable primary amides and a new class of heterocycle, 4-hydroxy-2-pyrroline-5-one.

Financial support from DST (SR/NM/NS-29/2010 and SR/S1/OC-22/2006), CRNN, CSIR-SPMF (K. S. G.) and CSIR-SRF (T. S.) of India are gratefully acknowledged.

Notes and references

1 (*a*) P. Ball, *H_2O: A Biography of Water*, Phoenix Press, London, 2000; (*b*) R. M. Daniel, J. L. Finney and M. Stoneham, *Philos. Trans. R. Soc. London, Ser. B*, 2004, **359**, 1143; (*c*) J. E. Klijn and J. B. F. N. Engberts, *Nature*, 2005, **435**, 746.

2 (*a*) M. Lancaster, in *Handbook of Green Chemistry and Technology*, ed. J. H. Clark and D. J. Macquarrie, Blackwell Publishing, Abingdon, 2002; (*b*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*c*) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725; (*d*) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302; (*e*) P. Pandit, K. S. Gayen, S. Khamarui, N. Chatterjee and D. K. Maiti, *Chem. Commun.*, 2011, **47**, 6933.

3 (*a*) Y. S. Lee, *Self-Assembly and nanotechnology: A Force Balance Approach*, John Wiley and Son, Inc., Hoboken, New Jersey, 2008; (*b*) S. K. Ghosh and T. Pal, *Chem. Rev.*, 2007, **107**, 4797; (*c*) M. Turner, V. B. Golovko, O. P. H. Vaughan, P. Abdulkin, A. Berenguer-Murcia, M. S. Tikhov, B. F. G. Johnson and R. M. Lambert, *Nature*, 2008, **454**, 981.

4 Application of Cu(0) NPs: (*a*) M. Kidwai, N. K. Mishra, V. Bansal, A. Kumar and S. Mozumdar, *Tetrahedron Lett.*, 2007, **48**, 8883; (*b*) A. Saha and B. Ranu, *J. Org. Chem.*, 2008, **73**, 6867–6870; (*c*) F. Benaskar, V. Engels, N. Patil, E. V. Rebrov, J. Meuldijk, V. Hessel, L. A. Hulshof, D. A. Jefferson, J. C. Schouten and A. E. H. Wheatley, *Tetrahedron Lett.*, 2010, **51**, 248; (*d*) S. Ahammed, A. Saha and B. C. Ranu, *J. Org. Chem.*, 2011, **76**, 7235.

5 (*a*) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (*b*) J. K. Gallos and A. E. Koumbis, *Curr. Org. Chem.*, 2003, **7**, 397; (*c*) N. Chatterjee, P. Pandit, S. Halder, A. Patra and D. K. Maiti, *J. Org. Chem.*, 2008, **73**, 7775.

6 (*a*) A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; (*b*) D. Muri and E. M. Carreira, *J. Org. Chem.*, 2009, **74**, 8695.

7 (*a*) J. W. Bode and E. M. Carreira, *Org. Lett.*, 2001, **3**, 1587; (*b*) D. Jiang and Y. Chen, *J. Org. Chem.*, 2008, **73**, 9181.

8 (*a*) G. K. Tranmer and W. Tam, *Org. Lett.*, 2002, **4**, 4101; (*b*) P. Aschwanden, L. Kværnø, R. W. Geisser, F. Kleinbeck and E. M. Carreira, *Org. Lett.*, 2005, **7**, 5741; (*c*) J. L. Lee, G. Schiffer and V. Jäger, *Org. Lett.*, 2005, **7**, 2317.

9 (*a*) I. Lisiecki and M. P. Pileni, *J. Am. Chem. Soc.*, 1993, **115**, 3887; (*b*) J. P. Cason and C. B. Roberts, *J. Phys. Chem. B*, 2000, **104**, 1217; (*c*) X. Zhang, H. Yin, X. Cheng, H. Hu, Q. Yu and A. Wang, *Mater. Res. Bull.*, 2006, **41**, 2041; (*d*) C.-S. Chen, C.-C. Chen, C.-T. Chen and H.-M. Kao, *Chem. Commun.*, 2011, **47**, 2288.

10 H. Zhu, C. Zhang and Y. Yin, *Nanotechnology*, 2005, **16**, 3079.

11 (*a*) S. I. Gorelsky, S. Ghosh and E. I. Solomon, *J. Am. Chem. Soc.*, 2006, **128**, 278; (*b*) G. Villar-Acevedo, E. Nam, S. Fitch, J. Benedict, J. Freudenthal, W. Kaminsky and J. A. Kovacs, *J. Am. Chem. Soc.*, 2011, **133**, 1419.

12 (*a*) J. T. Pulkkinen and J. J. Vepsäläinen, *J. Org. Chem.*, 1996, **61**, 8604; (*b*) S. E. Denmark and S. Fujimori, *Org. Lett.*, 2002, **4**, 3473; (*c*) G. Pousse, F. L. Cavelier, L. Humphreys, J. Rouden and J. Blanchet, *Org. Lett.*, 2010, **12**, 3582.

13 (*a*) C. D. Daub, D. Bratko, T. Ali and A. Luzar, *Phys. Rev. Lett.*, 2009, **103**, 207801; (*b*) Q. Chen, X. Shen and H. Gao, *Adv. Colloid Interface Sci.*, 2010, **159**, 32; (*c*) D. Spagnoli, J. P. Allen and S. C. Parker, *Langmuir*, 2011, **27**, 1821.

14 (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*b*) J. Deschamp and O. Riant, *Org. Lett.*, 2009, **11**, 1217; (*c*) R. K. Rao, A. B. Naidu and G. Sekar, *Org. Lett.*, 2009, **11**, 1923; (*d*) M. K. Ghorai and D. P. Tiwari, *J. Org. Chem.*, 2010, **75**, 6173; (*e*) A. Okano, S. Oishi, T. Tanaka, N. Fujii and H. Ohno, *J. Org. Chem.*, 2010, **75**, 3396.

15 (*a*) P. Pace, S. A. H. Spieser and V. Summa, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3865; (*b*) A. Raghuraman, E. Ko, L. M. Perez, T. R. Ioerger and K. Burgess, *J. Am. Chem. Soc.*, 2011, **133**, 12350.

16 (*a*) O. Einsle, A. Messerschmidt, R. Huber, P. M. H. Kroneck and F. Neese, *J. Am. Chem. Soc.*, 2002, **124**, 11737; (*b*) E. D. Lorance, W. H. Kramer and I. R. Gould, *J. Am. Chem. Soc.*, 2002, **124**, 15225.

17 (*a*) H. Tanaka, Y. Iwata, D. Takahashi, M. Adachi and T. Takahashi, *J. Am. Chem. Soc.*, 2005, **127**, 1630; (*b*) N. Zheng and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 4749; (*c*) S. Ahn and A. J. Matzger, *J. Am. Chem. Soc.*, 2010, **132**, 11364; (*d*) C. L. Allen and J. M. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405.

