ARTICLE

OBC
www.rsc.org/obc

A practical synthesis of D-*erythro*-sphingosine using a cross-metathesis approach †

Staffan Torssell and Peter Somfai*

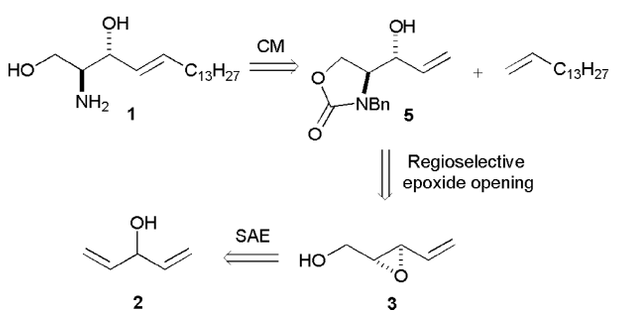
Organic Chemistry, KTH Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden. E-mail: somfai@kth.se; Fax: +46 8 7912333; Tel: +46 8 7906960

Received 9th March 2004, Accepted 26th March 2004
First published as an Advance Article on the web 20th April 2004

Starting from a vinylepoxide, a short and practical synthesis of D-*erythro*-sphingosine is described. The key transformations are a regioselective opening of the vinylepoxide and an *E*-selective cross-metathesis, affording the target molecule in **5** steps and 51% overall yield.

Introduction

Sphingolipids are constituents of cell membranes in all eukaryotic cells and the recent discovery of their biologically active metabolites *e.g.* sphingosine, ceramide and lysosphingolipids has generated interest in the physiological role of these molecules. D-*erythro*-Sphingosine (**1**, Scheme 1) and related compounds have been shown to inhibit protein kinase C, which affects cell regulation and signal transduction, and exhibits antitumor promoter activities in various mammalian cells. In addition, these compounds may function as modulators of cell function and possibly also as secondary messengers.[1–3] Due to the biological importance of **1** and its derivatives many synthetic routes to enantiopure sphingolipids have been described in the literature. Most of these utilize starting materials from the chiral pool *e.g.* L-serine or carbohydrates,[4–8] while asymmetric routes are more rare.[9–12]



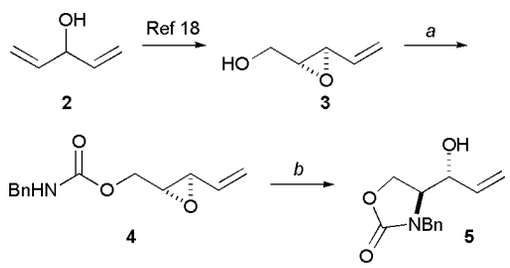
Scheme 1 Retrosynthetic analysis of D-*erythro*-sphingosine.

We became interested in assembling **1** by using a cross-metathesis reaction to introduce the required *E*-olefin moiety (Scheme 1). Such a strategy would be convenient compared to alternatives using more traditional C–C double bond forming reactions, since the required catalyst is commercially available and the metathesis usually proceeds with a low amount of byproduct formation.[13,14] The polar head group **5** should be available from epoxide **3**, which, in turn, is readily prepared from divinylcarbinol (**2**). The realization of this strategy yields a practical synthesis of **1** that is outlined below.

Results and discussion

Synthesis of oxazolidinone 5

The synthesis of oxazolidinone **5** starts from commercially available **2** (Scheme 2). Sharpless epoxidation of **2** followed by base-induced Payne rearrangement gave **3** in high yield and excellent enantiomeric purity (>99% ee[15]), as described previously.[16–18] It was expected that intermolecular reaction of **3** with various nitrogen nucleophiles would, due to electronic influences, result in a preferential ring-opening at the allylic position.[19] To circumvent this the C-2 amino functionality was introduced through a two-step procedure. Alkyl isocyanates have previously been used as nitrogen nucleophiles to give regioselective attack at the C-2 position of epoxy alcohols.[20,21] Consequently, when epoxy alcohol **3** was treated with benzyl isocyanate and Et_3N in a sealed tube benzyl carbamate **4** was obtained in excellent yield. The subsequent intramolecular ring-opening of **4** using NaH proceeded sluggishly and gave a poor yield of oxazolidinone **5**.[20,21] Gratifyingly, when using NaHMDS in THF at low temperature instead, **5** was obtained in 88% yield.[22]



Scheme 2 Synthesis of oxazolidinone **5**. *Reagents and conditions: a.* BnNCO, Et_3N, Et_2O, 60 °C, 98%; *b.* NaHMDS, THF, −15 °C, 88%.

