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A dual role for acetohydrazide in Pd-catalyzed controlled C(sp^3)–H acetoxylation of aldehydes†

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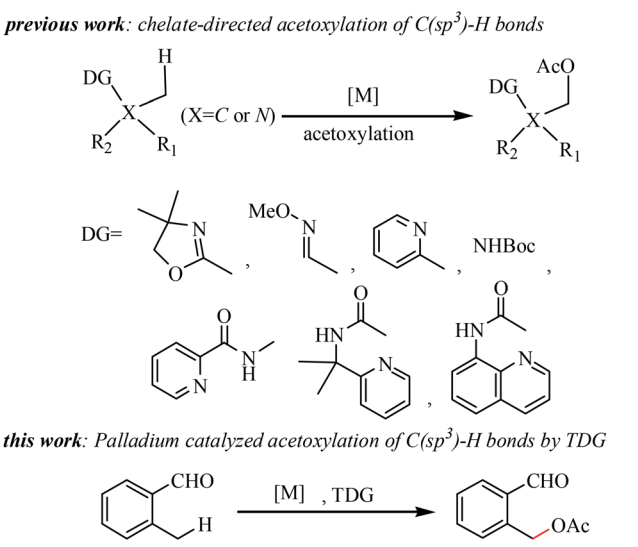
The palladium catalyzed aldehyde directed acetoxylation of C(sp^3)–H bonds was realized by a transient directing group approach for the first time. Crucial to the successful outcome of this reaction is the dual role of acetohydrazide as a directing group for the catalytic C(sp^3)–H activation process and as a protecting group for the CHO functional group. The applicable methodology exhibits good functional group tolerance and occurs readily under mild conditions.

Introduction

Due to the ubiquitous nature of C–H bonds in organic molecules, selective functionalization of C(sp^3)–H bonds emerged as a powerful tool in step-economical organic synthesis, featuring applications in pharmaceutical agent construction, bioactive molecules, and materials.[1] Recently, the direct formation of a C–O bond *via* C(sp^3)–H activation, particularly acetoxylation, has attracted much attention in organic synthesis[2] because organic molecules bearing acetoxy group(s) are important structural features in drugs[3] and agricultural chemicals.[4] Various directing groups, such as oxazoline,[2a,5] *o*-methyl oxime,[6] pyridine,[6,7] Boc-protected amines,[8] Bts-protected amines,[9] primary amines,[10] quinazolinones[11] and bidentate auxiliary groups,[12] have been successfully employed for stoichiometric chelate-directed acetoxylation of C(sp^3)–H bonds (see Scheme 1). Despite this significant progress, the development of oxidizable groups, such as aldehydes, for the directed acetoxylation of C(sp^3)–H bonds is arguably highly desirable. There are a number of remaining challenges in the selective C(sp^3)–H acetoxylation of aldehydes: (1) the tendency of CHO functional groups to undergo undesired oxidation; (2) competitive metal insertions into formyl C–H bonds; and (3) the weak coordinating ability of this group. To date only one example of aldehyde-directed *ortho*-hydroxylations of benzaldehydes *via* C(sp^2)–H activation has been reported.[13]

Very recently, the transient directing group (TDG) approach has been extended to the palladium-catalyzed *ortho*-C(sp^3)–H bond arylations of aldehydes by the groups of Yu,[14] Hu[15], Chen,[16] Bull,[17] Ge,[18] Wang[19] and Wei.[20] Notably, all these processes called for stoichiometric quantities of silver salts as oxidants and the CHO functional group is not oxidized in the reaction process. In these processes, the TDG plays a dual role, one role is to act as a directing group of the catalytic cycle, another is to act as a protecting group of the CHO functional group. Inspired by this concept, we questioned whether aldehyde-directed C(sp^3)–H oxidation could be achieved using the TDG approach.

Herein, we describe a novel palladium catalyzed TDG approach for the direct and selective C(sp^3)–H acetoxylation of aldehydes. This developed methodology provides a catalysis route for C–O bond formation in a straightforward fashion, which successfully suppresses the undesired oxidation of the –CHO group and the acetoxylation products could be transformed into various biologically active compounds such as indeno[1,2-*b*]quinolines,[21] five-membered azacyclic compounds,[22] mycophenolic acid which is an important



Scheme 1 The development of C(sp^3)–H acetoxylation.

