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Gold-catalyzed intermolecular oxidation of chiral homopropargyl sulfonamides: a reliable access to enantioenriched pyrrolidin-3-ones†

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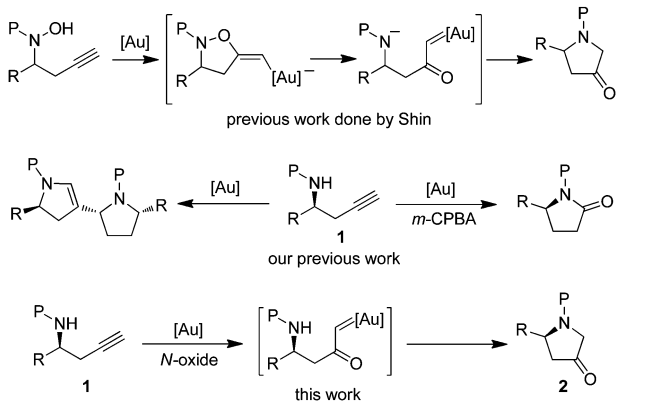
A gold-catalyzed intermolecular oxidation of chiral homopropargyl sulfonamides has been developed, which provides a reliable access to synthetically useful chiral pyrrolidin-3-ones with excellent ee, by combining the chiral *tert*-butylsulfinimine chemistry and gold catalysis. This methodology has also been used in the facile synthesis of natural product (−)-irniine. The use of readily available starting materials, a broad substrate scope, a simple procedure and the mild nature of this reaction render it a viable alternative for the synthesis of enantioenriched pyrrolidin-3-ones.

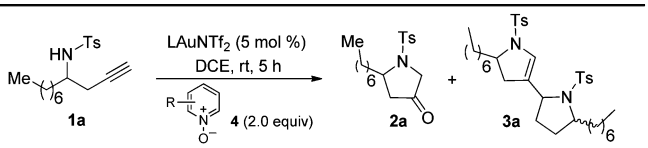
The pyrrolidin-3-one moiety has received considerable interest because of its frequent occurrence in a large number of bioactive natural and non-natural molecules and has therefore been used as a privileged structural subunit for the design of several pharmaceutical agents.[1] In addition, pyrrolidin-3-ones also served as valuable building blocks for the construction of complex molecules due to their latent reactivity and the large panel of highly selective transformations they can undergo.[2] However, despite numerous preparative methods developed during the past decade,[3] there are very few examples of enantioselective synthesis of pyrrolidin-3-ones, especially those with high enantioselectivity, flexibility and good modularity.[4]

Recent rapid development in gold-catalyzed oxygen-atom transfer reactions offers easy access to an incredible variety of functionalized carbo- and heterocycles.[5–8] In this regard, Shin and co-workers reported an elegant protocol for the synthesis of functionalized pyrrolidin-3-ones involving a gold-catalyzed intramolecular oxygen-transfer



Scheme 1 Formation of pyrrolidin-3-ones through gold-catalyzed oxygen-atom transfer to alkynes.

Table 1 Optimization of reaction conditions[a]



