Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Palladium-Catalyzed Regio-selective Oxidative C-H Bond Acylation of Azoxybenzenes with Alcohols

Cite this: DOI: 10.1039/xoxxoooooox

Lekai Hou,[b] Xiangxiang Chen,[b] Shuang Li, Suxian Cai, Yanxia Zhao, Meng Sun*[a] and Xiao-Juan Yang

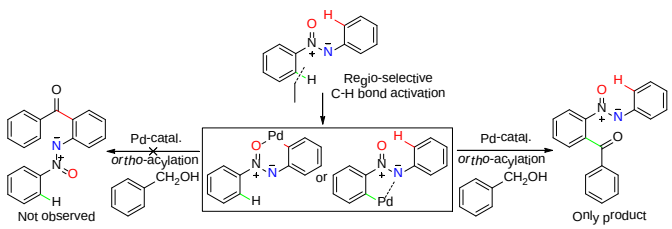
Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

A palladium-catalyzed regio-selective acylation of C-H bond of azoxybenzenes with alcohols was developed using *tert*-butyl hydroperoxide (TBHP) as oxidant. Alcohol derivatives can act as effective acyl precursors *in situ*, which were low toxic, inexpensive, stable, and commercially available. These transformations proceeded smoothly and could tolerate a variety of functional groups.

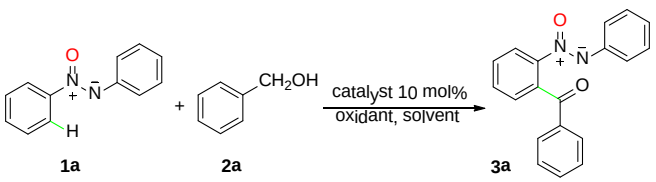
General methods for selective transformation of unreactive C-H bonds have enjoyed tremendous advances owing to their widespread application to the rapid construction of carbon-carbon or carbon-heteroatom bonds, particularly in the fields of many useful polyfunctional compounds.[1,2] Directing-group-assisted strategy was one of the most efficient methods to realize the regioselectivity of C-H bond cleavage and its further transformation.[3] As well as the oxygen-containing groups,[4] a variety of nitrogen-containing groups have been extensively investigated, such as amides,[5] imines,[6] amines,[7] oximes,[8] pyridine[9] and other nitrogen-containing heterocycles.[10] However, although significant progress in C-H bonds functionalization has been achieved with the assistance of diverse directing groups, there are rare studies on the regioselectivity control of functionalization of compounds with unique functional groups, which binds with transition metal to form different rings by making use of the two or more possible orthogonal co-ordination modes. Hence, it is very necessary to develop knowledge and associated strategies for overcoming these hurdles. As far as we know, the azoxy compounds with an unique directing group, which could be used as anchors to form two different cyclometalated intermediates followed by further transformations, are rarely reported in the C-H activation/functionalization process.[11]



Scheme 1 Pd-catalyzed *ortho*-acylation of azoxybenzenes with alcohols.

Azoxy compounds are widely used in electronic devices due to their wonderful liquid crystalline properties,[12] and are also key materials of polymer inhibitors, stabilizers and dyes.[13] Although numerous methods for the synthesis of azoxy compounds have been developed,[14] reports on the *ortho*-selective functionalization of

Table 1. Optimization of the reaction conditions[a]