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antiparasitic, antineoplastic and antiviral agent,[23] an intermediate of coleophomone which has antifungal activity and shows inhibition of human heart chymase,[24] varitriol which is associated with high levels of biological activity toward renal, CNS, and breast cancer cell lines[25] and an *s-trans*-heterodiene framework[26] (see Scheme 2). Therefore, the methodology of aldehyde-directed selective acetoxylation of C(sp^3)–H bonds can greatly reduce the steps of the total synthesis of these biologically active compounds.

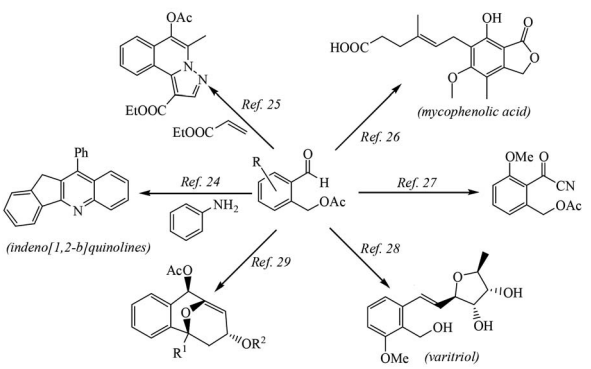
Experimental

General procedure for $Pd(OAc)_2$ catalyzed C(sp^3)–H acetoxylation reaction

A mixture of *o*-methylbenzaldehyde **1a** (0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol%), acetohydrazide (40 mol%), MCM-48 (24 mg, 0.40 mmol), H_2O (9 μL, 0.50 mmol) and $K_2S_2O_8$ (108.2 mg, 0.40 mmol) in AcOH (2.0 mL) was added to a 25 mL oven dried reaction tube. The reaction mixture was heated and refluxed for 48 h at 110 °C. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1 : 5 to 1 : 10 as an eluent) to afford the desired product **2a**. All the products were also confirmed by comparing the ^{1}H NMR and ^{13}C NMR data with authentic samples.

Gram-scale synthesis

In a gram-scale reaction, *o*-methylbenzaldehyde **1a** (1 g, 8.33 mmol), $Pd(OAc)_2$ (186.67 mg, 10 mol%), acetohydrazide (246.67 mg, 40 mol%), MCM-48 (1 g, 16.67 mmol), H_2O (375.0 μL, 0.50 mmol) and $K_2S_2O_8$ (4.50 g, 16.67 mmol) in AcOH (60.0 mL) were added to a 100 mL oven dried round flask. The reaction was carried out at 110 °C for 48 h in an oil bath under air conditions. After being cooled to room temperature, the reaction solution was evaporated *in vacuo*. The residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1 : 10 as an eluent) to afford the desired product **2a** (904.8 mg, 61% yield).

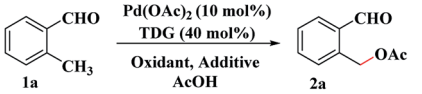


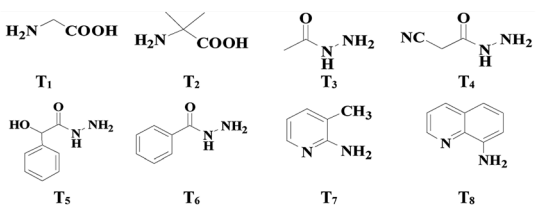
Scheme 2 Application of the acetoxylation product.

Results and discussion

The study commenced with 2-methylbenzaldehyde (**1a**) as a model substrate. We initially employed the $PhI(OAc)_2$/$Pd(OAc)_2$ catalyzed system which has been shown to be a favourable system for C–H bond acetoxylation[27] using glycine $\mathbf{T_1}$ as the TDG (see ESI, Table S1†). Unfortunately, we found that $PhI(OAc)_2$ as an oxidant and acetate source was totally unreactive (see Table 1, entry 1). Other oxidants and acetate sources were screened and finally AcOH was chosen to be the external acetate source and solvent (see ESI, Table S1†). Gratifyingly, when $K_2S_2O_8$ was used as the inorganic peroxide-based oxidant,[28] the desired C(sp^3)–H acetoxylation product, *o*-formylbenzyl acetate (**2a**) was isolated in 35% yield after refluxing **1a** in AcOH (entry 2). Using AcOH as the acetate source, organic peroxides and H_2O_2 all can facilitate the acetoxylation reaction albeit with low yields of **2a** (entries 3–5). The results indicated that the novel C(sp^3)–H acetoxylation of aldehydes probably involved a radical process. Then various TDGs, including amino acids, hydrazides, aminopyridine and aminoquinoline, were tested and acetohydrazide $\mathbf{T_3}$ gave the best performance (entries 6–12). A control experiment indicated that the transient

