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Unprecedented *ortho*-acylation of azoxybenzenes with α-oxocarboxylic acids by Pd-catalyzed C–H activation and decarboxylation†

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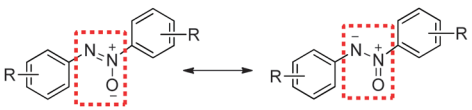
A palladium-catalyzed *ortho*-acylation reaction of azoxybenzenes with α-oxocarboxylic acids was developed in the presence of $K_2S_2O_8$. The established methodology provides a direct approach to obtain acylated azoxybenzenes in good yields.

Transition metal-catalyzed C–H bond activation and functionalization[1] in recent years have been broadly explored for the efficient construction of complex molecules and natural products.[2] In particular, the employment of directing groups in substrates can facilitate C–H activation and control the reaction selectivity, because the function group often binds with transition metal to form an active species which can furnish the catalytic cycle.[3] The utilization of directing groups in transition metal-catalyzed C–H activation has been successfully applied in construction of C–C and C–heteroatom bonds, and these groups mainly include pyridines, azobenzenes, amides, oximes, alcohols, amines, carboxylic acids, esters, aldehydes, ketones, nitriles, triazenes, alkenes and so on.[4] Presently, we successfully realized the *ortho*-C–H functionalization of azobenzenes.[4o] Based on these findings, we envisioned that the azoxy compounds, with two proposed resonance structures (Scheme 1),[5] can also provide a coordinating site (oxygen or nitrogen) to complex with transition metal[4] and enable the next *ortho*-C–H bond functionalization.

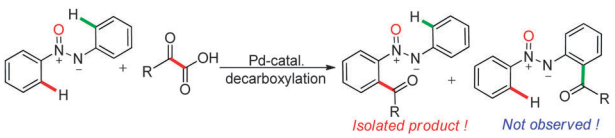
We recently noted that the decarboxylative cross-coupling reactions, involving readily available carboxylic acids as coupling partners, have been paid much attention in organic synthesis.[6,7] For example, Myers,[7a,b] Goossen,[7c–g] Li,[7h] Liu[7i] and Miura[7j] completed the decarboxylative biaryl coupling, alkynylation, olefination and ketone formation. Most recently, Ge,[8] Duan,[9] Kim[10] and Tan[11] developed the decarboxylative acylation of unactivated arenes with α-oxocarboxylic acids *via* group-directed C–H activation and functionalization. Additionally, it is well known that azoxy compounds are key materials in electronic devices because of their liquid crystalline properties[12] and have also been used as polymer inhibitors, stabilizers and dyes.[13] In spite of numerous methods for the preparation of azoxy compounds being developed,[14] reports on the synthesis of sterically hindered *ortho*-acylated azoxybenzenes are rare.



Scheme 1 Resonance structures for azoxybenzenes.

As far as we know, the azoxy group has never been studied in group-directed C–H activation. It should be noted that two kinds of potential C–H bonds exist in the azoxybenzene, which may be involved in the subsequent C–H functionalization (Scheme 2). Hence, the control of C–H activation and functionalization is extremely challenging in azoxybenzenes. As part of our ongoing interest in C–H activation and decarboxylation reaction,[4o,15] we herein report the first Pd-catalyzed site-selective *ortho*-acylation of azoxybenzenes with α-oxocarboxylic acids under mild reaction conditions.

Initially, we examined the model acylation of azoxybenzene (**1a**) with 2-oxo-2-phenylacetic acid (**2a**) in DCE using $Pd(OAc)_2$ as catalyst at 60 °C for 24 h, as shown in Table S1 (ESI†). We found that the acylated product **3a** was isolated in 16% yield when using $(NH_4)_2S_2O_8$ as an oxidant (Table S1, entry 1). Gratifyingly, 72% yield of **3a** was obtained in the presence of $K_2S_2O_8$ (entry 2). However, the use of $Cu(OAc)_2$ as an oxidant did not improve the yield of **3a** (entry 3). Other inorganic oxidants, such as AgOAc and $Mn(OAc)_3$, were found to be ineffective in the reaction (entries 4 and 5). Meanwhile, it was also found that TBHP (*tert*-butyl hydroperoxide) or DTBP (di-*tert*-butyl peroxide) could not promote the reaction (entries 6 and 7). When the reaction was performed under 1.0 atm of an oxygen atmosphere,



Scheme 2 Site-selective *ortho*-acylation of azoxybenzenes with α-oxocarboxylic acids.