Entry	L	Oxidant (R)	Acid	Yield[b] (%) 2a	3a
1	PPh_3	**4a** (2-Br)	1.1 equiv. MsOH	37	<2
2	PPh_3	**4b** (3,5-Cl_2)	1.1 equiv. MsOH	28	8
3	PPh_3	**4c** (2,6-Br_2)	1.1 equiv. MsOH	32	15
4	PPh_3	**4d** (3-Cl)	1.1 equiv. MsOH	39	12
5	PPh_3	**5**[d]	1.1 equiv. MsOH	35	<5
6	XPhos	**4a** (2-Br)	1.1 equiv. MsOH	50	<2
7	Cy-JohnPhos	**4a** (2-Br)	1.1 equiv. MsOH	34	<2
8	BrettPhos	**4a** (2-Br)	1.1 equiv. MsOH	43	<2
9	$(4\text{-}CF_3C_6H_4)_3P$	**4a** (2-Br)	1.1 equiv. MsOH	26	<2
10	**Et_3P**	**4a (2-Br)**	**1.1 equiv. MsOH**	**72**	**<2**
11	IPr	**4a** (2-Br)	1.1 equiv. MsOH	42	<2
12	Mor-DalPhos	**4a** (2-Br)	1.1 equiv. MsOH	65	<2
13	Au(III)[c]	**4a** (2-Br)	1.1 equiv. MsOH	20	<2
14	Et_3P	**4a** (2-Br)	0.5 equiv. MsOH	48	<2
15	Et_3P	**4a** (2-Br)	/	43	<2
16	Et_3P	**4a** (2-Br)	1.8 equiv. MsOH	55	<2
17	Et_3P	**4a** (2-Br)	1.1 equiv. CF_3CO_2H	69	<2
18	Et_3P	**4a** (2-Br)	1.1 equiv. $HNTf_2$	36	<2

[a] Reaction conditions: [**1a**] = 0.05 M; DCE: 1,2-dichloroethane. [b] Estimated by ^1H NMR using diethyl phthalate as an internal reference. [c] Dichloro(2-picolinato)gold(III). [d] 8-methylquinoline 1-oxide.

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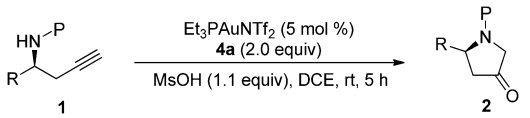
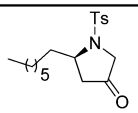
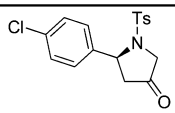
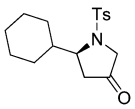
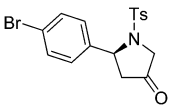
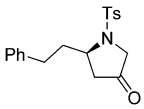
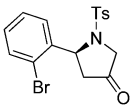
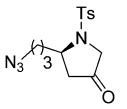
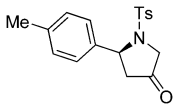
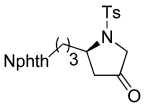
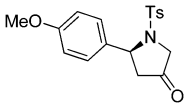
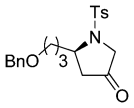
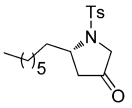
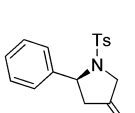
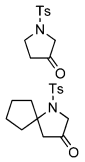
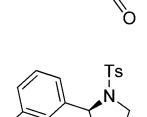
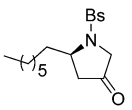
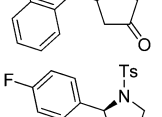
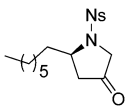
redox cyclization (Scheme 1).[9] In our recent study toward gold-catalyzed 5-*endo*-dig cyclization of terminal alkynes, we reported gold-catalyzed tandem cycloisomerization–oxidation and tandem cycloisomerization–dimerization from readily available chiral homopropargyl sulfonamides, leading to the efficient formation of enantioenriched γ-lactams and pyrrolidines, respectively.[10] Inspired by these results, we envisioned that enantioenriched pyrrolidin-3-ones might be accessed directly from chiral homopropargyl sulfonamides through a gold-catalyzed intermolecular oxygen-transfer redox cyclization, providing a flexible and alternative way for the preparation of versatile pyrrolidin-3-one derivatives (Scheme 1). In this communication, we describe herein the realization of such a gold-catalyzed intermolecular alkyne oxidation, affording chiral pyrrolidin-3-ones in moderate to good yields and excellent enantioselectivities by successful combination of the chiral *tert*-butylsulfinimine chemistry with gold catalysis. The synthetic utility of this protocol was demonstrated by the enantioselective total synthesis of natural product (−)-irniine.

