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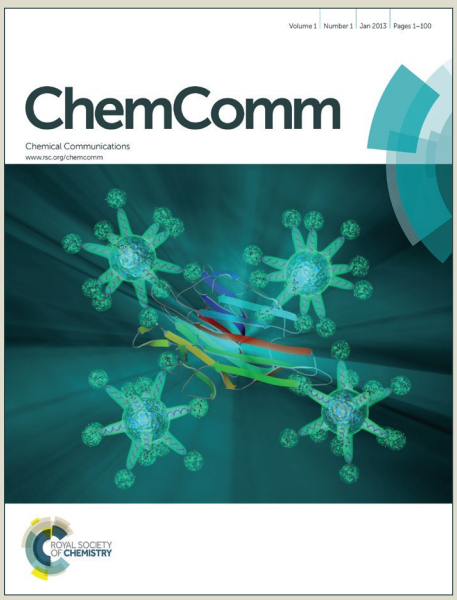

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ARTICLE TYPE

Pd-Catalyzed α-Selective C(sp^3)-H Acetoxylation of Amides through an Unusual Cyclopalladation Mechanism

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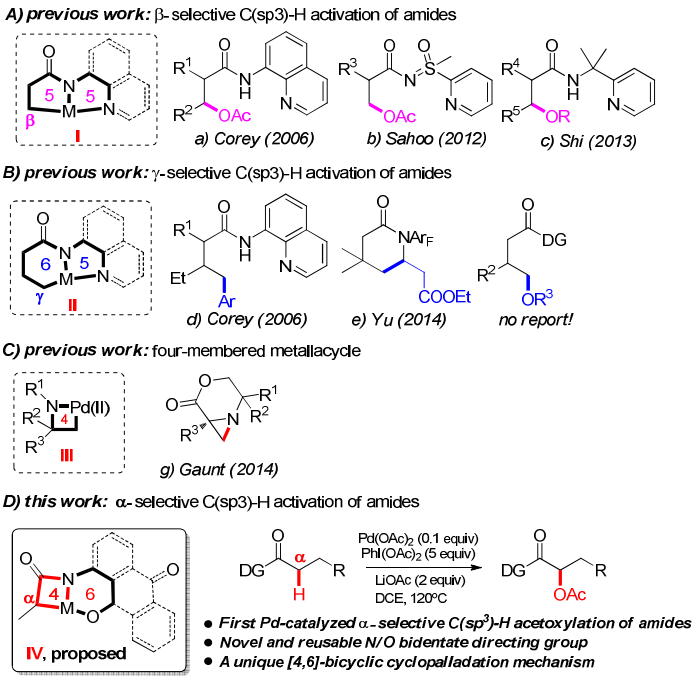
We report the first example of Pd-catalyzed site-selective α-C(sp^3)-H oxidation/acetoxylation of amides through an unusual [4,6]-bicyclic metallacycle intermediate with 1-aminonanthraquinone as a new bidentate directing group. In addition to the distinct mechanism and high efficiency, the reaction is highly appealing due to the ample commercial source, low-costing, as well as easy removal and recycling of the auxiliary group.

Recent years have witnessed explosive advances in the field of directed C-H activation/functionalization.[1] However, functionalization of C(sp^3)-H bonds remains a challenging task.[2] Fortunately, bidentate directing groups (BDGs)[3] have been introduced as a new option to promote activation of many C(sp^3)-H bonds. 8-Aminoquinoline[4] as the earliest BDG was reported by Daugulis[4b] in 2005 and opened a new avenue for C(sp^3)-H activation. Later on, a few analogous BDGs have been developed and used in numerous C(sp^3)-H activation and subsequent transformations.[4,5]

Notably, nearly all BDGs prefer to assist β-selective C(sp^3)-H bond activation through a fused [5,5]-bicyclic metallacycle intermediate **I** (Scheme 1A).[3] For example, Corey's laboratory achieved β-selective C(sp^3)-H acetoxylation of various protected amino acid derivatives with 8-aminoquinoline as the BDG in 2006 (Scheme 1A, a).[4e] Sahoo[5a] and Shi's[5b] groups respectively developed substituted pyridine BDGs for the selective acetoxylation and alkoxylation at the β-positions of amides in 2012 and 2013 (Scheme 1A, b and c). In comparison to the majority of β-selective C-H functionalization, a few examples of γ-arylation and olefination were reported as well although limited to substrates either with bulky tertiary β-C-H bonds (Scheme 1B, d)[4e] or in the absence of β-C-H bonds (Scheme 1B, e).[6] While γ- or α-oxidation of amides controlled by BDGs, to the best of our knowledge, has not been explored yet.

