Isomerization of *meso* Diamines into their C_2 Symmetrical *d,l* Isomers

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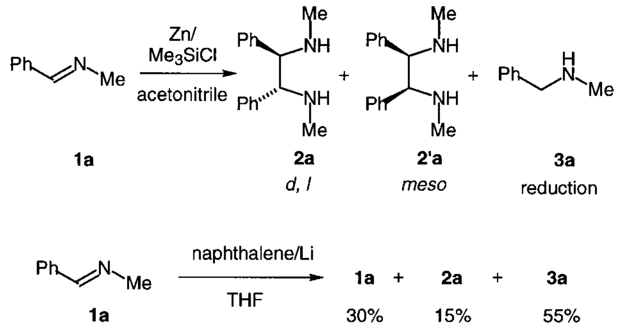
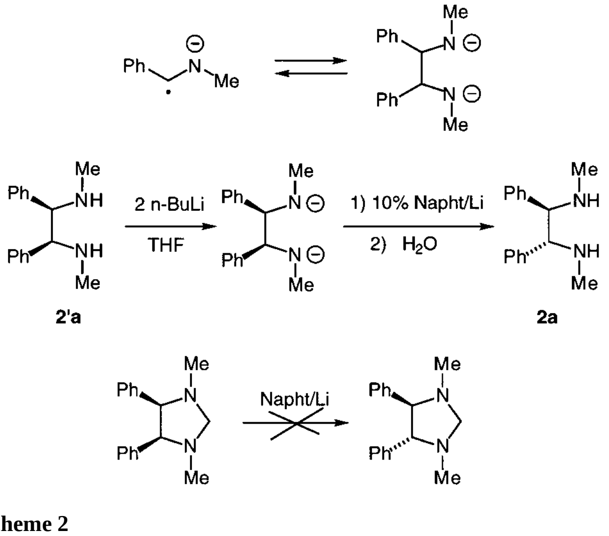
Abstract : An efficient isomerization method is disclosed which allows the obtention of the useful *d,l* isomers of C_2 symmetrical diamines, starting from their *meso* isomer.

In the preceding article, we described an efficient and practical method for the synthesis of C_2 symmetrical diamines through reductive coupling of imines by the combination Zn/TMSCl. Despite the formation of a 1/1 ratio of the *d,l* and *meso* diastereomers, we used this technique for the synthesis of large amounts of *d,l* N,N'-dimethyl-1,2-diphenylethane-1,2-diamine. Thus, we accumulated a large amount of *meso* diamine and investigated ways to isomerize it into the useful *d,l* isomers.



Scheme 1

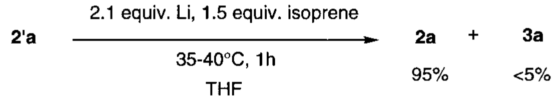
Despite our efforts using anionic (by analogy to the isomerization of 1,2-diphenylethanediol),[1] cationic, radical or photochemical ways, we could not observe any significant amount of isomerization. However, during our attempts to disclose new coupling methods, we observed that naphthalene/Li or naphthalene/Na gave rise to exclusively the *d,l* isomer (see Scheme 1), albeit in very low yield, due to the large formation of reduction product. In addition, the reaction was not complete. This result may be explained by Smith's hypothesis of a reversible formation of the bis-amide from the radical anion[2] (see Scheme 2).



Scheme 2

We therefore formed the bis lithium amide of the *meso* diamine **2a'**, with 2 equiv. n-BuLi, in THF, and we added a catalytic amount (10%) of naphthalene/Li, in order to be under the same experimental conditions stated in Scheme 2. After 1h at room temperature, all the *meso* diamine was isomerized into the *d,l* one **2a**, in quantitative yield. It should be pointed out that the bis-amide is required ; the corresponding aminal of formaldehyde does not isomerize, even with one full equiv. of naphthalene/Li.

To improve the isomerization and to avoid the large volumes of solvent generated by 1.6 M commercial n-BuLi solutions, we used another way to form the bis amide. According to Gaudemar[3] and Reetz,[4] lithium amides may be formed with 1 atom equivalent of Li and 0.5 equivalent of an electron acceptor such as styrene or even isoprene,[5] which also acts as proton acceptor. Accordingly, our optimized procedure is the following one:

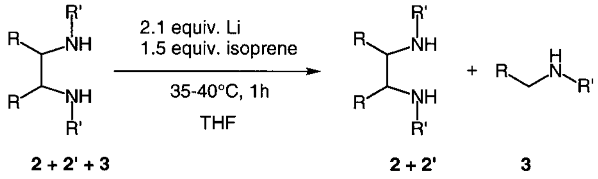


Scheme 3

Several solvents were also tried, but THF was the best one in our hands. It should be pointed out that the reduction product **3** is also formed in slight amounts. However, its amount increases as the reaction time is prolonged, and after 12h only **3** is obtained. If Li is replaced by Na, the isomerization process is much faster and only the reduction product was produced. It is probable that the radical anion postulated in Scheme 2, or the dianion formed by further reduction, is slowly protonated by the solvent. Therefore, the isomerization reaction should be carefully monitored to avoid larger amounts of reduction product.

An interesting question is which driving force is responsible for the reaction to occur. To address this point, we submitted anoptically pure sample of diamine **2** to the standard isomerization conditions. After 1h, a small amount of reduction product appeared (<5%) and the starting diamine was recovered in, still, 50% ee. This result means that the rate of isomerization of the *d,l* diamine is much slower than that of the *meso* one, thus allowing the accumulation of the *d,l* isomer in the reaction mixture.