Cross-metathesis and completion

Due to the lipid chain and the hydrophilic head group, compound **1** exhibits surfactant-like properties such as low solubility in organic solvents at low temperature, and problems with flash chromatography due to aggregation of the material on the silica gel column.[12] The late introduction of the aliphatic chain by a cross-metathesis reaction overcomes many of these problems and has advantages over several of the existing strategies of **1** where the lipid chain is introduced at an early stage of the synthetic route.

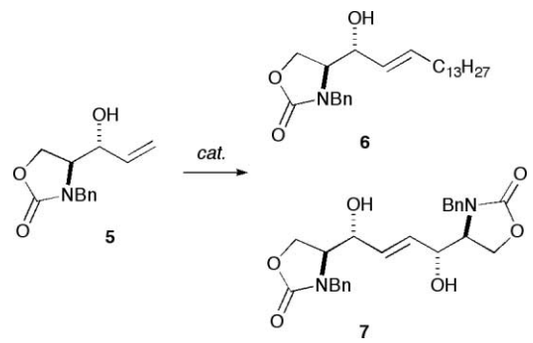
Compound **6** was synthesized by coupling allylic alcohol **5** with 1-pentadecene using Ru-catalysts A–C (Fig. 1 and Table 1).

The initial coupling attempts under standard conditions[14] using catalyst **A** or **B** resulted in no reaction or required prolonged reaction times, giving **6** in moderate yield and *E* : *Z* selectivity (Table 1, entries 1–3). When using toluene[23] as solvent homodimer **7** precipitated as a white solid and thereby shifted the equilibrium toward **7** (entry 4). This could be resolved by addition of $Ti(O^iPr)_4$ to the reaction mixture and **6** was isolated in 52% yield (78% based on recovered starting material) with 16 : 1 *E* : *Z* selectivity (entry 7). The *E* : *Z* isomers

† Electronic supplementary information (ESI) available: spectroscopic data for compounds **1** and **4**–**8**. See http://www.rsc.org/suppdata/ob/b4/b403568b/

DOI: 10.1039/b403568b

Table 1 Cross-metathesis



Entry	Catalyst (mol%)	Conditions[a]	Product (Yield %[b])	$E : Z$
1	**A** (5)	40 °C, 43 h	No reaction	N.A.
2	**B** (5)	rt, 3 d	**6** (35)	14 : 1
3	**B** (5)	40 °C, 24 h	**6** (49)	5 : 1
4[c]	**B** (10)	50 °C, 1.5 h	**6** (7)	12 : 1
			7 (57)	*E*
5[d]	**A** (5)	40 °C, 40 h	**6** (7)	N.A.
6[d]	**B** (10)	40 °C, 22 h	**6** (30)	N.A.
7[d]	**B** (10)	40 °C, 45 min	**6** (52)	16 : 1
8	**C** (10)	rt, 48 h	**6** (53)	13 : 1
9	**C** (10)	40 °C, 1.5 h	**6** (59)	17 : 1

[a] 2 equiv. 1-pentadecene in CH_2Cl_2. [b] Isolated yield. [c] 2 equiv. of 1- pentadecene in PhMe [d] 2 equiv. $Ti(O^iPr)_4$ was added prior to the catalyst.

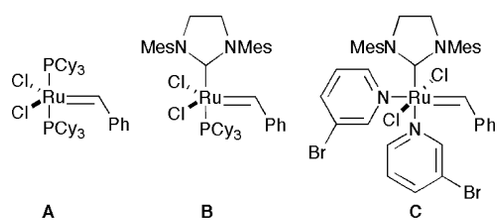
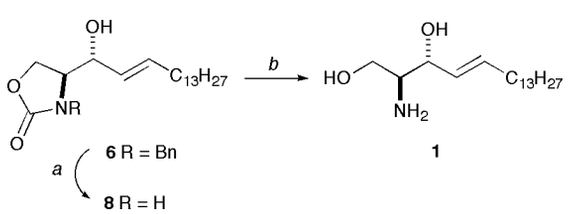


Fig. 1 Ru-catalysts used in the cross-metathesis reaction.

