Tetrahedron Letters 50 (2009) 4710–4713

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of 3-substituted tetrahydroisoquinolines from phthalan and chiral *N*-sulfinylimines

Daniel García, Benjamín Moreno, Tatiana Soler, Francisco Foubelo *, Miguel Yus *

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

ARTICLE INFO

Article history:
Received 5 May 2009
Revised 2 June 2009
Accepted 2 June 2009
Available online 6 June 2009

Keywords:
Reductive ring opening
Phthalan
DTBB-catalysed lithiation
Chiral sulfinylimines
Organozincates
Diastereoselective addition

ABSTRACT

The reaction of the dianionic intermediate [resulting from the reductive opening of phthalan (**1**) with lithium] with chiral *N*-*tert*-butylsulfinyl aldimines **3** in the presence of $ZnMe_2$ gives, after hydrolysis, *N*-*tert*-butylsulfinyl amino alcohols **4** with high diastereoselectivity. Successive treatment of compounds **4** with hydrogen chloride in methanol, thionyl chloride in chloroform and sodium hydroxide yields 3-substituted tetrahydroisoquinolines **6**.

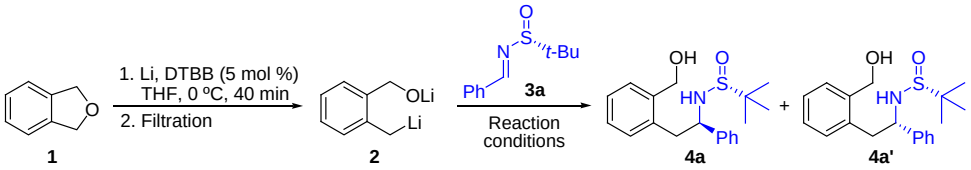
Isoquinoline alkaloids[1] are widespread represented in nature. In many cases, these natural products are cytotoxic agents that display antitumor and antimicrobial activities, which are closely related to the tetrahydroisoquinoline unit. For this reason the asymmetric synthesis[2] of substituted tetrahydroisoquinolines has been of great interest for synthetic organic chemists in the aim of discovering new drugs. One of the most direct and reliable methods for the asymmetric synthesis of amine derivatives is the addition of an organometallic reagent (mainly organomagnesium,[3] organolithium,[4] organozinc[5] and organoindium[6] derivatives) to the C=N bond of enantiopure sulfinylimines. In this context, *N*-*tert*-butylsulfinyl derivatives have found high applicability in synthesis[7] as electrophiles due to the possibility of preparing both enantiomers in large-scale processes[8] and also because the chiral auxiliary can be easily removed under acidic conditions.[4b] In addition, practical processes for recycling the *tert*-butylsulfinyl group upon deprotection of *N*-*tert*-butylsulfinylamines have been reported recently, making this chiral auxiliary even more attractive.[9] On the other hand, functionalised organolithium compounds[10] are accessible through different procedures, among them, the reductive ring opening of heterocycles[11] using an arene-catalysed lithiation.[12] The benzylic carbon–oxygen bonds are susceptible to suffering reductive cleavage by means of a lithiating reagent to generate benzylic organolithium compounds. In the case of phthalan (**1**), the resulting dianionic intermediate **2**[13] (Table 1) has shown a wide use in organic synthesis. For instance, the reaction of **2** with keto derivatives of some protected monosaccharides (glucose and fructose),[14] as well as steroids (estrone and cholestanone),[15] gives the expected selectively functionalised natural products. Racemic 3-substituted tetrahydroisoquinolines were obtained upon cyclisation of the resulting amino alcohols after reaction of **2** with non-enolisable *N*-trimethylsilylaldimines.[16] Intermediate **2** has also been transformed into the corresponding functionalised organozinc derivative by a lithium–zinc transmetallation process with zinc bromide and its reactivity towards different electrophiles was studied.[17] Substituted phthalans at both the five-membered heterocyclic ring[18] and the aromatic ring[19] undergo in most cases a regioselective reductive cleavage leading to the corresponding functionalised benzylic organolithium compounds. In addition, García Ruano and co-workers found that benzylic organolithium derivatives reacted with *N*-*p*-tolylsulfinylimines with high stereoselectivity.[20] With these antecedents, we considered of interest to explore the reactivity of the anionic intermediate **2** resulting from the reductive opening of phthalan (**1**) with chiral *N*-*tert*-butylsulfinylimines in order to apply this methodology to the synthesis of substituted tetrahydroisoquinolines in a highly enantioselective manner.

