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Dynamic resolution of lithiated *ortho*-trifluoromethyl styrene oxide and the effect of chiral diamines on the barrier to enantiomerisation†‡

Rosmara Mansueto, Filippo Maria Perna, Antonio Salomone, Saverio Florio and Vito Capriati*

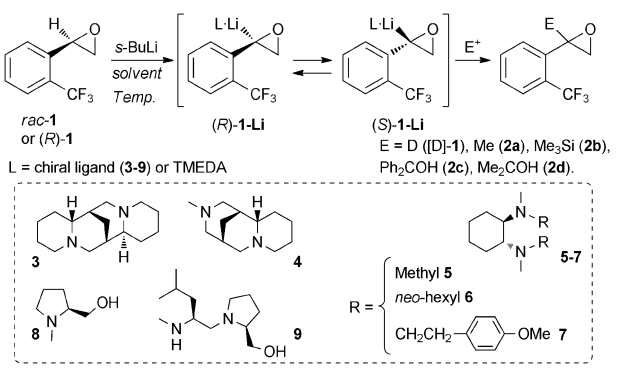
The first dynamic thermodynamic resolution of a racemic oxiranyllithium is described with selectivities of up to 82 : 18 from a selection of three types of chiral ligands (seven ligands in total). Both (−)-sparteine and its (+)-surrogate were surprisingly found to increase the enantiomerisation barrier.

Chiral functionalised organolithiums with a stereogenic lithiated carbon centre are of growing importance in the daily repertoire of synthetic organic chemistry because of their potential utility in enantioselective chemical synthesis.[1] Asymmetric substitution represents an effective alternative to asymmetric deprotonation[2] for the preparation of enantiomerically enriched products. It relies upon a chiral racemic organolithium which is, however, required to undergo equilibration in the presence of a chiral ligand in order that a dynamic resolution can take place. For a dynamic thermodynamic resolution (DTR), the rate of inter-conversion of the diastereomeric organolithium complexes is low compared to that of the subsequent electrophilic substitution; thus, the enantiomeric ratio (er) of the product is determined by the ratio of the above complexes. In contrast, in the case of a dynamic kinetic resolution, the rate of inter-conversion is fast, relatively to the rate of substitution and the organolithium may be resolved by means of the faster reaction of one of the two diastereomeric complexes, which is under Curtin–Hammett conditions.[3]

Enantiomerically enriched epoxides are important building blocks in the production of fine chemicals and pharmaceutical targets. Nowadays, they are usually efficiently prepared by catalytic epoxidation[4] or by a kinetic resolution promoted by chiral (salen)–Cr and (salen)–Co(III) complexes,[5] as well as by hydrolytic enzymes.[6] In light of this, we wondered whether the dynamic resolution of a racemic lithiated oxirane[7] could also be exploited for the preparation of enantiomerically enriched derivatives. To accomplish this goal, it is first required that the oxiranyllithium be configurationally labile, as the asymmetric substitution in the presence of a chiral ligand may benefit from its enantiomerisation. Second, "chemical stability" is also a factor to be taken into consideration, because oxiranyllithiums (which are in all respects lithium carbenoids)[8] may either undergo a faster decomposition as the temperature progresses or exhibit electrophilic behaviour according to the conditions employed.

As for α-lithiated aryl-substituted epoxides, our research group recently reported that, whereas electron-donating groups do not alter the configurational stability in THF and at low temperatures, electron-withdrawing groups trigger racemisation in THF at a rate which is dependent on their position on the phenyl ring.[9] Such a rate proved to be sensitive to both the presence of additives and the nature of the solvent. In particular, higher inversion barriers (that is, slower inter-conversion rates) were detected when TMEDA was used as the ligand jointly with an apolar solvent such as hexane, which is particularly promising for a dynamic resolution under thermodynamic control.

