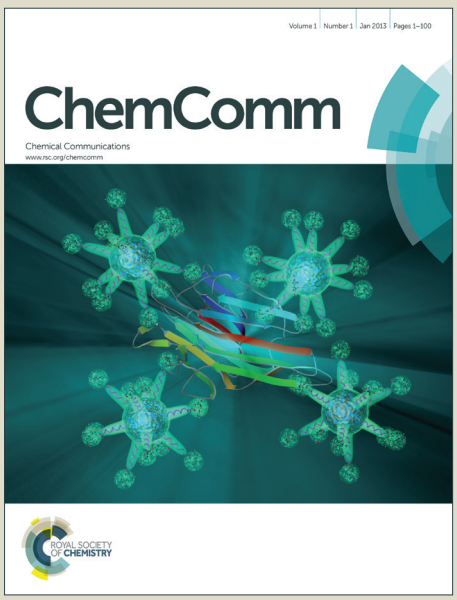
ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Copper-catalyzed oxygen atom transfer of *N*-oxides leading to a facile deoxygenation procedure applicable to both heterocyclic and amine *N*-oxides

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

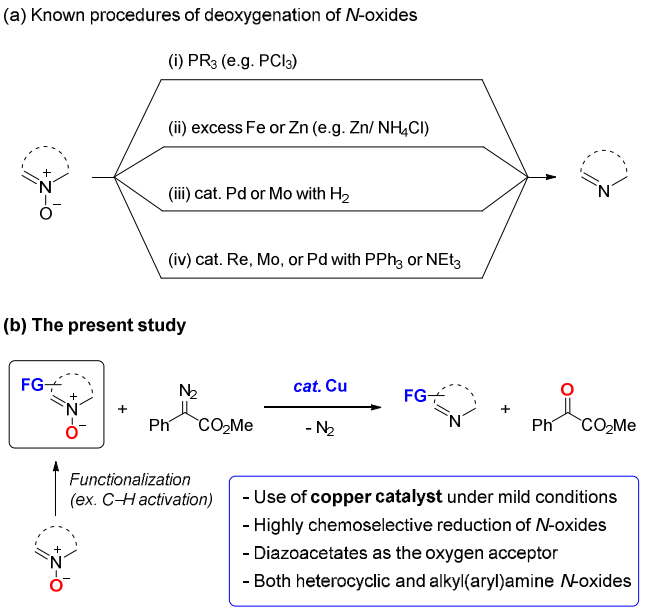
Jisu Jeong[ab], Donggun Lee[ab] and Sukbok Chang*[ba]

Deoxygenation of various types of *N*-oxides including both heterocyclic and alkyl(aryl)amine derivatives has successfully been developed by the copper-catalyzed oxygen atom transfer using diazo compounds as the oxygen acceptor. The reaction proceeds smoothly over a broad range of substrates with excellent functional group tolerance under mild conditions.

Heterocyclic *N*-oxides are important synthetic intermediates for the regioselective introduction of certain functional groups which cannot be achieved by direct methods starting from the parent heterocycles.[1] Indeed, significant advances have been made recently in the direct functionalization of oxygenated heterocyclic substrates *via* a C–H bond activation strategy using *N*-oxide as a directing group[2] including our own contributions.[3] Given the importance of *N*-heterocycles in medicinal and materials chemistry,[4] the development of an efficient and chemoselective deoxygenation method is highly desirable that can be used after the derivatization of heterocyclic *N*-oxides to afford functionalized heterocycles.

