A new and highly effective organometallic approach to 1,2-dehalogenations and related reactions

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

Abstract

We investigated the reductive elimination of several functionalized and non-functionalized *vic*-dibromides with 1,2-diphenyl-, 1,1,2,2-tetraphenyl- and 1-phenyl-2-(2-pyridyl)-1,2-disodioethane. The reaction, involving some of the less expensive organic and inorganic reagents, proceeds under mild conditions, and is tolerant of a variety of functional groups. Extension of this procedure to similar 1,2-disubstituted compounds was also investigated. Reductive eliminations run on stereochemical probe compounds strongly suggest that this reaction proceeds via a "single electron" reductive elimination reaction pathway.
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1. Introduction

Reductive dehalogenation of *vic*-dihalides is a useful and long time known reaction, and many reagents have been developed to achieve this goal [1]. Indeed, halogenation/dehalogenation of alkenes has been employed either to protect double bonds towards oxidations, reductions or electrophilic additions [2], or as a useful way to achieve alkene purification [3]. Furthermore, reductive dehalogenation allows the employment of 1,2-dihaloethenes as synthetic equivalents of acetylene in cycloaddition reactions [4–6]. Recently, the dehalogenation procedure was successfully employed in the synthesis of isotopically labelled compounds, like [1-^{14}C]-*E*-isomers of fatty acids [7] and [1-^{79}Br]-1-bromo- or [1-^{37}Cl]-1-chloro-2-fluoroethylene [8]. Finally, it is worth mentioning the application of reductive dehalogenation procedures to the abiotic degradation of organohalide contaminants [9].

We recently reported that reaction of 1,2-diarylethenes with Na metal in dry THF allows the generation of a wide array of 1,2-diaryl-1,2-disodioethanes, whose reaction with 1,3-dichloropropane led to a highly stereoselective synthesis of *trans*-1,2-diaryl-substituted cyclopentanes [10]. At odds with these results, reaction of 1,2-diaryl-1,2-disodioethanes with 1,2-dihaloethanes affords the parent *trans*-1,2-diarylethenes, probably with concurrent formation of ethene [11]. Although the ability of delocalized polycarbanions to act either as nucleophiles or reducing agents towards alkyl halides is well known [12], the latter reaction was never synthetically exploited.

Following our interest in the development of efficient alkali metal-mediated reaction procedures, and with the aim to expand the synthetic utility of these interesting *vic*-diorganometallics, we investigated the reductive dehalogenation of several *vic*-disubstituted compounds

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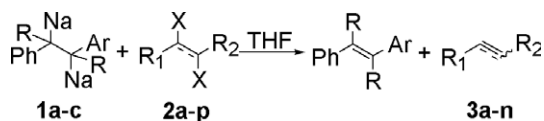
Scheme 1. Reductive eliminations of *vic*-disubstituted compounds. **1a**, Ar = Ph, R = H; **1b**, Ar = R = Ph; **1c**, Ar = 2-C₅H₄N, R = H; R₁, R₂, X = see text and Tables 1–3.

with 1,2-diphenyl-, 1,1,2,2-tetraphenyl- and 1-phenyl-2-(2-pyridyl)-1,2-disodioethane (Scheme 1). A preliminary communication on this topic already appeared [13].

2. Results and discussion

2.1. Reductive elimination reactions

0.1–0.2 M deep red solutions of 1,2-diaryl-1,2-disodioethanes (**1a–c**) were obtained by the reaction of *trans*-stilbene, tetraphenylethene or *trans*-stilbazole, respectively, with an excess of Na metal in dry THF, under Ar [10]. Yields of the diorganometals were determined by quenching samples of the resulting solutions with D₂O, followed by ¹H NMR analysis of crude reaction mixtures, to determine the percentage of deuterium incorporation in the arylmethyl positions. The same procedure was employed to determine that solutions of organometals **1a–c** can be stored under Ar in a freezer, for at least one week, without detrimental effects.

Solutions of **1** were decanted from excess metal immediately prior to use, a procedure allowing a simple way to recycle the excess of the metal [14].

Reductive eliminations were carried out by adding a solution of the appropriate *vic*-disubstituted compound **2** to a chilled solution of **1a–c**, followed by stirring the reaction mixture at the same temperature before aqueous work up. Inverse addition of the organometallic reagent to the substrate is usually equally effective. It is worth noting that the last procedure is particularly effective for those reactions requiring stoichiometric amounts of the reducing agent. Indeed, under these conditions, addition of the

diorganometal can be stopped as soon as a faint red colour persists in the reaction mixture.

Besides the desired unsaturated reaction products, reactions run with the disodium-derivative **1a** (or **1b**) led to the formation of *trans*-stilbene (or tetraphenylethene), as well as to the formation of minor amounts of 1,2-diphenylethane (or 1,1,2,2-tetraphenylethane), the product of protonation of **1a** (or **1b**). In a similar way, *trans*-stilbazole is the main by-product of reductions run with the pyridine derivative **1c**, usually accompanied by minor amounts of 2-phenethylpyridine (i.e., the product of protonation of **1c**); the relative basicity of these pyridine derivatives allowed their easy separation form the reaction mixture upon acid washings with 1 N HCl.

Results obtained in the reductive elimination of several simple *vic*-disubstituted compounds (Chart 1) are reported in Table 1.

Reaction of *meso*-1,2-dibromo-1,2-diphenylethane (**2a**) with 1.1 equiv. of dianion **1a** led, within 10 min at 0 °C, to the recovery of a reaction mixture containing *trans*-stilbene (**3a**) as the major reaction product, as well as a minor amount of 1,2-diphenylethane (Table 1, entry 1). Running this reaction without removing the excess of the metal, to check the feasibility of an operatively simpler reaction procedure, led to a comparable result.

Under similar reaction conditions, the dibromo derivative **2b** (as a 9:1 *erythro/threo* mixture of diastereoisomers) was quantitatively converted into *trans*-anetole (**3b**), which, however, was inseparable from *trans*-stilbene (Table 1, entry 2).

