

CrossMark
click for updatesCite this: *Chem. Sci.*, 2016, 7, 5384

Received 13th March 2016

Accepted 26th April 2016

DOI: 10.1039/c6sc01148a

www.rsc.org/chemicalscience

Pd-catalyzed dehydrogenative annulation approach for the efficient synthesis of phenanthridinones†

Xinyao Li,^a Jun Pan,^a Song Song^a and Ning Jiao^{*ab}

A novel Pd-catalyzed intermolecular dehydrogenative annulation of aryl iodides and aryl carbamic chlorides for the efficient synthesis of phenanthridinone derivatives was developed. Simple aryl iodides and carbamic chlorides readily made from various anilines, a broad substrate scope with hetero/polycycles, as well as high-value products, make this direct dehydrogenative annulation approach very practical and attractive.

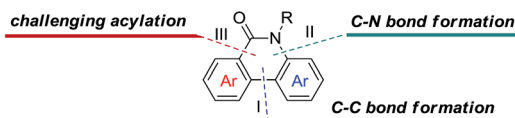
Introduction

Phenanthridinones are ubiquitous fused heterocyclic motifs found in many natural alkaloids and pharmaceutically active compounds, exhibiting broad biological activities such as antitumor, antiviral, and DNA topoisomerase I inhibition.¹ The rising use of these biologically significant fused phenanthridinones has stimulated considerable interest in developing their synthetic methods with enhanced generality, scope, and cost effectiveness. Accordingly, many synthetic approaches, including annulation of prefunctionalized substrates to construct phenanthridinones and their derivatives, were developed in the past decades.² Despite their significance, most of reported methods suffer from the prefunctionalized substrates low efficiency or limited substrate scope. Therefore, direct strategies for the efficient synthesis of diverse phenanthridinones are still highly demanded.

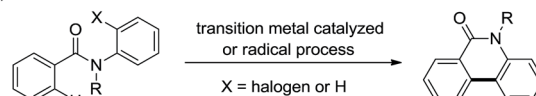
Transition-metal-catalyzed dehydrogenative annulation of simple substrates has proven to be a versatile and powerful synthetic strategy to construct polycyclic and heteroaromatic compounds.³ The retrosynthetic analysis of phenanthridinones through a dehydrogenative strategy could be orientated to typical C–C bond formation (I), amide directed C–N bond formation (II), or acylation (III) (Scheme 1a). Using a one chemical bond formation strategy, the intramolecular dehydrogenative cyclization of aryl amides *via* path I has been significantly developed by the groups of Åkermark,^{4a} Fagnou,^{4b} Dong,^{4c} Cheng,^{4d} and Curran^{4e} (Scheme 1b).

In order to disclose new approaches from more simple substrates, a strategy using two chemical bond formation is desired. Recently, Wang⁵ and Cheng⁶ independently developed elegant Pd- or Rh-catalyzed intermolecular dehydrogenative cyclization *via* C–C and C–N bond formation (pathways I and II) to prepare *N*-methoxy phenanthridinones (Scheme 1c). However, despite the significance, the requirement of stoichiometric oxidant and the CONHOMe directing group limit

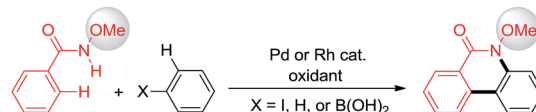
a) Retrosynthetic analysis through dehydrogenative strategy



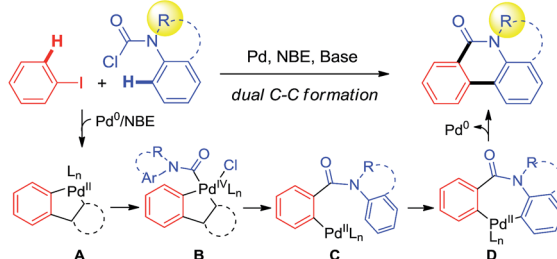
b) Previous intramolecular annulation *via* I bond formation



c) Previous intermolecular annulation *via* I & II bonds formation



d) This work: dehydrogenative annulation *via* I & III bonds formation



Scheme 1 Dehydrogenative annulation strategies for phenanthridinone construction.

