Asymmetric synthesis of 2-arylpyrrolidines starting from γ-chloro *N*-(*tert*-butanesulfinyl)ketimines†

Erika Leemans, Sven Mangelinckx‡ and Norbert De Kimpe*

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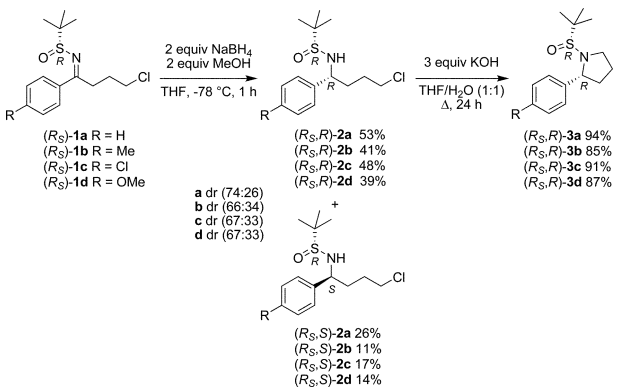
The enantioselective reductive cyclization of γ-chloro *N*-(*tert*-butanesulfinyl)ketimines towards the short and efficient synthesis of (*S*)- and (*R*)-2-arylpyrrolidines (ee >99%) is described for the first time by treatment with $LiBEt_3H$ and subsequent acid deprotection.

According to the established research work of the groups of Davis,[1] Ellman,[2] and others,[3] on the use of *N*-sulfinyl imines for the synthesis of a variety of N-containing compounds and in analogy with the synthesis of aziridines from α-chloro *N*-(*tert*-butanesulfinyl)imines,[4] γ-chloro *N*-(*tert*-butanesulfinyl)-ketimines were evaluated for the synthesis of chiral 2-aryl-pyrrolidines. In addition to their occurrence as pharmaceutical subunits,[5] pyrrolidines are an important class of biologically active naturally occurring compounds,[6] as exemplified by (*S*)-nicotine and its analogue 2-phenylpyrrolidine.[7] Therefore, considerable attention has been devoted in recent years to the synthesis of enantiopure pyrrolidine derivatives.[8] Furthermore, chiral 2-substituted pyrrolidines, such as 2-arylpyrrolidines,[9] are useful as chiral bases, chiral auxiliaries, and chiral ligands,[10] and have been made accessible *via* cyclization of 1-substituted 3-(1,3-dioxanyl)- and 3-(1,3-dioxolanyl)propyl-*tert*-butanesulfinamides, prepared *via* Grignard addition to *N*-(*tert*-butanesulfinyl)aldimines.[2e]

Only a few γ-chloro *N*-(*tert*-butanesulfinyl)- and *N*-(*p*-toluene-sulfinyl)imines have been synthesized and used in some specific nucleophile-induced cyclizations towards dimethyl (*R*)-1-(*S*)-*tert*-butanesulfinyl-2-phenylpyrrolidin-2-ylphosphonate[4g] and (2*R*,1′*S*)-*N*-[(*S*)-*p*-tolylsulfinyl]-2-[(2-*p*-tolylsulfinylphenyl)tri-isopropylsilyloxymethyl]pyrrolidine.[11] Simultaneous with our work, the asymmetric synthesis of 2-substituted pyrrolidines in 81–90% yield (from the starting imine) and in 95 : 5–97 : 3 dr (for the 1-(*tert*-butanesulfinyl)pyrrolidines) was reported very recently by Reddy and Prashad *via* addition of Grignard reagents across γ-chloro *N*-(*tert*-butanesulfinyl)aldimines.[12] However, a reactivity study of the former imines towards reducing agents has not been performed yet. The novel starting chiral γ-chloro *N*-(*tert*-butanesulfinyl)ketimines **1a–d** [(R_S) as well as (S_S)] were prepared from the readily available γ-chloroketones and one equiv. of (*R*)- or (*S*)-*tert*-butanesulfin-amide in the presence of two equiv. of titanium(IV) ethoxide in tetrahydrofuran at reflux temperature for 48–91 h. The successful synthesis of γ-chloroketimines **1** from the corresponding γ-chloroketones provides an important opportunity to extend our research on the application of ω-functionalized imines, and more specifically ω-chloroimines,[4a–d,h,13] for the synthesis of heterocyclic compounds.[14] Whereas α-, β- and δ-haloimines have been used successfully in the reductive cyclization to the corresponding aziridines,[4a,b,h] azetidines[13a] and piperidines,[13c,d] a similar approach towards the five-membered azaheterocycles *via* reduction of γ-halogenated imines has not been achieved so far.[14] Up to the present it was not possible to prepare γ-haloimines as stable compounds *via* condensation of γ-halocarbonyl compounds with a primary amine or *via* α-alkylation of imines with α,β-dihaloethanes. This important gap in the application of haloimines towards the synthesis of azaheterocycles is partly filled by the results presented herein.