Therefore, dehalogenation of **2b** was performed in the presence of 1.2 equiv. of dianion **1c**: after aqueous work up and acid washings to separate basic derivatives, *trans*-anetole (**3b**) was recovered in almost quantitative yield (Table 1, entry 3) [15].

The procedure was successfully applied to *vic*-dichlorides: in a first experiment (not reported in Table 1), treatment of dianion **1a** with 1 equiv. of 1,2-dichloroethane led to the quantitative recovery of stilbene. According to this preliminary finding, reduction of 1,2-dichlorododecane
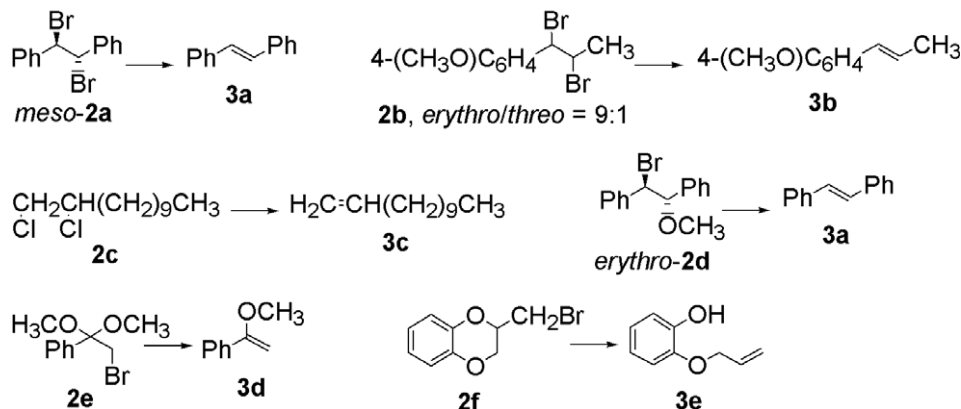

Chart 1. *Vic*-disubstituted compounds **2a–2f**, and resulting alkenes **3a–3e**.

Table 1
Reductive elimination of compounds **2a–2f**

Entry	Dianion (equiv.)	Substrate	T (°C)	t (min)	Product	Yield (%)[a]
1	**1a** (1.1)	*meso*-**2a**	0	10	**3a**	92[b,c]
2	**1a** (1.2)	**2b**, *erythro/threo* = 9:1	0	10	**3b**	>95[b]
3	**1c** (1.2)	**2b**, *erythro/threo* = 9:1	0	10	**3b**	91
4	**1c** (1.3)	**2c**	0	60	**3c**	>95[b]
5	**1c** (1.3)	*erythro*-**2d**	0	60	**3a**	90
6	**1c** (1.6)	**2e**	0	60	**3d**	70
7	**1b** (1.1)[d]	**2f**	0	10	**3e**	92

[a] Yields determined on isolated products, unless otherwise indicated.
[b] As determined by ^{1}H NMR of crude reaction mixture.
[c] **3a** is the product of dehalogenation of *meso*-**2a**, and the product of oxidation of **1a**; 8% of 1,2-diphenylethane was also recovered.
[d] Inverse addition, see text.

(**2c**) with dianion **1c** afforded 1-dodecene (**3c**) in satisfactory yields (Table 1, entry 4).

We next investigated the reduction of several simple α-haloethers.

Table 2
Reductive eliminations of compounds **2g–2k**

Entry	Dianion (equiv.)	Substrate	T (°C)	t (min)	Product	Yield (%)[a]
1	**1a** (2.0)	**2g**	0	10	**3f**	80
2	**1c** (1.6)	*threo*-**2h**	0	10	**3g**, $Z:E$ = 35:65[b]	90
3	**1c** (1.6)	*threo*-**2h**	−80	10	**3g**, $Z:E$ = 70:30[b]	90
4	**1c** (1.6)	*erythro*-**2h**	0	10	**3g**, $Z:E$ = <5: >95[b]	92
5	**1a** (2.0)	**2i**	0	10	**3h**	70
6	**1a** (2.0)	*threo*-**2j**	0	10	**3i**, $Z:E$ = 70:30[c]	65
7	**1a** (2.0)	*threo*-**2j**	−80	10	**3i**, $Z:E$ = 80:20[c]	65
8	**1c** (1.6)	**2k**, $Z:E$ = 23:77	0	10	**3j**	>95[c]

[a] Yields determined on isolated products, unless otherwise indicated.
[b] As determined by GC-MS analyses of the correspondig methyl ester, obtained by reacting crude reaction mixtures with diazomethane.
[c] As determined by ^{1}H NMR of crude reaction mixtures.

Reaction of 2-bromoethyl methyl ether with an excess of dianion **1a** led to the recovery of a relatively complex reaction mixture containing, besides a major amount of stilbene (68% by GC/MS), several unidentified by-products. Similar results were obtained reacting 2-bromoethyl methyl ether with **1b** (not reported in Table 1).

At variance with these preliminary results, satisfactory results were obtained in reactions leading to the formation of styrene derivatives (**3a** and **3d**, Table 1, entries 5 and 6), or involving a phenoxide as a leaving group (**3e**, Table 1, entry 7) [16]. These results strongly suggest that either the formation of a conjugated alkene or the presence of an efficient oxygen-leaving group is necessary to obtain good results in the reductive elimination of α-haloethers.

Table 2 reports a second set of results obtained in the reduction of several *vic*-dibromides bearing an acidic proton (compounds **2g–2j**, Chart 2), or leading to the formation of an acidic reaction product (**2k**, Chart 2).

Reduction of 10,11-dibromoundecanoic acid (**2g**) with an excess of **1a**, during 10 min at 0 °C, followed by aqueous work up and chromatographic purification of the reaction product, led to the formation of 10-undecenoic acid (**3f**) in 80% yield (Table 2, entry 1).

Application of a similar procedure to diastereoisomeric *threo*- and *erythro*-13,14-dibromodocosanoic acid (**2h**) allowed us to shed more light on the stereochemical outcome of our reductive dehalogenation procedure.