Table 1 Optimization of the reaction conditions[a]





Entry	TDG	Oxidant	Yield[b] %
1	$\mathbf{T_1}$	$PhI(OAc)_2$	NP
2	$\mathbf{T_1}$	$K_2S_2O_8$	35
3	$\mathbf{T_1}$	H_2O_2	11
4	$\mathbf{T_1}$	Cumene hydroperoxide	21
5	$\mathbf{T_1}$	CH_3CO_3H	15
6	$\mathbf{T_2}$	$K_2S_2O_8$	22
7	$\mathbf{T_3}$	$K_2S_2O_8$	46
8	$\mathbf{T_4}$	$K_2S_2O_8$	NP
9	$\mathbf{T_5}$	$K_2S_2O_8$	9
10	$\mathbf{T_6}$	$K_2S_2O_8$	23
11	$\mathbf{T_7}$	$K_2S_2O_8$	NP
12	$\mathbf{T_8}$	$K_2S_2O_8$	NP
13		$K_2S_2O_8$	NP
14[c]	$\mathbf{T_3}$	$K_2S_2O_8$	61
15[d]	$\mathbf{T_3}$	$K_2S_2O_8$	73

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), TDG (40 mol%), and AcOH (2.0 mL), 110 °C, 48 h. [b] Isolated yields. [c] MCM-48 (0.4 mmol, 24 mg) was added. [d] MCM-48 (0.4 mmol, 24 mg) and H_2O (9 μL, 0.5 mmol) were added.

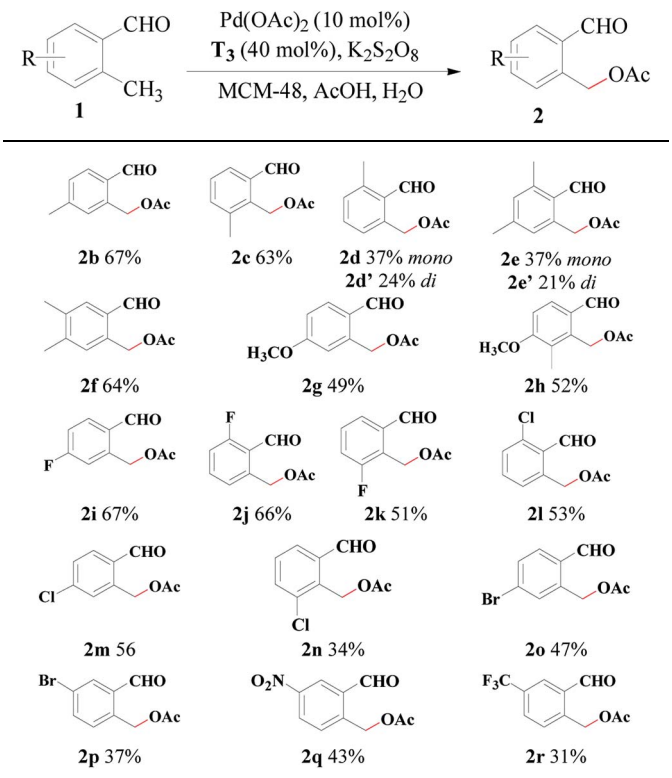
directing group had a vital role in this reaction (entry 13). With the aim of overcoming the lipophobicity of the inorganic oxidant, a molecular sieve (MCM-48) was added to the reaction solution and the yield of **2a** increased to 61% (entry 14). Adding small amounts of water also effectively promotes the reaction because the addition of water reduces the concentration of the imine intermediate and prevents decomposition during the reaction[14] (entry 15).

