Pergamon

Tetrahedron Letters 42 (2001) 4515–4518

TETRAHEDRON LETTERS

Deracemization of alkyl diarylmethanes using (−)-sparteine or a chiral proton source

Laurence Prat, Georges Dupas, Jack Duflos, Guy Quéguiner, Jean Bourguignon and Vincent Levacher*

Laboratoire de Chimie Organique Fine et Hétérocyclique associé au CNRS, IRCOF-INSA, rue Tenières BP 08, F-76131 Mont Saint Aignan Cedex, France

Received 2 March 2001; revised 11 May 2001; accepted 13 May 2001

Abstract—In a first stage, deracemization of 2-(1-phenylethyl)pyridine **1** and chlorpheniramine **2** was investigated in the presence of (−)-sparteine as a chiral ligand. Whereas (*R*)-2-(1-phenylethyl)pyridine **1** was obtained in 65% ee with 2,6-di-*tert*-butyl-4-methylphenol as a proton donor, the opposite stereoselection was observed with EtOH leading to (*S*)-2-(1-phenylethyl)pyridine **1** in 53% ee. A second methodology making use of (+)-(*R*)-1-[5-chloro-2-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline **4** as a chiral proton source gave higher enantioselectivities, affording (*R*)-**1** and (*R*)-**2** in up to 84 and 75% ee, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

While deracemization processes have been widely developed in the field of enolate chemistry,[1] little work has been devoted to extend the scope of this methodology to other substrates.[2] In the course of a project aimed at obtaining enantiomerically pure alkyl diarylmethane derivatives, a framework present in many active principles of important drugs, we recently studied the deracemization of 4-phenyl-1,2,3,4-tetrahydroisoquinoline using (−)-sparteine as a chiral inductor.[2b] As a part of this research program, we wish to report the use of (−)-sparteine and chiral protonating agents in the deracemization of 2-(1-phenylethyl)pyridine **1**[3] and chlorpheniramine **2**,[4] one of the most important antihistaminic agents (Fig. 1).

The preparation of *rac*-2-(1-phenylethyl)pyridine **1** was accomplished by methylation of 2-benzylpyridine according to a literature procedure.[2b] Concurrently, we considered the ability of (−)-sparteine to promote an asymmetric induction during this methylation step. For this purpose the deprotonation–methylation sequence was conducted in the presence of (−)-sparteine in various solvents (Scheme 1).

As can be seen in Table 1, polar solvents such as THF or Et_2O are good candidates to deprotonate **1**, however, with a poor stereoselectivity (Table 1; entries 1 and 2). Enantiomeric excesses of the methylated product **1** were somewhat higher when the reaction was

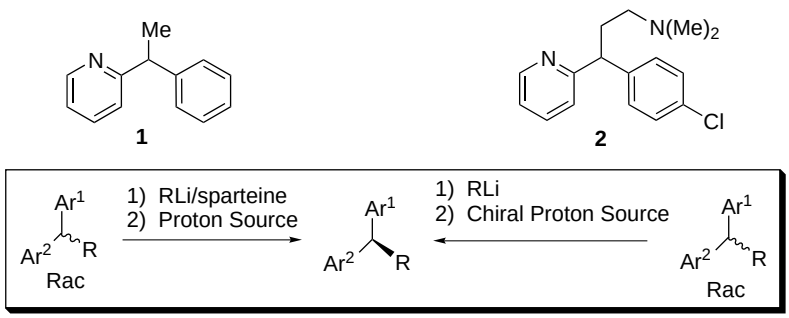
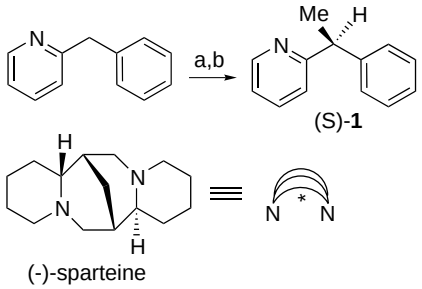


Figure 1.

Keywords: deracemization; asymmetric protonation; (−)-sparteine; chiral proton donor.

* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00784-5



Scheme 1. *Reagents and conditions*: (a) *sec*-BuLi (1.5 equiv.)/(−)-sparteine (1.5 equiv.)/−78°C/1 h; (b) MeI (3.5 equiv.)/3 h/−78°C.