Indeed, reaction of *threo*-13,14-dibromodocosanoic acid, *threo*-**2h**, with 1.6 equiv. of **1c** at 0 °C, afforded the corresponding unsaturated carboxylic acid, **3g**, as a Z/E = 35:65 mixture of diastereoisomers (Table 2, entry 2), whilst a similar reaction, run at −80 °C, afforded the same compound as a Z/E = 70:30 mixture of diastereoisomers (Table 2, entry 3).

On the contrary, reductive dehalogenation of *erythro*-13,14-dibromodocosanoic acid, *erythro*-**2h**, run at 0 °C in the presence of 1.6 equiv. of **1c**, afforded almost exclusively *E*-**3g** (Table 2, entry 4). The reliability of these stereochemical results was assured by observing the stereochemical
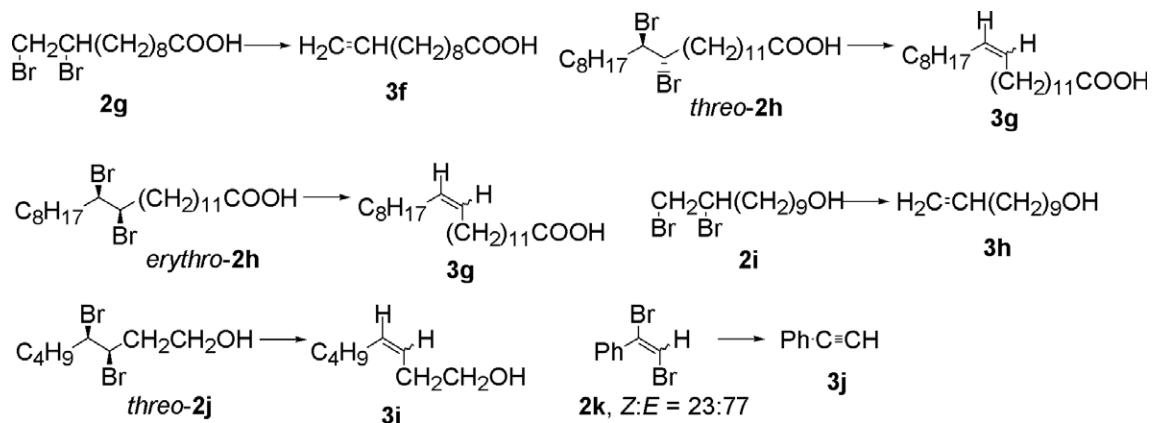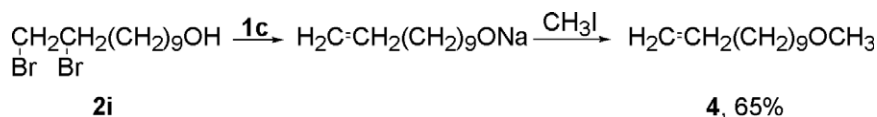

Chart 2. Functionalized *vic*-disubstituted compounds **2g–2k**, and resulting elimination products **3f–3j**.

Scheme 2. Synthesis of methyl 10-undecenyl ether, **4**.

stability of acid Z-**3g** under the above reported reaction conditions.

A similar procedure was successfully applied to the reductive dehalogenation of dibromoalcohols: reaction of 10,11-dibromoundecan-1-ol (**2i**) with 2 equivs. of **1a** led, after aqueous work up, to the recovery of 10-undecen-1-ol (**3h**) in 70% yield (Table 2, entry 5). The last reaction can be successfully run without removing the excess of the metal (not reported in Table 2).

A further debromination of alcohol **2i**, run according to the general procedure, was quenched with 2.2 equivs. of CH$_3$I thus allowing, after aqueous work up and acid washings with 1 N HCl, the recovery of methyl 10-undecenyl ether (**4**) in 65% yield (Scheme 2).

Reaction of threo-3,4-dibromooctan-1-ol, threo-**2j**, with 2 equivs. of **1a** afforded, after 10 min at 0 °C, a 70:30 Z/E mixture of the corresponding unsaturated alcohol, **3i** (Table 2, entry 6). It is worth noting that a similar reaction run at −80 °C led to the formation of the unsaturated alcohol **3i**, as a 80:20 Z/E mixture of diastereoisomers (Table 2, entry 7). Comparable results were obtained running the reductive debromination of threo-**2j** with the disodium derivative of stilbazole (**1c**) (not reported in Table 2).

We finally investigated the dehalogenation of 1,2-dibromo-1-phenylethene (**2k**) (as a 23:77 Z/E mixture of diastereoisomers); a first reaction, run with 1 equiv. of **1c**, led to the recovery of a reaction mixture containing an almost 1:1 mixture of phenylacetylene (**3j**) and starting material (not reported in Table 2). Increasing the relative amount of **1c** to 1.6 equivs. led to recover acetylene **3j** in

almost quantitative yield (Table 2, entry 8), thus suggesting deprotonation at C(2) of the reaction product.

Our procedure was successfully extended to several vic-disubstituted compounds bearing a carbonyl substituent (Chart 3). These results are reported in Table 3.

Debromination of amide **2l** with 1 equiv. of **1a**, during 10 min at −80 °C, followed by aqueous work up and chromatographic purification of the reaction product, led to the

Table 3
Reductive eliminations of compounds **2l**–**p**

Entry	Dianion (equiv.)	Substrate	T (°C)	t (min)	Product	Yield (%)[a]
1	**1a** (1.0)	**2l**	−80	10	**3k**	90
2	**1c** (1.0)	**2m**	−80	60	**3l**	58[b,c]
3	**1c** (1.1)[d]	**2m**	−80	30[e]	**3l**	80
4	**1b** (1.1)[d]	**2m**	−20	30[e]	**3l**	70[f]
5	**1a** (1.1)[d]	**2n**	0	30[e]	**3m**	36[b]
6	**1a** (1.1)[d]	**2n**	−40	30[e]	**3m**	90
7	**1a** (1.1)[d]	**2o**	−40	30[e]	**3m**	90
8	**1b** (1.1)[d]	**2o**	0	30[e]	**3m**	>95[c]
9	**1b** (1.1)[d]	**2p**[g]	−80	30[e]	**3n**[g]	94