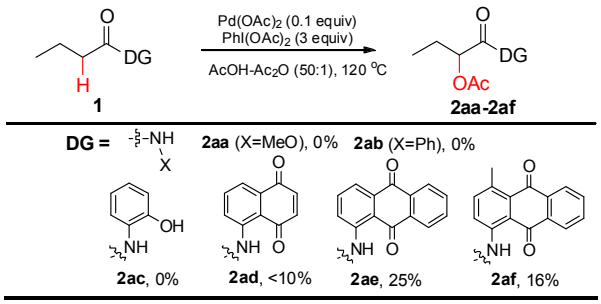
Transition metal-catalyzed α-arylation and alkylation have been reported through enolate intermediate.[7,8] However, in the case of α-C(sp^3)-H bond oxidation of amides, only traditional enolate oxidations are available, in which strong bases, such as LiHMDS or NaHMDS, anhydrous condition, and much low temperature are generally necessary.[9] Therefore, we decide to take advantage of the C-H activation strategy[4,5,10] by developing an appropriate BDG to facilitate α-C(sp^3)-H bond activation/acetoxylation of amides in a more economic and convenient fashion.



Scheme 1. DG-controlled site-selective acetoxylation of carbonates.

The major obstacle of α-C(sp^3)-H bond activation via a bidentate auxiliary directing procedure other than an enolization intermediate lies in the difficulty in the formation of a proposed [4,6]-bicyclic metallacycle intermediate **IV** (scheme 1D), which is structurally distinct from the common and thermodynamically more stable [5,5]-bicyclic counterpart (e.g. **I**) for β-C(sp^3)-H bond activation, or the [6,5]-bicyclic intermediate (e.g. **II**) for γ-C(sp^3)-H bond activation. To reach our goal, we first attempted to discover a new type of BDGs, which has the capacity to provide a larger coordination angle to allow forming the expected six-membered metallacycle as in **IV** (Scheme 1D). This expanded six-membered BDG-metal coordination would then likely force the metal complex to insert into the α-C(sp^3)-H via a highly strained four-membered metallacycle intermediate (as in **IV**). Very recently, Gaunt's group communicated on Nature a Pd-catalyzed C-H activation of aliphatic amines through a unique four-membered ring cyclopalladation intermediate **III** (Scheme 1C) for the first time.[11] This extraordinary work convinced us the likelihood of achieving α-C(sp^3)-H bond activation/acetoxylation

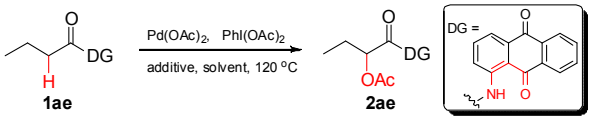
via a four-six-membered bicyclic metallacycle **IV**.



Scheme 2. Effect of the directing groups

We first screened a number of widely used MDGs (monodendate directing groups) and BDGs (Scheme 2). No reactions were observed using MDGs (**2aa** and **2ab**), or 2-aminophenol as a BDG (**2ac**). Gratifyingly, the expected α-acetoxylated product **2ad** was obtained when 1-aminonaphthoquinone was used as the BDG, albeit in a low yield of 10%. Slightly higher yields were obtained by using the tricyclic 1-aminoanthraquinones as the BDGs (**2ae** and **2af**).