With the optimal reaction conditions in hand, we explored the scope with respect to the *o*-methylbenzaldehyde derivatives (see Table 2). The reaction can tolerate various functional groups, including alkyl, alkoxy, halogen (F, Br and Cl), trifluoromethyl, and nitro groups. Both electron-withdrawing (**2b–2h**) and electron-donating substituents (**2i–2r**) were tolerated in the C(sp^3)–H acetoxylation reaction, and their reactivities did not exhibit a significant difference. Substrates with a 3-substituted group (**2c**, **2h**, **2k**, **2n**) were well-tolerated, thus indicating a high steric tolerance of this system. When there is a methyl group at both the *ortho*-positions of the formyl group, mono-acetoxylation (**2d**, **2e**) and bis-acetoxylation products (**2d′**, **2e′**) were isolated.

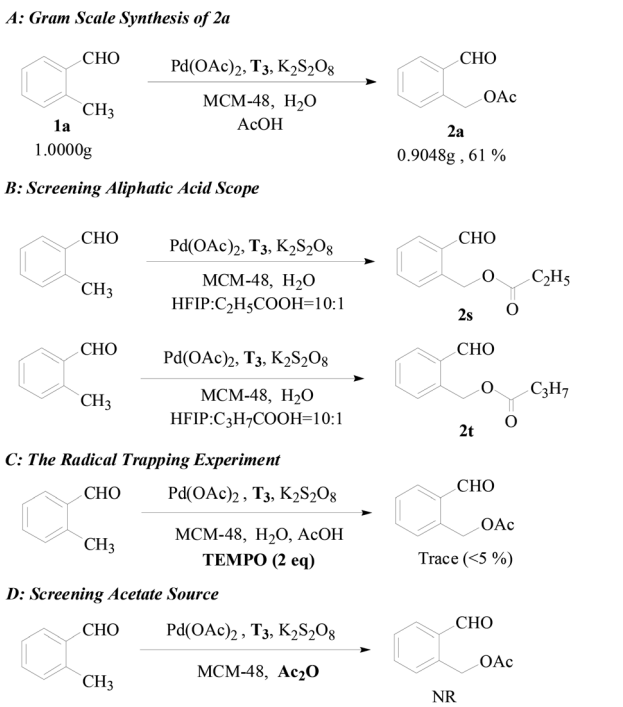
To further establish the general utility of this transformation and shed some light on the reaction mechanism, some control experiments were conducted. To our delight, the gram-scale synthesis of the acetoxylation product **2a** was carried out without significant lost in efficiency under the same reaction conditions (see Scheme 3A). As shown in Scheme 3B, propionic acid and butyric acid were all moderate reaction partners with a minor modification of the standard reaction conditions giving the corresponding product propionate **2s** and butyrate **2t**, respectively, and no acetoxylation product was observed, which confirmed that the acetate group of $Pd(OAc)_2$ is not involved in the reaction process. A radical trapping experiment was carried out to judge the possibility of a radical process (Scheme 3C). When the model reaction was carried out in the presence of TEMPO [(2,2,6,6-tetramethyl-piperidin-1-yl)oxy, 0.4 mmol], a radical scavenger, only a trace (<5% yield) of the acetoxylation product was observed, but the captured benzyl radical was not detected. This result further confirmed that the reaction probably involves a radical process but it may be irrelevant to the C–H activation step. When Ac_2O was employed as the solvent and acetate source instead of AcOH, the reaction could not proceed (Scheme 3D). In view of the fact that Ac_2O is a more effective acetate source than AcOH under the palladium catalyst,[6b,8,12b,12d] we have reason to believe that AcOH may participate in the radical process while it is harder for Ac_2O to generate radicals.

