CHEMISTRY
A EUROPEAN JOURNAL

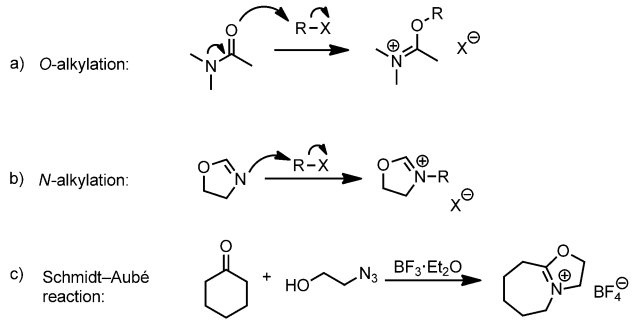
ChemPubSoc
Europe

DOI: 10.1002/chem.201203293

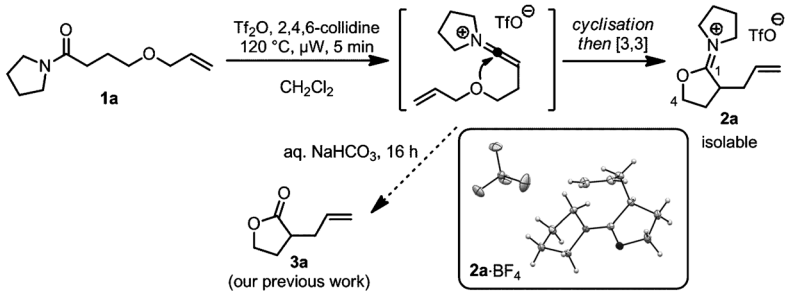
Dual Nucleophilic/Electrophilic Capture of In Situ Generated Iminium Ethers: Towards the Synthesis of Functionalized Amide Building Blocks

Bo Peng, Daniel H. O'Donovan, Igor D. Jurberg, and Nuno Maulide*[a]

Iminium ethers (or oxazacarbenium ions) are desirable reactive intermediates due to their ambident electrophilicity and ability to react with a wide range of nucleophiles.[1] These species are ideally suited to applications that require the rapid generation of structural diversity because a single iminium ether can potentially give rise to a large variety of different products. Iminium ethers have also been used for the preparation of natural products and bioactive molecules.[2] However, their synthetic utility has been limited by the relatively small range of useful methods for their generation. Common procedures rely on the inter- or intramolecular *O*-alkylation of amides by using strong electrophiles (Scheme 1 a),[3] the *N*-alkylation of oxazolines (Scheme 1 b),[4] and more recently, Aubé's procedure for preparing iminium ethers through the Schmidt reaction of ketones with 2-azidoethanol (Scheme 1 c).[5] Many of these methods are limited to a narrow range of substrates and therefore new and more flexible approaches for the generation of iminium ethers remain highly desirable.



Scheme 1. Traditional strategies for the preparation of iminium ethers.

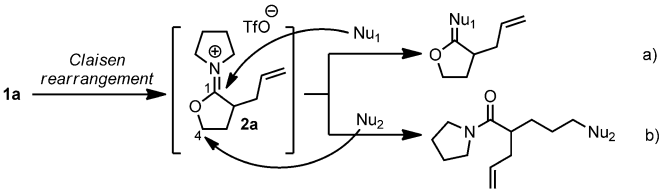


Scheme 2. Formation of the iminium ether **2a** by the Claisen rearrangement of amide **1a**.

Our group has recently described the domino Claisen rearrangement of ω-allyloxy, -propargyloxy and -benzyloxy amides through the corresponding keteniminium salts for the synthesis of α-substituted lactones in the presence of triflic anhydride (Tf_2O) and 2,4,6-collidine.[6] During recent investigations, we were surprised to observe that iminium ether **2a** could be isolated from this reaction in pure form by omitting the final hydrolysis step (Scheme 2). Mechanistically, the formation of **2a** can be explained by an intramolecular cyclization onto the transient keteniminium salt followed by a [3,3] Claisen rearrangement. After purification and counter-ion exchange we were able to unambiguously confirm the structure of iminium ether **2a** by X-ray crystallography.