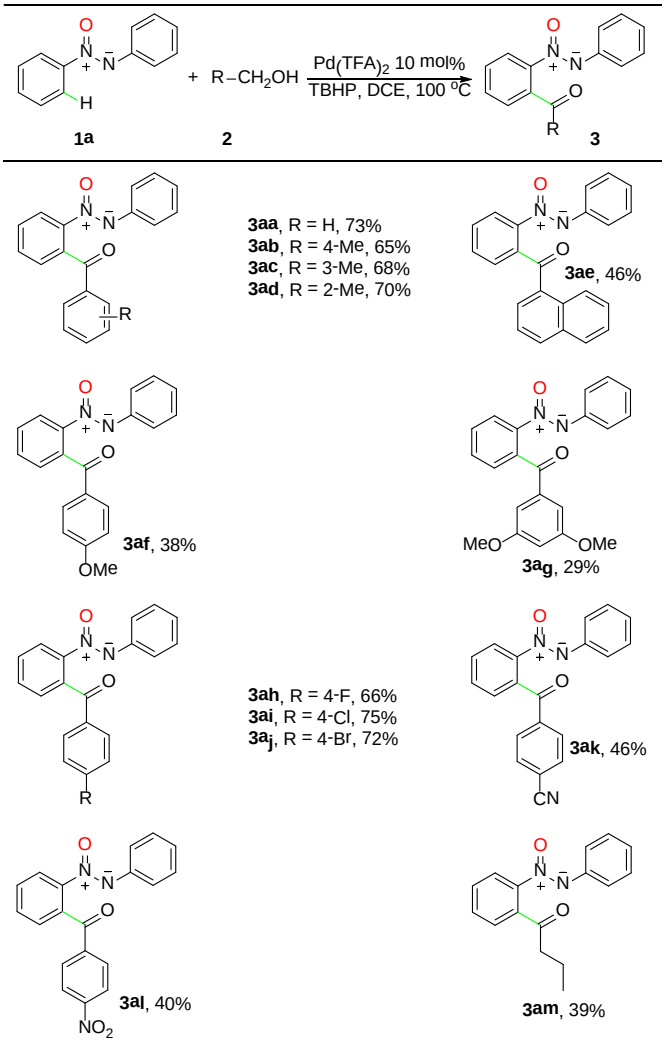


1a 2a 3a

Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	TBHP	DCE	20%
2	$Pd(TFA)_2$	TBHP	DCE	32%
3	$PdCl_2$	TBHP	DCE	14%
4	$PdCl_2(MeCN)_2$	TBHP	DCE	14%
5	$Pd(PPh_3)_4$	TBHP	DCE	13%
6	none	TBHP	DCE	0
7	$Pd(TFA)_2$	DTBP	DCE	7%
8	$Pd(TFA)_2$	DDQ	DCE	trace
9	$Pd(TFA)_2$	$K_2S_2O_8$	DCE	trace
10	$Pd(TFA)_2$	$PhI(OAc)_2$	DCE	trace
11	$Pd(TFA)_2$	H_2O_2	DCE	trace
12	$Pd(TFA)_2$	TBHP	Toluene	20%
13	$Pd(TFA)_2$	TBHP	Dioxane	n.r.
14	$Pd(TFA)_2$	TBHP	PhCl	23%
15	$Pd(TFA)_2$	TBHP	AcOH	trace
16	$Pd(TFA)_2$	TBHP	neat	24%
17	$Pd(TFA)_2$	TBHP	DME	trace
18	$Pd(TFA)_2$	TBHP	DMF	n.r.
19	$Pd(TFA)_2$	TBHP	DMSO	n.r.
20	$Pd(TFA)_2$	TBHP	DCE	56%[c]
21	**$Pd(TFA)_2$**	**TBHP**	**DCE**	**73%[d]**
22	$Pd(TFA)_2$	TBHP	DCE	58%[e]
23	$Pd(TFA)_2$	TBHP	DCE	54%[d,f]
24	$Pd(TFA)_2$	TBHP	DCE	60%[d,g]

[a] All the reactions were carried out in the presence of 0.2 mmol of **1a**, 0.6 mmol of **2a** and 0.6 mmol of TBHP in 1.0 mL DCE at 100 °C under air condition. [b] Isolated yields. [c] 6.0 equiv of TBHP was added. [d] 7.0 equiv of TBHP was used. [e] 8.0 equiv of TBHP was used. [f] At 80 °C. [g] At 120 °C.