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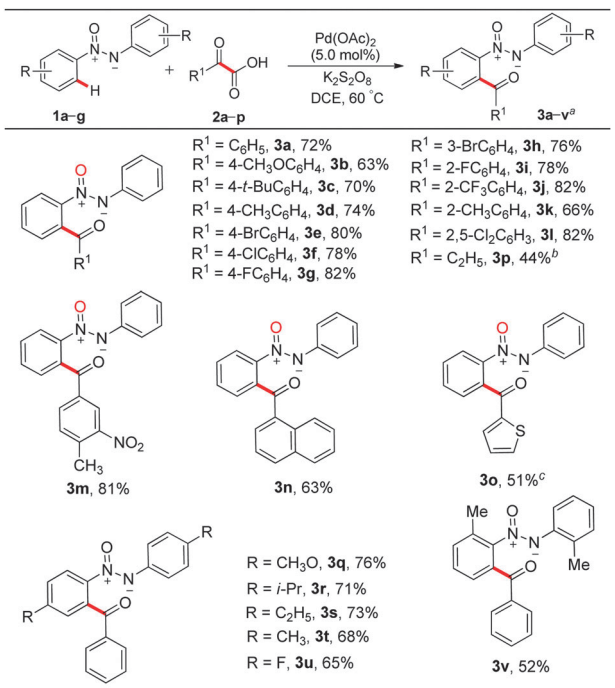
3a was isolated in 30% yield (entry 8). The effect of the palladium source on the reaction was also examined, and the results demonstrated that $Pd(TFA)_2$ gave lower yield of **3a**, compared with $Pd(OAc)_2$ (entry 2 *vs.* 9). However, other commercially available Pd catalysts, such as $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$ and $PdCl_2$, exhibited poor performance in the model reaction (entries 10–12). The general additives, Ag_2O and PivOH, were also investigated and the results indicated that the addition of Ag_2O into the reaction did not affect the yield of **3a** obviously (entry 13). In addition, the introduction of PivOH resulted in an inferior yield of **3a** (entry 14). Furthermore, the optimization of reaction time did not help in promoting the model reaction under the above reaction conditions (entries 15 and 16). To further optimize the reaction conditions for the reaction of **1a** with **2a**, a variety of solvents were examined. DCE was found to be the best one for the reaction and the detailed results are listed in Table S2 (ESI†). The optimized reaction conditions were obtained as follows: 5.0 mol% of $Pd(OAc)_2$ as catalyst, $K_2S_2O_8$ as oxidant, and DCE as solvent, at 60 °C under air for 24 h.