Encouraged by the isolation of **2a**, we sought to develop this reaction as a novel method for the generation of α-allyl iminium ethers and to exploit their unique reactivity to facilitate the conversion of linear amides such as **1a** into branched, highly functionalized products in a single operation (Scheme 3).

In line with the ambident electrophilicity of iminium ethers, we envisaged that "hard" (non-stabilized) nucleo-



Scheme 3. The generation and reaction of iminium ethers to afford α-allylated products.

[a] Dr. B. Peng, Dr. D. H. O'Donovan,[+] Dr. I. D. Jurberg,[+]
Dr. N. Maulide
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 2083062999
E-mail: maulide@mpi-muelheim.mpg.de

[+] These authors contributed equally to this work.

philes would react with the central sp^2 oxazacarbenium atom C1 under ionic control (Nu_1, Scheme 3 a), whereas "softer" or more hindered nucleophiles might react at C4, accompanied by ring opening and cleavage of the O–C4 bond (Nu_2, Scheme 3 b). Herein, we report the development of a one-pot procedure for the generation of iminium ethers via the Claisen rearrangement of amides and their subsequent reaction with a diverse range of nucleophiles.

Amides **1a**, **1b**, and **1c** were subjected to the Claisen rearrangement by using conditions previously reported by our group.[6] In a one-pot procedure, the crude iminium ether was then reacted in situ with the appropriate nucleophilic reagent (Table 1).

This sequence could be used for the preparation of a broad range of products, including α-allyl lactones **3**, β-allyl-α,ω-amino alcohols **4**, and α-allyl amide derivatives **5**–**10**. Both classes of nucleophiles (Nu_1 and Nu_2, Scheme 3) reacted with linear amides **1a** and **1b**, whereas the branched substrate **1c** could only be successfully united with the first class of nucleophiles (Nu_1, H_2O, and $NaBH_4$), presumably due to the added steric hindrance at C4.

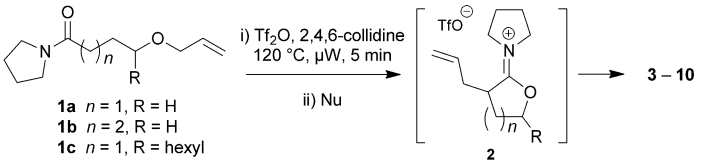
The reduction product **4c** was generated with a diastereoisomeric ratio (d.r.) of >9:1, whereas the corresponding lactone **3c** was formed with a slighlty lower d.r. of 5:1. It is likely that the mildly basic hydrolytic conditions used to prepare **3c** facilitate epimerization of the intermediate iminium ether.

Notably, different reactions required some modification of conditions, with solvent effects proving to be particularly important. Acetonitrile was usually superior for reactions the involving six-membered iminium ether **2b**, which we ascribe to the improved rate of nucleophilic substitution (versus degradation) of intermediate **2b** in a polar aprotic solvent. Similarly, the yields of reactions involving the five-membered iminium ether **2a** were usually higher than those involving **2b**. This is likely due to the fact that the latter six-membered species proved less stable than its homologue under most conditions.

By an appropriate choice of nucleophile, this sequence can be used to generate new C–S (using NaSPh), C–N (NaN_3, aliphatic amines) and even C–C bonds (NaCN). NaN_3 proved to be a particularly effective nucleophile; its reactions proceeded at room temperature whereas all other nucleophiles targeting the C4 position (Nu_2, Scheme 3) required microwave irradiation. We observed that increasing the amount of NaN_3 employed from 1.1 to 2.0 equivalents generally led to the formation of deallylated products, possibly via S_N2' nucleophilic attack by the azide anion on the allyl chain of the iminium ether. Reactions involving triphenylphosphine (Table 1, entry 4) are also noteworthy, as this nucleophile has not been previously reported to react with iminium ethers. The products if these reactions are particularly interesting as they provide structurally elaborate precursors ripe for subsequent Wittig reactions.

We then proceeded to examine the reaction of diastereomeric iminium ether **2d** with the same series of nucleophiles (Scheme 4). Our previous studies[6] showed that lactone **3d**

Table 1. Iminium ether generation and subsequent nucleophilic capture to form amides **3**–**10**.