Table 2. Scope of the *ortho*-acylation of azoxybenzene with different alcohols [a,b]



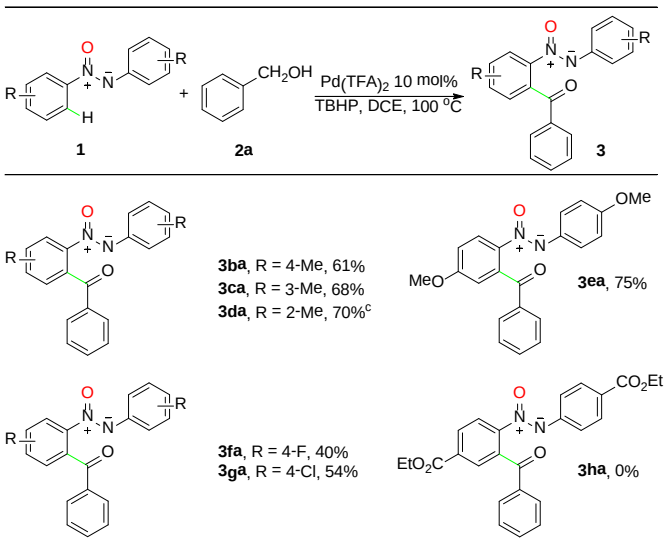
[a] All the reactions were carried out in the presence of 0.2 mmol of **1a**, 0.6 mmol of **2a** and 1.4 mmol of TBHP in 1.0 mL DCE at 100 °C under air. [b] Isolated yields.

azoxybenzenes are scarce.[11] Besides, it is well known that aryl ketones are very important structural motifs of natural products and pharmaceuticals.[15] During the development of preparation of aryl ketones, the emergence of direct functionalization of C-H bonds provides an atom-economic and highly efficient strategy[16] compared with the traditional methods of Friedel-Crafts acylation relying on Lewis acids or Bronsted acid[17] and various oxidants.[18] To the best of our knowledge, there are only two reports on the acylation of azoxybenzenes,[11a,11c] and this restriction has greatly limited the method to preparation of azoxy ketones. Consideration of the limitations and extremely challenge in the control of two different kinds of C-H bonds, it is necessary to develop a new method to realize regio-selective acylation of C-H bond of azoxy compounds. Herein, we describe a facile synthesis of azoxy ketones by Pd-catalyzed *ortho*-C-H bond acylation employing alcohol derivatives as the reliable coupling partners,[19] which show obvious advantage of high stability, easy to handle and low cost compared with α-oxocarboxylic acid and aldehydes.

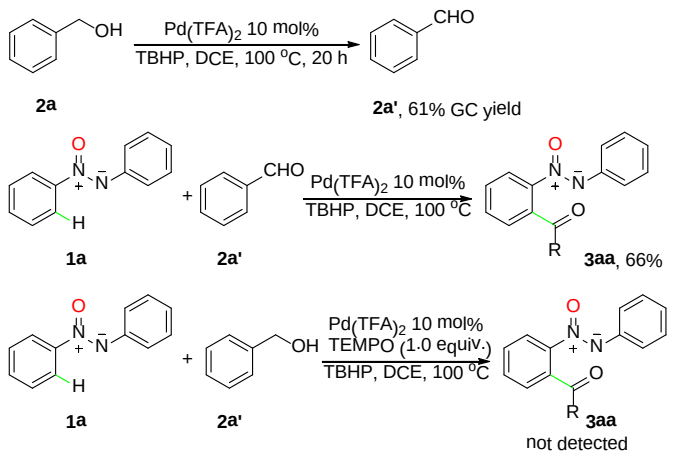
We initially used azoxybenzenes (**1a**) and benzoyl alcohol (**2a**) as the model substrates to optimize the reaction conditions. To our delight, when the mixture of azoxybenzene (0.20 mmol) and benzoyl alcohol (0.6 mmol) was treated with 3.0 equiv. of TBHP in DCE (1.0 mL) at 100 °C for 20 h in the presence of 10 mol% $Pd(OAc)_2$, the desired product **3a** was isolated in 20% yield (Table 1, entry 1). Further catalyst screening showed that an obvious increasing yield was achieved when $Pd(TFA)_2$ was used in the reaction, and the corresponding product was obtained in 32% yield (Table 1, entry 2). However, other catalysts such as $PdCl_2$, $PdCl_2(MeCN)_2$ and $Pd(PPh_3)_4$ were less effective (Table 1, entry 3-5). Subsequently, different oxidants were investigated in this transformation and TBHP was the most suitable oxidant compared with other oxidants including DTBP, DDQ, $K_2S_2O_8$, $PhI(OAc)_2$, H_2O_2, etc. (Table 1, entry 7-11). Notably, no desired product was detected in the absence of catalyst even in high temperature (Table 1, entry 6). Additionally, the effect of solvents on this transformation was also tested, and DCE proved to be crucial, while a slight lower yield was also isolated in PhCl and comparative yield was achieved under neat condition (Table 1, entry 12-19). It should be noted that increasing the stoichiometry of TBHP significantly increased the yield of the corresponding azoxy ketones. The best result was observed in 73% with 7 equiv of TBHP, while increasing or lowering the amount of oxidant suppressed the efficiency (Table 1, entry 20-24). Finally, the optimized reaction conditions for the *ortho*-C-H acylation of azoxy compound were obtained as follows: 10 mol% $Pd(TFA)_2$ as catalyst, 7.0 equiv of TBHP as oxidant, and DCE as solvent, at 100 °C under air for 20 h.