In an initial attempt to synthesize chiral pyrrolidines, similar reduction conditions were used as in the conversion of chiral (R_S)-*N*-*tert*-butanesulfinyl α-haloimines to the corresponding chiral aziridines.[4a,b,h] Treatment of (R_S)-*N*-[1-aryl-4-chloro-butylidene]-*tert*-butanesulfinamides **1a–d** with two equiv. of sodium borohydride and two equiv. of methanol in tetrahydro-furan at −78 °C for one hour afforded a mixture of two diastereomeric *N*-[1-aryl-4-chlorobutyl]-*tert*-butanesulfin-amides (R_S,*R*)-**2a–d** and (R_S,*S*)-**2a–d** in a diastereomeric ratio of 66 : 34–74 : 26 (Scheme 1). The obtained diastereoisomers **2** could be separated *via* column chromatography in 39–53% yield for isomers (R_S,*R*)-**2a–d** and 11–26% yield for isomers (R_S,*S*)-**2a–d**. Subsequent ring closure of (R_S,*R*)-*N*-[1-aryl-4-chlorobutyl]-*tert*-butanesulfinamides **2a–d** upon treatment with three equiv. of potassium hydroxide in tetrahydrofuran–water (1 : 1) at reflux temperature for 24 h afforded (R_S,*R*)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** in 85–94% yield.



Scheme 1 $NaBH_4$ reduction of (R_S)-γ-chloroimines **1**.

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium. E-mail: norbert.dekimpe@UGent.be; Fax: +329264 6243; Tel: +329264 5950

† Electronic supplementary information (ESI) available: Spectral and analytical data of compounds **1a–d**, (R_S,*R*)-**2a–d**, (R_S,*S*)-**2a–d**, (R_S,*R*)-**3a–d**, (S_S,*R*)-**3a–d**, **4a–d**, **5a–d**. See DOI: 10.1039/b925209f

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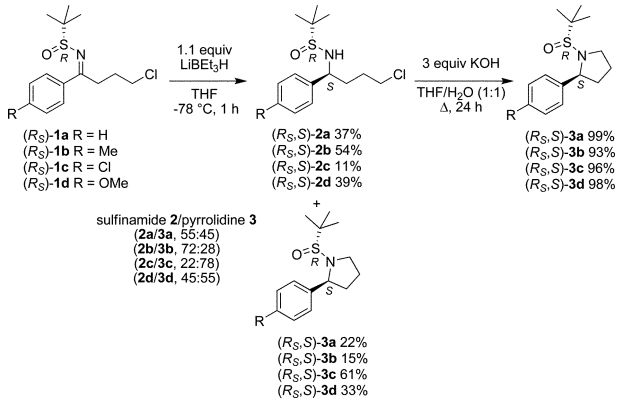


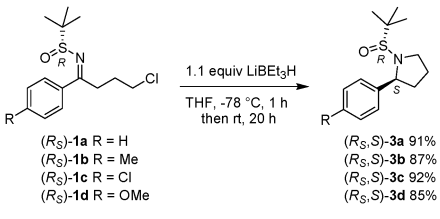
Scheme 2 $LiBEt_3H$ reduction of (R_S)-γ-chloroimines **1**.