Under the above optimized reaction conditions, we then examined the scope of decarboxylative acylation reactions with respect to α-oxocarboxylic acids, and the results are summarised in Scheme 3. It was found that substrates with both electron-donating and electron-withdrawing groups on the benzene rings of 2-oxo-2-arylacetic acids were tolerated and afforded good yields of the corresponding acylated products. Notably, compared to the electron-donating groups, including MeO, *t*-Bu and Me, the electron-withdrawing groups, such as halogens at the *para*-positions of the phenyl rings in α-oxocarboxylic acids, exhibited higher activity when they reacted with azoxybenzenes, furnishing the corresponding products in enhanced yields (**3e–g**). The steric hindrance effect was observed when *meta*- and *ortho*-substituted α-oxoarylcarboxylic acids were used as substrates in the reaction (**3d** *vs.* **3k**, **3e** *vs.* **3h**, and **3g** *vs.* **3i**). However, when azoxybenzene (**1a**) was coupled with more steric and electron attractive 2-oxo-2-(2-(trifluoromethyl)phenyl)acetic acid (**2j**) under the optimized reaction conditions, a satisfactory yield of the corresponding product **3j** was achieved. Fortunately, a representative structure of **3j** was confirmed by X-ray single-crystal analysis.[16] It was worth noting that the use of disubstituted α-oxocarboxylic acids **2l** and **2m** provided the desired products in 82% (**3l**) and 81% (**3m**) yields, respectively. When 2-(naphthalen-1-yl)-2-oxoacetic acid **2n** was tested in the reaction, 63% of the product **3n** was obtained. Encouraged by the above results, the heterocyclic-substituted α-oxocarboxylic acid **2o** was evaluated and a moderate yield of the product **3o** was obtained at the enhanced reaction temperature. Finally, it was observed that the simple aliphatic α-oxocarboxylic acids **2p** could react with azoxybenzene (**1a**) at 100 °C, affording the acylated product **3p** in 44% yield. To expand the scope of this method, some typical disubstituted azoxybenzenes were synthesized and examined. The results demonstrated that the disubstituted azoxybenzenes with electron-donating and electron-withdrawing substituents at the *para*-positions of phenyl rings, such as MeO, i-Pr, Et, Me and F, afforded the desired products (**3q–u**) in good yields. Obviously, the steric hindrance effect of the azoxy compound, **1g**, was observed, and its reaction with 2-oxo-2-phenylacetic acid (**2a**) led to lower yield of product **3v** under the present reaction conditions.

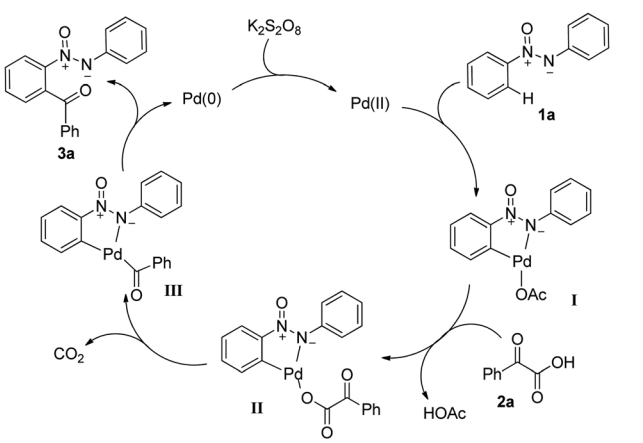
Although the exact reaction mechanism is not clear to date, a possible pathway is described in Scheme 4. It is known that N is generally considered to be a better coordinating atom than O when complexed with Pd(II). Hence, azoxybenzene **1a** firstly reacted with $Pd(OAc)_2$ to form an active complex **I** through the *ortho*-C–H insertion,[17] which accounts for the high regioselectivity in the reactions. Then, the obtained **I** underwent an anion exchange with α-keto acid **2a** to generate a cyclopalladated complex **II** along with release of HOAc. Subsequently, the decarboxylation of complex **II** led to CO_2[18] and a complex **III**, which underwent reductive elimination to afford the acylated product **3a** and Pd(0). Finally, the regeneration of Pd(II) from Pd(0) was realized in the presence of $K_2S_2O_8$. However, the Pd(III) or Pd(IV) intermediate could not be absolutely ruled out in the system.[19]

Moreover, the further transformation of the acylated azoxybenzenes into an indazole backbone was examined.[4o,4q]

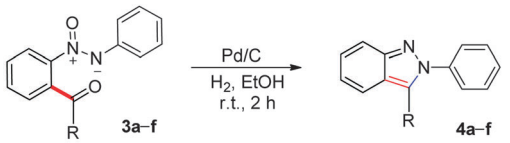


Reaction conditions: azoxybenzene (**1**, 0.20 mmol), α-oxocarboxylic acid (**2**, 0.30 mmol), $Pd(OAc)_2$ (5.0 mol%), $K_2S_2O_8$ (0.30 mmol) in DCE (1.0 mL) at 60 °C under air for 24 h. [a] Isolated yields. [b] 100 °C. [c] 80 °C.