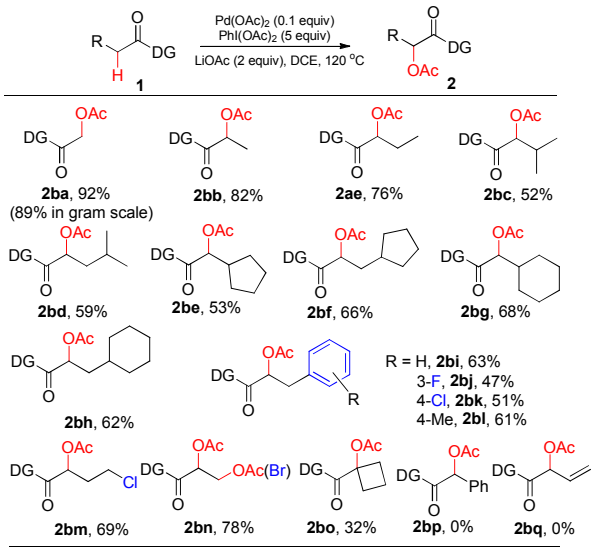
Table 1. Optimization of reaction conditions.[a,b]



Entry	Additive (2 equiv)	Solvent	Yield (%)
1	-	AcOH-Ac_2O (50:1)	25
2	-	Toluene	12
3	-	DCE	38
4	-	Dioxane	0
5	-	DMF	5
6	$K_2S_2O_8$	DCE	17
7	MeCOOO*t*-Bu	DCE	8
8	AgOAc	DCE	58
9	Ag_2O	DCE	48
10	CuI	DCE	5
11	LiOAc	DCE	62
12[c]	LiOAc	DCE	76
13	NaO*t*-Bu	DCE	47
14[d]	LiOAc	DCE	0
15[e]	LiOAc	DCE	0

[a]N-anthraquinon-1-ylbutyramide **1ae** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), $PhI(OAc)_2$ (3 equiv) and additive (2 equiv) in solvent (0.5 mL) in a sealed tube at 120 °C for 12 h. [b]Isolated yields were listed. [c]5 equiv $PhI(OAc)_2$ were used. [d]Without $Pd(OAc)_2$. [e]Without $PhI(OAc)_2$.

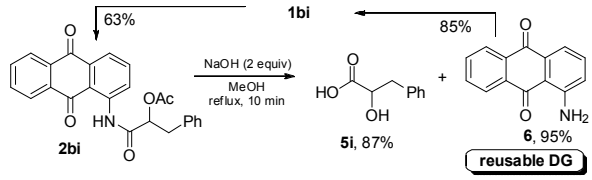
Further optimization of the reaction conditions was set out using **1ae** as the model substrate (Table 1). Screening of solvents showed that DCE gave the highest yield (entries 1-5). The yield of **2ae** was increased slightly when Ag_2O (entry 9) or NaO*t*-Bu (entry 13) was added, but decreased much when $K_2S_2O_8$ (entry 6), $MeCO_3t$-Bu (entry 7), or CuI (entry 10) was used. It was of interest that addition of AgOAc (entry 8) or LiOAc (entry 11) led to dramatically increased yield. Finally, a high yield of 76% was achieved by using $Pd(OAc)_2$ (0.1 equiv), $PhI(OAc)_2$ (5 equiv), and LiOAc (2 equiv) in DCE at 120 °C for 12 h (entry 12).



Scheme 3. Acetoxylation of α-C(sp^3)-H bonds of amides.[a,b]
[a]The reactions were performed with **1** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), $PhI(OAc)_2$ (5 equiv) and LiOAc (2 equiv) in DCE (0.5 mL) in a sealed tube at 120 °C for 12 h. [b]Isolated yields were listed.