Conventional methods for the deoxygenation of *N*-oxides are the use of trivalent phosphorous compounds[1,5] or the employment of excessive metals such as iron or zinc.[6] A range of catalytic procedures has also been developed by using transition metals in combination with hydrogen gas.[7] Recently, a catalytic route to *N*-heterocycles from their *N*-oxides has been reported with the combined use of rhenium, molybdenum, or palladium catalysts with triphenylphosphine or triethylamine as the oxygen atom acceptor (Scheme 1a).[8] However, the developed procedures are often suffered from (i) the requirement of toxic reagents such as PCl_3; (ii) the use of stoichiometric amounts of transition metals; (iii) concomitant undesirable reduction of other functional groups such as olefin, nitro, cyano or carbonyl groups; or (iv) harsh reaction conditions with lack of functional group tolerance. As a result, the development of mild and selective deoxygenation of *N*-oxides will be important, especially considering the recent significant advance made in the direct C–H functionalization of heterocycles.[2-3]

Herein, we report the Cu-catalyzed highly facile deoxygenation of heterocyclic *N*-oxides via an oxygen atom transfer from *N*-oxides to *in situ* generated copper-carbenoid (Scheme 1b). Since the procedure is compatible with various functional groups, our new method is anticipated to be widely used for the derivatization of *N*-heterocycles in combination with the direct C–H functionalization of heterocyclic *N*-oxides. It is also demonstrated that the present method is applicable to the deoxygenation of alkyl(aryl)amine *N*-oxides.

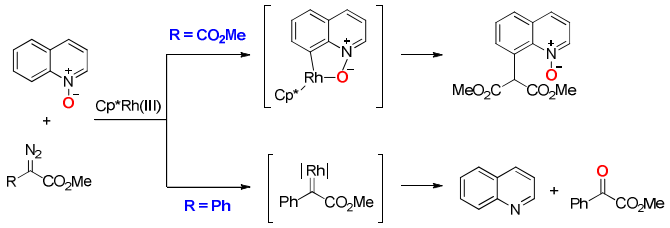


Scheme 1 Deoxygenation of *N*-oxides.

During the course of our previous works on the Rh-catalyzed carbenoid functionalization of quinoline *N*-oxides at the C8 position,[3d,9] we observed that the use of methyl phenyldiazoacetate as a coupling partner gave rise to methyl benzoylformate along with quinoline while the anticipated C8-alkylated quinoline *N*-oxide was obtained only when dimethyl diazomalonate was employed. Since the substituent effects of metal-carbenoids were widely recognized,[10] we assumed that a donor/acceptor-substituted diazo compound would selectively give a Rh-carbenoid followed by subsequent attack of an oxygen atom of quinoline *N*-oxide at the electrophilic carbene carbon. This was reasoned by the fact that the formation of donor/acceptor-substituted metal-carbenoids would be more facile than the acceptor/acceptor-substituted counterparts presumably due

ChemComm Accepted Manuscript

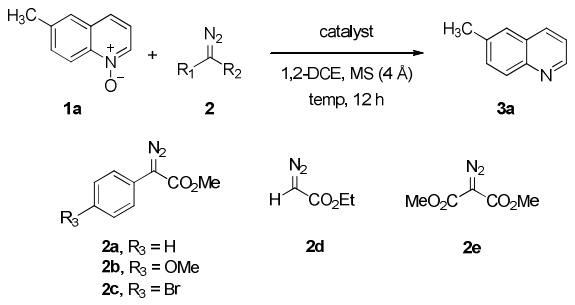
to the interactions between electron-deficient carbene carbon and adjacent electron-donating group. In contrast, since the acceptor/acceptor-substituted diazo compounds are not facile in giving the corresponding metal-carbenoids under the similar conditions, those compounds instead will react with a five-membered rhodacyclic intermediate which is generated *in situ via* C–H bond activation of quinoline *N*-oxides, eventually leading to the C8-alkylated products.



Scheme 2 Different reactivity depending on diazo compounds employed in the presence of a Cp*Rh(III) catalyst.

Based on our initial observations and consequent working hypothesis that metal carbenoids would mediate the deoxygenation reaction, we commenced our study by examining a reaction of 6-methylquinoline *N*-oxide (**1a**) with methyl phenyldiazoacetate (**2a**) under various catalytic conditions (Table 1).