were easily separated by flash chromatography. The need for $Ti(O^iPr)_4$ could be explained by the heteroatom density in **5**, as Ru catalyst **B** can form inactive chelates with Lewis-basic sites in the substrate.[23] The presence of $Ti(O^iPr)_4$ decreases the amount of Ru-substrate chelates and increases the amount of desired product.[24–26] When employing Grubbs' phosphine-free 3-bromopyridine catalyst **C**[27] (Fig. 1) the yield and $E : Z$ selectivity were increased to 59% (82% based on recovered starting material) and 17 : 1 respectivly (Table 1, entry 9). Catalyst **C** was easily made from the commercially available **B** and has shown increased reactivity in various cross-metathesis reactions.[28–30]

Removal of the benzyl group in **6** with sodium in liquid ammonia gave oxazolidinone **8** which was then hydrolyzed with KOH to afford D-*erythro*-sphingosine (**1**) in quantitative yield over two steps (Scheme 3). Analytical data of **1** were in good agreement with literature data.[4–12]



Scheme 3 Deprotection of **1**. *Reagents and conditions: a.* 1 M KOH, H_2O : EtOH 1 : 1, 100 °C, 100%; *b.* Na, NH_3(l), −78 °C, 100%.

Conclusions

In conclusion, an efficient and practical route for the synthesis of D-*erythro*-sphingosine (**1**), based on a cross-metathesis approach, has been developed. The required stereochemistry was introduced *via* a regioselective epoxide opening while the aliphatic chain of **1** was introduced with a highly *E*-selective cross-metathesis in the presence of Grubbs' phosphine free catalyst **C**. Two quantitative deprotection steps completed the synthetic route, furnishing **1** in 51% yield over five steps. The strategy is flexible and would permit the synthesis of sphingolipids with different aliphatic chains by using other olefins in the cross-metathesis reaction.

Experimental

For general experimental procedures see ref 12.

((2*R*,3*R*)-3-Vinyloxiran-2-yl)methyl benzylcarbamate (4)

To a solution of ((2*R*,3*R*)-3-vinyloxiran-2-yl)methanol[18] (509 mg, 5.08 mmol) in Et_2O (20 cm^3) was added freshly distilled Et_3N (1.42 cm^3, 10.16 mmol) followed by BnNCO (0.94 cm^3, 7.62 mmol). The resultant mixture was heated to 60 °C in a sealed tube for 17 h, cooled to rt and quenched with sat. NH_4Cl (15 cm^3). The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2 ⟶ CH_2Cl_2 + 1% MeOH) of the residue gave **4** (1.161 g, 98%) as a low melting white solid: δ_H(400 (MHz; $CDCl_3$) 3.14 (1 H, m), 3.29 (1 H, d, *J* 6.6), 4.01 (1 H, dd, *J* 12.2 and 6.0), 4.39 (2 H, d, *J* 6.0), 4.46 (1 H, dd, *J* 12.2 and 3.1), 5.08 (1 H, br s), 5.31–5.34 (1 H, m), 5.63–5.48 (2 H, m) and 7.26–7.37 (5 H, m); δ_C(100 (MHz; $CDCl_3$) 45.2, 56.4, 57.5, 64.8, 120.3, 127.6, 127.7, 128.8, 134.5, 138.4 and 156.1; $[a]_D^{20}$ +26.2 (*c* 0.39 in CHCl $CHCl_3$) [lit.[21] $[a]_D^{20}$ +25.7 (*c* 0.39 in $CHCl_3$)].

(*S*)-3-Benzyl-4-((*R*)-1-hydroxyallyl)oxazolidin-2-one (5)

To a stirred solution of urethane **4** (1.022 g, 4.38 mmol) in THF (50 cm^3) at −15 °C was added dropwise NaHMDS (6.57 cm^3, 6.57 mmol, 1 M in THF). The resultant mixture was slowly allowed to reach 0 °C (5 h) and then quenched by addition of sat. NH_4Cl (20 cm^3). The phases were separated and the aqueous layer was extracted twice with Et_2O, dried over $MgSO_4$