The lithiation of the phthalan (**1**) with an excess of lithium (1:10 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 5 mol %) in THF at 0 °C for 40 min led to a solution of the corresponding intermediate **2**. After filtration of the excess of lithium at room temperature, to the resulting solution of the functionalized organolithium compound **2** was added a THF solution of the

* Corresponding authors. Fax: +34 965 903549 (M.Y.).
E-mail addresses: foubelo@ua.es (F. Foubelo), yus@ua.es (M. Yus).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.010

Table 1
Screening and optimisation of the reaction conditions[a]



Entry	Reaction conditions			Product	
	Additives (1.1 equiv)	*T* (time)	Hydrolysis	Yield[b] (%)	**4a**:**4a**′ ratio[c]
1	—	−78 to 20 °C (12 h)	−78 to 20 °C	47	78:22
2	$AlMe_3$	−65 °C (12 h)	−65 to 20 °C	25	95:5
3	$AlMe_3$	−55 °C (12 h)	−55 to 20 °C	42	69:31
4	$ZnMe_2$	−65 °C (12 h)	−65 to 20 °C	78	86:14
5	$ZnMe_2$	−30 °C (12 h)	−30 to 20 °C	69	83:17
6	$ZnMe_2$	−5 °C (12 h)	−5 to 20 °C	61	67:33
7	$ZnEt_2$	−65 °C (12 h)	−65 to 20 °C	27[d]	63:37

[a] Phthalan (**1**, 3 equiv) was treated with an excess of lithium in the presence of a catalytic amount of DTBB at 0 °C. After filtration of the excess of lithium, the corresponding additive was added at room temperature and after 15 min, the reaction mixture was cooled down and aldimine **3a** (1 equiv) was added.
[b] Yield of the major reaction product **4a** based on the starting aldimine **3a**.
[c] Diastereomeric mixture was determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Sulfinamide **5** was obtained in 37% yield.

chiral aldimine (*R*)-**3a** [easily prepared from benzaldehyde and (*R*)-*tert*-butylsulfinamide][21] at −78 °C and the reaction mixture was allowed to reach the room temperature for 12 h. Final hydrolysis led to a mixture of diastereomeric *N*-*tert*-butylsulfinyl amino alcohols **4a** and **4a**′ in a 78:22 ratio, the major diastereoisomer **4a** being isolated in a 47% yield (Table 1, entry 1). In order to improve, both diastereoselectivity and the yield of the reaction, $AlMe_3$ was added to the THF solution of intermediate **2** and the mixture was stirred for 15 min at room temperature prior to the addition of aldimine (*R*)-**3a** at −65 °C. Under these reaction conditions, aminoalcohols **4** were obtained with a higher diastereoselectivity (95:5 dr) but in a very low yield due to a poor conversion (Table 1, entry 2). It has been reported that yields and diastereoselectivities are improved when the addition of organolithium compounds to ketimines is performed in the presence of $AlMe_3$.[3b] When the reaction was performed with the same additive at −55 °C, through an inverse addition, that means addition of organolithium intermediate **2** to a solution of aldimine (*R*)-**3** and $AlMe_3$, the yield increased to 54% but diastereomeric ratio was 69:31 (Table 1, entry 3). In our research group we found out recently that the reaction of triorganozincates with *N*-*tert*-butylsulfinylimines gives the expected α-branched sulfinamides in good to excellent yields with diastereomeric ratios of up to 98:2, however, no reaction was observed with dialkylzincs.[22] Thus, when $ZnMe_2$ was used as additive, the reaction of the resulting mixed organozincate with aldimine **3a** at −65 °C for 12 h gave, after hydrolysis, the expected mixture of amino alcohols **4a** and **4a**′ in 78% yield and 86:14 ratio (Table 1, entry 4).[23] Due to the slow transfer rate of the methyl group, it can be used as a non-transferable one in these processes. Yields and stereoselectivities were lower when the process was performed with the same additive and at −30 °C and −5 °C (Table 1, entries 5 and 6). A mixture of the expected compounds **4** and sulfinamide **5** (Chart 1) was obtained when $ZnEt_2$ was used as an additive. Compound **5** results from the addition of the ethyl group to the imine (Table 1, entry 7). For the resulting mixed zincate in this case, there is a competition between the benzyl and the ethyl groups which both are transferable. Regarding the stereochemistry of the major isomer **4a**, it was unambiguously determined by single X-ray analysis[24] and the obtained structure showed that the configuration of the new stereogenic centre was *R* (Chart 1). This result is consistent with an approach of the nucleophile from the