[a] Yields determined on isolated products, unless otherwise indicated.
[b] As determined by ^{1}H NMR of crude reaction mixture.
[c] 37% of **2m** and 5% of alcohol **3h** were also detected.
[d] Inverse addition, see text.
[e] Time needed to perform a slow addition of the reducing agent to the substrate.
[f] 7% of alcohol **3h** was also detected.
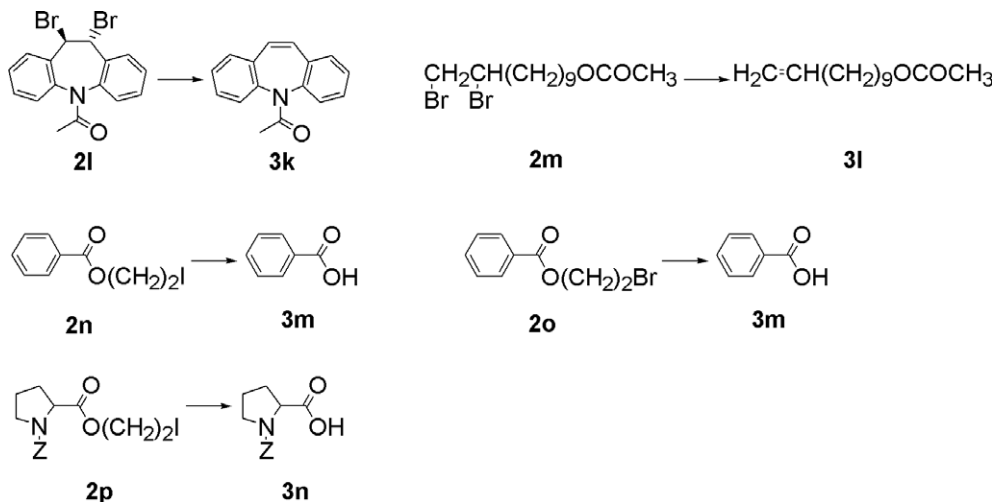[g] Z = Benzyloxycarbonyl.

Chart 3. Functionalized vic-disubstituted compounds **2l**–**2p**, and resulting elimination products **3k**–**3n**.

formation of amide **3k**, in almost quantitative yield (Table 3, entry 1).

We next investigated the reaction of 10,11-dibromoundecyl acetate (**2m**) with 1 equiv. of dianion **1c** at −80 °C: under these reaction conditions, aqueous work up and acid washing (1 N HCl) to separate basic derivatives, allowed to recover, besides the desired unsaturated ester **3l** and some unreacted starting material, a minor amount of 11-undecen-1-ol (**3h**) (Table 3, entry 2).

Interestingly, alcohol **3h** was the main product (63%, as determined by ^{1}H NMR) of a reaction run in the presence of 1.7 equivs. of the reducing agent (not reported in Table 3).

This behaviour can be rationalized by assuming that dianion **1c** is acting towards the dibromoester **2m**, both as a reducing agent, leading to the formation of dehalogenated products, as well as a nucleophile towards the ester moiety, eventually leading to the formation of alcohol **3h**. Accordingly, the desired unsaturated ester **3l** was recovered in 80% yield, by reacting dibromide **2m** with 1.1 equiv. of **1c**, under inverse addition reaction conditions at −80 °C (Table 3, entry 3).

Finally, we found it possible to selectively dehalogenate ester **2m** under milder reaction conditions. Indeed, the reduction of **2m** was successfully performed at −20 °C, with the sterically hindered, hence poorly nucleophilic, dianion **1b**. Under inverse addition reaction conditions, the unsaturated ester **3l** was recovered in 70% isolated yield (Table 3, entry 4).

Interestingly, under the above reported reaction conditions (Table 3, entries 2–4), the reductive dehalogenation of ester **2m** never led to the formation of the corresponding acyloin, i.e., the product of the reaction of an alkyl (or aryl) ester with Na metal in THF [17].

The relative stability of the ester group under the above reported reaction conditions, as well as the possibility to obtain the reductive elimination of *vic*-halide-oxygen disubstituted compounds (Table 1, entries 5–7), prompted us to investigate the reductive deprotection of β-haloethyl esters [18].

The reaction of the 2-iodoethyl ester of benzoic acid (**2n**) with 1.1 equivs. of dianion **1a** was investigated as a function of reaction temperature. A reaction run at 0 °C, under inverse addition reaction conditions, led to the recovery of benzoic acid, **3m** in modest yield, probably due to a competitive nucleophilic reaction of the dianion with the ester group (Table 3, entry 5). A much better result was obtained performing the reaction at −40 °C; indeed, under these reaction conditions, the desired acid was recovered in 90% isolated yield (Table 3, entry 6). A similar result was obtained performing this reaction at −80 °C (not reported in Table 3).

Besides the 2-iodoethyl ester **2n**, also the less reactive 2-bromoethyl ester of benzoic acid [19], **2o**, was efficiently deprotected under the above reported reaction conditions; indeed, this ester was almost quantitatively converted into benzoic acid, **3m**, either by reduction with the disodium derivative **1a**, at −40 °C (Table 3, entry 7), or by reduction with the poorly nucleophilic dianion **1b**, at 0 °C (Table 3, entry 8).

As an additional advantage, all reactions leading to the formation of acid **3m** were easily purified by acid-basic washings.

The above described procedure was successfully applied to the regioselective deprotection of the 2-iodoethyl ester of *N*-benzyloxycarbonylproline (**2p**). Indeed, inverse addition of dianion **1b** to a THF solution of compound **2p**, chilled at −20 °C, allowed the recovery of Z-proline, **3n**, in 62% isolated yield (not reported in Table 3), whilst a similar reaction, run at −80 °C, afforded the desired product in almost quantitative yield (Table 3, entry 9).

