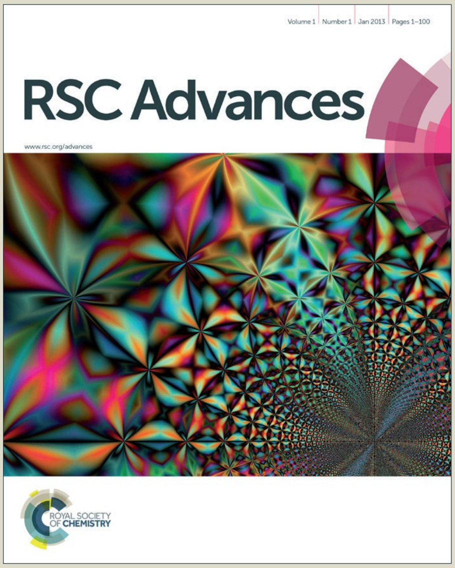
RSC Advances



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

One-pot synthesis of *α*-iodoketones from alcohols using ammonium iodide and Oxone® in water

Marri Mahender Reddy[a], Peraka Swamy[a,b], Mameda Naresh[a,b], Kodumuri Srujana[a], Chevella Durgaiah[a], Tumula Venkateshwar Rao[a] and Nama Narender[a,b]*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A novel protocol for the synthesis of *α*-iodoketones from alcohols has been developed. Using water as the reaction medium, ammonium iodide and Oxone® was proven to be efficient reagent system for this reaction and afforded the corresponding *α*-iodoketones in moderate to good yields. The generality of this reaction was demonstrated with various secondary alcohols such as benzylic alcohols and aliphatic alcohols (acyclic and cyclic).

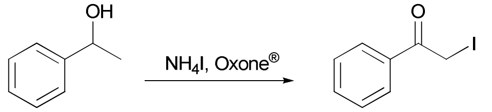
Strong efforts have been made in the field of green chemistry to accept methods that are step economic, produce fewer by-products and use less energy and less toxic chemicals.[1] In particular, the use of water as a solvent for organic synthesis has become popular and received substantial interest because water is a green and abundant natural resource which can be easily obtained.[2] Moreover, the tandem reactions have also become a powerful tool for performing several chemical reactions in only one operation often yielding products with significantly increased molecular complexity from simple starting materials.[3] The main advantages of tandem reactions are reduction of overall steps by avoiding isolation of often highly reactive intermediates, minimization of waste compared to stepwise reactions, the amount of solvents, reagents, adsorbents and energy can be dramatically decreased.

It is hard to envision organic chemistry without organo-halogen compounds because the halo-substituted organic compounds are widely used as intermediates in carbon-carbon, carbon-oxygen and carbon-nitrogen bond formation reaction. Moreover, iodinated compounds are generally used in medical diagnostics as contrast agents or radioactively-labelled markers.[4] *α*-Iodoketones are among the most versatile intermediates in organic synthesis and their high reactivity makes them prone to react with large number of nucleophiles to provide a variety of useful compounds.[5] As the iodine atom has poor electrophilic nature, the selective introduction of iodine into organic molecules has received significant attention among the scientific community.[6] Most of the known methods of preparing *α*-iodoketones proceed indirectly by oxidative iodination of olefins,[7] electrophilic iodination of ketone derivatives (enol ethers, and acetates)[8] or by halogen interchange of bromo compounds with sodium iodide.[9] Due to the difficulties in the synthesis and purification of enol silyl ethers and acetates, in recent years various modified reagents have been discovered for the synthesis of *α*-iodoketones from carbonyl compounds using different iodonium donating systems.[10-22] However, most of these methods have one or more drawbacks, such as use of expensive, hazardous or toxic reagents, tedious work-up procedures and high reaction temperatures. Therefore, the development of an efficient, environmentally friendly, atom economic (100% with respect to iodine) and selective procedure for the direct synthesis of *α*-iodoketones is still desirable.