With the optimized reaction conditions in hand, the applicability of this protocol was subsequently investigated with regard to different alcohols as the *in situ* generated acyl source. It was found that a variety of alcohols with both electron-donating and electron-withdrawing groups substituted on aromatic ring were tolerated and moderate to good yields were obtained for most case. For example, the substrates with electron donating methyl group on the aromatic ring gave the desired products in good yields (Table 2, **3ab**-**3ad**), while *para* electron-withdrawing group-substituted benzyl alcohols afforded comparative results (Table 2, **3ah**-**3aj**). It is worth noting that *ortho*-hindered benzyl alcohol was feasible coupling partner in this catalytic system. Moreover, lower yields were obtained when 4-

Table 3. Scope of azoxy compounds in *ortho*-acylation reactions [a,b]



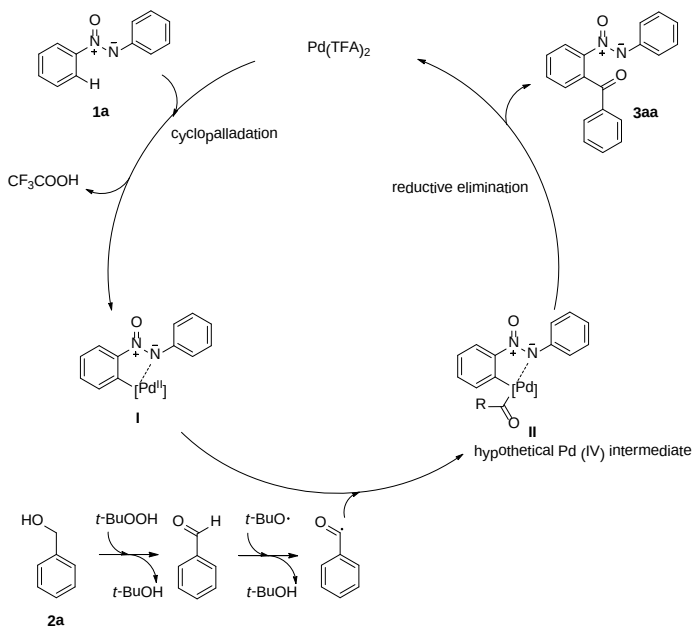
[a] All the reactions were carried out in the presence of 0.2 mmol of **1**, 0.6 mmol of **2a** and 1.4 mmol of TBHP in 1.0 mL DCE at 100 °C under air. [b] Isolated yields. [c] At 120 °C, 36 h.



Scheme 2 Control reactions.

methoxybenzyl alcohol and 3,5-dimethoxybenzyl alcohol were involved, and the corresponding azoxy ketones were achieved in 38% and 29% yields, respectively, presumably due to the difficult C-H bond cleavage of aldehydes generated *in situ*. In particular, the bromo group remained intact during the course of the reaction, which could be further transformed into other important structures. To our delight, a representative structure of **3ai** was confirmed by X-ray single-crystal analysis (see Supporting Information (**SI**) for more details), which proved the single isomer product. Encouraged by these positive results, we also extended the substrate scope to benzyl alcohol derivatives with strong electron-withdrawing groups and aliphatic alcohols, and obtained the desired acylated azoxy compounds in moderate yields (Table 2, **3ak**-**3am**). Unfortunately, heterocyclic-substituted alcohols could not participate in this procedure, which often showed positive results in acylation reactions.