^aState Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, China. E-mail: jiaoning@pku.edu.cn

^bState Key Laboratory of Elemento-organic Chemistry, Nankai University, Weijin Rd. 94, Tianjin 300071, China

† Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c6sc01148a

the substrate scope and their application in the construction of hetero and polycycles. Alternatively, a straightforward approach through two C–C bond formation (pathways I and III) (Scheme 1a) enables the use of various functional groups including some heterocyclic partners from corresponding readily available aniline precursors (Scheme 1d). However, to the best of our knowledge, this strategy is still unknown and poses a challenge due to the adjacent dual C–C bond construction *via* C–H bond cleavage.⁷

Recently, Pd/norbornene (NBE) chemistry has been demonstrated to be a significant protocol that allows activation of both the *ipso* and *ortho*-positions of arenes.^{8,9} In continuation of our interest in dehydrogenative annulation for the construction of heterocycles,¹⁰ we envisioned that if a proper carbonyl reagent could be employed to form Pd^{IV} intermediate **B** through the palladacycle **A** species generated *in situ* from aryl iodides in the presence of NBE, acylation at the *ortho*-position would be realized and produce the aryl-Pd intermediate **C**. Subsequently, if species **C** could undergo the CMD¹¹ process, followed by reductive elimination to realize arylation,¹² the desired phenanthridinone derivatives would be constructed (Scheme 1d). Very recently, Dong,^{13a} Gu,^{13b} and Liang^{13c} independently reported unprecedented *ortho* C–H acylation of aryl iodides through Pd/NBE chemistry. These results encouraged us to test the above dehydrogenative design. Nevertheless, three challenges have to be solved: (1) the carbonyl reagent not only needs to provide the carbonyl group but also has to be a stronger oxidant than aryl halides, to avoid homo-Catellani coupling,¹⁴ for oxidizing **A**. (2) The subsequent dehydrogenative annulation that implicates the intermediacy of seven-membered palladacycle **D** should be favoured over other quenched processes. (3) Multiple steps including acylation and annulation have to take place successively under mild conditions. Herein, we report the discovery of a novel Pd-catalyzed dehydrogenative annulation of aryl iodides and aryl carbamic chlorides for the efficient synthesis of phenanthridinones (Scheme 1d).

Results and discussion

Initially, we endeavoured to realize the Pd-catalyzed dehydrogenative annulation reaction using iodobenzenes and anilines with norbornene under CO, however, only the *ipso* position of the iodobenzenes was carbonylated, providing liner amides without cyclization. We hypothesized that properly pre-functionalized carbonyl anilines may inhibit the carbonylation at the *ipso* position in order to preclude the by-products. As we expected, when 1-iodo-2-methylbenzene (**1a**) was reacted with methyl(phenyl)carbamic chloride (**2a**), the intermolecular annulation performed well affording the desired phenanthridinone **3a** (Table S1, see ESI†). The desired product, **3a**, could be obtained in up to 98% yield when using Pd(OAc)₂/PPh₃ as the metal/ligand combination, NBE, and Cs₂CO₃ as the base in DCE at 95 °C (**3a**, Table 1). A series of control experiments indicated that the palladium, phosphine ligand, NBE, and base were all essential for this transformation (entries 2–5, Table S1, see ESI†).

Table 1 Scope of aryl carbamic chlorides with different substituents^a

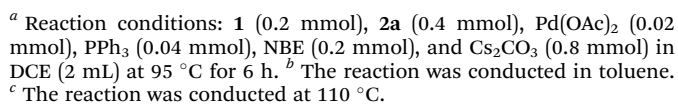
3a , 98%	3b , 96%	3c , 99% (11:1) ^b	3d , 98%
3e , 93%	3f , 93%	3g , 84%	3h , 30%
3i , 98%	3j , 93%	3k , 97%	3l , 95%
3m , 66%, 72% ^c	3n , n = 1, 32% ^c	3p , 41% ^c	3q , 69% ^c

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)₂ (0.02 mmol), PPh₃ (0.04 mmol), NBE (0.2 mmol), and Cs₂CO₃ (0.8 mmol) in DCE (2 mL) at 95 °C for 6 h. ^b Regioselectivity ratio (the major isomer is substituted at the 3-position as drawn). ^c The reaction was conducted in toluene.