and then concentrated *in vacuo*. Flash chromatography (pentane : EtOAc 3 : 2) of the residue gave **5** (899 mg, 88%) as a colorless oil. ν_{max}(film)/cm^{-1} 3216, 1745, 1265 and 739; δ_H(400 MHz; $CDCl_3$) 2.20 (1 H, d, *J* 3.5), 3.70 (1 H, ddd, *J* 9.2, 6.2 and 2.6), 4.15 (1 H, t, *J* 8.8), 4.25 (1 H, dd, *J* 8.8 and 6.3), 4.36 (1 H, A-part of ABq, *J* 15.2), 4.37 (1 H, s), 4.73 (1 H, B-part of ABq, *J* 15.2), 5.28 (1 H, dd, *J* 10.6 and 1.3), 5.41 (1 H, dd, *J* 17.2 and 1.3), 5.66 (1 H, ddd, *J* 17.2, 10.6 and 4.9) and 7.32–7.37 (5 H, m); δ_C(100 MHz; $CDCl_3$) 46.8, 58.4, 62.4, 69.2, 118.2, 128.2, 128.3, 129.2, 134.6, 136.3 and 159.3; $[\alpha]_D^{20}$ +4.7 (*c* 1.04 in $CHCl_3$); *m*/*z* (FAB+) 234.1134 (M + H) $C_{13}H_{16}NO_3$ requires 234.1130).

(*S*)-3-Benzyl-4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)oxazolidin-2)-one (6)

Typical cross-metathesis protocol. To a solution of allylic alcohol **5** (34.8 mg, 0.15 mmol) in CH_2Cl_2 (1.0 cm^3) was added 1-pentadecene (43.6 mm^3, 0.30 mmol). To the resultant mixture at reflux was added catalyst **C**[28](13.2 mg, 0.015 mmol) in CH_2Cl_2 (0.5 cm^3) and the resulant mixture was stirred at reflux for 1.5 h and then cooled to rt. The solvent was evaporated to give a brown residue with 17.4 : 1 *E* : *Z* selectivity (crude NMR). Flash chromatography (pentane : EtOAc 4 : 1) of the residue gave isomerically pure **6** (36.5 mg, 59%) as a white solid and recovered **5** (8 mg, 23%).

Typical cross-metathesis protocol using Ti(O^{i}Pr)$_4$. To a solution of allylic alcohol **5** (827 mg, 3.55 mmol) in CH_2Cl_2(20 cm^3) was added Ti(O^{i}Pr)$_4$ (2.10 cm^3, 7.09 mmol) and the resultant mixture was refluxed for 30 min. To the mixture was then added 1-pentadecene (1.040 cm^3, 7.09 mmol) and catalyst **B** (301 mg, 0.35 mmol) in CH_2Cl_2 (10 cm^3) and the resultant mixture was refluxed for 45 min and then cooled to rt. The solvent volume was reduced to approx. 4 cm^3 and the resultant mixture was subjected to flash chromatography (pentane : EtOAc 4 : 1) to give **6** (*E* : *Z* 16 : 1) as a white solid and recovered **5** (280 mg, 34%). The *E* : *Z*-isomers were separated with a second flash chromatography (pentane : EtOAc 4 : 1) to give isomerically pure **6** (761 mg, 52%): mp 54–56 °C (lit.[31] mp 56–57 °C); δ_H(400 (MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.9), 1.27 (22 H, m), 2.01 (2 H, q, *J* 7.3), 2.06 (1 H, s), 3.66 (1 H, ddd, *J* 9.1, 6.2 and 2.9), 4.17 (1 H, t, *J* 8.8), 4.25 (1 H, dd, *J* 8.8 and 6.3), 4.28 (1 H, s), 4.33 (1 H, A-part of ABq, *J* 15.2), 4.74 (1 H, B-part of ABq, *J* 15.2), 5.27 (1 H, dd, *J* 15.5 and 6.1), 5.79 (1 H, ddt, *J* 15.4, 6.9 and 1.2) and 7.31–7.36 (5 H, m); δ_C(125 (MHz; $CDCl_3$) 14.3, 22.8, 29.1, 29.3, 29.5, 29.6, 29.71, 29.78, 29.80, 29.81, 32.1, 32.5, 46.8, 58.7, 62.8, 69.7, 69.8, 126.22, 126.24, 128.2, 128.3, 129.1, 135.65, 135.68, 135.72, 136.4 and 159.3; $[\alpha]_D^{20}$ −12.5 (*c* 1.07 in $CHCl_3$) [lit.[31] $[\alpha]_D^{20}$ −11.8 (*c* 1.07 in $CHCl_3$)]; *m*/*z* (FAB+) 416.3174 (M + H. $C_{26}H_{42}NO_3$ requires 416.3165).