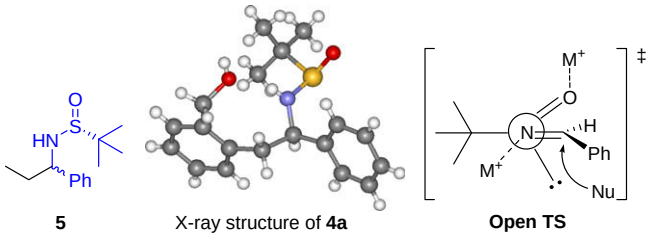
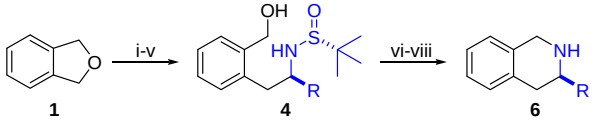


Chart 1.

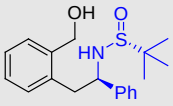
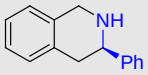
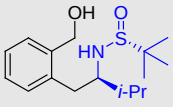
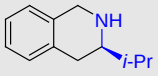
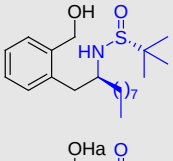
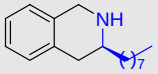
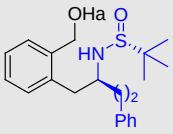
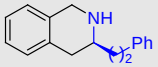
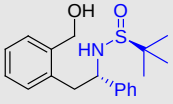
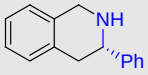
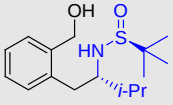
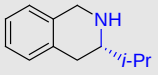
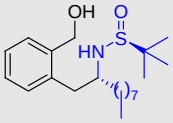
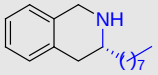
re-face of C=N through an open transition state in the twofold Lewis acid coordinated (*Rs*)-sulfinylimine, due to the large excess of lithium cations and organozinc compounds (Chart 1). Theoretical calculations support that a like *s*-*cis* conformation of these sulfinylimines is the most stable conformation.[7g,25]

The reaction of the dianionic intermediate **2** with different chiral *N*-sulfinyl aldimines **3** was performed under the previously optimised conditions (Table 1, entry 4). Compounds **4** were obtained in rather good yields and high diastereoselectivities (Scheme 1 and Table 2). The major diastereomers were isolated after column chromatography and fully characterised in all cases. The nucleophilic attack occurs predominantly to the *re*-face of the imine unit for R_S-isomers (Table 2, entries 1–4) and to the *si*-face in the case of S_S-derivatives (Table 2, entries 5-7) according to the proposed open transition state. The *tert*-butylsulfinyl group was easily removed under acidic conditions, yielding the corresponding amino alcohols in quantitative yields. These amino alcohols are adequate precursors of tetrahydroisoquinolines **6** after



Scheme 1. Reagents and conditions: (i) Li, DTBB (5 mol %), THF, 0 °C, 40 min; (ii) filtration; (iii) $ZnMe_2$, 20 °C, 15 min; (iv) RCH=NS(O)*t*-Bu (**3**), −65 °C, 12 h; (v) H_2O, −65 to 20 °C; (vi) HCl/dioxane (4 M), MeOH, 20 °C; (vii) Cl_2SO, $CHCl_3$, 50 °C; (viii) NaOH/H_2O (5 M), THF, 20 °C.