Synthesis of *α*-iodoketones from alcohols instead of ketones in a single step is a challenging task. Recently, Barluenga et al. reported the *α*-iodoketones from alcohols under acidic condition[23]. However, main disadvantage of this method is the use of strong mineral acid. From the green chemical point of view there is a need to reduce the chemical waste and promote simple synthetic methods involving readily available, inexpensive and less toxic reactants to synthesize *α*-iodoketones selectively. To contribute to the development of an environmentally benign organic chemistry, we are focusing our research on the replacement of the volatile common organic reaction media with water (green solvent). As part of our ongoing research programme to develop 'greener' methods for halogenation,[24] earlier we have reported a method for the *α*-iodination of carbonyl compounds using NH_4I–Oxone® system[25] and to the best of our knowledge there are no reports for the synthesis of *α*-iodoketones from alcohols using NH_4I and Oxone®. Herein, we report a novel and environmentally benign procedure for the direct synthesis of *α*-iodoketones from alcohols using NH_4I and Oxone® in water without employing any catalyst.

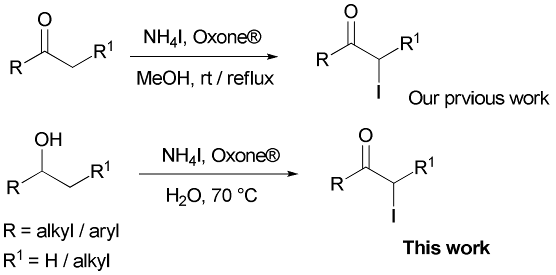
Initially, we investigated suitable reaction conditions for the synthesis of *α*-iodoketones using 1-phenylethanol as the model substrate with NH_4I-Oxone® reagent system and the results are described in Table 1. Several solvents (H_2O, CH_3OH, EtOH, *iso*-propanol, *tert*-butanol, acetone, CH_3CN, ethyl acetate, THF, $CHCl_3$, CH_2Cl_2, CCl_4 and hexane) were investigated and results revealed that the reaction proceeded only in polar protic solvents (Table 1). The best results were obtained when water was used as a solvent among others in terms of reaction yields and time (Table 1, entries 4-16). Next, we examined the temperature effect on this reaction, by varying the reaction temperature from RT to 70 °C a gradual improvement of reaction yield (23 to 72%) was observed (Table 1, entries 1-4). The above results showed that the optimum reaction conditions to get the highest yield for this reaction are 1-phenylethanol (1 mmol), NH_4I (1.1 mmol)

Table 1 Optimization of reaction conditions[a]



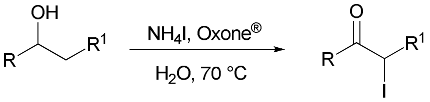
Entry	Solvent	Time (h)	Yield[b] (%)
1	H_2O	48[c]	23
2	H_2O	24[d]	35
3	H_2O	14[e]	41
4	H_2O	3.5[f]	72
5	CH_3OH	24[g]	20
6	EtOH	24[g]	-
7	*iso*-Propanol	24[g]	-
8	*tert*-Butanol	24[g]	-
9	Acetone	24[g]	-
10	CH_3CN	24[g]	-
11	AcOEt	24[g]	-
12	THF	24[g]	-
13	$CHCl_3$	24[g]	-
14	CH_2Cl_2	24[g]	-
15	CCl_4	24[g]	-
16	Hexane	24[g]	-