Attempts to improve the stereoselectivity of the reduction of (R_S)-*N*-[4-chloro-1-phenylbutylidene]-*tert*-butanesulfinamide **1a** with two equiv. of sodium borohydride at −78 °C for one hour in different solvents failed. The use of methanol gave a diastereomeric ratio of 35 : 65 for (R_S,R)-**2a** : (R_S,S)-**2a** whereas addition of 2 equiv. of methanol in dichloromethane or toluene failed to give reduction.

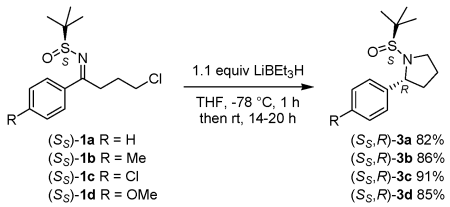
On the other hand, when reducing the (R_S)-*N*-[1-aryl-4-chlorobutylidene]-*tert*-butanesulfinamides **1a–d** using 1.1 equiv. of a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran at −78 °C for one hour, the corresponding (R_S,S)-*N*-[1-aryl-4-chlorobutyl]-*tert*-butanesulfinamides **2a–d** were obtained as a single diastereoisomer, next to a variable amount of the ring closed (R_S,S)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** in a 22 : 78–72 : 28 ratio (R_S,S)-**2** : (R_S,S)-**3** (Scheme 2). Again, the two compounds could be separated *via* column chromatography and (R_S,S)-*N*-[1-aryl-4-chlorobutyl]-*tert*-butanesulfinamides **2a–d** were ring closed under basic conditions (three equiv. KOH, THF–H_2O (1 : 1), Δ, 24 h) to give (R_S,S)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** in 93–99%yield.

Moreover, when (R_S)-*N*-[1-aryl-4-chlorobutylidene]-*tert*-butanesulfinamides **1a–d** were reduced with 1.1 equiv. of lithium triethylborohydride in tetrahydrofuran at −78 °C for one hour, subsequently allowed to warm up to room temperature and kept at this temperature for 20 h, the corresponding (R_S,S)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** were obtained in an excellent yield (85–92%) (Scheme 3).

In view of the excellent results obtained under the aforementioned reduction conditions, *i.e.* 1.1 equiv. of $LiBEt_3H$, THF, −78 °C, 1 h then rt, 14–20 h, the enantiomeric (S_S)-*N*-[1-aryl-4-chlorobutylidene]-*tert*-butanesulfinamides **1a–d** were



Scheme 3 Synthesis of (R_S,S)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3**.

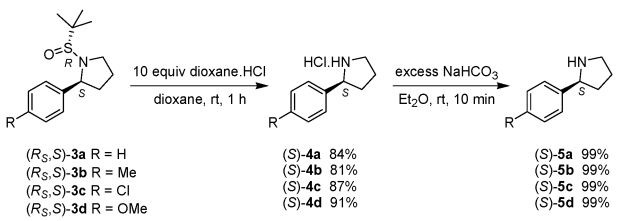


Scheme 4 Synthesis of (S_S,R)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3**.

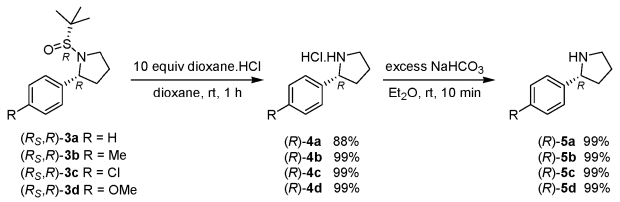
converted into the (S_S,R)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** in 82–91% yield after purification by means of recrystallization or column chromatography (Scheme 4).