According to the present experimental results and the commonly accepted mechanism from the literature, a plausible reaction mechanism is proposed (see Scheme 4). First, *o*-methylbenzaldehyde reacts with acetohydrazide to form acetohydrazone **I**, which serves as a directing group in the next step. Second, bidentate coordination of the acetohydrazone moiety in

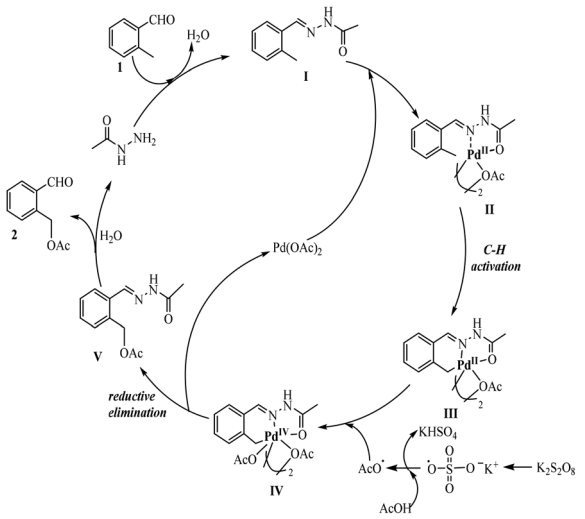
Table 2 Substrate scope of C(sp^3)–H acetoxylation of *o*-methylbenzaldehyde derivatives[a]



[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), acetohydrazone (0.08 mmol), MCM-48 (0.4 mmol), H_2O (0.5 mmol), AcOH (2.0 mL), 110 °C, 48 h.



Scheme 3 (A) Gram scale synthesis of **2a**, (B) screening the aliphatic acid scope, (C) the radical trapping experiment, and (D) screening the acetate source.



Scheme 4 A plausible catalytic cycle.

I to $Pd(OAc)_2$ occurs to form the five-membered palladium-ring **II** and then generate intermediate **III** *via* C–H activation. Then, intermediate **III** reacts with an acetate radical which resulted from the reaction of AcOH with $K_2S_2O_8$, leading to an Pd^{IV} intermediate **IV**.[29] The final step consists of the reductive elimination of intermediate **IV** to release compound **V** and Pd^{II} to complete the catalytic cycle. Compound **V** is then hydrolyzed to the desired product **2** and acetohydrazide.

Conclusions

In summary, we solved the puzzle of oxidizable group-aldehyde directed selective acetoxylation of $C(sp^3)$–H bonds for the first time. Using $Pd(OAc)_2$ as a catalyst and acetohydrazide as both the TDG and protecting group, a broad scope of *o*-formylbenzyl acetates were synthesized under neutral and mild conditions. The methodology has good generality and tolerates various functional groups, including alkyl, alkoxy, halogen (F, Br and Cl), trifluoromethyl, and nitro groups. A mechanism study indicated that the reaction may involve a radical process. Further synthetic applications and additional mechanistic studies are currently under investigation in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J. Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (*b*) J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224; (*c*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*d*) F. Bellina and R. Rossi, *Chem. Rev.*, 2009, **110**, 1082; (*e*) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (*f*) D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749.

2 For examples, see: (*a*) 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; (*b*) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (*c*) D. H. Wang, X. S. Hao, D. F. Wu and J. Q. Yu, *Org. Lett.*, 2006, **8**, 3387.

3 J. A. May, H. Ratan, J. R. Glenn, W. Losche, P. Spangenberg and S. Heptinstall, *Platelets*, 1998, **9**, 227.

4 E. P. Fuerst, C. J. Arntzen, K. Pfister and D. Penner, *Weed Sci.*, 1986, **34**, 344.

5 R. Giri, X. Chen and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 2112.

6 (*a*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (*b*) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542.

7 (*a*) H. Jiang, H. Chen, A. Wang and X. Liu, *Chem. Commun.*, 2010, **46**, 7259–7261; (*b*) J. Zhang, E. Khaskin, N. P. Anderson, P. Y. Zavalij and A. N. Vedernikov, *Chem. Commun.*, 2008, 3625–3627.

8 D. H. Wang, X. S. Hao, D. F. Wu and J. Q. Yu, *Org. Lett.*, 2006, **8**, 3387–3390.

9 Y. Zheng, W. Song, Y. Zhu, B. Wei and L. Xuan, *J. Org. Chem.*, 2018, **83**, 2448–2454.

10 K. Chen, D. Wang, Z. W. Li, Z. Liu, F. Pan, Y. F. Zhang and Z. J. Shi, *Org. Chem. Front.*, 2017, **4**, 2097–2101.

11 D. N. Garad and S. B. Mhaske, *J. Org. Chem.*, 2017, **82**, 10470–10478.

12 (*a*) Z. Wang, Y. Kuninobu and M. Kanai, *Org. Lett.*, 2014, **16**, 4790–4793; (*b*) L. Ju, J. Yao, Z. Wu, Z. Liu and Y. Zhang, *J. Org. Chem.*, 2013, **78**, 10821–10831; (*c*) M. Wang, Y. Yang, Z. Fan, Z. Cheng, W. Zhu and A. Zhang, *Chem. Commun.*, 2015, **51**, 3219–3222; (*d*) R. K. Rit, M. R. Yadav and A. K. Sahoo, *Org. Lett.*, 2012, **14**, 3724.