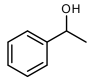
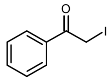
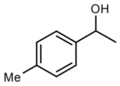
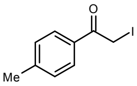
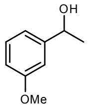
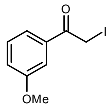
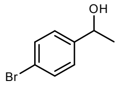
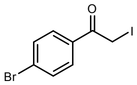
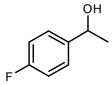
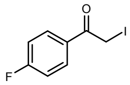
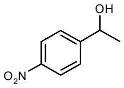
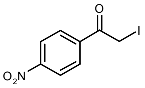
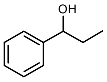
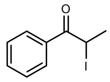
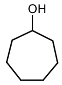
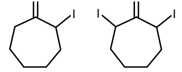
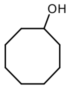
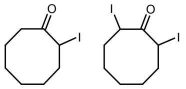
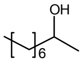
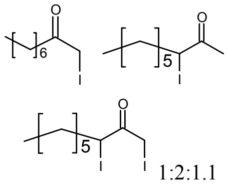
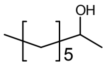
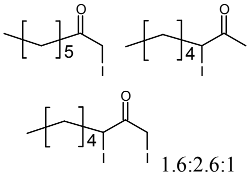
[a] Reaction conditions: substrate (2 mmol), NH_4I (2.2 mmol), Oxone® (2.2 mmol), Solvent (10 ml).[b] products were characterized by ^1H NMR, Mass spectra and quantified by GC. [c] RT. [d] 50 °C. [e] 60 °C. [f] 70 °C. [g] Reflux temperature.

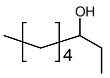
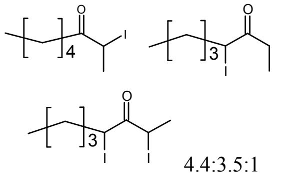
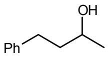
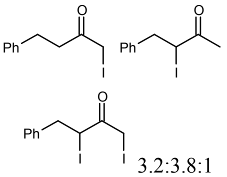


Scheme 1 Synthesis of α-iodoketones.

Table 2 Synthesis of α-iodoketones from alcohols[a]



Entry	Substrate	Time (h)	Product	Yield[b] (%)
1		3.5		72
2		24		10
3		6		-
4		20		40
5		9		25
6		24		15
7		1		66
8		24	 3.8:1	77
9		24	 3.2:1	72
10		24	 1:2:1.1	78
11		24	 1.6:2.6:1	79

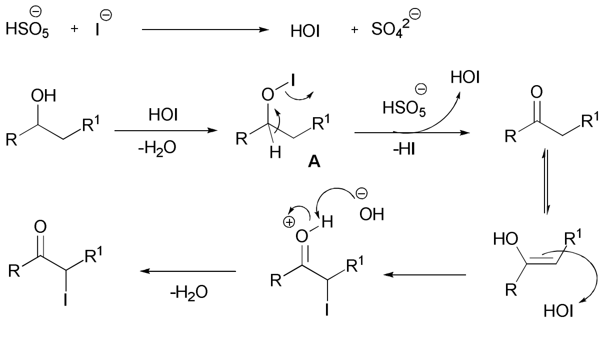
12		24	 4.4:3.5:1	89
13		24	 3.2:3.8:1	80

[a] Reaction conditions: substrate (2 mmol), NH_4I (2.2 mmol), Oxone® (2.2 mmol), Water (10 ml), 70 °C. [b] products were characterized by ^1H NMR, Mass spectra and quantified by GC.

and Oxone® (1.1 mmol) in water (10 ml) at 70 °C.

With the optimized conditions in hand, the scope and limitations of the method was explored (scheme 1) with a variety of secondary alcohols (benzylic and aliphatic secondary alcohols) and the results are summarized in Table 2. 1-Phenylethanol produced the corresponding *α*-iodoproduct in high yield (Table 2, entry 1). In order to determine the influence of substitution on aromatic ring of 1-phenylethanol on the reaction path with this reagent system, we studied the reaction with different substitutions (Table 2, entries 2-6). Moderately activating group present on aromatic ring of 1-phenylethanol i.e. 1-(4-methylphenyl)ethanol provided lower yield (10%) (Table 2, entry 2). Whereas, highly activated 1-phenylethanol i.e. 1-(3-methoxyphenyl)ethanol gave a complex mixture of unidentified products, which contained virtually no *α*-iodoproduct (Table 2, entry 3). Halo substituted 1-phenylethanols such as 1-(4-bromophenyl)ethanol and 1-(4-fluorophenyl)ethanol were gave the corresponding *α*-iodinated products in 40% and 25% yields, respectively (Table 2, entries 4 and 5). Highly deactivated 1-(4-nitrophenyl)ethanol also furnished lower yield of the corresponding product (Table 2, entry 6). Interestingly, 1-phenylpropanol showed good reactivity with this reagent system and yielded the corresponding *α*-iodoproduct in good yield (66%) within 1 h (Table 2, entry 7).