2.2. Reaction mechanism

Alternative reductive dehalogenations mechanisms are usually described as "single electron" or as "concerted two electron" reaction pathways [20]. More recently, the "single electron" pathway was described as an "outer-sphere" redox process, whilst the "concerted two electron" pathway was described as an "inner-sphere" redox process [1i].

As recently emphasized [9a], it is possible to discriminate between these mechanisms by examining the reduction of a series of stereochemical probe compounds. Indeed, a "concerted two electron" reaction pathway should proceed with *anti* stereospecificity (E2-like process, also termed[1i] E2(R) process), with *erythro*- and *meso*-starting materials leading to the formation of *E*-reaction products, and *dl*- and *threo*-compounds being reduced to the corresponding *Z*-alkenes.

On the contrary, "single electron" reductive eliminations are characterized by a great variety of stereochemical results. Indeed, the stereochemical outcome of this reduction pathway strongly depends on the relative configurational stability of reaction intermediates, as well as on their chemical behaviour [1b,1i,1l,9a]. Interestingly, reductive dehalogenations promoted by radical anions and carbanions are usually considered to proceed via "single electron" reaction pathways [1b], mostly in the case of carbanions with a negative redox potential [1i].

From this point of view, we observed *anti* stereospecificity in the reductive eliminations of *meso*-**2a** (Table 1, entry 1), *erythro*-**2d** (Table 1, entry 5) and *erythro*-**2h** (Table 2, entry 4), and a lack of stereospecifity in the reductive dehalogenations of **2b**, employed as a 9:1 *erythro/threo* mixture of diastereoisomers (Table 1, entries 2 and 3), as well as of *threo*-**2h** (Table 2, entries 2 and 3) and *threo*-**2j** (Table 2, entries 6 and 7).
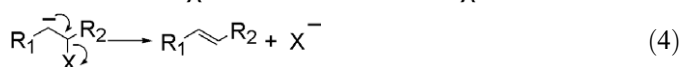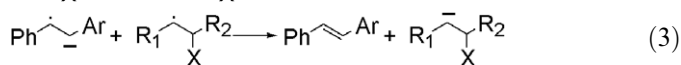
According to these stereochemical findings, a "concerted two electron" reaction pathway, i.e., an "inner-sphere" redox process, can be ruled out, and the actual mechanism should involve an "outer-sphere" redox process, leading to the formation of transient species behaving in a non-stereospecific way.

We therefore suggest that our reductive eliminations proceed via a "single electron" reaction pathway, as depicted in Eqs. (1)–(4).

A first single electron transfer (SET) from the dianion to the *vic*-disubstituted substrate generates two radical anions

(Eq. (1)); the halide-substituted radical anion immediately (or contemporary to the SET step [21]) loses a halide anion leading to the formation of a radical (Eq. (2)); a second SET, from the 1,2-diaryl-substituted radical anion to the radical, afforded the 1,2-diarylethene and a β-substituted carbanion (Eq. (3)); the last one is finally transformed into the corresponding alkene (Eq. (4)).

$$\text{Ph}\overset{-}{\diagdown}\text{Ar} + R_1\overset{X}{\diagup}\overset{}{\diagdown}R_2 \longrightarrow \text{Ph}\overset{-}{\diagdown}\text{Ar} + R_1\overset{X}{\diagup}\overset{-}{\diagdown}R_2 \tag{1}$$

$$R_1\overset{X}{\diagup}\overset{-}{\diagdown}R_2 \longrightarrow R_1\overset{}{\diagup}\overset{}{\diagdown}R_2 + X^- \tag{2}$$

$$\text{Ph}\overset{}{\diagdown}\text{Ar} + R_1\overset{}{\diagup}\overset{}{\diagdown}R_2 \longrightarrow \text{Ph}\diagdown\text{Ar} + R_1\overset{-}{\diagup}\overset{}{\diagdown}R_2 \tag{3}$$

$$R_1\overset{}{\diagup}\overset{}{\diagdown}R_2 \longrightarrow R_1\diagdown R_2 + X^- \tag{4}$$
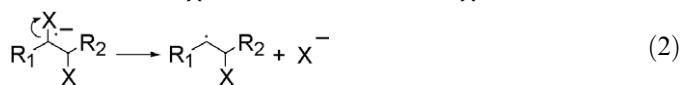
As already argued, our stereochemical results can be rationalized taking into account, besides a lack of stereospecificity in reactions leading to the formation of both the haloalkyl radical and carbanion, the possibility for these intermediates to undergo rotameric relaxation [22], thus favouring preferential or exclusive formation of *E*-reaction products.

The results obtained running the reductive dehalogenations of acid *threo*-**2h** (Table 2, entries 3 and 4) and alcohol *threo*-**2j** (Table 2, entries 6 and 7) at different temperatures, further supp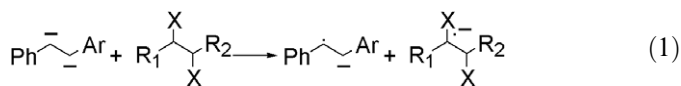ort this hypothesis. In both cases, a higher percentage of the *Z* stereoisomer of the reaction product was obtained running each reduction at the lower temperature investigated, i.e., under conditions which should significantly slow down rotameric relaxation of reactive intermediates [11,9a].

3. Concluding remarks

Our results show that 1,2-diaryl-1,2-disodium ethanes are effective reductive elimination reagents presenting several useful and interesting features.

A first remark concerns their easy preparation from readily available starting materials. Indeed, Na is by far one of the less expensive inorganic reagents, whilst *trans*-stilbene and tetraphenylethene are relatively inexpensive organic starting materials. Concerning *trans*-stilbazole, it can be prepared in a multigram scale via a Wittig-type reaction, as already described [10].

A comparison with known alkali metal-based reductive elimination reagents, shows some of the advantages of our procedure.