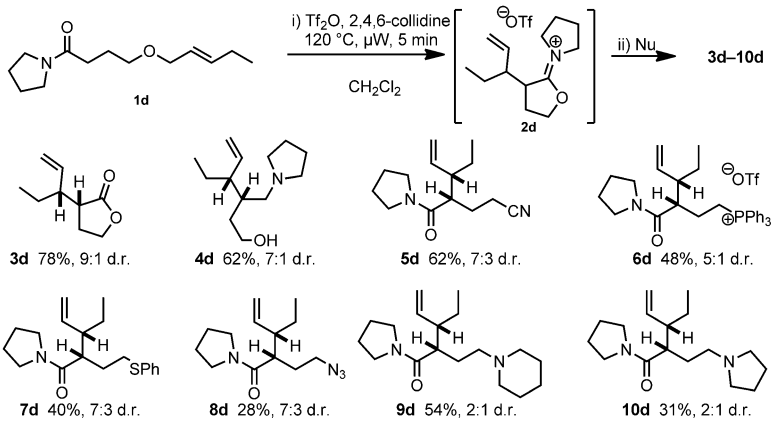


1a *n* = 1, R = H
1b *n* = 2, R = H
1c *n* = 1, R = hexyl

2

Entry	Nu (conditions)	Product, yield [%] (d.r.)
1	H_2O (aq. $NaHCO_3$, RT, 16 h)	**3a**, 90[a] **3b**, 57[a] **3c**, 71 (5:1)[a]
2	$NaBH_4$ (MeOH, RT, 16 h)	**4a**, 72[b] **4b**, 41[b] **4c**, 73 (>9:1)[b]
3	NaCN (120 °C, μW, 5 min)	**5a**, 62[c] **5b**, 82[d]
4	PPh_3 (120 °C, μW, 1 h)	**6a**, 58[e] **6b**, 40[d]
5	NaSPh (120 °C, μW, 5 min)	**7a**, 72[c] **7b**, 85[d]
6	NaN_3 (RT, 24 h)	**8a**, 56[c] **8b**, 42[d]
7		**9a**, 73[e]
	(120 °C, μW, 5 min)	**9b**, 47[d]
8		**10a**, 47[e]
	(120 °C, μW, 5 min)	**10b**, 46[d]

[a] i) CH_2Cl_2, ii) biphasic mixture of CH_2Cl_2/aq. $NaHCO_3$ (1:1). [b] i) CH_2Cl_2, ii) MeOH. [c] i) CH_2Cl_2, ii) DMF. [d] i) and ii) MeCN. [e] i) and ii) CH_2Cl_2.



Scheme 4. Reactions of the diastereo-enriched iminium ether **2d**.

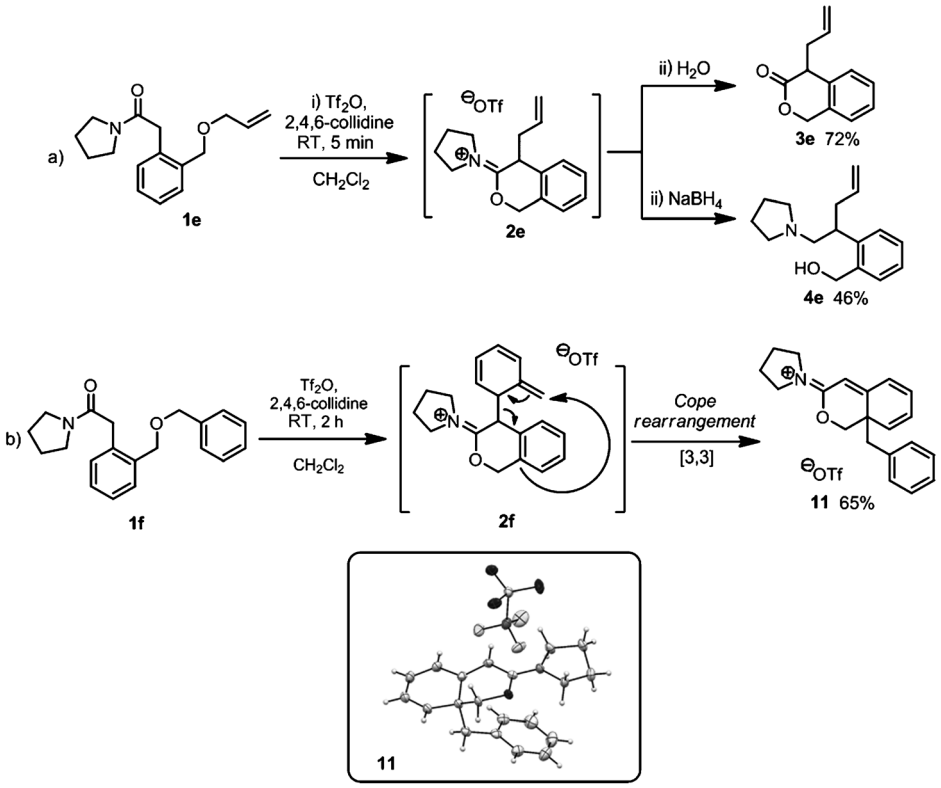
was generated with a diastereomeric ratio of 9:1 following hydrolysis of **2d** with bicarbonate solution. Although switching to nucleophiles other than water generally provided a lower degree of diastereomeric enrichment, the d.r. remained relatively high in the case of poorly basic nucleophiles such as triphenylphosphine (5:1) and sodium borohydride (7:1). However, nucleophiles necessitating longer reaction times or more basic nucleophiles such as piperidine generally led to reduction of the d.r., likely due to epimerization of the intermediate iminium ether.