Further, we investigated the efficiency of this method with aliphatic alcohols. In case of cyclic alcohols such as, cycloheptanol and cyclooctanol were reacted under the similar conditions to afford corresponding *α*-iodoproducts in 61% and 55% yields, along with *α,α'*-diiodoproducts in 16% and 17% yields, respectively (Table 2, entries 8 and 9). Notably, the acyclic alcohols, such as 2-nonanol, 2-octanol and 3-octanol were rendered the mixture of *α*-iodinated products (two monoiodinated regiomers and *α,α'*-diiodoproducts) in > 77% yield (Table 2, entries 10-13). For example, 2-nonanol delivered the 1-iodo-2-nonanone, 3-iodo-2-nonanone and 1,3-diiodo-2-nonanone in 19%, 38% and 21% yields, respectively (Table 2, entry 10). 4-Phenyl-2-butanol was also provided the mixture of *α*-iodinated products in 80% yield (Table 2, entry 13).



Scheme 2 The probable reaction mechanism for the formation of *α*-iodoketones from alcohols.

In a blank experiment, no reaction occurred between acetophenone and NH_4I without Oxone® (oxidant) under similar reaction conditions. Thus the role played by the Oxone® is justified. In absence of NH_4I also we did not observe any reaction between Oxone® and alcohol. Based on the above experimental observations and literature reports[23, 25,26], we propose a probable reaction mechanism for the formation of α-iodoketones from alcohols is shown in Scheme 2. It is assumed that the $I^{\ominus}$(NH_4I) is oxidized with Oxone® to generate the $I^{\oplus}$(HOI) *in situ.* $I^{\oplus}$(HOI) plays multiple roles in this reaction. First, it acts as the oxidizing agent to convert alcohol into ketone via intermediate **A**. Then, Oxone® oxidizes the generated $I^{\ominus}$(NH_4I) to $I^{\oplus}$(HOI), which ($I^{\oplus}$(HOI)) acts as iodinating agent and further reacts with enol form of carbonyl compound to afford the corresponding α-iodinated product.

Conclusions

In conclusion, we have developed an efficient and green protocol for the synthesis of *α*-iodoketones directly from secondary alcohols using NH_4I and Oxone® without metal or mineral acid catalyst in aqueous media. Various secondary alcohols, such as benzylic alcohols and aliphatic alcohols (acyclic and cyclic) can be oxidized-iodinated by this reagent system under mild conditions and affording the corresponding *α*-iodoproducts in moderate to good yields. Remarkably, the process conducted in water (green solvent) and offers several advantages, such as commercial availability of the reagents, simple reaction conditions, high atom economy (100% with respect to iodine), good yields, easier setup/work-up procedures and environmentally friendly nature makes our method more valuable from preparative point of view.

Experimental section

General procedure for the synthesis of *α*-iodoketones: Oxone® (2.2 mmol) was slowly added to a well stirred solution of NH_4I (2.2 mmol) and alcohol (2 mmol) in water (10 ml) and the reaction mixture was allowed to stir at 70 °C. After disappearance of the alcohol (reaction was monitored by TLC) or after the appropriate time, the organic product mixture was extracted with DCM (3 x 25 mL). The organic layer was washed with 5% aqueous sodium thiosulfate solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel using n-hexane-ethyl acetate as eluent to give desired products. All the products were identified by their ^{1}H NMR, ^{13}C NMR and mass spectra.

Acknowledgements

We thank the CSIR Network project CSC-0125 for financial support. M.M.R., M.N. and Ch.D acknowledge the financial support from CSIR, India in the form of fellowships. P.S. and K.S. acknowledge the financial support from UGC, India in the form of fellowship.