With the optimized reaction conditions in hand, we next explored the scope of aryl carbamic chlorides **2** (Table 1). *o*-, *m*-, *p*-Methyl substituents on the phenyl ring of **2** were well tolerated and the desired phenanthridinones **3b–d** were isolated in excellent yields. Among them, **3c** was synthesized with good regioselectivity. A series of **2**, bearing electron-donating groups or weak electron-withdrawing groups such as F and Cl, and OCF₃, were tested and showed excellent performance in this reaction, giving the corresponding products in high yields (**3d–g**). It is worthy to note that *N*-alkyl and aryl groups were compatible in this transformation with almost equivalent transformation into corresponding products (**3i–l**). Furthermore, methyl(naphthalen-1-yl)carbamic chloride (**2m**) and polycyclic carbamic chlorides (**2n–q**) were smoothly converted into polycyclic phenanthridinones (**3m–q**) in moderate to good yields, which are the common core structural motifs in some natural products and bioactive compounds. For these substrates, the reaction proceeded better in toluene than in DCE.

In order to explore the effect of substituents on iodobenzenes, a variety of aromatic and heteroaromatic iodides





(1)

1a **2r**: R = PMB
2s: R = Bn **3r**, 92%
3s, 99% R = PMB **5**, 91%

(2)

1a **2t** **6a**, 80% **6b**, 15%

(3)

1a **2u** **7a**, 75% **7b**, 6%

(4)

1a **2a/2a-d₅** **3a/3a-d₄**
 1 h KIE = 1.3

Scheme 2 Other substrates and isotope-labeling experiment.

Based on our preliminary mechanistic studies, and assuming a 1 : 1 stoichiometry between all reaction components in the catalyst turnover to simplify the discussion, we conducted a density functional theory (DFT) calculation investigation into the direct dehydrogenative annulation of **1a** and **2a** to better understand the mechanism of this transformation (Fig. 2).^{16,17} The phenyl groups in the ligand are replaced by methyl groups to save computational time but without sacrificing credibility. Initially, the oxidative addition of **1a** with Pd⁰ could occur on the bisphosphine or monophosphine complex.¹⁸ The calculations

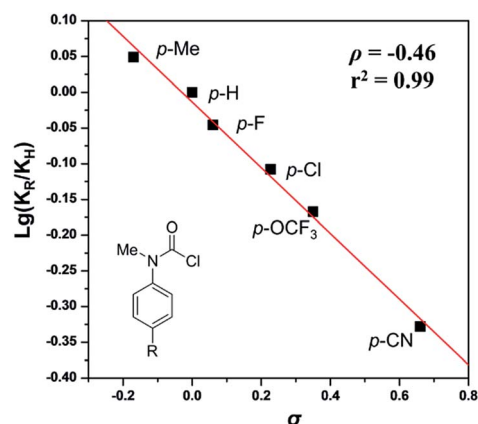


Fig. 1 Hammett plot of the annulation of 2.