Our initial investigation focused on the reaction of homopropargyl sulfonamide substrate **1a** with pyridine *N*-oxide **4** in DCE at room temperature in the presence of a gold(I) complex (5 mol%). To our delight, the desired pyrrolidin-3-one **2a** was indeed formed under the optimal conditions established by Zhang for propargylic alcohol substrates (Table 1, entry 1).[6h] However, the yield of this reaction was only 37%, indicating that the sulfonamide here behaved very differently from its

Table 2 Reaction scope for the formation of enantioenriched pyrrolidin-3-ones[a]



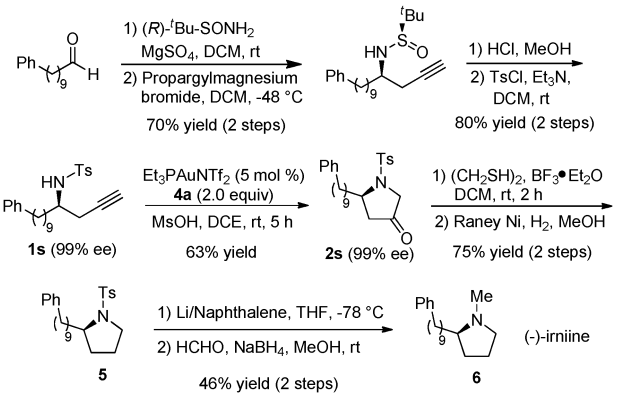
Entry	Product	2	Yield ee (%)	Entry	Product	2	Yield ee (%)
1		**2a**	69 99	10		**2j**	61 99
2		**2b**	52 99	11		**2k**	57 99
3		**2c**	62 99	12		**2l**	63 98
4		**2d**	67 99	13		**2m**	61 99
5		**2e**	70 99	14		**2n**	60 99
6		**2f**	60 99	15[b]		**2a′**	63 99
7		**2g**	60 99	16		**2o** **2p**	70 55
8		**2h**	63 99	17		**2q**	70 99
9		**2i**	62 99	18		**2r**	65 99

[a] Reactions run in vials; [**1**] = 0.05 M; isolated yields are reported; ees are determined using HPLC on a chiral stationary phase. [b] Using (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl amide **1a′** as the substrate.

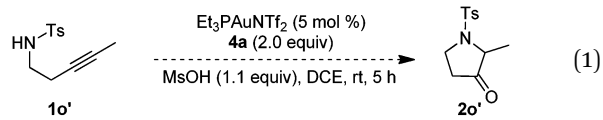
alcohol counterpart. Varying the oxidants did not improve the reaction (Table 1, entries 2–5). Here, it should be mentioned that a significant amount of dimer **3a** was formed through gold-catalyzed tandem cycloisomerization–dimerization in some cases.[10a] Correlated with our previously reported gold-catalyzed tandem cycloisomerization–oxidation reaction,[10b] we speculate that the differential reactivity of the starting materials mainly depends on the nucleophilicity of the oxidants. More nucleophilic oxidants such as pyridine *N*-oxides here would attack the gold-activated alkynes directly to deliver the α-oxo gold carbenoids, which finally led to the formation of 3-pyrrolidones. However, in the presence of less nucleophilic oxidants such as *m*-CPBA, the reaction would proceed through a gold-catalyzed cycloisomerization and subsequent oxidation, while a tandem cycloisomerization–dimerization occurred in the absence of the oxidant. Screening of different gold catalysts (Table 1, entries 6–13) revealed that $Et_3PAuNTf_2$ was best suited for this reaction (Table 1, entry 10), followed by Mor-DalPhosAuNTf$_2$ (Table 1, entry 12).[6a,b] In addition, the effect of acid was also investigated and it was found that the use of other acids failed to improve the yield (Table 1, entries 14–18). Notably, no pyrrolidin-3-one was observed under acidic conditions in the absence of the gold catalyst, and $PtCl_2$ was not effective in promoting this reaction.