Scheme 3 The scope of azoxybenzenes and α-oxocarboxylic acids in the reaction.



Scheme 4 Proposed reaction mechanism.



R = C_6H_5, **4a**, 96% R = 4-$CH_3OC_6H_4$, **4b**, 98%
R = 4-*t*-BuC_6H_4, **4c**, 96% R = 4-$CH_3C_6H_4$, **4d**, 96%
R = 4-BrC_6H_4, **4e**, 99% R = 4-ClC_6H_4, **4f**, 98%

Reaction conditions: acylated azoxybenzene (**3**, 0.20 mmol), Pd/C (10.0 mg, 5.0 wt. %, containing 0.0047 mmol of Pd), EtOH (0.50 mL), H_2 (1.0 atm), room temperature, 2 h, isolated yields.

Scheme 5 Transformation of acylated azoxybenzenes into indazoles.

When the commercially available Pd/C catalyst was used to catalyze the reduction of acylated azoxybenzenes **3** under a hydrogen atmosphere (1.0 atm) at room temperature, the transformation of acylated azoxybenzenes (**3a–f**) into indazoles **4** was completed in 2 h with excellent yields (Scheme 5).

In summary, we have disclosed an *ortho*-acylation reaction of azoxybenzenes with α-oxocarboxylic acids through palladium-catalyzed direct C–H activation and decarboxylation in the presence of $K_2S_2O_8$. This simple methodology employs readily available azoxy compounds and α-oxocarboxylic acids as starting materials to obtain acylated azoxybenzenes in good yields with high regioselectivity. The detailed mechanistic investigations and further applications of these azoxybenzenes are still underway in our laboratory.

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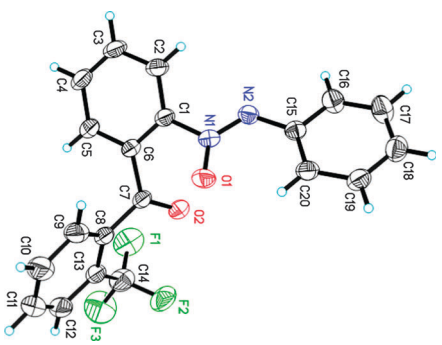
Notes and references