A further substrate class that we examined incorporates a phenyl ring within the alkyl tether, thereby restricting conformational freedom in the substrate. Interestingly, the *O*-allyl amide **1e** was quantitatively converted to iminium ether **2e** after just five minutes at room temperature (Scheme 5); these conditions are remarkably mild given that the same transformation for iminium ethers **2a**–**d** generally requires microwave irradiation at 120 °C in order to proceed. The facility with which this reaction takes place is likely a result of reduced conformational flexibility, resulting in significant pre-organization for the cyclization/Claisen rearrangement events, perhaps combined with the favorable formation of a conjugated keteniminium salt intermediate. Nucleophilic capture of **2e** was also possible (Scheme 5), giving rise to isochromanone **3e** or the aromatic aminoalcohol **4e**.

The *O*-benzyl analogue **1f** was found to react under similarly mild conditions. However, the major product of this transformation was not the expected iminium ether **2f** or its rearomatized congener;[7e] instead, the isomeric compound **11** was generated in 65% yield (Scheme 5). Although **11** proved inert to hydrolysis and did not afford the expected lactone product, it was possible to confirm its structural assignment by X-ray crystallography.

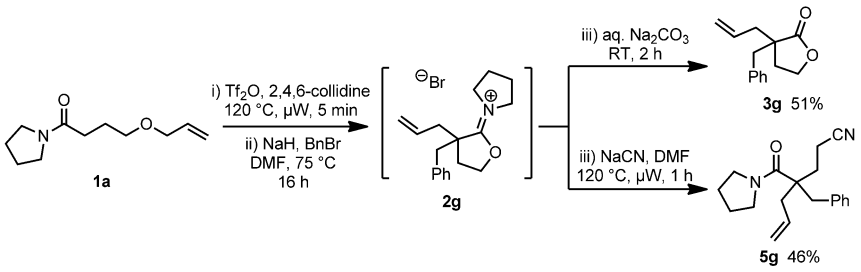
The formation of **11** can be explained by initial generation of iminium ether **2f** through the expected benzyl-Claisen rearrangement, followed by a Cope-type sigmatropic rearrangement.[8] Remarkably, this reaction sacrifices aromaticity in one of the two phenyl rings, while simultaneously generating a sterically-crowded quaternary carbon center, and proceeds under mild conditions at room temperature.

We also envisaged that iminium ethers generated by the Claisen rearrangement might behave as competent pro-nucleophiles through deprotonation at C2, thereby generating an *N*,*O*-ketene aminal.[9] After some experimentation, we found that it is possible to deprotonate the in situ formed



Scheme 5. Claisen–Cope rearrangement of **1f** to produce iminium ether **11**. An ORTEP drawing of **11**·OTf is shown, ellipsoids are presented at the 50% probability level.