The chiral homopropargyl sulfonamide substrates were then prepared with excellent enantiomeric excesses according to Ellman's *tert*-butylsulfinimine chemistry.[11] With these substrates in hand, we then probed the generality of the current reaction. As shown in Table 2, homopropargyl sulfonamides **1** could undergo smooth cyclization to produce the corresponding pyrrolidin-3-ones **2** in moderate to good yields. Of note, a range of functional groups were well tolerated during the cyclization reaction, including phenyl (Table 2, entry 3), azido (Table 2, entry 4), protected amino (Table 2, entry 5), and hydroxy (Table 2, entry 6). Importantly, excellent enantioselectivities could be achieved in all cases and essentially no epimerization was observed, constituting a good combination of chiral *tert*-butylsulfinimine chemistry with gold catalysis. In addition, the use of (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl sulfonamide **1a′** also furnished the corresponding pyrrolidin-3-one **2a′** with the opposite enantioselectivity (Table 2, entry 15). Thus, this protocol allows a rapid and practical access to both enantiomers of pyrrolidin-3-one **2** just by the choice of the starting chiral source. This chemistry can also be extended to the preparation of parent pyrrolidin-3-one **2o** and 5,5-disubstituted pyrrolidin-3-one **2p** in fairly good yields (70% and 55% isolated yields, Table 2, entry 16). Besides the tosyl group, it was found that the reaction could proceed well for Bs and Ns protected substrates **1q–1r**, resulting in good yields of the desired products **2q–2r** (70% and 65% isolated yields, Table 2, entries 17 and 18) with excellent ees, providing an easier way for its later removal.

As shown in eqn (1), attempts to expand this chemistry to internal alkynes were not successful presumably due to the competing gold-catalyzed hydration reaction and 1,2-C–H insertion *via* an α-oxo gold carbene intermediate.[6f,8k] Notably, no migration of the sulfonyl group was observed in this case, as previously described in Shin's Chemistry.[9]



Scheme 2 Enantioselective total synthesis of (−)-irniine.



(1)

The significance of this methodology is additionally demonstrated by its application to the enantioselective total synthesis of (−)-irniine (Scheme 2).[12] Chiral homopropargyl sulfonamide substrate **1s** was prepared from 10-phenyldecanal in a four-step process according to our well-established sequence. Then, the treatment of substrate **1s** under the previously optimized reaction conditions allowed the formation of pyrrolidin-3-one **2s** in 63% yield with excellent enantioselectivity. The removal of the carbonyl group, followed by replacement of the tosyl group with the methyl group, furnished the final (−)-irniine **6**. Thus, the preparation of (−)-irniine was accomplished in 9 steps from readily available 10-phenyldecanal in 12.2% overall yield. Importantly, this protocol represents a new access to versatile optically active *N*-methyl pyrrolidine derivatives,[13] and nicely complements the method we have developed very recently.[10b]

In summary, we have developed a gold-catalyzed intermolecular oxidation of chiral homopropargyl sulfonamides, allowing the convenient synthesis of optically active pyrrolidin-3-ones in combination with chiral *tert*-butylsulfinimine chemistry. With this newly established methodology, the enantioselective total synthesis of natural product (−)-irniine could be easily achieved in a highly efficient and concise manner. Further investigations into the synthetic applications of the current protocol are in progress in our laboratory.

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Notes and references

1 (*a*) T. Kawakami, T. Ishizawa and H. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 12297; (*b*) D. Siegel, S. Merkel, W. Bremser, M. Koch and I. Nehls, *Anal. Bioanal. Chem.*, 2010, **397**, 453; (*c*) X. Liu and C. T. Walsh, *Biochemistry*, 2009, **48**, 11032; (*d*) S. Collina, D. Rossi, G. Loddo, A. Barbieri, E. Lanza, L. Linati, S. Alcaro, A. Gallelli and O. Azzolinaa, *Bioorg. Med. Chem.*, 2005, **13**, 3117; (*e*) H. Poschenrieder,

H.-D. Stachel, G. Höfner and P. Mayer, *Eur. J. Med. Chem.*, 2005, **40**, 391; (*f*) M. Bouygues, M. Medou, G. Quéléver, J. C. Chermann, M. Camplo and J. L. Kraus, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 277.