13 F. Yang, K. Rauch, K. Kettelhoit and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 11285–11288.

14 F. L. Zhang, K. Hong, T. J. Li, H. Park and J. Q. Yu, *Science*, 2016, **351**, 252–256.

15 F. Ma, M. Lei and L. Hu, *Org. Lett.*, 2016, **18**, 2708–2711.

16 B. B. Gou, H. F. Liu, J. Chen and L. Zhou, *Org. Lett.*, 2019, **21**, 7084–7088.

17 S. St John-Campbell, A. J. P. White and J. A. Bull, *Chem. Sci.*, 2017, **8**, 4840–4847.

18 K. Yang, Q. Li, Y. Liu, G. Li and H. Ge, *J. Am. Chem. Soc.*, 2016, **138**, 12775–12778.

19 X. L. Zhang, G. F. Pan, X. Q. Zhu, R. L. Guo, Y. R. Gao and Y. Q. Wang, *Org. Lett.*, 2019, **21**, 2731–2735.

20 C. Dong, L. Wu, J. Yao and K. Wei, *Org. Lett.*, 2019, **21**, 2085–2089.
21 M. Chen, N. Sun and Y. Liu, *Org. Lett.*, 2013, **15**, 5574–5577.
22 D. B. Huple, C. H. Chen, A. Das and R. S. Liu, *Adv. Synth. Catal.*, 2011, **353**, 1877–1882.
23 (*a*) A. Covarrubias-Zúnniga, *Tetrahedron*, 2003, **59**, 1989–1994; (*b*) A. Covarrubias-Zúnniga and A. Gonzalez-Lucas, *Tetrahedron Lett.*, 1998, **39**, 2881–2882; (*c*) M. V. Paradkar, S. A. Kulkarni, A. R. Joseph and A. A. Ranade, *J. Chem. Res.*, 2000, 364–366; (*d*) A. Covarrubias-Zúnniga, J. Diaz-Dominguez and J. Olguín-Uribe, *Synth. Commun.*, 2001, **31**, 1373–1381.
24 (*a*) K. C. Nicolaou, T. Montagnon, G. Vassilikogiannakis and C. J. N. Mathison, *J. Am. Chem. Soc.*, 2005, **127**, 8872–8888; (*b*) K. C. Nicolaou, T. Montagnon and G. Vassilikogiannakis, *Chem. Commun.*, 2002, 2478–2479.
25 G. Sudhakar and J. Raghavaiah, *J. Org. Chem.*, 2013, **78**, 8840–8846.
26 T. M. Teng, A. Das, D. B. Huple and R. S. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 12565–12567.
27 (*a*) Z. Ren, J. E. Schulz and G. Dong, *Org. Lett.*, 2015, **17**, 2696–2699; (*b*) H. Zhang, R. B. Hu, X. Y. Zhang, S. X. Lia and S. D. Yang, *Chem. Commun.*, 2014, **50**, 4686–4689; (*c*) C. S. Buettner, D. Willcox, B. G. N. Chappell and M. J. Gaunt, *Chem. Sci.*, 2019, **10**, 83–89; (*d*) A. K. Cook, M. H. Emmert and M. S. Sanford, *Org. Lett.*, 2013, **15**, 5428–5431; (*e*) F. R. Gou, X. C. Wang, P. F. Huo, H. P. Bi, Z. H. Guan and Y. M. Liang, *Org. Lett.*, 2009, **11**, 5726–5729.
28 L. V. Desai, H. A. Malik and M. S. Sanford, *Org. Lett.*, 2006, **8**, 1141–1144.
29 G. W. Wang, T. T. Yuan and X. L. Wu, *J. Org. Chem.*, 2008, **73**, 4717–4720.