Among the various fluorinated derivatives, α-lithiated *ortho*-trifluoromethyl styrene oxide **1-Li** (Scheme 1) undergoes the fastest racemisation in THF, the half-life being 1.6 s at 157 K, corresponding to an inversion barrier $\Delta G^{\neq}_{enant}$ of 9.5 ± 0.1 kcal mol^{-1} (entry 1, Table 2).[9a] We have now ascertained that the two α-lithiated enantiomers, (*R*)-**1-Li** and (*S*)-**1-Li**, undergo inter-conversion also in an apolar solvent, and the rate proved to be sensitive to the presence of ligands. Indeed, running the deprotonation of a 0.2 M solution of



Scheme 1

Dipartimento di Farmacia – Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., via E. Orabona 4, I-70125 Bari, Italy.
E-mail: vito.capriati@uniba.it; Fax: +39 080 5442539; Tel: +39 080 5442174

† Dedicated to Professor Francesco Naso on the occasion of his 75th birthday.

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enantiomerically enriched (*R*)-**1** (95 : 5 er) (Scheme 1) with *s*-BuLi (1.5 equiv.)–TMEDA (1 equiv.) in hexane, [D]-**1** could be recovered with 76 : 24 er (in favour of the *R* enantiomer) upon quenching the reaction mixture with MeOD, 3 min being the reaction time at 195 K. The barrier to enantiomerisation of **1-Li** was then calculated upon quenching with a deuterium source and upon aging the enantioenriched **1-Li** for different times at 195 K. The obtained first-order plot indicated an estimated racemisation half-life ($t_{1/2}$) of 115 s, which equates to an enantiomerisation barrier ($\Delta G^{\neq}_{enant}$) of 13.5 ± 0.1 kcal mol^{-1} at 195 K (entry 2, Table 2) (see the ESI‡). In the perspective of a dynamic resolution, racemic epoxide **1** was thus chosen as a model substrate.

We began our study testing (−)-sparteine as the chiral ligand (ligand **3**, Scheme 1) to see whether there was a preference to complex to one enantiomer of the inter-converting organolithiums. A preformed mixture of *rac*-**1** (1 equiv.) and (−)-sparteine (1.2 equiv.) in pentane was preliminarily cooled to −120 °C, then treated with *s*-BuLi (1.2 equiv.), followed by quenching after 2 min with MeOD. This procedure afforded a 50 : 50 mixture of (*S*)- and (*R*)-[D]-**1** (86% D) (entry 1, Table 1) (Scheme 1). Once the reaction time was extended to 30 min, α-deuterated (*R*)-[D]-**1** was formed with an er of 75 : 25 (84% D) (entry 2, Table 1). These results intimate that the equilibration between the two organolithium (−)-sparteine complexes is prevented at least at short reaction times (2 min), but it occurs slowly at longer reaction times even at a temperature as low as −120 °C.

Running the deprotonation of *rac*-**1** at −78 °C in hexane (that is the upper limit value before decomposition of **1-Li** starts off) for a reaction time of 30 min, the detected er was again 75 : 25 upon quenching with MeOD (entry 3, Table 1). This ratio could not be improved, either by allowing the two diastereomeric complexes first to equilibrate for 30 min at −78 °C before cooling to −90 °C or at longer reaction times of up to 1 h; thus, it reflects the relative population of the two diastereomeric organolithiums once the equilibrium has been reached. In contrast, completely racemic [D]-**1** was recovered upon deprotonating a mixture of *rac*-**1** (1 equiv.) and (−)-sparteine (1.2 equiv.) with *s*-BuLi (1.2 equiv.) at −78 °C in THF, with a 15 min reaction time (entry 4, Table 1). This result may be explained in terms of a competition of (−)-sparteine with bulk THF for coordination sites on lithium.[10]