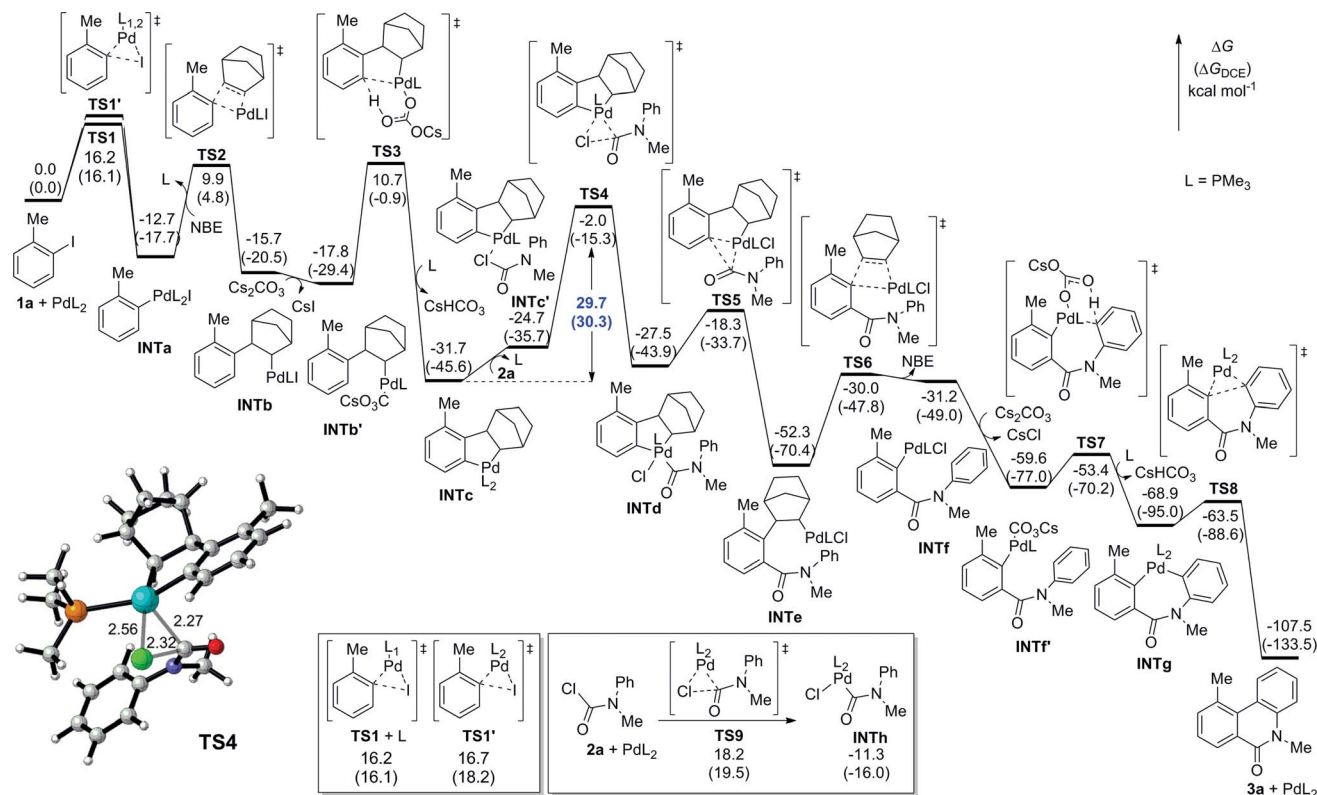


Fig. 2 DFT-computed energy profiles for Pd-catalyzed dehydrogenative acylation and annulation of **1a** and **2a**.

show that the oxidative addition on the monophosphine complex *via* transition state **TS1** is slightly favoured over that on the bisphosphine complex *via* **TS1'**, indicating that the monophosphine complex is the dominant active species, while the bisphosphine complex is the minor one (see ESI† for details). However, both pathways are facile, requiring an activation free energy of only 16.2 and 16.7 kcal mol⁻¹ to form Pd^{II} species **INTa** exergonically. The next step, corresponding to the insertion of NBE, is reversible to afford **INTb**. After base exchange, the formed **INTb'** undergoes a CMD process to provide the stable intermediate palladacycle **INTc** irreversibly. Then, oxidative addition takes place through transition state **TS4** with an activation free energy of 29.7 kcal mol⁻¹ to deliver Pd^{IV} intermediate **INTd**. The following reductive elimination of Pd^{IV} is facile and exergonic. After acylation, β-C elimination of NBE occurs endergonically. The subsequent CMD step readily proceeds to furnish cyclic intermediate **INTg**. Finally, the reductive elimination of **INTg** is also facile to give the final phenanthridinone **3a**, whilst regenerating the Pd⁰ catalyst. Reviewing the whole energy profile, we find that the direct oxidative addition of the *in situ* formed palladacycle with aryl carbamic chloride is the rate-determining step, in good agreement with the experimental observation of the Hammett plot.

Conclusions

In conclusion, we have demonstrated the first Pd-catalyzed intermolecular direct dehydrogenative annulation of aryl

iodides and aryl carbamic chlorides through dual C–H bond activation for the efficient synthesis of phenanthridinone derivatives. This protocol is easy to handle with simple aryl iodide and aryl carbamic chloride substrates readily prepared from various anilines. The use of various functional groups, including some heterocyclic partners, makes this approach very attractive for the construction of high-value and biologically significant phenanthridinone heterocycles. Preliminary experiments and DFT calculations suggest that the *in situ* formed palladacycle **INTc** could undergo oxidative addition of aryl carbamic chloride to generate a Pd^{IV} intermediate in the rate-determining step. Efforts toward expanding the reaction scope of other fused heterocycles are underway.

