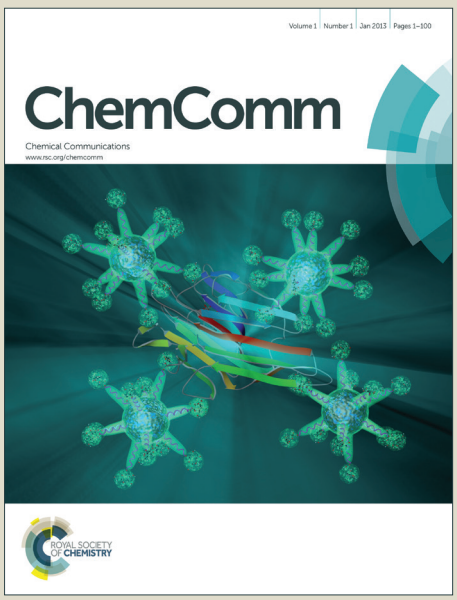
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/chemcomm

ARTICLE TYPE

Gold-Catalyzed Intermolecular Oxidation of Chiral Homopropargyl Sulfonamides: A Reliable Access to Enantioenriched Pyrrolidin-3-ones

Chao Shu, Long Li, Yong-Fei Yu, Shuang Jiang and Long-Wu Ye*

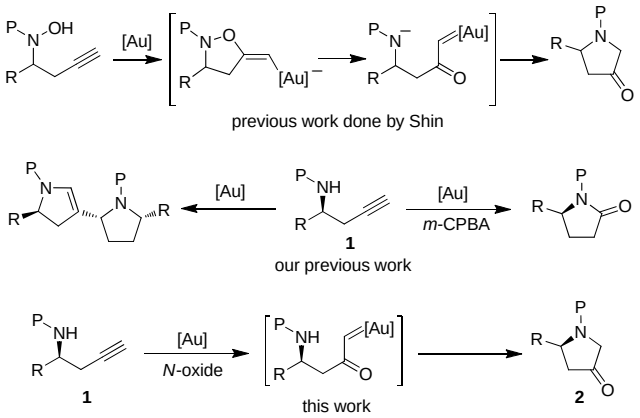
Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

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, broad substrate scope, a simple procedure and 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 have been 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 redox cyclization (Scheme 1).[9] In our recent study toward gold-catalyzed 5-endo-dig cyclization of teminal alkyne, 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 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.

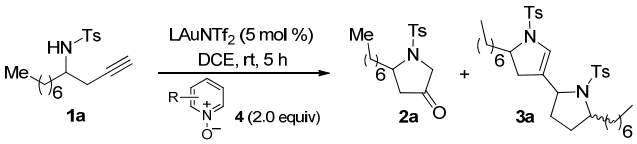


Scheme 1 Formation of pyrrolidin-3-ones through gold-catalyzed oxygen-atom transfer to alkynes.

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 disired pyrrolidin-3-one **2a** was indeed formed under the optimal conditions established by Zhang for propargylic alcohol substrates (Table 1, entry 1).[6j] However, the yield of this reaction was only 37%, indicating that the sulfonamide here behaved very differently from its alcohol counterpart. Varying the oxidants could 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 differential reactivity of the starting materials mainly depends on the nucleophilicity of the oxidants. With more nucleophilic oxidants such as pyridine *N*-oxides as the oxidants, the oxidants 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).[6b-6c] In addition, the effect of acid was also investigated and it was found that the use of other acid 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.

Table 1 Reaction conditions optimization[a]