Next, the scope of this transformation with regard to a range of azoxybenzenes was then explored with benzyl alcohol under our best conditions. The results of the reaction with the azoxy derivatives bearing electron-donating groups were better than with those bearing electron-withdrawing groups (Table 3). For example, 4,4'-dimethyl azoxybenzene and 4,4'-azoxydianisole gave the corresponding azoxy ketones in good yields, while sharp reducing yields were observed with electron-deficiency substituents at the *para*-positions of azoxybenzenes, especially for the CO_2Et, no C-H cross-coupling reaction occurred at all.



Scheme 3 Proposed reaction mechanism.

To further investigate the possible mechanism, some control experiments were performed to obtain mechanistic insight (Scheme 2). It is observed that benzaldehyde was formed under our reaction conditions in the absence of azoxy compound. Very recently, we have developed a method to realize the *ortho*-acylation of azoxybenzene with benzaldehyde under similar reaction conditions.[11c] Moreover, treatment of azoxybenzene (**1a**) and benzyl alcohol (**2a**) in the presence of the radical scavenger TEMPO suppressed the reaction completely, which indicated that a radical process was possibly involved in this procedure.[20]

Based on the previous literatures[19,21] and above-mentioned control experiments, a plausible mechanism pathway for this transformation is depicted in Scheme 3. First, the active palladium catalyst reacts with azoxybenzene to generate intermediate **I**[22] by chelation-directed C-H activation with N atom, which is generally considered to be a better coordinating atom than O. At the same time, aldehyde was formed via the oxidation of the alcohol by TBHP, followed by transferred to an acyl radical according to the literature. Second, the Pd(II) intermediate **I** would react with the acyl radicals to afford the Pd(IV) intermediate **II**.[23,24] Finally, the intermediate **II** underwent reductive elimination to afford the *ortho*-acylated product and the active Pd(II) was regenerated.

In summary, we have developed a novel catalytic system for the synthesis of *ortho*-acetyl functionalization of azoxybenzenes via regio-selective directing-group-assisted strategy. Alcohol derivatives can be employed as effective acyl precursors in the oxidative coupling between two C-H bonds. Further exploration of the synthetic utility of this chemistry and other functionalization of azoxy compounds are currently underway in our lab.

We are grateful to the Northwest University (PR13089, NF14020) and National Found for Fostering Talents of Basic Science (NFFTBS-J1103311, J1210057) for financial support.

Notes and references

[a]Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, P. R. China
[b]These two authors contributed equally to this work.
*E-mail: sunmeng@nwu.edu.cn

† Electronic supplementary information (ESI) available: CCDC 1037307. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

1 For selected reviews, see: (*a*) G. Dyker, *Handbook of C-H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (*b*) K. I. Goldberg and A. S. Goldman, Eds. *Activation and Functionalization of C-H Bond*, ACS Symposium Series 885, American Chemical Society, Washington, DC, 2004. (*c*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (*d*) J.-Q. Yu and Z.-J. Shi, *C-H Activation*, Springer, Berlin, Germany, 2010.

2 (*a*) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529; (*b*) D. A. Colby, R.

G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*c*) S. Conejero, M. Paneque, M. L. Poveda, L. L. Santos and E. Carmona, *Acc. Chem. Res.*, 2010, **43**, 572; (*d*) M. M. Daz-Requejo and P. J. Prez, *Chem. Rev.*, 2008, **108**, 3379; (*e*) C. I. Herreras, X. Yao, Z. Li and C.-J. Li, *Chem. Rev.*, 2007, **107**, 2546; (*f*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*g*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*h*) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518.

3 (*a*) N. Chatani, *Directed Metallation*, Springer, Berlin, Germany, 2008; (*b*) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (*c*) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910; (*d*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (*e*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651.