Table 2
Preparation of 3-substituted tetrahydroisoquinolines **6**

Entry	Aldimines **3**		Compounds **4**[a]				Tetrahydroisoquinolines **6**[a,b]		
	No.	R	No.	Structure	Yield[c] (%)	dr[d]	No.	Structure	Yield[e] (%)
1	(*R*)-**3a**	Ph	**4a**		78	86:14	**6a**		72
2	(*R*)-**3b**	*i*-Pr	**4b**		69	77:23	**6b**		74
3	(*R*)-**3c**	$CH_3(CH_2)_7$	**4c**		79	85:15	**6c**		80
4	(*R*)-**3d**	$Ph(CH_2)_2$	**4d**		71	87:13	**6d**		79
5[f]	(*S*)-**3a**	Ph	**4e**		54	77:23	**6e**		67
6	(*S*)-**3b**	*i*-Pr	**4f**		57	71:29	**6f**		78
7	(*S*)-**3c**	$CH_3(CH_2)_7$	**4g**		55	85:15	**6g**		80

[a] Products **4** and **6** were ≥95% pure (GLC and 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR and LRMS/HRMS).
[b] ee ≥ 97% determined by HPLC using a ChiralCel OJ column.
[c] Isolated yield of the major diastereoisomer based on the starting aldimine **3**.
[d] Diastereomeric mixture was determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] Isolated yield from compounds **4**.
[f] The reaction was performed in the absence of $ZnMe_2$ as additive.

intramolecular dehydration when they were successively treated with thionyl chloride in chloroform at 50 °C and then with a 5 M aqueous solution of sodium hydroxide in THF at room temperature (Scheme 1 and Table 2).[26] The ee values of chiral tetrahydroisoquinolines **6** were determined by chiral HPLC analysis, being in all cases higher than 97%.

In conclusion, we describe here a straightforward synthesis of 3-substituted tetrahydroisoquinolines **6** with high enantiomeric purity starting from phthalan (**1**) and chiral *N*-*tert*-butylsulfinyl aldimines **3**, through a two-pot strategy: (1) Reaction of the dianionic intermediate **2** resulting from the reductive opening lithiation of phthalan (**1**) with chiral aldimines **3** in the presence of $ZnMe_2$ and (2) cyclisation of the amino alcohol resulting from the removal of the *tert*-butylsulfinyl unit.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; Grant Nos. CSD2007-00006, CTQ2004-01261 and Consolider Ingenio 2010). D.G. thanks the University of Alicante for a predoctoral fellowship. We also thank Medalchemy S. L. and Chemetall GmbH for a gift of enantiopure *tert*-butylsulfinamides (*S* and *R*) and lithium, respectively.

References and notes

1. For a review, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. For reviews, see: (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J. *Curr. Org. Chem.* **2003**, *7*, 1775–1792; (b) Bracca, A. B. J.; Kaufman, T. S. *Tetrahedron* **2004**, *60*, 10575–10610; (c) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676–2690.
3. (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914; (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883–8904; (c) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396–3397; (d) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645–1647; (e) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599–2602; (f) Dirscherl, G.; Rooshenas, P.; Schreiner, P. R.; Lamaty, F.; König, B. *Tetrahedron* **2008**, *64*, 3005–3016.
4. (a) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268–269; (b) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904; (c) Davis, F. A.; Melamed, J. Y.; Sharik, S. S. *J. Org. Chem.* **2006**, *71*, 8761–8766.
5. (a) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244–8250; (b) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983–986; (c) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269–5278; (d) Chemla, F.; Ferreira, F. *Synlett* **2006**,

2613–2616; (e) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979–4982; (f) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291–9294; (g) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235–1241; (h) Voituriez, A.; Pérez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931–934.