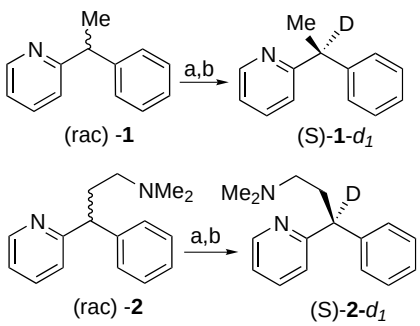
Table 1. Enantioselective methylation of 2-(1-phenylethyl)-pyridine in the presence of (−)-sparteine in different solvents

Entry	Solvent	Yield (%)	ee%[a]
1	THF	72	0
2	Et_2O	88	20 (*S*)
3	Toluene	70	30 (*S*)
4	Cumene	53	30 (*S*)
5	Hexane	44	52 (*S*)
6	Pentane	27	34 (*S*)

[a] Enantiomeric excesses were measured by chiral HPLC. See Ref. 5.

conducted in toluene or cumene (Table 1; entries 3 and 4). The poor enantioselectivity observed in THF may be imputed to the strong complexing properties of the solvent which competes with (−)-sparteine in the complexation of the lithiated diarylmethane species. After optimization, the best enantioselectivity was attained in hexane affording (*S*)-2-(1-phenylethyl)pyridine **1** in 52% ee and 44% isolated yield (Table 1; entry 5).

Given the difficulty encountered to attain high asymmetric induction by alkylation, we turned our interest in a deracemization process in the presence of (−)-sparteine. Firstly, we studied the influence of the solvent on both deprotonation rate and asymmetric induction. Deracemization of (*rac*)-**1** and (*rac*)-**2** was conducted in different solvents at −78°C, followed by addition of MeOD to quench the reaction (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) *sec*-BuLi (1.5 equiv.)/(−)-sparteine (1.5 equiv.)/−78°C/2 h/Et_2O; (b) MeOD/−78°C.

The deprotonation was complete within 2 h in THF, affording **1**-d_1 and **2**-d_1 in 100% yield after addition of MeOD. However, as was the case for the methylation process, no stereoselectivity was observed in that solvent (Table 2; entry 1). When the deprotonation of **1** was carried out in Et_2O without (−)-sparteine, 70% of deuterium incorporation was obtained. The presence of sparteine improved somewhat the deprotonation rate, affording **1**-d_1 with a higher deuterium incorporation (95%), however, in only 36% ee (Table 2; entry 2). In contrast to **1**, it was found that deprotonation of **2** occurs readily in Et_2O without (−)-sparteine, giving rise to **2**-d_1 in 100% yield. This enhancement may be ascribed to the presence of the pendant *N*,*N*-dimethylethylamine moiety which would assist in the deprotonation step via the formation of a pre-complex with *sec*-BuLi. As recorded with **1**, (−)-sparteine is not efficient to promote an asymmetric induction with **2** in that solvent (Table 2; entry 2). Finally, attempts to deracemize both substrates **1** and **2** in toluene or hexane were unsuccessful (Table 2; entries 3 and 4).

In a last attempt to improve this deracemization process by the aid of (−)-sparteine, various protonating agents were also examined in Et_2O. The nature of the proton donor was found to have a pronounced effect on the enantioselectivity, leading in some cases to an inversion of stereoselectivity with both substrates, however, in lower enantioselectivity with **2** (Table 3; entries 1 and 2). In order to clear up this reversal of stereoselectivity, it may be asked whether the pK_a value or the steric features of the protonating agent could influence the stereochemical outcome of the protonation step. As can be observed in Table 3, no relationship could be established between the pK_a value and the degree of enantioselectivity. Indeed, whereas *tert*-BuOH and *tert*-Bu(Me_2)SiOH possess different pK_a values and show comparable steric hindrance, both protonating agents provide the same sense of asymmetric induction with the same level of enantioselectivity (Table 3; entries 2 and 5). In the same way, H_2O, AcOH and AcOEt manifest similar stereoselectivities, although they possess different acid strengths (Table 3; entries 6–8). On the other hand, one may observe that sterically hindered proton sources lead preferentially to (*R*)-**1**, while the least sterically hindered ones afford (*S*)-**1**.