Table 1 Optimization of the reaction conditions[a]



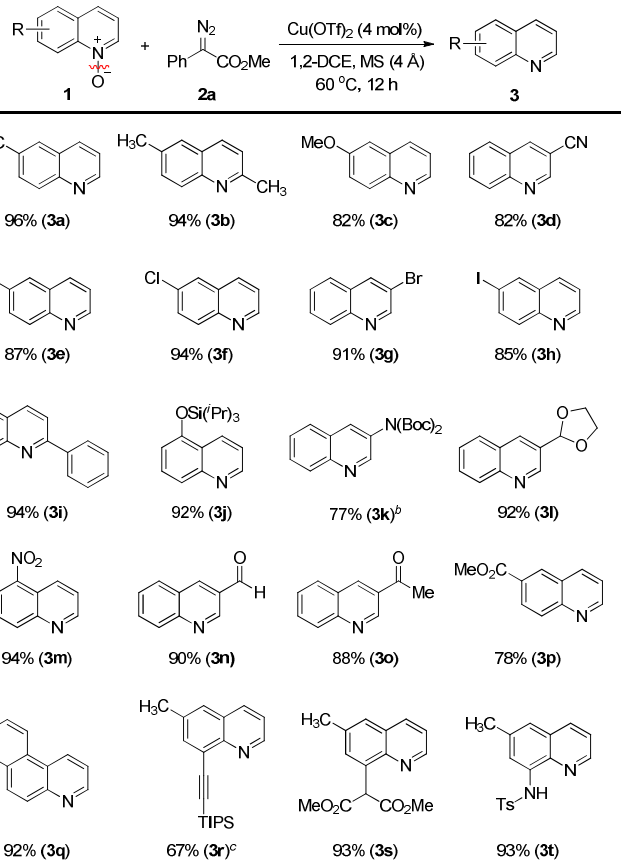
Entry	Catalyst (mol%)	Diazo	Temp (°C)	Yield (%)[b]
1	$Cu(OTf)_2$ (4)	**2a**	25	7
2	$Cu(OTf)_2$ (4)	**2a**	40	17
3	**$Cu(OTf)_2$ (4)**	**2a**	**60**	**95**
4	$Rh_2(OAc)_4$ (2)	**2a**	60	98
5	$(RhCp^*Cl_2)_2$(2)/ $AgSbF_6$ (8)	**2a**	60	98
6	$Cu(OAc)_2$ (4)	**2a**	60	66
7	none	**2a**	60	12
8	$Cu(OTf)_2$ (4)	**2b**	60	98
9	$Cu(OTf)_2$ (4)	**2c**	60	98
10	$Cu(OTf)_2$ (4)	**2d**	60	55
11	$Cu(OTf)_2$ (4)	**2e**	60	0

[a] **1a** (0.20 mmol) and **2** (1.1 equiv.) in 1,2-DCE (0.5 mL) for 12 h. [b] HPLC yield of crude reaction mixture (1,3,5-trimethylbenzene as an internal standard).

Among the various transition metals examined as catalysts in the metal-carbenoid chemistry,[11] copper species is especially attractive in that it is an inexpensive and abundant first-row transition metal.[12] Therefore, we started to optimize the reaction condition with $Cu(OTf)_2$ as a catalyst for the practical purpose. To our delight, $Cu(OTf)_2$ displayed catalytic activity that was found to be dependent on the reaction temperatures, thus leading to 95% yield at 60 °C (entries 1–3). Furthermore, as we initially hypothesized, methyl benzoylformate was observed indeed to form in 94% determined by ^{1}H NMR of the crude reaction mixture, thus showing another interesting aspect of this synthetic procedure (entry 3). Although $Rh_2(OAc)_4$ and $(RhCp^*Cl_2)_2/AgSbF_6$ also displayed notable catalytic reactivity (entries 4 and 5), we decided to choose copper species as a catalyst in this reaction for the reasons described above. In addition, inseparable side product was often generated from the Rh-catalyzed deoxygenation during the study of substrate scope presumably due to the fact that an undesired reaction between diazo compounds and H_2O is facile in this case.[13]

When the reaction was carried out with different copper catalysts such as $Cu(OAc)_2$, the desired product **3a** was obtained in 66% yield (entry 6). The deoxygenation was observed to occur only slightly under metal-free conditions to prove the importance of metal species for this process (entry 7).[14] In addition, substituents of diazo compounds were found to display significant effects on the reaction efficiency. Methyl phenyldiazoacetate bearing electron-donating or withdrawing groups in the phenyl moiety showed similar product yields (entries 8 and 9). While commercially available ethyl diazoacetate gave the deoxygenated product in moderate yield (entry 10), dimethyl diazomalonate bearing acceptor/acceptor substituents did not give any reactivity (entry 11).