To test for DTR, the two organolithium (−)-sparteine complexes were kept for 30 min at −78 °C in hexane before being quenched, in a first run, with 5 equiv. MeI, and, in a second run (with pentane as the solvent), with 10 mol% MeI, the enantiomeric ratios of the corresponding α-methylated adduct **2a** being 76 : 24 (*R* : *S*) (70% yield) and 52 : 48 (10% yield), respectively (entries 5 and 6, Table 1). A difference in the er of the product resulted in a changed stoichiometry of the electrophile, which provides evidence for a dynamic resolution under thermodynamic control. In particular, the racemic mixture detected for **2a** when using MeI in sub-stoichiometric amounts is consistent with the thermodynamically less populated (less stable) diastereomeric complex to react faster than the other. In cases like this, re-equilibration to further successive warm–cool cycles is known to be detrimental to the final er. Evaluation of the use of different solvents (Et_2O and toluene) resulted in lower er in the (*R*)-**2a** (range 60–63 : 40–37, 70–72% D). A variety of chiral ligands were also screened at −78 °C in hexane using deuterium as the electrophile. As for chiral diamines **4–7**, the readily accessible (+)-sparteine surrogate (O'Brien's diamine) (ligand **4**, Scheme 1)[11] gave enantioenriched (*S*)-[D]-**1** (er 25 : 75) (90% D) with the opposite absolute stereochemistry (entry 7, Table 1), whereas ligands **5–7**[12] (Scheme 1) furnished [D]-**1** essentially as a racemic mixture (entries 8–10, Table 1). A 50 : 50 mixture of the two enantiomers of [D]-**1** was detected, as well, using different types of ligands such as amino alcohol **8** and diamino alcohol **9**[3c] (Scheme 1) at −78 °C, regardless of the solvent system employed (toluene, hexane, Et_2O, and THF) (entries 11 and 12, Table 1).

We next probed the scope of the reaction with other electrophiles under the best conditions found in terms of ligands and solvents. Lithiation/substitution of *rac*-**1** in hexane at −78 °C in the presence of (−)-sparteine using the electrophiles Me_3SiCl, Ph_2CO and Me_2CO all resulted in the formation of the expected enantio-enriched derivatives **2b–d** in both reasonable yields (65–85%) and selectivity (er 72–77 : 28–23) (entries 13–15, Table 1) (Scheme 1). From these data it can be seen that the enantioselectivity does not significantly depend on the electrophile used, as expected in the case of a DTR. Interestingly, an er higher than that fixed by the thermodynamic ratio of the two diastereomeric complexes (*ca.* 75 : 25) could also be achieved using a sacrificial electrophile. Addition to **1-Li** at −78 °C in hexane of 20 mol% Me_2CO, and then quenching with MeOD (5 equiv.), provided **2d** essentially racemic (er 52 : 48, *R* : *S*) in 15% yield, but allowed the recovery of enantioenriched (*R*)-[D]-**1** with good enantioselectivity (er 82 : 18, *R* : *S*, 86% D, 75% yield) (entry 16, Table 1).

We also investigated the influence of chiral ligands on the racemisation rate of (*R*)-**1-Li**, obtained upon deprotonating a 0.2 M solution of enantiomerically enriched (*R*)-**1** (er 95 : 5) (1 equiv.) in hexane with *s*-BuLi (1.2 equiv.) at 195 K (−78 °C). Interestingly, the

Table 1 Enantiomeric ratio of [D]-**1** and **2a–d** by DTR using ligands **3–9**

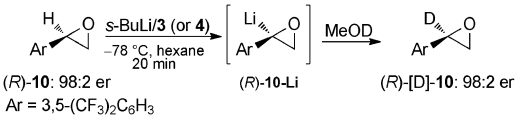
Entry	Time (min)	Solvent	E^+ (equiv.)	Ligand	[D]-**1**[a] (%)	Product[b] (%)	er[c] (*R*/*S*)
1	2[d]	Pentane	MeOD (5)	**3**	86	—	50 : 50
2	30[d]	,,	,,	,,	84	—	75 : 25
3	,,[e]	Hexane	,,	,,	70	—	75 : 25
4	15[e]	THF	,,	,,	87	—	50 : 50
5	30[e]	Hexane	MeI (5)	,,	—	**2a** (70)	76 : 24
6	,,[f]	Pentane	MeI (0.1)	,,	—	**2a** (10)	52 : 48
7	,,[e]	,,	MeOD (5)	**4**	90	—	25 : 75
8	,,[e]	,,	,,	**5**	77	—	44 : 57
9	,,[e]	,,	,,	**6**	55	—	56 : 44
10	,,[e]	,,	,,	**7**	50	—	50 : 50
11	,,[e]	,,	,,	**8**[g]	70	—	50 : 50[h]
12	,,[e]	Toluene	,,	**9**[g]	35	—	50 : 50[h]
13	,,[e]	Hexane	Me_3SiCl (5)	**3**	—	**2b** (85)	24 : 76[i]
14	,,[e]	,,	Ph_2CO (5)	,,	—	**2c** (65)	77 : 23
15	,,[e]	,,	Me_2CO (5)	,,	—	**2d** (85)	72 : 28
16	,,[f]	Pentane	Me_2CO (0.2)	,,	86	**2d** (15)	52 : 48[j]