4 For selective examples of different oxygen-containing groups directed C-H functionalization, see: (*a*) Y. Lu, D.-H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916; (*b*) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (*c*) F. Kakiuchi, Y. Matsuura, S. Kan and N. Chatani, *J. Am. Chem. Soc.*, 2005, **127**, 5936; (*d*) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1064; (*e*) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 460; (*f*) P. Novak, A. Correa, J. Gallardo-Donaire and R. Martin, *Angew. Chem., Int. Ed.*, 2011, **50**, 12236; (*g*) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 468; (*h*) J. J. Mousseau, F. Vallee, M. M. Lorion and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 14412.

5 For selected examples, see: (*a*) J. Park, E. Park, A. Kim, Y. Lee, K.-W. Chi, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Lett.*, 2011, **13**, 4390; (*b*) S. Sharma, E. Park, J. Park and I. S. Kim, *Org. Lett.*, 2012, **14**, 906; (*c*) S. Sharma, J. Park, E. Park, A. Kim, M. Kim, J. H. Kwak, Y. H. Jung and I. S. Kim, *Adv. Synth. Catal.*, 2013, **355**, 332.

6 For selected examples, see: (*a*) T. Fukutani, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Commun.*, 2009, **34**, 5141; (*b*) K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2011, **133**, 400; (*c*) M. J. Tredwell, M. Gulias, N. G. Bremeyer, C. C. C. Johansson, B. S. L. Collins and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 1076; (*d*) L. Ackermann, N. Hofmann and R. Vicente, *Org. Lett.*, 2011, **13**, 1875; (*e*) D. A. Colby, A.-S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814.

7 For selected examples, see: (*a*) F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani and S. Murai, *Chem. Lett.*, 2002, **365**, 396; (*b*) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342; (*c*) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 16184; (*d*) H. Li, G.-X. Cai and Z.-J. Shi, *Dalton Trans.*, 2010, **39**, 10442; (*e*) B. Haffemayer, M. Gulias and M. J. Gaunt, *Chem. Sci.*, 2011, **2**, 312; (*f*) H. Zhang, X. Cui, X. Yao, H. Wang, J. Zhang and Y. Wu, *Org. Lett.*, 2012, **14**, 3012.

8 For selected examples, see: (*a*) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542; (*b*) C.-L. Sun, N. Liu, B.-J. Li, D.-G. Yu, Y. Wang and Z.-J. Shi, *Org. Lett.*, 2010, **12**, 184; (*c*) C.-W. Chan, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.*, 2010, **12**, 3926; (*d*) Y. Yang, B. Zhou and Y. Li, *Adv. Synth. Catal.*, 2012, **354**, 2916.

9 For selected examples, see: (*a*) N. Chernyak, A. S. Dudnik, C. Huang and V. Gevorgyan, *J. Am. Chem. Soc.*, 2010, **132**, 8270; (*b*) H. Mizuno, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2011, **133**, 1251; (*c*) T. W. Lyons, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 4455; (*d*) Y. Li, B.-J. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Cheng and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 2115; (*e*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (*f*) J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272; (*g*) A. Garcia-Rubia, M. A. Fernandez-Ibanez, R. G. Arrayas and J. C. Carretero, *Chem. Eur. J.*, 2011, **17**, 3567; (*h*) A. Garcia-Rubia, B. Urone, R. G. Arrays and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2011, **50**, 10927; (*i*) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648.

10 For selected examples, see: (*a*) R. Giri, X. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 2112; (*b*) L. Ackermann, A. Althammer and R. Born, *Angew. Chem., Int. Ed.*, 2006, **45**, 2619; (*c*) N. Umeda, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 7094; (*d*) M. K. Lakshman, A. C. Deb, R. Ram Chamala, P. Pradhan and R. Pratap, *Angew. Chem., Int. Ed.*, 2011, **50**, 11400.

11 (*a*) H. J. Li, P. H. Li, Q. Zhao and L. Wang, *Chem. Commun.*, 2013, **49**, 9170; (*b*) H. J. Li, X. Y. Xie and L. Wang, *Chem. Commun.*, 2014, **50**, 4218; (*c*) M. Sun, L.-K. Hou, X.-X. Chen, X.-J. Yang, W. Sun and Y.-S. Zang, *Adv. Synth. Catal.*, 2014, **356**, 3789.