Table 2 Cu-catalyzed deoxygenation of quinoline *N*-oxides[a]



[a] **1** (0.20 mmol) and **2a** (1.1 equiv.) in 1,2-DCE (0.5 mL): isolated yields. [b] 22% of 3-(*tert*-butoxycarbonyl)aminoquinoline was obtained. [c] at 80 °C.

With the optimized conditions in hand, we next examined the substrate scope of quinoline *N*-oxides (Table 2). The deoxygenation

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 2012

reaction proceeded smoothly irrespective of electronic variation of substrates (**3a**–**d**). Halogenated compounds bearing fluoro, chloro, bromo, or iodo group were well-tolerated to the reaction conditions to afford the corresponding quinolines in good yields (**3e**–**h**). 2-Phenylquinoline *N*-oxide was deoxygenated without difficulty even in the presence of steric hindrance around *N*-oxide (**3i**). The fact that an wide range of functional groups was compatible with the conditions including silyloxy, carbamate, acetal, nitro, aldehyde, ketone, and ester (**3j**–**p**) is significant in that such reducible functional groups as nitro or carbonyl were not tolerated in the previously reported methods.[7,15]

Polyaromatic heterocycle such as benzo[*f*]-quinoline *N*-oxide (**3q**) was readily deoxygenated in excellent yield. In addition, the present procedure was applicable to the deoxygenation of C8-functionalized quinoline *N*-oxides obtained from the direct C–H functionalization (**3r**–**s**) according to our methods.[3d] At the beginning of this study, we were curious to see whether deoxygenation of 8-amidated quinoline *N*-oxide could be readily achieved because the starting material **1t** has an intramolecular hydrogen-bonding interaction between the oxygen atom and sulfonamide group; 1.78 Å of the NH···O bond length (Figure 1). Therefore, it was significant that the desired deoxygenation occurred successfully to give 8-amidated quinoline (**3t**) in 93% yield.

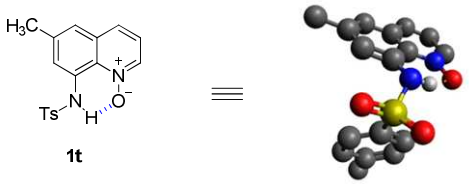
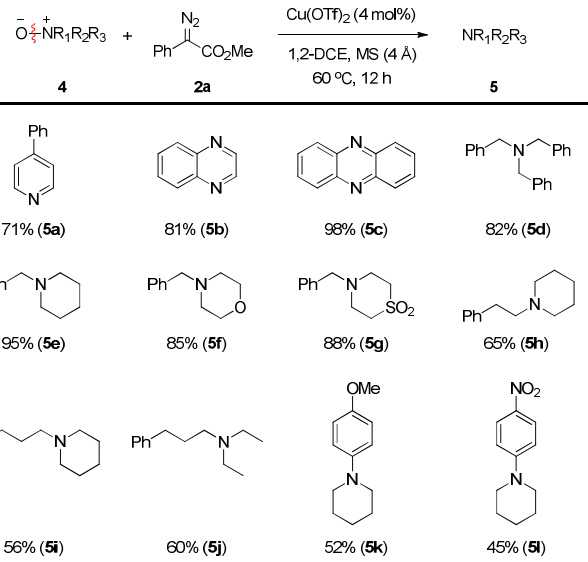


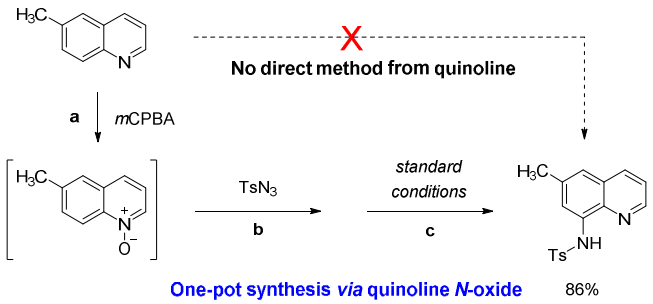
Figure 1 Intramolecular hydrogen-bonding interaction of the 6-methyl-8-(4-methylphenylsulfonamido)quinoline *N*-oxide.