[a] Calculated by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield by column chromatography. [c] For the absolute configuration of the major enantiomer, see the ESI. [d] Temp. = −120 °C. [e] Temp. = −78 °C. [f] Lithiation performed at −78 °C, then cooling to −120 °C before quenching with the electrophile. [g] Pre-treated with *s*-BuLi in hexane. [h] A racemic mixture was also obtained in Et_2O in the case of ligand **8** (70% D), and in Et_2O (86% D) and THF (92% D) in the case of ligand **9**; the latter was proved to be insoluble in hexane. [i] The change in the absolute configuration was only due to a change in the relative priorities of the substituent groups. [j] Upon quenching the mixture with MeOD (5 equiv.), the remaining **1-Li** was recovered as [D]-**1** in 75% yield and with an er of 82 : 18 (*R* : *S*).

Table 2 Influence of ligands on the enantiomerisation barrier of **1-Li**

Entry	Ligand	Temperature (K)	$\Delta G^{\neq}$ (kcal mol^{-1})
1	—	157[a]	9.5 ± 0.1
2	TMEDA	195	13.5 ± 0.1
3	**3**	,,	14.5 ± 0.1 ($R \rightarrow S$) 14.1 ± 0.1 ($S \rightarrow R$)
4	**4**	,,	14.0 ± 0.1 ($R \rightarrow S$) 14.3 ± 0.1 ($S \rightarrow R$)

[a] Reaction performed in THF–Et_2O (3 : 2).



Scheme 2

time-dependent deuteration (see the ESI‡) of **1-Li** in the presence of stoichiometric (1.2 equiv.) chiral ligands **3** and **4** revealed in both cases slower enantiomerisation kinetics in comparison to TMEDA (*vide supra*) (entries 3 and 4, Table 2). To date, there have been relatively a few data on the effects of chiral diamines on the barrier to enantiomerisation of chiral organolithiums.[3a,13]

The above results are noteworthy because, in the case of *N*-Boc-2-lithiopyrrolidine, a chiral ligand such as (−)-sparteine contributes to lower the enantiomerisation barrier, thereby accelerating the rate of inversion.[14] In an effort to generalise this result, optically active aryloxirane (*R*)-**10** (er 98 : 2), having two CF_3 groups in a *meta*, *meta′* orientation, was also subjected to lithiation. Previous studies showed that deprotonation of (*R*)-**10** (er 98 : 2) with *s*-BuLi–TMEDA (1 equiv.) in hexane at −78 °C, followed by quenching with MeOD, gave enantio-enriched (*R*)-[D]-**10** with er 90 : 10 after a deprotonation time of 40 s. Running the same reaction with ligands **3** and **4**, in place of TMEDA, a more dramatic effect was noted upon quenching with MeOD: enantio-enriched (*R*)-[D]-**10** could be recovered, in each case, with the same enantiopurity of the starting oxirane (er 98 : 2) after a reaction time of 20 min (Scheme 2).

In conclusion, the chiral ligand (−)-sparteine, widely used for asymmetric deprotonation,[2] was found to promote a DTR of a highly reactive lithiated oxirane such as **1-Li** with a range of electrophiles, albeit with moderate final er (*ca.* 75 : 25). By using a sacrificial electrophile, the er in the recovered [D]-**1** increased up to 82 : 18. Interestingly, both chiral ligands **3** and **4** proved also to be more effective than TMEDA in hampering the progress of racemisation of lithiated aryloxiranes (*R*)-**1-Li** and (*R*)-**10-Li** when employed in hexane at a temperature as low as −78 °C. Elucidation of the structure–reactivity relationship[15] of the above lithiated oxiranes would certainly be helpful in unravelling their mechanism of enantiomerisation in the presence of different ligands.[16] Solid structure and stereodynamics of lithiated oxirane **1-Li** will be discussed in a forthcoming paper from our group.

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