Acknowledgements

Financial support from the National Basic Research Program of China (973 Program) (grant No. 2015CB856600), National Natural Science Foundation of China (No. 21325206), and National Young Top-notch Talent Support Program are greatly appreciated. We thank Xiaojin Wen in this group for reproducing the results of **3l** and **4e**.

Notes and references

- (a) D. Weltin, V. Picard, K. Aupeix, M. Varin, D. Oth, J. Marchal, P. Dufour and P. Bischoff, *Int. J. Immunopharmacol.*, 1995, **17**, 265; (b) S. Patil, S. Kamath,



- T. Sanchez, N. Neamati, R. F. Schinazi and J. K. Buolamwini, *Bioorg. Med. Chem.*, 2007, **15**, 1212; (c) M. Nakamura, A. Aoyama, M. T. A. Salim, M. Okamoto, M. Baba, H. Miyachi, Y. Hashimoto and H. Aoyama, *Bioorg. Med. Chem.*, 2010, **18**, 2402.
- 2 (a) T. N. Le, S. G. Gang and W.-J. Cho, *J. Org. Chem.*, 2004, **69**, 2768; (b) B. O. Ashburn, R. G. Carter and L. N. Zakharov, *J. Org. Chem.*, 2008, **73**, 7305; (c) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, 1957, **79**, 5479; (d) S. Prabhakaran, A. M. Loba and M. R. Tavares, *J. Chem. Soc., Chem. Commun.*, 1978, 884; (e) M. G. Banwell, D. W. Lupton, X. Ma, J. Renner and M. O. Sydnes, *Org. Lett.*, 2004, **6**, 2741; (f) R. Ferraccioli, D. Carenzi, O. Rombola and M. Catellani, *Org. Lett.*, 2004, **6**, 4759; (g) D. Liang, Z. Hu, J. Peng, J. Huang and Q. Zhu, *Chem. Commun.*, 2013, **49**, 173; (h) V. Rajeshkumar, T.-H. Lee and S.-C. Chuang, *Org. Lett.*, 2013, **15**, 1468; (i) Y.-F. Chen, Y.-S. Wu, Y.-H. Jhan and J.-C. Hsieh, *Org. Chem. Front.*, 2014, **1**, 253; (j) M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14960.
- 3 For reviews on the dehydrogenative annulations, see: (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (b) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (c) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (d) J.-W. Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (e) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (f) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (g) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281.
- 4 (a) B. Åkermark, L. Ebersson, E. Jonsson and E. Pettersson, *J. Org. Chem.*, 1975, **40**, 1365; (b) L. C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581; (c) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (d) R. P. Korivi and C.-H. Cheng, *Chem.-Eur. J.*, 2010, **16**, 282; radical cyclization; (e) D. P. Curran and A. I. Keller, *J. Am. Chem. Soc.*, 2006, **128**, 13706.
- 5 G.-W. Wang, T.-T. Yuan and D.-D. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 1380.
- 6 (a) J. Karthikeyan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 9880; (b) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 12343.
- 7 (a) U. Umeda, H. Tsurugi, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2008, **47**, 4019; (b) F. W. Patureau, T. Besset, N. Kuhl and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2154; (c) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3948; (d) J. Zhang, A. Ugrinov and P. Zhao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6681.
- 8 (a) M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 119; (b) M. Lautens and S. Piguel, *Angew. Chem., Int. Ed.*, 2000, **39**, 1045; (c) M. Catellani, E. Motti and S. Baratta, *Org. Lett.*, 2001, **3**, 3611; (d) M. Catellani, E. Motti and N. Della Ca', *Acc. Chem. Res.*, 2008, **41**, 1512; (e) A. Martins, B. Mariampillai and M. Lautens, *Top. Curr. Chem.*, 2010, **292**, 1; (f) X. Sui, R. Zhu and Z. Gu, *Synlett*, 2013, **24**, 2023.