Table 3 Cu-catalyzed deoxygenation of various *N*-oxides[a]



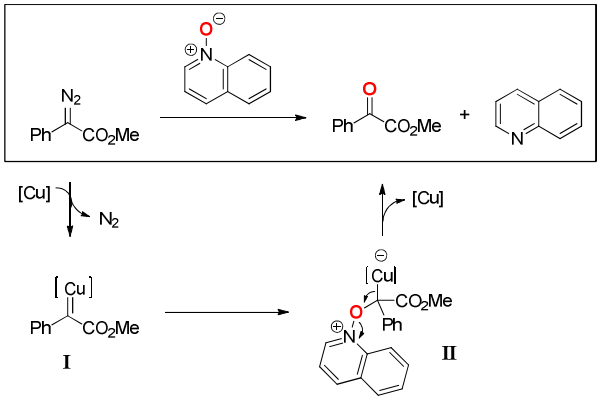
[a] **4** (0.20 mmol) and **2a** (1.1 equiv.) in 1,2-DCE (0.5 mL): isolated yields.

The scope of various *N*-oxide compounds was subsequently investigated (Table 3). As anticipated, 4-phenylpyridine *N*-oxide and mono-oxides of quinoxaline and phenazine were deoxygenated without difficulty (**5a**–**c**). After successful exploration of the deoxygenation of *N*-oxides of quinoline and additional heterocycles, we turned our attention to *alkylamine N-oxides* to broaden the substrate scope. Previously, to the best of our knowledge, only one example of catalytic deoxygenation of trimethylamine *N*-oxide was reported by using oxorhenium catalyst.[8b] To our delight, the desired reduction of tribenzylamine *N*-oxide was observed to occur smoothly to afford the corresponding amine product in high yield (**5d**). Additionally, *N*-oxides of *N*-benzylpiperidine, morpholine, and thiomorpholine 1,1-dioxide were readily deoxygenated irrespective of the presence of heteroatoms such as oxygen or sulfur (**5e**–**g**). Cyclic and acyclic amine *N*-oxides underwent the deoxygenation in moderate yields (**5h**–**j**). Alkylarylamine *N*-oxides turned out to be also suitable substrates for the developed deoxygenation under the standard conditions (**5k**–**l**), although electrophilic aromatic substitution of diazo compounds was observed as a side reaction in this case.[16]



Scheme 3 One-pot three-step synthesis of 8-amidated quinoline. a) 6-methylquinoline (0.20 mmol), *m*CPBA (1.0 equiv.), 1,2-DCE, 50 °C, 12 h; b) $[IrCp^*Cl_2]_2$ (2 mol%), $AgNTf_2$ (8 mol%), TsN_3 (1.0 equiv.), 50 °C, 6 h; c) $Cu(OTf)_2$ (4 mol%), methyl phenyldiazoacetate (1.1 equiv.), 60 °C, 12 h.