6. (a) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823–3825; (b) Wang, Z.-Q.; Feng, C.-Q.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336–5337; (c) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259–1262; (d) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777–2780; (e) Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Heterocycles* **2008**, *76*, 569–581.
7. For reviews, see: (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (c) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39–46; (d) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030; (e) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905; (f) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831–840; (g) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.
8. (a) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317–1320; (b) Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157–165.
9. (a) Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646–2650; (b) Aggarwal, V. K.; Barbero, N.; McGarrigle, E. M.; Mickle, G.; Navas, R.; Suárez, J. R.; Unthank, M. G.; Yar, M. *Tetrahedron Lett.* **2009**, *50*, 3482–3484.
10. For reviews on functionalised organolithium compounds, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181; (b) Nájera, C.; Yus, M. *Org. Prep. Proc. Int.* **1995**, *27*, 383–457; (c) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67–96; (d) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107; (e) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926; (f) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255–9303; (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722; (h) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139–3176; (i) See also the special issue of Tetrahedron Symposium in Print (Eds.: Nájera, C; Yus, M.) devoted to 'Functionalised Organolithium Compounds', *Tetrahedron* **2005**, *61*, issue no. 13.; (j) Yus, M.; Foubelo, F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. Chapter 2; (k) Foubelo, F.; Yus, M. *Chem. Soc. Rev.* **2008**, *37*, 2620–2633.
11. For reviews, see: (a) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107; (b) Yus, M.; Foubelo, F. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2002; pp 136–171; (c) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453–1475; (d) Yus, M.; Foubelo, F. *Adv. Heterocycl. Chem.* **2006**, *91*, 135–158.
12. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; (c) Yus, M. *Synlett* **2001**, 1197–1205; (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79–92; (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 75–115; (f) Yus, M.. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, 2004; Vol. 1,. Part 2, Chapter 11.
13. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3351–3364.
14. (a) Soler, T.; Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3939–3943; (b) Soler, T.; Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 493–517.
15. (a) Falvello, L. R.; Foubelo, F.; Soler, T.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2063–2066; (b) Foubelo, F.; Soler, T.; Yus, M. *Tetrahedron: Asymmetry* **2001**, *12*, 801–810.
16. Foubelo, F.; Gómez, C.; Gutiérrez, A.; Yus, M. *J. Heterocycl. Chem.* **2000**, *37*, 1061–1064.
17. (a) Pastor, I. M.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 1589–1592; (b) Pastor, I. M.; Yus, M. *Tetrahedron* **2001**, *57*, 2371–2378; (c) Yus, M.; Gomis, J. *Tetrahedron Lett.* **2001**, *42*, 5721–5724; (d) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2002**, 1989–1995; (e) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2003**, 2043–2048.
18. Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913–4919.