12 T. Ikeda and O. Tsu, *Science* 1995, **268**, 1873.

13 (*a*) J. M. Huang, J. F. Kuo and C. Y. Chen, *J. Appl. Polym. Sci.*, 1995, **55**, 1217; (*b*) D. Campbell, L. R. Dix and P. Rostron, *Dyes Pigm.*, 1995, **29**, 77.

14 For selected examples, see: (*a*) Z. Hou, Y. Fujiware and H. Taniguchi, *J. Org. Chem.*, 1988, **53**, 3118; (*b*) N. Sakai, K. Fuji, S. Nabeshima, R. Ikeda and T. Konakahara, *Chem. Commun.*, 2010, **46**, 3173.

15 (*a*) H. G. Franck, *Industrial Aromatic Chemistry*, Springer, Berlin, 1988; (*b*) H. Surburg and J. Panten, *Common Fragrance and Flavor Materials*, 5th edn., Wiley-VCH, Weinheim, 2006.

16 For selected examples, see: (*a*) O. Basle, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; (*b*) P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898; (*c*) Y. Wu, P. Y. Choy, F. Mao and F. Y. Kwong, *Chem. Commun.*, 2013, **49**, 689; (*d*) Y. Wu, B. Li, F. Mao, X. Li and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 3258; (*e*) Z. Yin and P. Sun, *J. Org. Chem.*, 2012, **77**, 11339.

17 (*a*) G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, 1973; (*b*) G. Sartori and R. Maggi, *Chem. Rev.*, 2006, **106**, 1077; (*c*) G. Sartori and R. Maggi, *Advances in Friedel–Crafts Acylation Reactions*, CRC Press, Boca Raton, FL, 2010.

18 (*a*) M. Hudlicky, *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, 1990; (*b*) M. Fernandez and G. Tojo, *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*, Ed. E. Tojo, Springer, New York, 2006; (*c*) R. Liu, X. Liang, C. Dong and X. Hu, *J. Am. Chem. Soc.*, 2004, **126**, 4112; (*d*) X. He, Z. Shen, W. Mo, N. Sun, B. Hu and X. Hu, *Adv. Synth. Catal.*, 2009, **351**, 89; (*e*)Y. Yuan, X. Shi and W. Liu, *Synlett* 2011, **4**, 559.

19 For selected examples, see: (*a*) F. Xiao, Q. Shuai, F. Zhao, O. Basle, G. Deng and C.-J. Li, *Org. Lett.*, 2011, **13**, 1614; (*b*) Y. Yuan, D. Chen and X. Wang, *Adv. Synth. Catal.*, 2011, **353**, 3373; (*c*) H. Tang, C. Qian, D. Lin, H. Jiang and W. Zeng, *Adv. Synth. Catal.*, 2014, **356**, 519; (*d*) J. Park, A. Kim, S. Sharma, M. Kim, E. Park, Y. Jeon, Y.

Lee, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Biomol. Chem.*, 2013, **11**, 2766; (*e*) Q. Ding, H. Ji, C. Ye, J. Wang, J. Wang, L. Zhou and Y. Peng, *Tetrahedron* 2013, **69**, 8661.

20 (*a*) J. J. Warren and J. M. Mayer, *J. Am. Chem. Soc.*, 2010, **132**, 7784; (*b*) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737.

21 (*a*) J. M. Racowski, A. R. Dick and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 10974; (*b*) D. C. Powers and T. Ritter, *Nat. Chem.*, 2009, **1**, 302.

22 (*a*) S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759; (*b*) H. Horino and N. Inoue, *J. Org. Chem.*, 1981, **46**, 4416.

23 (*a*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234; (*b*) C. F. Rosewall, P. A. Sibbald, D. V. Liskin and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 9488; (*c*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945; (d) J. M. Racowski, A. R. Dick and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 10974; (g) P. L. Arnold, M. S. Sanford and S. M. Pearson, *J. Am. Chem. Soc.*, 2009, **131**, 13912; (h) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177.

24 However, a Pd(II) intermediate can not be ruled out at this stage, since the formation of cyclopalladation, insertion of aldehyde into the C-Pd bond and β-hydride elimination are precedented transformations for Pd(II) species.