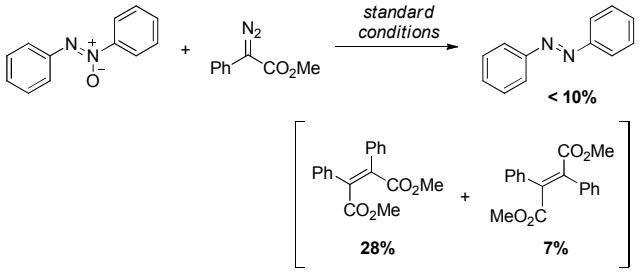
A one-pot synthesis of 8-amidated quinoline starting from quinoline was examined to prove a practical aspect of the present method. To our best knowledge, there is no direct route to 8-amidated products in one-pot process by directly using quinolines.[2d,17] Upon oxidation of quinoline with *meta*-chloroperoxybenzoic acid (*m*CPBA), we applied our previous C8-amidation procedure to quinoline *N*-oxide by employing tosyl azide (1.0 equiv.), $[IrCp^*Cl_2]_2$ (2 mol%), and $AgNTf_2$ (8 mol%). Since *meta*-chlorobenzoic acid (*m*CBA) generated from the first *N*-oxidation step could accelerate the C8-amidation reaction,[3c] no external additive was required in this one-pot process. Finally, the deoxygenation occurred smoothly under the standard conditions to afford the corresponding 8-aminoquinoline product in 86% yield (three steps).



Scheme 4 Proposed mechanistic pathway

ChemComm Accepted Manuscript

Based on the precedent literature,[18] a plausible deoxygenation pathway is shown in Scheme 4. It is first postulated that diazoacetate reacts with copper species to afford copper-carbenoid **I**. Generation of a copper-carbenoid species was evidenced by the observation that a dimeric mixture of diazoacetate was formed as a byproduct[19] when a deoxygenation was not efficiently occurred (Scheme 5). Subsequent attack at the electrophilic carbene carbon by the oxygen atom of quinoline *N*-oxide generates an oxonium ylide **II**. It is believed that the decomposition of intermediate **II** will take place as the final step to afford methyl benzoylformate and deoxygenated product.



Scheme 5 Deoxygenation of azoxybenzene

In conclusion, the deoxygenation of *N*-oxides including both heterocyclic and alkyl(aryl)amine derivatives has been successfully developed by the copper-catalyzed oxygen atom transfer using diazo compounds as the oxygen atom acceptor. The reaction was highly mild, efficient, and chemoselective to allow for high functional group tolerance. As proved by the convenient one-pot synthesis of 8-functionalized quinoline from quinoline, this new method is anticipated to be highly useful especially when it is combined with the direct C–H functionalization of heterocyclic compounds.

Acknowlegments

This research was supported by the Institute for Basic Science (IBS-R010-D1).

Notes and references

[a] Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, Korea
[b] Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Korea

† Electronic Supplementary Information (ESI) available: CCDC 1051440. For experimental procedures and characterization data, see DOI: 10.1039/c000000x/

1 *(a)* T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles, 2nd ed.*, Wiley-VCH: Weinheim, Germany, 2003; *(b)* E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534; *(c)* E. Howard, Jr. and W. F. Olszewski, *J. Am. Chem. Soc.*, 1959, **81**, 1483.

2 *(a)* L.-C. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020; *(b)* T. Shibata and Y. Matsuo, *Adv. Synth. Catal.*, 2014, **356**, 1516; *(c)* G. Yan, A. J. Borah and M. Yang, *Adv. Synth. Catal.*, 2014, **356**, 2375; *(d)* X. Zhang, Z. Qi and X. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 10794; *(e)* D. E. Stephens, J. Lakey-Beitia, A. C. Atesin, T. A. Ateşin, G. Chavez, H. D. Arman and O. V. Larionov, *ACS catal.*, 2015, **5**, 167.

3 *(a)* S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254; *(b)* J. Ryu, S. H. Cho and S. Chang, *Angew. Chem. Int. Ed.*, 2012, **51**, 3677; *(c)* H. Hwang, J. Kim, J. Jeong and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 10770; *(d)* J. Jeong, P. Patel, H. Hwang and S. Chang, *Org. Lett.*, 2014, **16**, 4598; *(e)* U. Sharma, Y. Park and S. Chang, *J. Org. Chem.*, 2014, **79**, 9899.