Having the chiral (R_S,S)- and (R_S,R)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3** in hand, the *N*-*tert*-butanesulfinyl group was removed by simple treatment with a saturated solution of anhydrous HCl in 1,4-dioxane (Schemes 5–6). Stirring for one hour at room temperature afforded the (*S*)- and (*R*)-2-arylpyrrolidine hydrochlorides **4** in 81–91% and 88–99% yield, respectively, after precipitation from diethyl ether. The absolute configuration of compound (*R*)-**4a** and (*R*)-**4d** was determined by comparison of the optical rotation ($[\alpha]_D$ = −9.25 (*c* 1.01, MeOH) for (*R*)-**4a** and $[\alpha]_D$ = −12.4 (*c* 1.01, MeOH) for (*R*)-**4d**) with literature values ($[\alpha]_D$ = −9.10 (*c* 1.00, MeOH) for (*R*)-**4a**,[2e] $[\alpha]_D$ = −15.3 (*c* 0.86, MeOH) for (*R*)-**4a**,[15] $[\alpha]_D$ = −15.7 (*c* 0.96, MeOH) for (*R*)-**4a**,[16] and $[\alpha]_D$ = −14.3 (*c* 0.98, MeOH) for (*R*)-**4d**).[16]

When a saturated solution of sodium bicarbonate was added to a stirring suspension of the hydrochlorides **4** in diethyl ether at room temperature for ten minutes, the corresponding (*S*)- and (*R*)-2-arylpyrrolidines **5** were obtained in quantitative yield without further purification. The absolute configuration of pyrrolidines (*R*)-**5a** and (*S*)-**5a** was confirmed by comparison of the optical rotations {(*R*)-**5a**: $[\alpha]_D$ = +29.7 (*c* 0.32, MeOH), (*S*)-**5a**: $[\alpha]_D$ = −27.9 (*c* 0.38, MeOH)} with literature values {(*R*)-**5a**: $[\alpha]_D$ = +24.3 (*c* 0.30, MeOH) for an enantiomeric excess of 75%,[17] (*S*)-**5a**: $[\alpha]_D$ = −22 (*c* 0.30, MeOH)}.[15,17,18] The absolute configuration of 2-arylpyrrolidines can also easily be determined by inspection of the multiplicity of the NMR signal of the methine proton of the pyrrolidine ring in the corresponding Mosher's amides.[19,20] 2-Phenylpyrrolidines (*S*)-**5a** and (*R*)-**5a** were reacted with 2.5 equiv. of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher's acid chloride) in the presence of 2.5 equiv. of diisopropylethylamine in dichloromethane at room temperature for 16 h. The ^1H NMR spectra (300 MHz, DMSO-d_6) of the synthesized Mosher's amides were identical to those reported in the literature.[20c] For the (2*R*)-2-phenylpyrrolidine-(*S*)-MTPA-amide, the H2 methine proton couples with the



Scheme 5 Synthesis of (*S*)-arylpyrrolidines **5**.



Scheme 6 Synthesis of (*R*)-arylpyrrolidines **5**.

vicinal protons at C3 with different coupling constants (8.1 and 3.7 Hz), resulting in a doublet x doublet at 5.13 ppm {literature value for the enantiomeric (2*S*)-2-phenylpyrrolidine-(*R*)-MTPA-amide: 5.14 ppm (d x d, J = 7.9, 3.7 Hz)}. The H2 methine proton of (2*S*)-2-phenylpyrrolidine-(*S*)-MTPA-amide gave a triplet with a coupling of 7.3 Hz at 5.06 ppm {literature value: 5.09 ppm (t, J = 7.6 Hz)}.

The enantiomeric purity of (*S*)-2-(4-methylphenyl)pyrrolidine **5b** was confirmed *via* NMR experiments using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol) as a chiral solvating agent.[21] When 1.7 equiv. of (*R*)-Pirkle alcohol was added to (*S*)-2-(4-methylphenyl)pyrrolidine **5b**, no chemical shift nonequivalences could be observed in the ^{1}H NMR spectrum. However, upon addition of a small amount of (*R*)-2-(4-methylphenyl)pyrrolidine **5b** to the solution of (*S*)-**5b**, a well-resolved spectral nonequivalence of the signal from the CH_3-protons appeared in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$).