2a and combine it with benzyl bromide to afford the alkylated intermediate **2g**, which, following hydrolysis, leads to the corresponding lactone **3g** (Scheme 6). This transformation represents a sequential addition of both an electrophile (BnBr) and a nucleophile (H_2O) to the iminium ether **2a** that was generated initially. It was also possible to react the putative, newly formed iminium ether **2g** with nucleophiles other than water, as evidenced by the preparation of nitrile **5g**. Remarkably, product **5g** is formed as a result of three distinct C–C bond-forming events (Claisen rearrangement,



Scheme 6. Formation of the iminium ether **2g**, followed by reaction with H_2O or NaCN.

benzylation, and cyanation) in one pot with a very reasonable overall yield of 46%. These transformations provide expedient access to all-carbon quaternary centers with four different functional groups from a simple linear precursor.

In summary, we have developed a new method for the preparation of α-allylated iminium ethers by the electrophilic Claisen rearrangement of amides. The generated iminium ethers can be reacted in situ with a diverse range of nucleophiles to afford branched, highly-functionalized compounds through the concomitant transfer of the *O*-allyl chain and formation of a new C–S, C–N, C–P, or C–C bond in a single operation. The investigation of conformationally restricted substrates incorporating an aromatic ring (**1e** and **1f**) revealed that this modification greatly facilitates the formation of the iminium ether, even leading to intriguing products of dearomatization. We have also demonstrated that the iminium ethers may be utilized in a deprotonation–alkylation sequence followed by reaction with nucleophiles, thereby carrying out three complexity-generating reactions in a single, one-pot operation. The ability to use amide electrophilic activation to generate reactive intermediates that are amenable to complexity-increasing cascades of bond-forming events is an exciting line of research, which is currently being further pursued in our laboratories.

Acknowledgements

We are grateful to the Max-Planck-Society and the Max-Planck-Institut für Kohlenforschung for generous support of our research programs. This work was funded by the Ecole Polytechnique (Fellowship to I.D.J.) and the Fonds der Chemischen Industrie (Sachkostenzuschuss to N.M.). We further acknowledge the invaluable support of our NMR, HPLC, and GC Departments and Dr. R. Goddard (MPI Mülheim) for crystallographic analysis. The authors also acknowledge J.-W. Lee (MPI Mülheim) for his valuable advice regarding the aromatic substrates discussed in Scheme 5.

Keywords: amides · Claisen rearrangement · iminiums · keteniminium · rearrangement

[1] For reviews on iminium ethers, see: a) S. Hünig, *Angew. Chem.* **1964**, *76*, 400–412; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 548–560; b) C. U. Pittman, S. P. McManus, J. W. Larsen, *Chem. Rev.* **1972**, *72*, 357–438; c) *Stereoelectronic Effects in Organic Chemistry* (Ed.: P. Deslongchamps), Pergamon, Oxford, **1983**, pp. 101–162; for the use of iminium ethers in the Claisen rearrangement, see: d) J. T. Welch, S. Eswarakrishnan, *J. Org. Chem.* **1985**, *50*, 5909–5910; e) M. J. Kurth, O. H. Decker, *J. Org. Chem.* **1985**, *50*, 5769–5775.

[2] For synthetic applications of iminium ethers, see: a) J. Sheu, M. B. Smith, K. Matsumoto, *Synth. Commun.* **1993**, *23*, 253–262; b) T. N. Lambert, S. Chittamuru, H. K. Jacobs, A. S. Gopalan, *Tetrahedron Lett.* **2002**, *43*, 7379–7383; c) L. Hedvati, A. Nudelman, E. Falb, B. Kraiz, R. Zhuk, M. Sprecher, *Eur. J. Med. Chem.* **2002**, *37*, 607–616; d) G. Grassi, F. Risitano, F. Foti, M. Cordaro, G. Bruno, F. Nicolò, *Chem. Commun.* **2003**, 1868–1869; e) W. Zhu, P. Wu, X. Liang, Y. Dong, J. Zhang, H. Yuan, S. Qi, X. Meng, J. Wu, F. Chen, D. Wang, *J. Agric. Food Chem.* **2008**, *56*, 6547–6553.