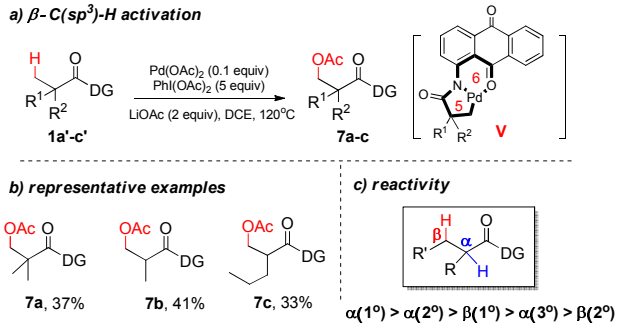
With the optimized reaction conditions, we explored the reaction scope and generality with various amide substrates **1**. The results were summarized in Scheme 3. It was found that substrates containing primary α-C(sp^3)-H bonds gave excellent yields (**2ba**, 92%). Amides containing α-methylene C(sp^3)-H bonds, which were more difficult to cleave than primary ones, also proceeded smoothly under the optimal conditions, although with somewhat lower yields (**2bb-2bd**, 52-82%). Excellent α-selectivity was achieved under the standard conditions, especially for substrate **2bb**, which contained a primary β-C(sp^3)-H bond while no β-product was observed. Amides **1** with larger cyclic aliphatic substituents were tolerant as well, and gave corresponding products **2be-2bh** in 53-68% yields. Substrates with aromatic substituents were also tested, and all reactions went through smoothly providing products **2bi-2bl** in moderate yields (47-63%). No significant differences were observed between electron-neutral, electron-deficient, and electron-rich substituents. Chloro substituent was well survived (**2bm**, 69%), while bromo substituent on the substrate was acetoxylated simultaneously, leading to diacetate **2bn** in 78% yield. It was worth mentioning that acetoxylated product **2bo** containing an α-tertiary carbon center was also obtained through the proposed Pd-catalyzed α-C-H functionalization. However, phenyl acetamide and but-3-enamide were found unstable in the standard reaction conditions, and decomposition of the amide bond occurred in both cases (**2bp**, **2bq**).

To evaluate the efficiency and practicality of this catalytic process, a scale-up experiment (1.0 g of **1ba**) was carried out. As a result, gram-scale preparation of **2ba** was achieved in 89% yield (Scheme 3). Encouraged by the successful acetoxylation of α-C(sp^3)-H bonds, we further expanded the reaction protocol to the *ortho* C(sp^2)-H bond activation and obtained the corresponding aryl acetates in high yields (ESI). The new BDG - 1-aminoanthraquinone could be easily cleaved and recycled. As shown in Scheme 4, refluxing product **2bi** in MeOH with 2 equiv NaOH for 10 minutes gave the α-hydroxyl acid **5i** in 87% yield, together with 1-aminoanthraquinone (**6**) recovered in nearly quantitative yield (95%). The recycled crude 1-aminoanthraquinone was then used directly in the preparation of amides **1** for further C-H activation without significant loss of yields.



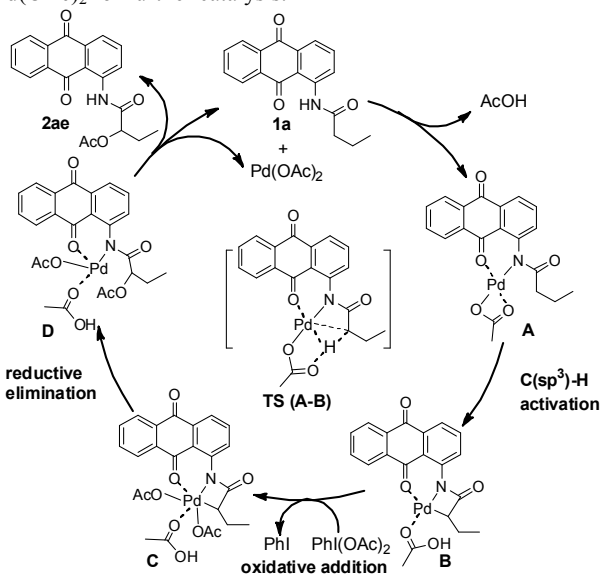
Scheme 4. Reusability of the directing group (DG).

With the aim to rule out a Pd-enolate mechanism, as well as to explore the practical utility of our BDG, blocking experiments at the α-position were conducted. As shown in Scheme 5, substrate with α-position fully blocked (**1a'**) gave β-acetoxylation product **7a**, indicating that β-acetoxylation is a competitive path to the α-acetoxylation, although it is unfavorable (37%) in our current condition. To compare the reactivity of β(1°)-C-H and α(3°)-C-H bonds, methyl propanamide **1b'** and methyl pentanamide **1c'** were tested as well. β-Acetoxylated products **7b** and **7c** were obtained in 41 and 33% yields, respectively through the intermediate **V**, but no α-acetoxylated products were detected. This result ruled out the possibility of a traditional Pd-enolate process involved in current protocol. These findings, together with that from Scheme 3, suggested a C-H activation preferring sequence as α(1°) > α(2°) > β(1°) > α(3°) > β(2°) (Scheme 5C).