Indeed, bulk Li [23] or Na [24] metal in THF are usually employed in large excess and for relatively long reaction times, whilst our reagents are employed in stoichiometric amounts (or in a slight excess), and drive reactions to completion within a very short reaction time, under mild conditions. Na naphthalenide [1m,25] is a particularly effective reagents towards aliphatic (or alicyclic) dihalides, but

reduction of stilbene dibromides led to the formation of complex reaction mixtures. Other methods, involving the employment of Na in liquid NH$_3$ [26] or the K-graphite intercalate C$_8$K [27], appear less attractive form a practical point of view.

Furthermore, depending on the nature of the substrate to be reduced, the arylalkene employed to generate the diorganometals can often be easily separated from the reaction product by acid–base washings, thus avoiding laborious work-up procedures.

It is also worth noting that our procedure is tolerant of several functional groups (alcohols, carboxylic acids, alkynes, esters, amides and urethanes), and shows promising applications as a new and selective protocol to be employed in the reductive removal of protecting groups.

From this point of view, the deprotection of benzoic acid 2-bromoethyl ester (**2o**) (Table 3, entries 7 and 8) appears as a particularly interesting reaction. Indeed, it has been reported that reductive removal of 2-bromoethyl ester is a problematic reaction, and extremely slow and inefficient when Zn, or even SmI$_2$ [19], are employed as reducing agents.

As a conclusion, we can say that 1,2-diaryl-1,2-disodioethanes can be considered as synthetic equivalents of an activated, selective, and highly reactive form of Na metal, functioning under homogeneous reaction conditions.

4. Experimental

4.1. General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. THF was distilled from Na/K alloy under N$_2$ immediately prior to use. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in CDCl$_3$ (unless otherwise indicated) with SiMe$_4$ as internal standard on a Varian VXR 300 spectrometer. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of crude reaction mixtures, as described in Ref. [10]. IR spectra were recorded on pure samples on a FT-IR Jacso 480 P. GC-MS spectra were measured at 70 eV on a Trace GC-Polaris Q spectrometer. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

4.2. Starting materials

Starting materials **2** are either known compounds, prepared according to standard procedures and characterized according to the literature [28], or commercially available

(**2a**, **2f**, **2o**). The stereochemistry of starting materials was assigned by comparison with commercially available samples and/or literature data [28]; the *trans* stereochemistry of amide **2l** was assigned by comparison with the stereochemistry of the corresponding *N*-carboxamide and *N*-carbonyl chloride, prepared under similar reaction conditions [29].

Other products were synthesized and characterized as follows.

4.2.1. Synthesis of threo-3,4-dibromoocta-1-ol (threo-2j)

A solution of (*Z*)-3-octen-1-ol (2.00 g, 15.6 mmol) in dry CCl_4 (20 mL) was placed in a two-necked flask, equipped with reflux condenser, $CaCl_2$ tube and magnetic stirrer, and chilled to −5 °C. To this solution was added dropwise a solution of Br_2 (0.8 mL, 2.50 g, 15.6 mmol) dissolved in CCl_4 (2 mL). The mixture was stirred 30 min at −5 °C, then 2 h at r.t. The reaction mixture was evaporated, and the resulting brown oil was purified by vacuum distillation, to give the pure product (3.00 g, 9.9 mmol, 63%), which was characterized as follows: light yellow oil, b.p. 120–125 °C/ 1 mmHg; IR (neat): 3345 cm^{-1}; δ_H 0.93 (3H, t, $J =$ 7.2 Hz, CH$_3$), 1.24–2.38 (9H, m, 4× CH$_2$, OH), 3.79–3.95 (2H, m, CH$_2$O), 4.20–4.27 (1H, m, CHBr), 4.46–4.54 (1H, m, CHBr); δ_C 13.9, 21.9, 29.8, 35.1, 37.8, 55.6, 59.6, 60.2. Anal Calc. for $C_8H_{16}Br_2O$: C, 33.36; H, 5.60. Found: C, 33.25; H, 5.79%.

4.2.2. Synthesis of 10,11-dibromoundecyl acetate (2m)

A solution of 10,11-undecenyl acetate, **3l**, (4.0 g, 18.8 mmol) in dry CCl_4 (20 mL) was placed in a two-necked flask, equipped with reflux condenser, $CaCl_2$ tube and magnetic stirrer, and chilled to −5 °C. To this solution was added dropwise a solution of Br_2 (0.97 mL, 3.01 g, 18.8 mmol) dissolved in CCl_4 (2 mL). The mixture was stirred 30 min at −5 °C, then 40 min at r.t. The reaction mixture was evaporated, and the resulting brown oil was purified by vacuum distillation, to give the pure product (5.0 g, 13.4 mmol, 72%), which was characterized as follows: light yellow oil, b.p. 150–155 °C/1 mmHg; IR (neat): 1737 cm^{-1}; δ_H: 1.27–1.40 (14 H, m, 7× CH$_2$), 1.70–1.84 (1H, m, CH), 2.05 (3H, s, CH$_3$), 2.05–2.20 (1H, m, CH), 3.63 (1H, t, $J = 9.9$ Hz, CHBr), 3.85 (1H, dd, $J = 10.2$, 4.5 Hz, CHBr), 4.05 (2H, t, $J = 6.6$ Hz, CH$_2$O), 4.12–4.22 (1H, m, CHBr); δ_C: 21.0, 25.8, 26.7, 28.5, 28.7, 29.1, 29.2, 29.3, 35.9, 36.3, 53.1, 64.6, 171.2. Anal. Calc. for $C_{13}H_{24}Br_2O_2$: C, 41.96; H, 6.50. Found: C, 41.71; H, 6.79%.