Homodimer (7)

To a solution of allylic alcohol **5** (29.0 mg, 0.12 mmol) in toluene (1 cm^3) was added 1-pentadecene (36.4 mm^3, 0.25 mmol) and catalyst **B** (10.6 mg, 0.012 mmol) in toluene (0.5 cm^3) and the resultant mixture was heated to 50 °C for 1.5 h and then cooled to rt. The white precipitate was filtered off and washed with toluene to give **7** (15.6 mg, 57%). Flash chromatography (pentane : EtOAc 4 : 1) of the residue gave **6** (3.6 mg, 7%, *E* : *Z* 12 : 1) as a white solid and recovered **5** (8 mg, 28%): mp 158.9–159.9 °C (dec); ν_{max}(film)/cm^{-1} 3056, 1712, 1267 and 739; δ_H(500 (MHz; d_6-acetone) −3.76 (1 H, m), 4.16 (2 H, m), 4.24 (1 H, A-part ABq, *J* 15.4), 4.58 (2 H, m), 4.74 (1 H, B-part of ABq, *J* 15.4), 5.82 (1H, d, *J* 1.3) and 7.28–7.36 (5 H, m); δ_C(125 (MHz; d_6-acetone) 46.4, 58.5, 62.8, 68.67, 68.76, 128.4, 128.9, 129.5, 131.2, 137.8 and 159.2; $[\alpha]_D^{20}$ −51.8 (*c* 0.83 in acetone); *m*/*z* (FAB+) 439.1877 (M + H. $C_{24}H_{27}N_2O_6$ requires 439.1864).

(*S*)-4-((*R*,*E*)-1-Hydroxyhexadec-2-enyl)oxazolidin-2-one (8)

To a solution of Na (excess) in freshly distilled NH_3 (45 cm^3) at −78 °C was cannulated oxazolidinone **6** (558 mg, 1.34 mmol) in Et_2O (10 cm^3). The resultant blue solution was stirred at −78 °C for 4 h and then carefully quenched with sat. NH_4Cl. The $NH_3$was then slowly evaporated under a stream of N_2. The phases were separated and the aqueous layer was extracted three times with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo* to give **8** (437 mg, 100%) as a white solid: mp 71–72 °C (lit.[32] 73–74 °C); δ_H(400 MHz; $CDCl_3$) 0.81 (3 H, t, *J* 6.8), 1.20–1.37 (22 H, m), 2.04 (2 H, q, *J* 7.0), 2.92 (1 H, br s), 3.86 (1 H, m), 4.12 (1 H, m), 4.33 (1 H, dd, *J* 8.8 and 5.2), 4.39 (1 H, t, *J* 8.8), 5.37 (1 H, ddt, *J* 15.4, 6.8 and 1.2), 5.83 (1 H, ddt, 15.4, 6.8 and 0.8) and 6.11 (1 H, s); δ_C(100 (MHz; $CDCl_3$) 14.2, 22.8, 29.1, 29.4, 29.5, 29.6, 29.74, 29.79, 29.81, 32.1, 32.5, 56.4, 66.4, 73.3, 126.3, 126.6, 136.6 and 160.5; $[\alpha]_D^{20}$ −1.3 (*c* 1.75 in $CHCl_3$) [lit.[32] $[\alpha]_D^{20}$ − 0.8 (*c* 2.0 in $CHCl_3$)].

D-*erythro*-Sphingosine (1)

Oxazolidinone **8** (425.8 mg, 1.31 mmol) in 1 M KOH (20 cm^3, H_2O : EtOH 1 : 1) was heated to reflux for 2.5 h, cooled to rt and then 2 M NaOH (10 cm^3) was added. The mixture was extracted with EtOAc (3 × 20 cm^3) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* giving **1** (390.1 mg, 100%) as a white solid: mp 72–75 °C (lit.[7] mp 70 °C, lit.[12] mp 73–75 °C); δ_H(500 (MHz; $CDCl_3$) 0.87 (3 H, t, *J* 6.9), 1.25–1.38 (22 H, m), 2.05 (2 H, q, *J* 7.0), 2.27 (4 H, br s), 2.85 (1 H, m), 3.63 (1 H, dd, *J* 10.9 and 5.8), 3.67 (1 H, dd, *J* 10.9 and 4.6), 4.04 (1 H, t, *J* 6.3), 5.47 (1 H, dd, *J* 15.4 and 7.2) and 5.75 (1 H, dt, *J* 15.4 and 6.7); δ_C(100 (MHz; $CDCl_3$) 14.3, 22.8, 29.3, 29.4, 29.5, 29.6, 29.76, 29.80, 29.82, 32.1, 32.5, 56.3, 64.2, 75.8, 129.4 and 134.9; $[\alpha]_D^{20}$ −1.6 (*c* 1.0, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ −1.2 (*c* 1.74 in $CHCl_3$), lit.[8] $[\alpha]_D^{20}$ −1.5 (*c* 0.52, $CHCl_3$)].