Scheme 5. Acetoxylation of β-C(sp^3)-H bonds of amides and C-H insertion propensity of different types of C-H bonds.

On the basis of these results, a plausible mechanism was depicted in Scheme 6. First, the 1-aminoanthraquinone component serves as a BDG that coordinates with palladium to form intermediate **A** by proton abstraction, followed by the key α-C(sp^3)-H activation step via a concerted metallation-deprotonation (CMD)[12,13] mechanism (**TS (A-B)**), thus leading to the cyclopalladated intermediate **B**. Next, oxidation of Pd(II) to Pd(IV) by PhI($OAc)_2$ forms intermediate **C**. Subsequent reductive elimination delivers the acetoxylation product **2a** and releases $Pd(OAc)_2$ for further catalysis.



Scheme 6. Proposed mechanism.

To further validate the α-selectivity in our C(sp^3)-H acetoxylation of amides, the density functional theory (DFT) calculations were performed with the Gaussian-09 software package.[12] Based on CMD transition states[13] of α- and β-C-H activation, participation of three-center two-electron agostic intermediates are suggested (Figure 1, **TS (A-B)**, **TS (A-B')**).

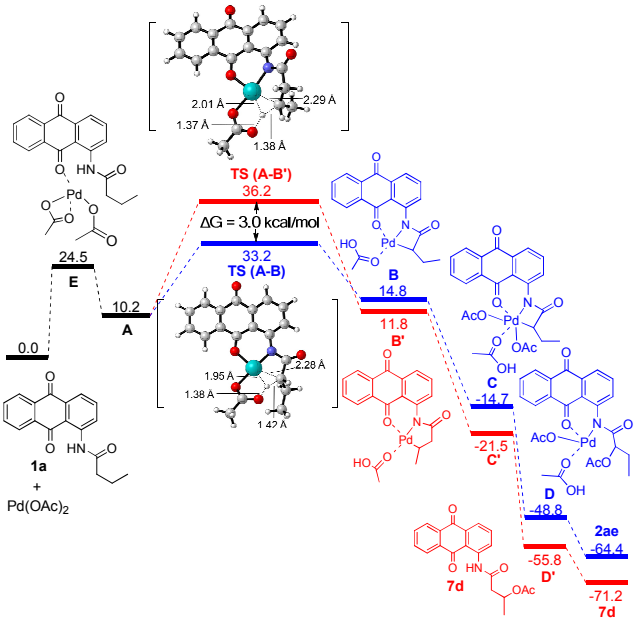


Figure 1. Free energy profile. Energies ΔG in kcal/mol.

The calculated distances between the palladium atom and the C-H σ bond were 1.95 Å in **TS (A-B)** and 2.01 Å in **TS (A-B')**, respectively, obviously within the distance of a three-center two-electron agostic interaction. Besides, a lower energy discrepancy of about 3.0 kcal/mol was observed for **TS (A-B)** over **TS (A-B')**, suggesting a favorable α-selectivity in this C(sp^3)-H bond activation, which was in agreement with our experiment results. Further investigation on the geometry of the optimized intermediate **A** revealed that the 5,6-fused palladacycle is difficult to be formed as it requires a significant rotation of the C(O)-C(α) bond, which increases molecular energy apparently (See ESI).

Conclusions

In conclusion, we have successfully developed a novel removable bidentate directing group (BDG)-controlled α-C(sp^3)-H acetoxylation via a unique [4,6]-bicyclic cyclopalladation pathway. This is the first example of α-C(sp^3)-H oxidation/acetoxylation of amides through a Pd-catalyzed BDG-induced C-H activation process. The cheap and ample commercial source of the newly discovered BDG, together with its easy on-and-off property, makes this reaction with great practical utility.

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Notes and references

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1 Selected reviews on directed C-H activations: (a) Y. J. Park and C.-H. Jun, *Bull. Korean Chem. Soc.*, 2005, **26**, 871; (b) T. M. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (c) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (d) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814.

2 Selected reviews of C(sp^3)-H functionalization: (a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutaer and O. Baudoin, *Chem.-Eur. J.*, 2010, **16**, 2654; (b) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902.