4 *(a)* T. J. Egan, D. C. Ross and P. A. Adams, *FEBS Lett.*, 1994, **352**, 54; *(b)* M. Foley and L. Tilley, *Pharmacol. Ther.*, 1998, **79**, 55; *(c)* G. Hughes and M. R. Bryce, *J. Mater. Chem.*, 2005, **15**, 94; *(d)* A. Kimyonok, X. Y. Wang and M. Weck, *Polym. Rev.*, 2006, **46**, 47; *(e)* J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 166; *(f)* V. R. Solomon and H. Lee, *Curr. Med. Chem.*, 2011, **18**, 1488.

5 D. Wenkert and R. B. Woodward, *J. Org. Chem.*, 1983, **48**, 283.

6 *(a)* J. M. Essery and K. Schofield, *J. Chem. Soc.*, 1960, 4953; *(b)* D. Konwar, R. C. Boruah and J. S. Sandhu, *Synthesis*, 1990, 337; *(c)* Y. Aoyagi, T. Abe and A. Ohta, *Synthesis*, 1997, 891; *(d)* J. S. Yadav, B. V. S. Reddy and M. M. Reddy, *Tetrahedron Lett.*, 2000, **41**, 2663; *(e)* B. W. Yoo, J. W. Choi and C. M. Yoon, *Tetrahedron Lett.*, 2006, **47**, 125; *(f)* S. K. Singh, M. S. Reddy, M. Mangle and K. R. Ganesh, *Tetrahedron*, 2007, **63**, 126.

7 *(a)* A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 1958, 1263; *(b)* P. M. Reis and B. Royo, *Tetrahedron Lett.*, 2009, **50**, 949; *(c)* For a selected example of catalytic hydrogen transfer agents, see: R. Balicki, *Synthesis*, 1989, 645.

8 *(a)* H. Nakagawa, T. Higuchi, K. Kikuchi, Y. Urano and T. Nagano, *Chem. Pharm. Bull.*, 1998, **46**, 1656; *(b)* Y. Wang and J. H. Espenson, *Org. Lett.*, 2000, **2**, 3525; *(c)* R. Sanz, J. Escribano, Y. Fernández, R. Aguado, M. R. Pedrosa and F. J. Arnáiz, *Synlett*, 2005, 1389; *(d)* M. Toganoh, K. Fujino, S. Ikeda and H. Furuta, *Tetrahedron Lett.*, 2008, **49**, 1488; *(e)* J. A. Fuentes and M. L. Clarke, *Synlett*, 2008, 2579.

9 For a review article on C–H functionalization with diazo compounds, see: F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, DOI: 10.1039/c5cc00497g.

10 *(a)* H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; *(b)* Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577; *(c)* H. M. L. Davies and J. R. Denton, *Chem. Soc. Rev.*, 2009, **38**, 3061.

11 M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley: New York, 1998.

12 X. Zhao, Y. Zhang and J. Wang, *Chem. Commun.*, 2012, **48**, 10162.

13 J. W. Bode, M. P. Doyle, M. N. Protopopova and Q.-L. Zhou, *J. Org. Chem.*, 1996, **61**, 9146.

14 J. Kim, Y. Ohk, S. H. Park, Y. Jung and S. Chang, *Chem. Asian J.*, 2011, **6**, 2040.

15 *(a)* S. Youssif, ARKIVOC, 2001, 242; *(b)* S. Chandrasekhar, Ch. R. Reddy, R. J. Rao and J. M. Rao, *Synlett*, 2002, 349; *(c)* N. B. Gowda, G. K. Rao and R. A. Ramakrishna, *Tetrahedron Lett.*, 2010, **51**, 5690.

16 E. Tayama, T. Yanaki, H. Iwamoto and E. Hasegawa, *Eur. J. Org. Chem.*, 2010, 6719.

17 *(a)* J. Kwak, M. Kim and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 3780; *(b)* S. Konishi, S. Kawamorita, T. Iwai, P. G. Steel, T. B. Marder and M. Sawamura, *Chem. Asian J.*, 2014, **9**, 434.

18 *(a)* C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 5838; *(b)* N. Selander and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 2477.

19 C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu and A.-Q. Mi, *Chem. Commun.*, 2005, 2624.

ChemComm Accepted Manuscript

 This journal is © The Royal Society of Chemistry 2012