Acknowledgements

This work was supported financially by AstraZeneca, Södertälje, and the Swedish Research Council.

References

1 K.-A. Karlsson, *Trends Pharm. Sci.*, 1991, **12**, 265.
2 Y. Hannun and R. M. Bell, *Science*, 1989, **243**, 500.
3 Y. Hannun, *Science*, 1996, **274**, 1855.
4 P. M. Koskinen and A. M. P. Koskinen, *Synthesis*, 1998, 1075.
5 J. M. Gargano and W. J. Lees, *Tetrahedron Lett.*, 2001, **42**, 5845.
6 T. Nakamura and M. Shiozaki, *Tetrahedron*, 2001, **57**, 9087.
7 R. J. B. H. N. van der Berg, C. G. N. Korevaar, G. A. van der Marel, H. S. Overkleeft and J. H. van Boom, *Tetrahedron Lett.*, 2002, **43**, 8409.
8 J.-M. Lee, H.-S. Lim and S.-K. Chung, *Tetrahedron: Asymmetry*, 2002, **13**, 343.
9 T. C. Nugent and T. Hudlicky, *J. Org. Chem.*, 1998, **63**, 510.
10 L. L. He, H. S. Byun and R. Bittman, *J. Org. Chem.*, 2000, **65**, 7627.
11 E. J. Corey and S. Choi, *Tetrahedron Lett.*, 2000, **41**, 2765.
12 B. Olofsson and P. Somfai, *J. Org. Chem.*, 2003, **68**, 2514.
13 S. J. Connon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900.
14 A. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.
15 $[\alpha]_D^{20}$ −62.7 (*c* 0.92 in $CHCl_3$) for comparison see refs. 16–18.
16 S. L. Schreiber, T. S. Schreiber and D. B. Smith, *J. Am. Chem. Soc.*, 1987, **109**, 1525.
17 V. Jäger, D. Schröter and B. Koppenhoefer, *Tetrahedron*, 1991, **47**, 2195.
18 A. Romero and C.-H. Wong, *J. Org. Chem.*, 2000, **65**, 8264.
19 B. Olofsson, U. Khamrai and P. Somfai, *Org. Lett.*, 2000, **2**, 4087.
20 W. R. Roush and W. A. Adam, *J. Org. Chem.*, 1985, **50**, 3752.
21 V. Jäger, U. Stahl and W. Hummer, *Synthesis*, 1991, 776.
22 R. Martin, A. Moyano, M. A. Pericas and A. Riera, *Org. Lett.*, 2000, **2**, 93.
23 Reactions in toluene are substantially faster than in CH_2Cl_2. This increased reactivity is not only an effect of increased reaction temperature. See: A. Fürstner, O. R. Thiel, L. Ackermann and H-J. Schanz and S. P. Nolan, *J. Org. Chem.*, 2000, **65**, 2204.

24 A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130.
25 A. K. Ghosh, J. Cappiello and D. Shin, *Tetrahedron Lett.*, 1998, **39**, 4651.
26 S. Rodríguez, E. Castillo, M. Carda and J. A. Marco, *Tetrahedron*, 2002, **58**, 1185.
27 To a solution of 3-bromo pyridine (10 equiv.) was added catalyst **B**. The resultant mixture was stirred under N_2 at rt for 15 min. The pure product was precipitated using pentane to give **C** (95%) as a green crystalline solid. See ref 28.
28 J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2002, **41**, 4035.
29 B. Kang, D.-H. Kim, Y. Do and S. Chang, *Org. Lett.*, 2003, **5**, 3041.
30 T. Kanemitsu and P. H. Seeberger, *Org. Lett.*, 2003, **5**, 4541.
31 S. Katsumura, N. Yamamoto, E. Fukuda and S. Iwama, *Chem. Lett.*, 1995, 393.
32 R. Julina, T. Herzig, B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1986, **69**, 368.