2 (*a*) D. J. Rawson, D. Brugier, A. Harrison, J. Hough, J. Newman, J. Otterburn, G. N. Maw, J. Price, L. R. Thompson, P. Turnpenny and A. N. Warren, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3771; (*b*) F. A. Davis, J. Zhang and Y. Wu, *Tetrahedron Lett.*, 2011, **52**, 2054; (*c*) K. C. Nicolaou, A. Krasovskiy, U. Majumder, V. É. Trépanier and D. Y.-K. Chen, *J. Am. Chem. Soc.*, 2009, **131**, 3690; (*d*) S. Gupta and C. E. Schafmeister, *J. Org. Chem.*, 2009, **74**, 3652; (*e*) P.-Q. Huang, T.-J. Wu and Y.-P. Ruan, *Org. Lett.*, 2003, **5**, 4341; (*f*) T. Gallagher, M. Giles, R. S. Subramanian and M. S. Hadley, *J. Chem. Soc., Chem. Commun.*, 1992, 166.

3 For recent examples, see: (*a*) G. Frey, H.-T. Luu, P. Bichovski, M. Feurer and J. Streuff, *Angew. Chem., Int. Ed.*, 2013, **52**, 7131; (*b*) O. K. Karjalainen, M. Nieger and A. M. P. Koskinen, *Angew. Chem., Int. Ed.*, 2013, **52**, 2551; (*c*) T. Maegawa, K. Otake, K. Hirosawa, A. Goto and H. Fujioka, *Org. Lett.*, 2012, **14**, 4798; (*d*) J.-M. Yang, Z. Zhang, Y. Wei and M. Shi, *Tetrahedron Lett.*, 2012, **53**, 6173; (*e*) V. D. Pinho and A. C. B. Burtoloso, *J. Org. Chem.*, 2011, **76**, 289; (*f*) J. Robertson, A. J. Tyrrell, P. T. Chovatia and S. Skerratt, *Tetrahedron Lett.*, 2009, **50**, 7141; (*g*) A. Alex, B. Larmanjat, J. Marrot, F. Couty and O. David, *Chem. Commun.*, 2007, 2500; (*h*) W. Van Brabandt, R. Van Landeghem and N. De Kimpe, *Org. Lett.*, 2006, **8**, 1105; (*i*) F. A. Davis, Y. Wu, H. Xu and J. Zhang, *Org. Lett.*, 2004, **6**, 4523; (*j*) S. Berlin, C. Ericsson and L. Engman, *J. Org. Chem.*, 2003, **68**, 8386.

4 (*a*) S. Cai, B. K. Gorityala, J. Ma, M. L. Leow and X.-W. Liu, *Org. Lett.*, 2011, **13**, 1072; (*b*) S. Kaden, M. Brockmann and H.-U. Reissig, *Helv. Chim. Acta*, 2005, **88**, 1826; (*c*) J. Courcambeck, F. Bihel, C. De Michelis, G. Quéléver and J. L. Kraus, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1421.

5 For a review, see: J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226.

6 For selected work done by the Zhang research group, see: (*a*) K. Ji, Y. Zhao and L. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 6508; (*b*) Y. Luo, K. Ji, Y. Li and L. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 17412; (*c*) Y. Wang, K. Ji, S. Lan and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 1915; (*d*) W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8482; (*e*) L. Ye, W. He and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 3236; (*f*) B. Lu, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 14070; (*g*) L. Ye, W. He and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 8550; (*h*) L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258.