19. (a) Foubelo, F.; García, D.; Moreno, B.; Yus, M. *Tetrahedron Lett.* **2007**, *48*, 3379–3383; (b) García, D.; Foubelo, F.; Yus, M. *Tetrahedron* **2008**, *64*, 4275–4286.
20. (a) García Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736–2737; (b) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677–680; (c) García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513–4516; (d) García Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron* **2004**, *60*, 5383–5392; (e) Arroyo, Y.; Meana, A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García Ruano, J. L. *J. Org. Chem.* **2005**, *70*, 3914–3920; (f) García Ruano, J. L.; Alemán, J.; Parra, A. *J. Am. Chem. Soc.* **2005**, *127*, 13048–13054; (g) García Ruano, J. L.; Alemán, J.; Cid, M. B. *Synthesis* **2006**, 687–691; (h) Arroyo, Y.; Rodríguez, J. F.; Santos, M.; Sanz Tejedor, M. A.; García Ruano, J. L. *J. Org. Chem.* **2007**, *72*, 1035–1038; (i) Arroyo, Y.; Meana, A.; Sanz Tejedor, M. A.; Alonso, I.; García Ruano, J. L. *J. Org. Chem.* **2009**, *74*, 764–772.
21. See, for instance: Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
22. (a) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 603–606; (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484–2491.
23. *Typical procedure for the diastereoselective synthesis of compounds **4a** and **4a′***. To a blue suspension of lithium powder (140 mg, 20.0 mmol) and a catalytic amount of DTBB (80.0 mg, 0.3 mmol) in THF (5 mL) was added dropwise a solution of phthalan (**1**, 360 mg, 3.0 mmol) under argon and the mixture was stirred at 0 °C for 45 min. Then, the excess of lithium was filtered off and a solution of $ZnMe_2$ (3.0 mL, 1.0 M in hexane) was added dropwise and stirring was continued for 15 min at room temperature. After this, the reaction mixture was cooled down to −65 °C and a solution of aldimine (*R*)-**3a** (209 mg, 1.0 mmol) in THF (0.4 mL) was added dropwise. After 12 h at the same temperature, finally the reaction mixture was hydrolysed with water (5 mL), extracted with ethyl acetate (3 × 15 mL) once at rt, dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products **4a** and **4a′**. (*1R*,*R*$_S$)-*N*-*tert*-Butylsulfinyl-2-(2-hydroxymethylphenyl)-1-phenylethanamine (**4a**): mp 129–130 °C (pentane/dichloromethane); $[\alpha]_D^{20}$ −40 (*c* 0.16, CH_2Cl_2); R_f: 0.20 (*n*-hexane/EtOAc: 1:2); IR *ν* (KBr) 3450–3310, 2920 cm^{-1}; ^{1}H NMR *δ* 1.00 (s, 9H), 3.02 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.43 (dd, *J* = 13.6, 8.7 Hz, 1H), 4.22 (br s, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.59–4.65 (m, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 5.11 (br s, 1H), 7.10–7.15 (m, 1H), 7.16–7.24 (m, 2H), 7.23–7.32 (m, 4H), 7.41 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR *δ* 22.5 (CH_3), 40.2 (CH_2), 56.3 (C), 60.9 (CH_2), 63.0 (CH), 126.8, 127.2, 127.8, 127.9, 128.5, 129.6, 130.3, 136.7, 139.0, 142.5 (ArC); MS (MALDI-TOF): *m/z* 332 $(M+H)^+$; HRMS: $(M-H_2O)^+$ found 313.1487, $C_{19}H_{23}NOS$ requires 313.1500. (*1S*,*R*$_S$)-*N*-*tert*-Butylsulfinyl-2-(2-hydroxymethylphenyl)-1-phenylethanamine (**4a′**): mp 127–128 °C (pentane/dichloromethane); $[\alpha]_D^{20}$ −38 (*c* 0.48, CH_2Cl_2); R_f: 0.14 (*n*-hexane/EtOAc: 1:2); IR *ν* (KBr) 3430–3300, 2923 cm^{-1}; ^{1}H NMR *δ* 1.10 (s, 9H), 3.12 (dd, *J* = 11.8, 5.3 Hz, 1H), 3.20 (dd, *J* = 11.8, 6.3 Hz, 1H), 3.70 (br s, 1H), 4.10–4.16 (m, 1H), 4.62–4.71 (m, 3H), 7.11–7.16 (m, 1H), 7.26–7.34 (m, 8H); ^{13}C NMR *δ* 22.7 (CH_3), 42.1 (CH_2), 56.0 (C), 60.8 (CH_2), 63.3 (CH), 127.3, 127.5, 127.8, 128.5, 128.7, 130.2, 130.8, 136.2, 139.6, 142.6 (ArC); MS (MALDI-TOF): *m/z* 332 $(M+H)^+$.