[3] For intermolecular *O*-alkylation of amides, see: a) B. Hellmut, E. Franz, S. Gerhard, *Chem. Ber.* **1963**, *96*, 1350–1355; b) R. W. Saalfrank, F. Schütz, U. Moenius, *Synthesis* **1985**, *11*, 1062–1067; c) A. Ates, D. P. Curran, *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131; for intramolecular *O*-alkylation of amides, see: d) S. Yoshifuji, K. Tanaka, Y. Arata, *Tetrahedron Lett.* **1979**, *20*, 809–812; e) C. Chen, P. Beak, *J. Org. Chem.* **1986**, *51*, 3325–3334; f) V. Blot, V. Reboul, P. Metzner, *J. Org. Chem.* **2004**, *69*, 1196–1201.

[4] See ref. [1e] and: a) R. H. Wiley, L. L. Bennett, *Chem. Rev.* **1949**, *44*, 447–476; b) A. I. Meyers, E. W. Collington, *J. Am. Chem. Soc.* **1970**, *92*, 6676–6678; c) S. Brunel, Y. Chevalier, P. Le Perchec, *Tetrahedron* **1989**, *45*, 3363–3370; d) M. P. John, S. A. Hermitage, J. R. Titchmarsh, *Tetrahedron Lett.* **2002**, *43*, 6997–6999.

[5] a) J. L. Treece, J. R. Goodell, D. V. Velde, J. A. Porco Jr., J. Aubé, *J. Org. Chem.* **2010**, *75*, 2028–2038; b) E. Fenster, B. T. Smith, V. Gracias, G. L. Milligan, J. Aubé, *J. Org. Chem.* **2008**, *73*, 201–205; c) K. Sahasrabudhe, V. Gracias, K. Furness, B. T. Smith, C. E. Katz, D. S. Reddy, J. Aubé, *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922; d) V. Gracias, G. L. Milligan, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048.

[6] a) C. Madelaine, V. Valerio, N. Maulide, *Angew. Chem.* **2010**, *122*, 1628–1631; *Angew. Chem. Int. Ed.* **2010**, *49*, 1583–1586; b) V. Valerio, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2011**, *17*, 4742–4745.

[7] For the original, pioneering work in keteniminium chemistry, see: a) M. Delaunois, L. Ghosez, *Angew. Chem.* **1969**, *81*, 33–34; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 72–73; b) J. Marchand-Brynaert, L. Ghosez, *J. Am. Chem. Soc.* **1972**, *94*, 2869–2870; c) I. Marko, B. Ronsmans, A. M. Hesbain-Frisque, S. Dumas, L. Ghosez, B. Ernst, H. Greuter, *J. Am. Chem. Soc.* **1985**, *107*, 2192–2194; for reviews of keteniminium chemistry, see: d) B. B. Snider, *Chem. Rev.* **1988**, *88*, 793–811; e) C. Madelaine, V. Valerio, N. Maulide, *Chem. Asian J.* **2011**, *6*, 2224–2239.

[8] For reviews of Cope rearrangement, see: a) R. P. Lutz, *Chem. Rev.* **1984**, *84*, 205–247; b) S. Blechert, *Synthesis* **1989**, 71–82; c) L. A. Paquette, *Angew. Chem.* **1990**, *102*, 642–660; *Angew. Chem. Int. Ed.*

Engl. **1990**, *29*, 609–626; although Claisen–Cope rearrangements have been described before, these reactions generally require elevated temperatures to proceed, for examples, see: d) B. J. Newhouse, J. Bordner, D. J. Augeri, C. S. Litts, E. F. Kleinman, *J. Org. Chem.* **1992**, *57*, 6991–6995; e) N. Al-Maharik, N. P. Botting, *Tetrahedron* **2003**, *59*, 4177–4181; f) K. Nakabayashi, M. Ooho, T. Niino, T. Kitamura, T. Yamaji, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 157–164.

[9] *N,O*-Ketene aminals have been shown to react with strong electrophiles such as isocyanates and isothiocyanates, for examples, see: a) A. Zhou, L. Cao, H. Li, Z. Liu, H. Cho, W. P. Henry, C. U. Pittman, *Tetrahedron* **2006**, *62*, 4188–4200; b) A. Zhou, L. Cao, H. Li, Z. Liu, C. U. Pittman, *Synlett* **2006**, *2*, 201–206.

Received: September 14, 2012
Published online: November 14, 2012