Notes and references

[a] *I&PC Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: narendern33@yahoo.co.in; Fax: +91-40-27160387/27160757; Tel: +91-40-27191703*
[b] *Academy of Scientific and Innovative Research, India*

† Electronic Supplementary Information (ESI) available: characterization data and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

1 (a) P. Anastas, R. Kazlauskas and G. Sheldrake, *Green Chem.*, 2006, **8**, 677–678; (b) P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301–312.

2 (a) T. Maegawa, A. Akashi, K. Yaguchi, Y. Iwasaki, M. Shigetsura, Y. Monguchi and H. Sajiki, *Chem. Eur. J.*, 2009, **15**, 6953-6963; (b) K. Aplander, O. Hidestal, K. Katebzadeh and U. M. Lindstrom, *Green. Chem.*, 2006, **8**, 22–24; (c) C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82; (d) K. Kumaravel and G. Vasuki, Curr. *Org. Chem.*, 2009, **13**, 1820–1841; (e) N. Yan, C. Xiao and Y. Kou, *Coord. Chem. Rev.*, 2010, **254**, 1179-1218; (f) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302–6337.

3 (a) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1-21; (b) R. J. K. Taylor, M. Reid, J. Foot and S. A. Raw, *Acc. Chem. Res.*, 2005, **38**, 851-869; (c) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134-7186; (d) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115-136; (e) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed.*, 1993, **32**, 131-163; (f) E. Fernandez, A. Polo, A. Ruiz, C. Clavera and S. Castillon, *Chem. Commun.*, 1998, 1803-1804; (g) M. Arun Kumar, P. Swamy, M. Naresh, M. Mahender Reddy, C. N. Rohitha, S. Prabhakar, A. V. S. Sarma, J. R. Prem Kumar and N. Narender, *Chem. Commun.*, 2013, **49**, 1711-1713; (h) M. Mahender Reddy, M. Arun Kumar, P. Swamy, M. Naresh, K. Srujana, L. Satyanarayana, A. Venugopal and N. Narender, *Green Chem.*, 2013, **15**, 3474–3483.

4 (a) F. Bellina, A. Carpita, R. Rossi, *Synthesis*, 2004, 2419–2440; (b) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1470; (c) M. J. Welch, C. S. Redvanly, *Hand book of Radiopharmaceuticals, Radiochemistry and Applications*, Wiley, Chichester, 2003; (d) M. Sovak, *In Radiocontract Agents, Handbook of Experimental Pharmacology*, Springer, Berlin, 1993, 73.

5 A. W. Erian, S. M. Sherif and H. M. Gaber, *Molecules*, 2003, **8**, 793–865.

6 (a) Y. Sasson, *Formation of Carbon–Halogen Bonds (Cl, Br, I). In The Chemistry of Functional Groups,* Supplement D2, The Chemistry of Halides, Pseudo Halides and Azides, Part 2, Ed., S. Patai and Z. Rappoport, Wiley, Chichester, 1995 p. 535–620; (b) J. Barluenga, *Pure Appl. Chem.*, 1999, **71**, 431–436.

7 (a) R. D. Ascoli, M. D. Auria, L. Nucciarelli, G. Piancatelli and A. Seettri, *Tetrahedron Lett.*, 1980, **21**, 4521–4522; (b) G. Cardillo and M. Shimizu, *J. Org. Chem.*, 1977, **42**, 4268–4270; (c) R. D. Evans and J. H. Schauble, *Synthesis*, 1986, 727–730.

8 (a) R. C. Cambie, R. C. Hayward, J. L. Jurlina, P. S. Rutledge and P. D. Woodgate, *J. Chem. Soc., Perkin Trans.*, 1978, **1**, 126–130; (b) C. Djerassi, C. J. Grossman, G. A. Thomas, *J. Am. Chem. Soc.*, 1955, **77**, 3826–3829; (c) G. M. Rubottom, R. C. Mott, *J. Org. Chem.*, 1979, **44**, 1731–1734; (d) A. D. Cort, *J. Org. Chem.*, 1991, **56**, 6708–6709; (e) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, 1953, **75**, 3493–3495.