In conclusion, it is demonstrated that enantiopure 2-arylpyrrolidines are prepared in high yield *via* stereoselective reduction of γ-chloro *N*-sulfinylketimines. Depending on the chirality of the starting substrate, (R_S,*S*)- and (S_S,*R*)-2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** became accessible in high yield by reduction with lithium triethylborohydride. Treatment of the stereochemically pure 2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines **3a–d** with a saturated solution of HCl in dioxane afforded (*S*)- and (*R*)-2-arylpyrrolidine hydrochlorides **4a–d** in high yield which were further neutralized to the corresponding enantiomerically pure (*S*)- and (*R*)-2-arylpyrrolidines **5a–d** in quantitative yield.

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Notes and references

1 (*a*) F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P. S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou and P. J. Caroll, *J. Org. Chem.*, 1997, **62**, 2555; (*b*) P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003; (*c*) F. A. Davis, *J. Org. Chem.*, 2006, **71**, 8993 and references cited therein.

2 (*a*) D. A. Cogan, G. Liu and J. A. Ellman, *Tetrahedron*, 1999, **55**, 8883; (*b*) J. A. Ellman, T. D. Owens and T. P Tang, *Acc. Chem. Res.*, 2002, **35**, 984; (*c*) J. A. Ellman, *Pure Appl. Chem.*, 2003, **75**, 39; (*d*) T. Kochi and J. A. Ellman, *J. Am. Chem. Soc.*, 2004, **126**, 15652; (*e*) K. M. Brinner and J. A. Ellman, *Org. Biomol. Chem.*, 2005, **3**, 2109.

3 F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162 and references cited therein.

4 (*a*) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2007, **72**, 3211; (*b*) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2008, **73**, 5662; (*c*) B. Denolf, S. Mangelinckx, K. W. Törnroos and N. De Kimpe, *Org. Lett.*, 2006, **8**, 3129; (*d*) B. Denolf, S. Mangelinckx, K. W. Törnroos and N. De Kimpe, *Org. Lett.*, 2007, **9**, 187; (*e*) A. V. Malkov, S. Stončius and P. Kočovsk, *Angew. Chem., Int. Ed.*, 2007, **46**, 3722; (*f*) D. M. Hodgson, J. Kloesges and B. Evans, *Org. Lett.*, 2008, **10**, 2781; (*g*) Q. Chen, J. Li and C. Yuan, *Synthesis*, 2008, 2986; (*h*) E. Leemans, S. Mangelinckx and N. De Kimpe, *Synlett*, 2009, **8**, 1265; (*i*) D. M. Hodgson, J. Kloesges and B. Evans, *Synthesis*, 2009, 1923.

5 (*a*) R. L. Elliott, H. Kopecka, N.-H. Lin, Y. He and D. S. Garvey, *Synthesis*, 1995, 772; (*b*) N.-H. Lin, G. M. Carrera, Jr., and D. J. Anderson, *J. Med. Chem.*, 1994, **37**, 3542.

6 For examples, see: (*a*) A. Elbein and R. I. Molyneux, in *Alkaloids, Chemical and Biological Perspectives*, ed. S. W. Pelletier, John Wiley, New York, 1990; (*b*) *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, San Diego, 2000, vol. 54; (*c*) J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571 and references cited therein.

7 (*a*) F. Mesnard, S. Girard, O. Fliniaux, R. K. Bhogal, F. Gillet, J. Lebreton, M.-C. Fliniaux and R. J. Robins, *Plant Sci.*, 2001, **161**, 1011; (*b*) D. E. Martin, E. G. Robertson, J. G. MacLellan, P. D. Godfrey, C. D. Thompson and R. J. S. Morrison, *J. Am. Chem. Soc.*, 2009, **131**, 2638.