7 For selected work done by the Liu research group, see: (*a*) S. K. Pawar, C.-D. Wang, S. Bhunia, A. M. Jadhav and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 7559; (*b*) S. Ghorpade, M.-D. Su and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4229; (*c*) R. K. Kawade and R.-S. Liu, *Org. Lett.*, 2013, **15**, 4094; (*d*) S. Bhunia, S. Ghorpade, D. B. Huple and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 2939; (*e*) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, 7200; (*f*) D. Vasu, H.-H. Hung, S. hunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911.

8 For other examples, see: (*a*) P. Nösel, L. N. dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *J. Am. Chem. Soc.*, 2013, **135**, 15662; (*b*) L. Wang, X. Xie and Y. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13302; (*c*) G. Henrion, T. E. J. Chava, X. Le Goff and F. Gagosz, *Angew. Chem., Int. Ed.*, 2013, **52**, 6277; (*d*) J. Fu, H. Shang, Z. Wang, L. Chang, W. Shao, Z. Yang and Y. Tang, *Angew. Chem., Int. Ed.*, 2013, **52**, 4198; (*e*) S. Shi, T. Wang, W. Yang, M. Rudolph and A. S. K. Hashmi, *Chem.–Eur. J.*, 2013, **19**, 6576; (*f*) K.-B. Wang, R.-Q. Ran, S.-D. Xiu and C.-Y. Li, *Org. Lett.*, 2013, **15**, 2374; (*g*) M. Xu, T.-T. Ren and C.-Y. Li, *Org. Lett.*, 2012, **14**, 4902; (*h*) A. S. K. Hashmi, T. Wang, S. Shi and M. Rudolph, *J. Org. Chem.*, 2012, **77**, 7761; (*i*) D. Qian and J. Zhang, *Chem. Commun.*, 2012, **48**, 7082; (*j*) D. Qian and J. Zhang, *Chem. Commun.*, 2011, **47**, 11152; (*k*) P. W. Davies, A. Cremonesi and N. Martin, *Chem. Commun.*, 2011, **47**, 379.

9 H.-S. Yeom, E. So and S. Shin, *Chem.–Eur. J.*, 2011, **17**, 1764.

10 (*a*) Y.-F. Yu, C. Shu, C.-H. Shen, T.-Y. Li and L.-W. Ye, *Chem.–Asian J.*, 2013, **8**, 2920; (*b*) C. Shu, M.-Q. Liu, S.-S. Wang, L. Li and L.-W. Ye, *J. Org. Chem.*, 2013, **78**, 3292; (*c*) C. Shu, M.-Q. Liu, Y.-Z. Sun and L.-W. Ye, *Org. Lett.*, 2012, **14**, 4958.

11 (*a*) M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600; (*b*) J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984.

12 For enantioselective synthesis of (−)-irniine, see: (*a*) H. Takahata, K. Ihara, M. Kubota and T. Momose, *Heterocycles*, 1997, **46**, 349; (*b*) A. Jossang, A. Melhaoui and B. Bodo, *Heterocycles*, 1996, **43**, 755.

13 For recent selected natural products of the optically active *N*-methyl 2-alkylpyrrolidine alkaloids, see: (*a*) K.-J. Xiao, Y. Wang, K.-Y. Ye and P.-Q. Huang, *Chem.–Eur. J.*, 2010, **16**, 12792; (*b*) M. Jordan, M. Humam, S. Bieri, P. Christen, E. Poblete and O. Muñoz, *Phytochemistry*, 2006, **67**, 570; (*c*) C. J. Dunsmore, R. Carr, T. Fleming and N. J. Turner, *J. Am. Chem. Soc.*, 2006, **128**, 2224; (*d*) G. Ferretti, M. Dukat, M. Giannella, A. Piergentili, M. Pigini, W. Quaglia, M. I. Damaj, B. R. Martin and R. A. Glennon, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 733; (*e*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.