The isomerization reaction may be conveniently performed directly on the crude mixture(*d,l/meso* 1/1) obtained from the coupling reaction described in the preceding article. Thus, the combination of these two reactions allows a very efficient synthesis of the useful *d,l* diamines. A generalization of this process to other diamines is shown in the Table, according to the following Scheme :



Scheme 4

Table. Isomerization of various diamines **2** and/or **2'**

Entry	R	R '	N°	Initial composition d,l / meso / red	Isomerization conditions	Crude yield[a] %	Final composition d,l / meso / red	Yield[b] of pure d,l
1	Ph	Me	**a**	0 / 100 / 0	Li / isoprene, 35°C, 1h	100	93 / 2 / 3	89%
2	Ph	Me	**a**	0 / 100 / 0	Na / isoprene, 35°C, 1h	100	0 / 0 / 100	-
3	Ph	Me	**a**	49 / 48 / 3	Li / isoprene, 35°C, 1h	99	90 / 2 / 8	78%
4	p-Me-C_6H_4	Me	**b**	46 / 49 / 5	Li / isoprene, 35°C, 1h	99	83 / 9 / 8	71%
5	p-MeO-C_6H_4	Me	**c**	45 / 47 / 8	Li / isoprene, 45°C, 2h	94	88 / 1 / 11	68%
6	m-CF_3-C_6H_4	Me	**d**	50 / 50 / 0	Li / isoprene, 40°C, 30 min	30	32 / 29 / 39	-
7	m-CF_3-C_6H_4	Me	**d**	50 / 50 / 0	2 BuLi/10% Napht/Li, 35°C, 30 min	35	70 / 20 / 10	-
8	Ph	Ph	**e**	63 / 37 / 0	Li / isoprene, 35°C, 1h	99	63 / 37 / 0	-
9	Ph	Ph	**e**	63 / 37 / 0	Na / isoprene, 20°C, 22h	95	95 / 0 / 5	72%
10	Ph	i-Pr	**f**	38 / 39 / 23	Li / isoprene, 35°C, 1h	84	0 / 0 / 100	-
11	1-furyl	Me	**g**	50 / 50 / 0	Li / isoprene, 35°C, 30 min	0	polymers	-
12	1-pyridyl	Me	**h**	42 / 28 / 30	Li / isoprene, 35°C, 30 min	0	polymers	-

[a]. mass recovery. [b]. Isolated after treatment with racemic tartaric acid

Although standard silica gel chromatography allows the easy separation of the components of the reaction mixture, a simpler and more convenient way to obtain exclusively the pure *d,l* isomer was to treat the crude reaction mixture with *racemic* tartaric acid in EtOH. When the precipitated ammonium salt is neutralized with aqueous NaOH, only the *d,l* isomer is obtained.

The reaction works well in many cases, but some limitations were noticed. Functionalized diamines (entries 11 and 12) gave polymers. Extensive decomposition was also observed with a fluorinated diamine (entries 6 and 7). The i-PrN group (entry 10) seems to hinder the reassociation of the radical anion, and only the reduction product was formed. In contrast, the PhN group (entries 8 and 9) slows down the isomerization process, but replacement of Li by Na allows the reaction to proceed.

In summary, we have found an isomerization system which allows many symmetrical diamines to be obtained as their useful *d,l* isomer.[6] Combined with an efficient resolution procedure[7] (which is the case of the above stated diamines) a palette of chiral auxiliaries are available for asymmetric synthesis. The process is very convenient since any method which produces these diamines as mixture of isomers may become a good source for the *d,l* isomer.

References and Notes

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(3) Gaudemar-Bardone, F.; Gaudemar, M. *Synthesis* **1979**, 463-465.

(4) Reetz, M.T.; Maier, W.F. *Liebigs Ann. Chem.* **1980**, 1471-1473.

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(6) **Typical procedure for isomerization of 2b :** The crude mixture (0.1 mol, 27 g) of **2b**+**2'b**+**3b** obtained from the coupling reaction (see preceding article) was dissolved in THF (200 mL) under nitrogen atmosphere. Li metal (containing 1-2% Na, 1.8 g, 0.25 mol) cut in small pieces was added in one portion. Isoprene (15 mL, 0.15 mol) was then slowly added while the solution was vigorously stirred. The temperature was maintained around 35-40°C. After 1h, an aliquot indicated that the amount of *meso* isomer **2'b** was low. The reaction was cooled to 0°C and the excess Li removed. The dark red solution was carefully hydrolyzed with 2.5 N HCl (200 mL). The aqueous layer was washed once with Et_2O (100 mL), then made basic with aqueous 35% NaOH (50 mL). Two extractions with Et_2O (2x200 mL) allow the full recovery of the crude *d,l* diamine **2b** (26.5 g).

This crude diamine was dissolved in absolute EtOH (700mL), racemic tartaric acid (0.096 mol, 14.2 g) was added, and the heterogeneous mixture was brought to reflux for 30 min. After cooling to +20°C, the precipitate was collected by filtration and washed twice with EtOH (2x50 mL). This salt was poured to a mixture of 35% NaOH (60 mL), water (200 mL) and Et_2O (200 mL). After stirring for 30 min, the layers were separated, the aqueous phase extracted twice with Et_2O (2x200 mL), and the combined organic phases were dried over K_2CO_3. The solvents are evaporated and the pure *d,l* diamine **2b** was obtained in 71% yield (19 g).

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