4.2.3. Synthesis of N-benzyloxycarbonylproline 2-iodoethyl ester (2p)

A solution of Z-proline (2.00 g, 8.0 mmol) in dry CH_2Cl_2 (60 mL) was placed under N_2 in a two-necked flask, equipped with reflux condenser and magnetic stirrer, and chilled to 0 °C. To this solution, were added 2-iodoethanol (0.75 ml, 1.65 g, 9.6 mmol) and pyridine (1.3 mL, 1.27 g, 16.6 mmol). After 10 min stirring, DCC (1.82 g, 8.8 mmol)

was added in one portion, and the resulting mixture was stirred overnight at 0 °C in the dark. The reaction was quenched by the addition of oxalic acid (0.11 g, 1.2 mmol) dissolved in THF (2 mL), stirred at rt for 30 min, filtered, and the filter cake washed with CH_2Cl_2 (3 × 10 mL). The combined organic phases were collected, washed with 1 N HCl (2 × 10 ml), brine (10 mL), dried (MgSO$_4$), and the solvent evaporated. The resulting oil was purified by flash chromatography (AcOEt/petroleum ether 6:4), to give the pure product (2.37 g, 5.9 mmol, 74%), which was characterized as follows: light yellow oil; $R_f = 0.65$ (AcOEt/petroleum ether 6:4); IR (neat): 1748, 1707 cm^{-1}; δ_H mixture of rotamers 1.80–2.20 (2H, m, CH$_2$), 2.18–2.36 (1H, m, CH), 3.20–3.50 (5H, m, 2× CH$_2$, CH), 4.18–4.41 (3H, m, NCHCO, CH$_2$O), 4.87–5.16 (2H, m, CH$_2$Ph), 7.21–743 (5H, m, Ph); δ_C (mixture of rotamers) 2.4, 2.7, 23.1, 23.9, 29.5, 30.5, 46.2, 46.8, 58.4, 59.0, 64.7, 64.7, 66.1, 127.4, 127.5, 127.8, 127.9, 128.4, 128.5, 136.7, 136.9, 153.5, 154.0, 171.7, 172.0. Anal. Calc. for $C_{15}H_{18}INO_4$: C, 44.68; H, 4.50; N, 3.47. Found: C, 44.57; H, 4.76; N, 3.36%.

4.3. Generation of diorganosodium reagents 1a–c

Deep red solutions (0.1 M) of **1a** and **1c** were prepared by the reaction of freshly cut Na metal with *trans*-stilbene, or *trans*-stilbazole, respectively in dry THF, as described in Ref. [10]. These solutions were drained from excess metal under an Ar atmosphere, immediately prior to use.

4.3.1. Generation of 1,1,2,2-tetraphenyl-1,2-disodioethane (1b)

Two to three pieces of freshly cut Na metal (0.14 g, 4.5 mg atoms) were placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and were suspended in dry THF (10 mL). 1,1,2,2-Tetraphenylethene (0.50 g, 1.5 mmol), dissolved dry THF (5 mL), was added dropwise, and the resulting mixture was vigorously stirred at rt during 4 h. Yield of dianion **1b** (>95%) was determined by quenching an aliquot of the resulting deep violet solution with D_2O, and determining deuterium incorporation (tipically quantitative) as described in Ref. [10]. The excess of the metal was withdrawn, under an Ar atmosphere, immediately before use.

4.4. General reductive elimination procedure

To 10 ml of a 0.1 M solution of **1a**–**1c** (1 mmol) chilled at the temperature reported in Tables 1–3 was added a solution of the appropriate *vic*-disubstituted compound **2** (0.8–0.5 mmol), dissolved in 3 mL of dry THF. Inverse addition involves addition of the organometallic solution to a chilled solution of compounds **2**, under otherwise identical reaction conditions. After stirring for 10 min (except when otherwise indicated), the mixture was quenched by slow dropwise addition of H_2O (15 mL), the cold bath removed, and the resulting mixture extracted (3 × 10 mL) with an organic solvent (Et$_2$O for reactions run with

dianions **1a** and **1c**; AcOEt for reactions run with dianion **1b**). The organic phase was washed with brine (10 mL) then, in case of reactions with **1c**, with 1 N HCl (3 × 10 mL), dried (Na$_2$SO$_4$) and the solvent evaporated.

Crude products were purified by flash chromatography (Petroleum ether/AcOEt). However, all products obtained from reactions run with dianion **1c** (i.e., **3a**–**d**, **3g**, **3j**, **3l**) as well as phenol **3e** and carboxylic acids **3f**, **3m** and **3n** can be efficiently purified by acid–base washings.

Reaction products **3** and **4** were recognized by comparison with commercially available samples (**3a**–**c**, **3f**, ***Z*-3g**, **3h**, ***Z*-3i**, **3j**) or with literature data [30]. When necessary, the stereochemistry of reaction products was assigned by comparison with commercially available samples and/or literature data [30]. Diastereoisomeric mixtures of acid **3g**, as obtained according to the general reductive elimination procedure, were dissolved in CH$_2$Cl$_2$ and treated with diazomethane, according to the literature [31]; the resulting mixtures, containing the corresponding methyl esters, were analyzed by GC-MS to determine their diastereoisomeric compositions.

Acknowledgement

References

[1] (a) For a list of reagents employed in reductive dehalogenation, see: R.C. Larock, Comprehensive Organic Transformation, VCH Publishers, New York, 1989, pp. 133–135;
(b) For a review, see: E. Baciocchi, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Functional Groups, Supplement D, Part I, Wiley, New York, 1983, pp. 161–201;
(c) For a selection of relevant literature, see: J.M. Concellón, H. Rodríguez-Solla, Chem. Soc. Rev. 33 (2004) 599–609;
(d) B.C. Ranu, A. Das, A. Hajra, Synthesis (2003) 1012–1014;
(e) T.S. Butcher, M.R. Detty, J. Org. Chem. 63 (1998) 177–180;
(f) Y. Takagughi, A. Hosokawa, S. Yamada, J. Motoyoshiya, H. Aoyama, J. Chem. Soc., Perkin Trans. 1 (1998) 3147–3149;
(g) C. Malanga, S. Mannucci, L. Lardicci, Tetrahedron 54 (1998) 1021–1028;
(h) R. Yanada, N. Negoro, K. Yanada, T. Fujita, Tetrahedron Lett. 37 (1996) 9313–9316;
(i) T. Lund, C. Bjørn, H.S. Hansen, A.K. Jensen, T.K. Thorsen, Acta Chem. Scand. 47 (1993) 877–884;
(j) D. Landini, L. Milesi, M.L. Quadri, F. Rolla, J. Org. Chem. 49 (1984) 152–153;
(k) D. Savoia, E. Tagliavini, C. Trombini, A. Umani-Ronchi, J. Org. Chem. 47 (1982) 876–879;
(l) J.F. Garst, J.A. Pacifici, V.D. Singleton, M.F. Ezzel, J.I. Morris, J. Am. Chem. Soc. 97 (1975) 5242;
(m) W. Adam, J. Arce, J. Org. Chem. 37 (1972) 507–508.