24. Crystal data (excluding structure factors deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 727086): $C_{19}H_{25}NO_2S$, *M* = 331.46; monoclinic, *a* = 10.3893(9) Å, *b* = 18.4104(16) Å, *c* = 10.3906(9) Å, *β* = 106.513(2); *V* = 1905.5(3) Å^3; space group *P*2(1); *Z* = 4; D_c = 1.155 Mg m^{-3}; *λ* = 0.71073 Å; *μ* = 0.179 mm^{-1}; *F*(000) = 712; *T* = 23 ± 1 °C. Data collection was performed on a Bruker Smart CCD diffractometer, based on three *ω*-scan runs (starting = −34°) at values *φ* = 0°, 120°, 240° with the detector at 2*θ* = −32°. For each of these runs, 606 frames were collected at 0.3° intervals and 30 s per frame. An additional run at *φ* = 0° of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the program SAINT (SAINT Version 6.02A: Area-Detector Integration Software.; Siemens Industrial Automation, Inc.: Madison, WI, 1995) and the integrated intensities were corrected for Lorentz-polarisation effects with SADABS (Sheldrick, G. M. SADABS: Area-Detector Absorption Correction; Göttingen University, 1996). The structure was solved by direct methods[27] and was refined to all 7474 unique F_o by full matrix least squares.[27] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final wR_2 = 0.1176 for all data and 429 parameters; R_1 = 0.0454 for 6318 $F_o > 4\sigma(F_o)$.
25. (a) Bharatam, P. V.; Amita; Kaur, D. *J. Phys. Org. Chem.* **2002**, *15*, 197–203; (b) Bharatam, P. V.; Uppal, P.; Amita; Kaur, D. *J. Chem. Soc. Perkin Trans. 2* **2000**, 43–50.
26. *Typical procedure for stereoselective synthesis of compound **6a***. To a stirred solution of **4a** (165 mg, 0.50 mmol) in MeOH (6 mL) was added a 4 M HCl (1 mL) solution in dioxane at 0 °C. After 3 h stirring at this temperature, a saturated $NaHCO_3$ solution was added. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was taken up in chloroform (5 mL), and thionyl chloride (0.1 mL, 1.7 mmol) was added at 0 °C. The solution was stirred at 50 °C for 4 h. After this, solvents were evaporated (15 Torr) and the resulting residue was dissolved in THF (5 mL) and a 5 M sodium hydroxide solution (10 mL) was added. The resulting mixture was vigorously stirred for 10 h at 20 °C and then it was extracted with ethyl acetate (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, chloroform/methanol) to yield pure title product (*R*)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**6a**):[28] $[\alpha]_D^{20}$ +125 (*c* 0.55, CH_2Cl_2); R_f: 0.34 (chloroform/methanol: 10:1); HPLC analysis (HPLC analyses were performed on a JASCO 200-series equipped with a CHIRALCEL-OJ column, 1.0 mL/min, *λ* = 215 nm, 99:1 *n*-hexane/*i*-PrOH), t_R = 79.7 min; IR *ν* (KBr) 3420–3385, 3063, 3026, 2923, 2851 cm^{-1}; ^{1}H NMR *δ* 2.02 (br s, 1H), 3.02 (d, *J* = 7.5 Hz, 2H), 4.05 (t, *J* = 7.5 Hz, 1H), 4.17 (d, *J* = 15.5 Hz, 1H), 4.28 (d, *J* = 15.5 Hz, 1H), 7.07–7.18 (m, 4H), 7.29–7.40 (m, 3H), 7.44 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR *δ* 37.8 (CH_2), 49.3 (CH), 58.7 (CH_2), 126.1, 126.4, 126.8, 127.6, 128.6, 128.8, 129.2, 134.7, 134.8, 143.9 (ArC); MS: *m/z* 209 (M^+, 33%), 208 (26), 207 (26), 206 (31), 132 (16), 130 (12), 105 (22), 104 (100), 103 (29), 102 (14), 90 (10), 89 (21), 78 (29), 77 (26), 76 (10); HRMS: M^+ found 209.1204, $C_{15}H_{15}N$ requires 209.1204.
27. SHELX97 [includes SHELXS97, SHELXL97 and CIFTAB]—Programs for Crystal Structure Analysis (Release 97-2). Sheldrick, G. M., Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998.
28. Enders, D.; Braig, V.; Boudou, M.; Raabe, G. *Synthesis* **2004**, 2980–2990.