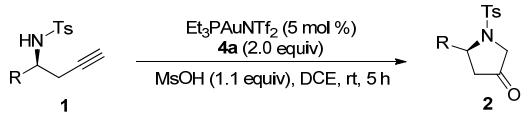


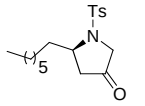
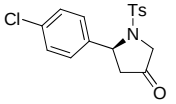
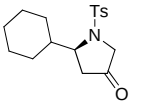
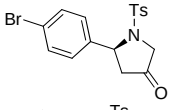
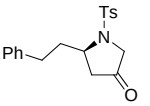
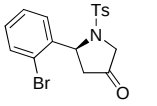
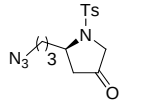
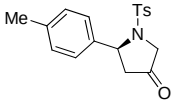
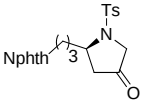
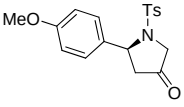
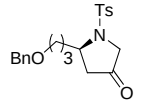
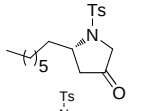
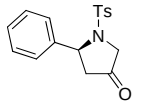
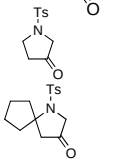
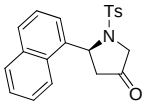
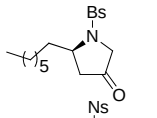
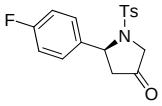
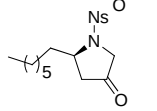
Entry	L	Oxidant (R)	Acid	Yield (%)[b]	
				2a	**3a**
1	PPh_3	**4a** (2-Br)	1.1 equiv MsOH	37	<2
2	PPh_3	**4b** (3,5-Cl_2)	1.1 equiv MsOH	28	8
3	PPh_3	**4c** (2,6-Br_2)	1.1 equiv MsOH	32	15
4	PPh_3	**4d** (3-Cl)	1.1 equiv MsOH	39	12
5	PPh_3	**5**	1.1 equiv MsOH	35	<5
6	XPhos	**4a** (2-Br)	1.1 equiv MsOH	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 ^{1}H NMR using diethyl phthalate as internal reference. [c] Dichloro(2-picolinato)gold(III).

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

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



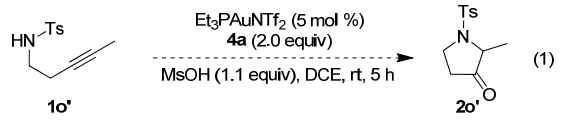
Entry	Product	2	Yield Ee	Entry	Product	2	Yield Ee
1		**2a**	69% 99%	10		**2j**	61% 99%
2		**2b**	52% 99%	11		**2k**	57% 99%
3		**2c**	62% 99%	12		**2l**	63% 98%
4		**2d**	67% 99%	13		**2m**	61% 99%
5		**2e**	70% 99%	14		**2n**	60% 99%
6		**2f**	60% 99%	15[b]		**2a'**	63% 99%
7		**2g**	60% 99%	16		**2o** **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.

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 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 17-18) with excellent ees, providing an easier way for its later removal.

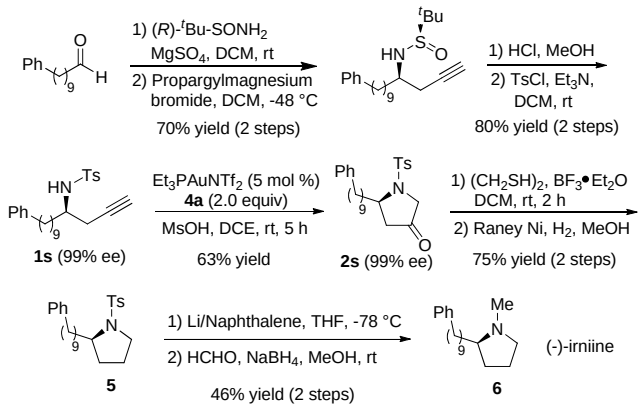
As shown in eq 1, attempts to expand this chemistry to internal

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]



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 previous optimized reaction conditions allowed the formation of pyrrolidin-3-one **2s** in 63% yield and excellent enantioselectivity. The removal of the carbonyl group, followed by replacement of tosyl group with 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.



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

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21102119 and 21272191), NFFTBS (No. J1310024) and PCSIRT.

Notes and references

State Key Laboratory for Physical Chemistry of Solid Surfaces, The Key Laboratory for Chemical Biology of Fujian Province and Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, 361005, Fujian, PR China. Fax: (+86) 592-218-5833; E-mail: longwuye@xmu.edu.cn

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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 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 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**, DOI: 10.1002/ange.201304700; (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, 7082; (j) D. Qian and J. Zhang, *Chem. Commun.,* 2011, 11152; (k) P. W. Davies, A. Cremonesi and N. Martin, *Chem. Commun.,* 2011, 379.

9 H.-S. Yeom, E. So, 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.