8 (*a*) S. Wu, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 715; (*b*) J. M. Andrés, I. H. Sierra, R. Pedrosa and A. P. Encabo, *Eur. J. Org. Chem.*, 2000, 1719; (*c*) A. J. Mota, A. Chiaroni and N. Langlois, *Eur. J. Org. Chem.*, 2003, 4187; (*d*) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (*e*) F. A. Davis, H. Xu, Y. Wu and J. Zhang, *Org. Lett.*, 2006, **8**, 2273; (*f*) P. Dubon, A. Farwick and G. Helmchen, *Synlett*, 2009, 1413.

9 (*a*) C. J. Rogers, T. J. Dickerson, A. P. Brogan and K. D. Janda, *J. Org. Chem.*, 2005, **70**, 3705; (*b*) S. E. Reisman, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2008, **130**, 7198; (*c*) E. A. Peterson and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6328.

10 (*a*) J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581; (*b*) P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1; (*c*) M. P. Doyle, R. J. Pieters, S. F. Martin, R. E. Austin, C. J. Olamann and P. J. Muller, *J. Am. Chem. Soc.*, 1991, **113**, 1423.

11 J. L. García Ruano, J. Alemán and M. B. Cid, *Synthesis*, 2006, 687.

12 L. R. Reddy and M. Prashad, *Chem. Commun.*, 2010, **46**, 222.

13 For selected examples, see: (*a*) P. Sulmon, N. De Kimpe, N. Schamp, B. Tinant and J. P. Declercq, *Tetrahedron*, 1988, **44**, 3653; (*b*) G. Verniest, S. Claessens, F. Bombeke, T. Van Thienen and N. De Kimpe, *Tetrahedron*, 2005, **61**, 2879; (*c*) G. Verniest, R. Surmont, E. Van Hende, A. Deweweire, F. Deroose, J. W. Thuring and N. De Kimpe, *J. Org. Chem.*, 2008, **73**, 5458; (*d*) M. D'hooghe, B. De Meulenaer and N. De Kimpe, *Synlett*, 2008, 2437; (*e*) N. De Kimpe and C. Stevens, *Synthesis*, 1993, 89.

14 (*a*) S. Mangelinckx, N. Giubellina and N. De Kimpe, *Chem. Rev.*, 2004, **104**, 2353 and references cited therein; (*b*) N. Giubellina, W. Aelterman and N. De Kimpe, *Pure Appl. Chem.*, 2003, **75**, 1433, and references cited therein.

15 F. Morlacchi, V. Losacco and V. Tortorella, *Gazz. Chim. Ital.*, 1975, **105**, 349.

16 (*a*) K. Higashiyama, I. Hiroaki and H. Takahashi, *Tetrahedron*, 1994, **50**, 1083; (*b*) M. Yus, T. Soler and F. Foubelo, *J. Org. Chem.*, 2001, **66**, 6207.

17 B. E. Maryanoff and D. F. McComsey, *J. Heterocycl. Chem.*, 1985, **22**, 911.

18 (*a*) F. Morlacchi and V. Losacco, *J. Heterocycl. Chem.*, 1976, **13**, 165; (*b*) A. I. Meyers and L. E. Burgess, *J. Org. Chem.*, 1991, **56**, 2294; (*c*) L. E. Burgess and A. I. Meyers, *J. Org. Chem.*, 1992, **57**, 1656.

19 (*a*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1968, **90**, 3732; (*b*) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; (*c*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; (*d*) G. R. Sullivan, J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 2143.

20 (*a*) T. R. Hoye and M. K. Renner, *J. Org. Chem.*, 1996, **61**, 8489; (*b*) J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17; (*c*) P. Vidal, C. Pedregal, N. Díaz, J. L. A. Broughton, A. Jiménez and J. F. Espinosa, *Org. Lett.*, 2007, **9**, 4123.

21 W. H. Pirkle, D. L. Sikkenga and M. S. Pavlin, *J. Org. Chem.*, 1977, **42**, 384.