1 For recent reviews, see: (*a*) *Activation and Functionalization of C–H Bond*, ed. K. I. Goldberg and A. S. Goldman, ACS Symposium Series 885, American Chemical Society, Washington DC; (*b*) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley–VCH, Weinheim, 2005; (*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*) T. Naota, H. Takaya and S. I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599; (*b*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*c*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*d*) X. Chen, K. M. Engle, D. H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*e*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*f*) I. Mkhalid, J. Barnard, T. Marder, J. Murphy and J. Hartwig, *Chem. Rev.*, 2010, **110**, 890.
3 (*a*) X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634; (*b*) L. Zhao, O. Basl and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4106; (*c*) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (*d*) K. Gao, P. S. Lee, T. Fujita and N. Yoshikai, *J. Am. Chem. Soc.*, 2010, **132**, 12249; (*e*) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 9902.
4 (*a*) M. D. K. Boele, G. P. F. Strijdonck, A. H. M. Vries, P. C. J. Kamer, J. G. Vries and P. W. N. M. Leeuwen, *J. Am. Chem. Soc.*, 2002, **124**, 1586; (*b*) D. H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315; (*c*) Y. Lu, D. H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916; (*d*) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3680; (*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*) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1064; (*g*) H. X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7222; (*h*) A. Garca-Rubia, B. Urones, R. G. Arrays and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2011, **50**, 10927; (*i*) C. H. Huang, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 12406; (*j*) K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144; (*k*) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466; (*l*) M. Mewald, J. A. Schiffner and M. Oestreich, *Angew. Chem., Int. Ed.*, 2012, **124**, 1797; (*m*) M. Mewald, J. A. Schiffner and M. Oestreich, *Angew. Chem., Int. Ed.*, 2012, **51**, 1763; (*n*) C. M. Wang, H. Chen, Z. F. Wang, J. Chen and Y. Huang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7242; (*o*) H. Li, P. Li and L. Wang, *Org. Lett.*, 2013, **15**, 620; (*p*) X.-T. Ma and S.-K. Tian, *Adv. Synth. Catal.*, 2013, **355**, 337; (*q*) Y. Lian, R. G. Bergman, L. D. Lavis and J. A. Ellman, *J. Am. Chem. Soc.*, 2013, **135**, 7122; (*r*) B. C. Chary, S. Kim, Y. Park, J. Kim and P. H. Lee, *Org. Lett.*, 2013, **15**, 2692.
5 (*a*) S. D. Kahn, W. D. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, 1987, **109**, 1871; (*b*) H. Basch and T. Hoz, *Mol. Phys.*, 1997, **97**, 789.
6 (*a*) J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2010, **111**, 1846; (*b*) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030; (*c*) W. I. Dzik, P. P. Lange and L. J. Gooßen, *Chem. Sci.*, 2012, **3**, 2671; (*d*) C. Y. Wang, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 4194; (*e*) C. Wang, S. Rakshit and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 14006; (*f*) S. Ranjit, Z. Duan, P. Zhang and X. Liu, *Org. Lett.*, 2010, **12**, 4134; (*g*) F. Z. Zhang and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 2768; (*h*) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang and W. Su, *Chem.–Eur. J.*, 2010, **16**, 5876; (*i*) R. Shang and L. Liu, *Sci. China: Chem.*, 2011, **54**, 1670.
7 (*a*) A. G. Myers, D. Tanaka and M. R. Mannion, *J. Am. Chem. Soc.*, 2002, **124**, 11250; (*b*) D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323; (*c*) L. J. Goossen, G.-J. Deng and L. M. Levy, *Science*, 2006, **313**, 662; (*d*) L. J. Goossen, N. Rodriguez, B. Melzer, C. Linder, G.-J. Deng and L. M. Levy, *J. Am. Chem. Soc.*, 2007, **129**, 4824; (*e*) L. J. Goossen, N. Rodriguez and C. Linder, *J. Am. Chem. Soc.*, 2008, **130**, 15248; (*f*) L. J. Goossen, F. Rudolphi, C. Oppel and N. Rodriguez, *Angew. Chem., Int. Ed.*, 2008, **47**, 3043; (*g*) L. J. Goossen, N. Rodriguez, P. P. Lange and C. Linder, *Angew. Chem., Int. Ed.*, 2010, **49**, 1111; (*h*) H.-P. Bi, L. Zhao, Y.-M. Liang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2009, **48**, 792; (*i*) R. Shang, Y. Fu, J.-B. Li, S.-L. Zhang, Q.-X. Guo and L. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 5738; (*j*) M. Yamashita, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **12**, 592.
8 (*a*) P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898; (*b*) M. Li and H. Ge, *Org. Lett.*, 2010, **12**, 3464.
9 H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.*, 2012, **14**, 4358.
10 M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 925.
11 Z. Yang, X. Chen, J. Liu, Q. Gui, K. Xie, M. Li and Z. Tan, *Chem. Commun.*, 2013, **49**, 1560.
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*) C. Li, L. Wang, P. Li and W. Zhou, *Chem.–Eur. J.*, 2011, **17**, 10208; (*b*) W. Zhou, H. Li and L. Wang, *Org. Lett.*, 2012, **14**, 4594; (*c*) D. Li, M. Wang, J. Liu, Q. Zhao and L. Wang, *Chem. Commun.*, 2013, **49**, 3640; (*d*) L. Yu, P. Li and L. Wang, *Chem. Commun.*, 2013, **49**, 2368.
16 X-ray single-crystal for acylated azoxybenzene **3j**



17 A. L. Balch and D. Petridis, *Inorg. Chem.*, 1969, **8**, 2247.
18 S. O. C. Mundle and R. Kluger, *J. Am. Chem. Soc.*, 2009, **131**, 11674.
19 (*a*) D. C. Power, M. A. L. Geibel, J. E. M. N. Klein and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 17050; (*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.