9 (a) Y. D. Vankar and G. Kumaravel, *Tetrahedron Lett.*, 1984, **25**, 233–236; (b) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *J. Am. Chem. Soc.*, 1950, **72**, 4077–4080.

10 M. S. Yusubov, R. Y. Yusubova, T. V. Funk, K.-W. Chi, A. Kirschning and V. V. Zhdankin, *Synthesis*, 2010, 3681–3685.

11 J. Iskra, S. Stavber and M. Zupan, *Tetrahedron Lett.*, 2008, **49**, 893–895.

12 G. Stavber, J. Iskra, M. Zupan and S. Stavber, *Adv. Synth. Catal.*, 2008, **350**, 2921–2929.

13 I. Pravst, M. Zupan and S. Stavber, *Tetrahedron*, 2008, **64**, 5191–5199.

14 J. S. Yadav, G. Kondaji, M. S. R. Reddy and P. Srihari, *Tetrahedron Lett.*, 2008, **49**, 3810–3813.

15 H. M. Meshram, P. N. Reddy, P. Vishnu, K. Sadashiv and J. S. Yadav, *Tetrahedron Lett.*, 2006, **47**, 991–995.

16 G. Yin, M. Gao, N. She, S. Hu, A. Wu and Y. Pan, *Synthesis*, 2007, 3113–3116.

17 J. Pavlinac, M. Zupan and S. Stavber, *Org. Biomol. Chem.*, 2007, **5**, 699–707.

18 M. L. N. Rao and D. N. Jadhav, *Tetrahedron Lett.*, 2006, **47**, 6883–6886.

19 M. A. Khalilzadeh, A. Hosseini, M. Shokrollahzadheh, M. R. Halvagar, D. Ahmadi, F. Mohannazadeh and M. Tajbakhsh, *Tetrahedron Lett.*, 2006, **47**, 3525–3528.

20 J. C. Lee, J. Y. Park, S. Y. Yoon, Y. H. Bae and S. J. Lee, *Tetrahedron Lett.*, 2004, **45**, 191–193.

21 S. Stavber, M. Jereb and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 2002, 488–489.

22 D. Yang, Y. L. Yan and B. Lui, *J. Org. Chem.*, 2002, **67**, 7429–7431.

23 J. Barluenga, M. Marco-Arias, F. Gonzalez-Bobes, A. Ballesteros and J. M. Gonzalez, *Chem. Commun.*, 2004, 2616–2617.

24 (a) K. V. V. Krishna Mohan and N. Narender, *Synthesis*, 2012, 15–26; (b) M. Arun Kumar, C. N. Rohitha, M. Mahender Reddy, P. Swamy and N. Narender, *Tetrahedron Lett.,* 2012, **53**, 191–195; (c) P. Swamy, M. Arun Kumar, M. Mahender Reddy and N. Narender, *Chem. Lett.,* 2012, **41**, 432-434; (d) M. Arun Kumar, C. N. Rohitha and N. Narender, *Tetrahedron Lett.,* 2012, **53**, 1401-1405; (e) M. Arun Kumar, M. Naresh, C. N. Rohitha and N. Narender, *Synth. Commun.,* 2013, **43**, 3121–3129; (f) M. Naresh, M. Arun Kumar, M. Mahender Reddy, P. Swamy, N. Jagadeesh Babu and N. Narender, *Synthesis*, 2013, 1497–1504; (g) M. Naresh, P. Swamy, M. Arun Kumar, M. Mahender Reddy, K. Srujana and N. Narender, *Tetrahedron Lett*., 2014, **55,** 3926–3933.

25 M. Mahender Reddy, M. Arun Kumar, P. Swamy and N. Narender, *Tetrahedron Lett.*, 2011, **52,** 6554-6559.

26 (a) R. E. Montgomery, *J. Am. Chem. Soc.*, 1974, **96**, 7820-7821; (b) H. W. You and K.-J. Lee, *Synlett*, 2001, 105–107.