Table 2. Deracemization of **1** and **2** in the presence of (−)-sparteine. Influence of the solvent on the stereoselectivity

Entry	Solvent	Substrate	% D	ee%
1	THF	**1**	100	0
		2	100	0
2	Et_2O	**1**	95[a]	36 (*S*)
		2	100[b]	26 (*S*)
3	Toluene	**1**	25	0
		2	20	2
4	Hexane	**1**	57	12
		2	60	0

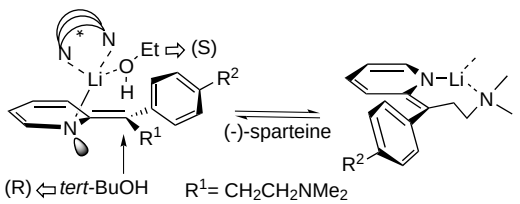
[a] Without (−)-sparteine: **1**-d_1/**1** = 70/30.
[b] Without (−)-sparteine: **2**-d_1 = 100%.

Table 3. Deracemization of **1** and **2** in the presence of (−)-sparteine. Influence of the achiral proton source on the stereoselectivity

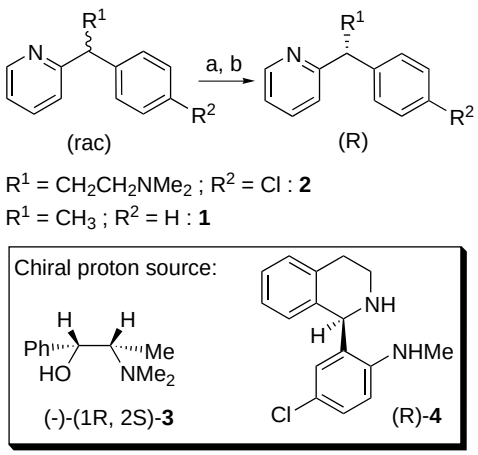
Entry	Substrate	Achiral proton source	pK_a[c]	ee%
1	**1**	EtOH	16	53 (*S*)
	2			22 (*S*)
2	**1**	*tert*-BuOH	18	50 (*R*)
	2			20 (*R*)
3	**1**	2,6-Di-*tert*-butyl-4-methylphenol	12	39 (*R*)[a]
				65 (*R*)[b]
4	**2**	2,6-Di-*tert*-butyl-4-methylphenol	12	18 (*R*)[a]
				19 (*R*)[b]
5	**1**	*tert*-Bu(Me$_2$)SiOH	12[d]	50 (*R*)
6	**1**	H_2O	15.7	20 (*S*)
7	**1**	AcOH	4.8	26 (*S*)
8	**1**	AcOEt	25	33 (*S*)

[a] Addition of a solution of 2,6-di-*tert*-butyl-4-methylphenol in THF.
[b] Addition of 2,6-di-*tert*-butyl-4-methylphenol (solid).
[c] Water pK_a values from March's Advanced Organic Chemistry.
[d] Estimated.

If one assumes that the lithiated species possesses an enamide type structure,[6] as depicted in Scheme 3, this suggests that the inversion of enantiofacial differentiation would originate from a competition between a steric and a chelation control in the protonation step. Interestingly, while powdered 2,6-di-*tert*-butyl-4-methylphenol afforded (*R*)-**1** in 65% ee, the same proton donor displayed lower enantioselectivities when it was added as a solution in THF (Table 3; entry 3).[7] Lastly, it should be noted that in all cases lower ee were recorded with **2** (Table 3; entries 1–4). This difference in behaviour may be due to the presence of the complexing side-chain which would displace sparteine from the lithiated species (Scheme 3).



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) *sec*-BuLi/−78°C/solvent/2 h; (b) chiral protonating agent.

The rather disappointing outcome of the deracemization of **2** with (−)-sparteine prompted us to consider whether the use of a chiral proton source could provide an interesting alternative to obtain a higher level of asymmetric induction. For this purpose, the commercially available (−)-(1*R*,2*S*)-*N*-methylephedrine **3**[8] and (+)-(*R*)-1-[5-chloro-2-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline **4**[9] were tested (Scheme 4).

Whatever the conditions used, *N*-methylephedrine **3** exhibits a low efficiency in the deracemization of both substrates **1** and **2** (Table 4; entries 1–4). In contrast, the chiral diamine **4** provided **1** in 73% ee when the deracemization was carried out in THF (Table 4, entry 5). However, in that solvent the enantioselectivity remains modest with **2** (Table 4, entry 5). Further increases in enantioselectivity were obtained in Et_2O affording **1** in 84% ee, while **2** was isolated in up to 75% ee (Table 4; entries 7 and 8).