3 Selected review on BDGs: G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726.

4 Selected examples on 8-aminoquinoline as BDGs: (a) M. Corbet and F. D. Campo, *Angew. Chem., Int. Ed.*, 2013, **52**, 9896; (b) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (c) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965; (d) L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5188; (e) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (f) Y. Feng, Y. Wang, B. Landgraf, S. Liu and G. Chen, *Org. Lett.*, 2010, **12**, 3414; (g) Y. Feng and G. Chen, *Angew. Chem., Int. Ed.*, 2010, **49**, 958; (h) S. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 12135; (i) Y. Ano, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 12984; (j) W. R. Gutekunst, R. Gianatassio and P. S. Baran, *Angew. Chem., Int. Ed.*, 2012, **51**, 7507; (k) R. Shang, L. Ilies, A. Matsumoto and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 6030; (l) R. Parella, B. Gopalakrishnan and S. A. Babu, *Org. Lett.*, 2013, **15**, 3238; (m) X. Wu, Y. Zhao and H. *Ge, Chem. Eur. J.*, 2014, **20**, 9530.

5 Selected examples on other BDGs: (a) R. K. Rit, M. R. Yadav and A. K. Sahoo, *Org. Lett.*, 2012, **14**, 3724; (b) F.-J. Chen, S. Zhao, F. Hu, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187; (c) N. Ghavtadze, F. S. Melkonyan, A. V. Gulevich, C. Huang and V. Gevorgyan, *Nature Chem.*, 2014, **6**, 122; (d) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 2124; (e) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 8070; (f) W. R. Gutekunst and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 19076; (g) E. T. Nadres and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 7; (h) N. Rodríguez, J. A. Romero-Revilla, M. A. Fernández-Ibáñez and J. C. Carretero, *Chem. Sci.*, 2013, **4**, 175; (i) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen and X. Shi, *Chem. Sci.*, 2013, 4, 3712. (j) R. K. Rit, M. R. Yadav, K. Ghosh, M. Shankar, and A. K. Sahoo, *Org. Lett.*, 2014, **16**, 5258.

6 S. Li, G. Chen, C.-G. Feng, W. Gong and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 5267.

7 Selected reviews on transition metal-catalyzed α-arylation of carbonyl compounds: (a) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676; (b) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082.

8 Transition metal-catalyzed α-alkylation of carbonyl compounds: F. Mo and G. Dong, *Science*, 2014, **345**, 68.

9 Selected reviews on α-oxidation of amides: (a) S. V. Ley, T. D. Sheppard, R. M. Myers and M. S. Chorghade, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 1451; (b) T. Vilaivan and W. Bhanthumnavin, *Molecules*, 2010, **15**, 917; (c) F. A. Davis and B.-C. *Chen, Chem. Rev.*, 1992, **92**, 919.

10 Selected examples on Pd-catalyzed C(sp^3)-H oxidation: (a) G. Shan, X. Yang, Y. Zong and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 13606; (b) G. He, Y. Zhao, S. Zhang, C. Lu and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 3; (c) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 7313; d) T. Cheng, W. Yin, Y. Zhang, Y. Zhang and Y. Huang, *Org. Biomol. Chem.*, 2014, **12**, 1405; (e) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (f) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542; (g) S. R. Neufeldt and M. S. Sanford, *Org. Lett.*, 2010, **12**, 532; (h) K. J. Stowers, A. Kubota and M. S. Sanford, *Chem. Sci.*, 2012, **3**, 3192; (i) R. Giri, J. Liang, J.-G. Lei, J.-J. Li, D.-H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7420; (j) D.-H. Wang, X.-S. Hao, D.-F. Wu and J.-Q. Yu, *Org. Lett.*, 2006, **8**, 3387; (k) Z. Ren, F. Mo and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 16991; (l) L. Zhou and W. Lu, *Org. Lett.*, 2014, **16**, 508.

11 A. McNally, B. Haffemayer, B. S. L. Collons and M. J. Gaunt, *Nature*, 2014, **510**, 129.

12 For computational details and references, see the Supporting Information.

13 (a) M. Lafrance, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 14570; (b) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 10706.