- 9 For some recent examples, see: (a) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334; (b) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887; (c) H. Zhang, P. Chen and G. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10174; (d) M. Sickert, H. Weinstabl, B. Peters, X. Hou and M. Lautens, *Angew. Chem., Int. Ed.*, 2014, **53**, 5147; (e) L. Jiao and T. Bach, *Angew. Chem., Int. Ed.*, 2013, **52**, 6080; (f) X. Sui, R. Zhu, G. Li, X. Ma and Z. Gu, *J. Am. Chem. Soc.*, 2013, **135**, 9318; (g) H. Weinstabl, M. Suhartono, Z. Qureshi and M. Lautens, *Angew. Chem., Int. Ed.*, 2013, **52**, 5305; (h) H. Liu, M. El-Salfiti and M. Lautens, *Angew. Chem., Int. Ed.*, 2012, **51**, 9846; (i) L. Jiao and T. Bach, *J. Am. Chem. Soc.*, 2011, **133**, 12990; (j) G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat and M. Catellani, *J. Am. Chem. Soc.*, 2011, **133**, 8574; (k) M.-H. Larrauffie, G. Maestri, A. Beaume, E. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacote, M. Catellani and M. Malacria, *Angew. Chem., Int. Ed.*, 2011, **50**, 12253; (l) R. Ferraccioli, D. Carenzi, E. Motti and M. Catellani, *J. Am. Chem. Soc.*, 2006, **128**, 722; (m) Z. Dong and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 18350; (n) H. Shi, D. J. Babinski and T. Ritter, *J. Am. Chem. Soc.*, 2015, **137**, 3775.
- 10 (a) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572; (b) Z. Shi, S. Ding, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 7895; (c) Z. Shi, B. Zhang, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 4036; (d) F. Chen, X. Huang, X. Li, T. Shen, M. Zou and N. Jiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 10495; (e) X. Li, X. Li and N. Jiao, *J. Am. Chem. Soc.*, 2015, **137**, 9246.
- 11 (a) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754; (b) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; (c) M. Lafrance and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 8754; (d) I. Ozdemir, S. Demir, B. Cetinkaya, C. Gurlauoen, F. Maseras, C. Bruneau and P. H. Dixneuf, *J. Am. Chem. Soc.*, 2008, **130**, 1156; (e) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137.
- 12 (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) C. Bressy, D. Alberico and M. Lautens, *J. Am. Chem. Soc.*, 2005, **127**, 13148; (c) C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico and M. Lautens, *Org. Lett.*, 2006, **8**, 2043; (d) C. Blaszykowski, E. Aktoudianakis, D. Alberico, C. Bressy, D. G. Hulcoop, F. Jafarpour, A. Joushaghani, B. Laleu and M. Lautens, *J. Org. Chem.*, 2008, **73**, 1888; (e) B. Laleu and M. Lautens, *J. Org. Chem.*, 2008, **73**, 9164; (f) M. Cheng, J. Yan, F. Hu, H. Chen and Y. Hu, *Chem. Sci.*, 2013, **4**, 526.
- 13 (a) Z. Dong, J. Wang, Z. Ren and G. Dong, *Angew. Chem., Int. Ed.*, 2015, **54**, 12664; (b) Y. Huang, R. Zhu, K. Zhao and Z. Gu, *Angew. Chem., Int. Ed.*, 2015, **54**, 12669; (c) P.-X. Zhou, Y.-Y. Ye, C. Liu, L.-B. Zhao, J.-Y. Hou, D.-Q. Chen, Q. Tang, A.-Q. Wang, J.-Y. Zhang, Q.-X. Huang, P.-F. Xu and Y.-M. Liang, *ACS Catal.*, 2015, **5**, 4927.



- 14 (a) E. Motti, N. Della Ca', S. Deledda, E. Fava, F. Panciroli and M. Catellani, *Chem. Commun.*, 2010, **46**, 4291; (b) A. Martins, D. A. Candito and M. Lautens, *Org. Lett.*, 2010, **12**, 5186.
- 15 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
- 16 All of the DFT calculations were performed with the Gaussian 09 program package at the M06 level of theory with the LACVP(d) basis set. All of the energies discussed in the paper are Gibbs free energies in the gas-phase (ΔG). Gibbs free energies with the CPCM solvation correction in DCE (ΔG_{DCE}) based on the structures in the gas phase with the same basis set are also given in parenthesis. Computational details and references are given in the ESI.†
- 17 G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat and M. Catellani, *J. Am. Chem. Soc.*, 2011, **133**, 8574.
- 18 (a) K. Vikse, T. Naka, J. S. McIndoe, M. Besora and F. Maseras, *ChemCatChem*, 2013, **5**, 3604; (b) K. J. Bonney and F. Schoenebeck, *Chem. Soc. Rev.*, 2014, **43**, 6609.