In summary, the deracemization of enolates widely reported in literature has been applied to alkyl diarylmethanes showing that this methodology could be extended to a new class of substrates. In a first approach, (−)-sparteine afforded (*R*)-**1** in 60% ee or (*S*)-**1** in 53% ee according to the proton donor used in the protonation step. This methodology gave only modest enantioselectivities with chlorpheniramine **2**. Another approach using the diamine **4** as a chiral proton source allowed the increase in stereoselectivity of this deracemization process, producing (*R*)-**1** and (*R*)-**2** in 84 and 75% ee, respectively. The chiral proton source **4** offers not only the advantage to provide higher stereoselectivities compared to the use of (−)-sparteine, but also to be available in both enantiomeric forms.[9c]

Table 4. Deracemization of **1** and **2** in the presence of a chiral proton source

Entry	Solvent	Substrate	Chiral proton source	ee%
1	THF	1	3	0
2	THF	2	**3**	5 (*R*)
3	Et_2O	1	**3**	4 (*R*)
4	Et_2O	2	**3**	1 (*R*)
5	THF	1	**4**	**73 (*R*)**
6	THF	2	**3**	23 (*R*)
7	Et_2O	1	**3**	**84 (*R*)**
8	Et_2O	2	**3**	**75 (*R*)**

Acknowledgements

This work was supported by grants from the Régions de Basse et Haute Normandie (Réseau Interrégional Normand de Chimie Organique Fine).

References

1. Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566–2587 and references cited therein.
2. For deracemization of other substrates via a deprotonation–reprotonation sequence, see: (a) Burton, A. J.; Graham, J. P.; Simpkins, N. S. *Synlett* **2000**, 1640–1642; (b) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509–2516; (c) Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517.
3. For further asymmetric syntheses of 2-(1-phenylethyl)pyridine **1**, see: (a) Oae, S.; Kawai, T.; Furukawa, N. *Tetrahedron. Lett.* **1984**, *25*, 9–72; (b) Oae, S.; Kawai, T.; Furukawa, N.; Iwasaki, F. *J. Chem. Soc., Perkin Trans. 2* **1987**, 405–411; Azzena, U.; Chelucci, G.; Delogu, G.; Gladiali, S.; Marchetti, M.; Soccolini, F.; Botteghi, C. *Gazz. Chim. Ital.* **1986**, *116*, 307–315.
4. For further asymmetric syntheses of chlorpheniramine **2**, see: (a) Marchetti, M.; Alberico, E.; Bertucci, C.; Botheghi, C.; Del Ponte, G. *J. Mol. Catal. A: Chem.* **1997**, 109–117; (b) Botteghi, C.; Del Ponte, G.; Marchetti, M. *J. Mol. Catal.* **1993**, L1–L4.
5. Chromatographic conditions. 2-(1-Phenylethyl)pyridine **1**: Chiracel OD column (250×4.6 mm; 10 μm). Injection: 20 μL (0.5 mg of **1** in 10 mL of hexane). Eluent: hexane/2-propanol: 99.5/0.5. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 17°C. UV detection: $\lambda = 230$ nm. Retention time: 7.4 min [(*R*)-enantiomer] and 8.0 min [(*S*)-enantiomer]. Chlorpheniramine **2**: ULTRON ES-OVM column (250×4.6 mm; 5 μm). Injection: 20 μL (0.5 mg of **2** in 10 mL of eluent). Eluent: KH_2PO_4 (20 mM)/CH_3CN (100/5 v/v). Flow rate: 1 mL/min. Pressure: 100 psi. Temperature: 20°C. UV detection: $\lambda = 230$ nm. Retention time: 8.3 min [(*R*)-enantiomer] and 12.9 min [(*S*)-enantiomer].
6. For NMR studies and crystal structures of lithiated diarylmethanes, see: Leung, W. P.; Weng, L. H.; Wang, R. J.; Mak, T. C. W. *Organometallics* **1995**, *14*, 4832–4836.
7. Based on the assumption that slow addition of the protonating agent is favourable to control the stereochemical outcome of the protonation, this is realized by addition of 2,6-di-*tert*-butyl-4-methylphenol that is solid and poorly soluble at −78°C in THF.
8. *N*-Methylephedrine and derivatives have been used as chiral proton sources in the enantioselective protonation of enolates. (a) Martin, J.; Lasne, M. C.; Plaquevent, J. C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181–7182; (b) Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909. Fehr, C.; Guntern, O. *Helv. Chim. Acta* **1992**, *75*, 1023.
9. Diamine **4** has been used with success as a chiral proton source in the deracemization of amide enolates: (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175–2176; (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792–2793; (c) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*, 6724–6729.