[2] D.W. Young, in: J.F.W. McOmie (Ed.), Protective Groups in Organic Chemistry, Plenum Press, London, 1973, pp. 309–320.

[3] See, for example: L.F. Fieser, M. Fieser, Advanced Organic Chemistry, Reinhold Publishing Corporation, New York, 1961, pp. 163–165.

[4] [2+2] cycloadditions: H.O. House, T.H. Cronin, J. Org. Chem. 30 (1965) 1061–1070.

[5] [4+2] cycloadditions: S.J. Cristol, N.L. Hause, J. Am. Chem. Soc. 74 (1952) 2193–2197.

[6] For a review on synthetic equivalents of acetylene in cycloaddition reactions, see: De O. Lucchi, G. Modena, Tetrahedron 40 (1984) 2585–2632.

[7] D. Georgin, F. Taran, C. Mioskowski, Chem. Phys. Lipids 125 (2003) 83–91.

[8] (a) A. Baldan, A. Tassan, Synth. Commun. 35 (2005) 1447–1453;
(b) A. Baldan, Synth. Commun. 34 (2004) 1229–1235.

[9] (a) L.A. Totten, U. Jans, A.L. Roberts, Environ. Sci. Technol. 35 (2001) 2268–2274, and references therein;
(b) E.C. Butler, K.F. Hayes, Environ. Sci. Technol. 34 (2000) 422–429.

[10] U. Azzena, G. Dettori, C. Lubinu, A. Mannu, L. Pisano, Tetrahedron 61 (2005) 8663–8668.

[11] (a) Ethene is a reasonable co-product of this reaction, but its formation was never ascertained J.W.B. Reesor, J.G. Smith, G.F. Wright, J. Org. Chem. 19 (1954) 940–956;
(b) U. Azzena, G. Dettori, M.V. Idini, L. Pisano, G. Sechi, Tetrahedron 59 (2003) 7961–7966.

[12] (a) C.E. Barry III, R.B. Bates, W.A. Beavers, F.A. Camou, B. Gordon III, H.F.-J. Hsu, N.S. Mills, C.A. Ogle, T.J. Siahaan, K. Suvannachut, S.R. Taylor, J.J. White, K.M. Yager, Synlett (1991) 207–212, and references therein;
(b) J.G. Smith, E. Oliver, T.J. Boettger, Organometallics 2 (1983) 1577–1582;
(c) J.G. Smith, J.R. Talvitie, A.R.E. Eix, J. Chem. Soc., Perkin Trans. 1 (1975) 1474–1479.

[13] U. Azzena, M. Pittalis, G. Dettori, S. Madeddu, E. Azara, Tetrahedron Lett. 47 (2006) 1055–1058.

[14] The residual metal is usually recovered as a single piece, which can be washed with a dry solvent (Et$_2$O or THF), weighed, and recycled to a successive reaction.

[15] Accordingly, trans-stilbazole can be recovered and purified by flash-chromatography (AcOEt/Petroleum Ether = 4:6) in 60–65% yield.

[16] (a) 2-Allyloxyphenol, **3e**, is a pyrocathecol monoprotected with a group known to be unstable under reductive electron transfer reaction conditions. J.J. Eisch, A.M. Jacobs, J. Org. Chem. 28 (1963) 2145–2146;
(b) E. Alonso, D.J. Ramon, M. Yus, Tetrahedron 53 (1997) 14355–14368.

[17] M. Makosza, K. Grela, Synlett (1997) 267–268, and references therein.

[18] T.W. Greene, P.G. Wuts, Protective Groups in Organic Synthesis, third ed., Wiley, New York, 1999, pp. 397–398.

[19] A.J. Pearson, K. Lee, J. Org. Chem. 59 (1994) 2257–2260, and references therein.

[20] See Ref. [1b] for a comparison between these mechanisms. See Ref. [1i] for an in-depth discussion on competitive "inner-" and "outer-sphere" redox processes.

[21] C.P. Andrieux, A. Le Gorande, J.-M. Savéant, J. Am. Chem. Soc. 114 (1992) 6892–6904, and references therein.

[22] α-Bromine-substituted radical intermediates are considered to be configurationally stabilized by bromine bridging. See Ref. [9a].

[23] J. Sicher, M. Havel, M. Svoboda, Tetrahedron Lett. 9 (1968) 4269–4272.

[24] Na in THF: H.O. House, R.S. Ro, J. Am. Chem. Soc. 80 (1958) 182–187.

[25] Na naphthalenide in 1,2-dimethoxyethane H.R. Pfaendler, F.X. Müller, Synthesis (1992) 350–352, and references therein.

[26] Na in liq. NH$_3$: E.L. Allred, B.R. Beck, K.J. Voorhees, J. Org. Chem. 39 (1974) 1426–1427.

[27] K graphite, C$_8$K: M. Rabinovitz, B. Tamarkin, Synth. Commun. 14 (1984) 377–379.

[28] (a) Literature references to starting materials: 2b: R.C. Fahey, H.-J. Schneider, J. Am. Chem. Soc. 90 (1968) 4429–4434;
(b) 2c: S.J. Lapporte, L.L. Ferstandig, J. Org. Chem. 26 (1961) 3681–3685;
(c) 2d: see Ref. [24];
(d) 2e: S.D. Higgins, C.B. Thomas, J. Chem. Soc. Perkin Trans. 1 (1982) 235–242;

(e) 2g: P. Vinczer, G. Baan, Z. Juvancz, L. Novak, C. Szantay, C. Synth. Commun. 15 (1985) 1257–1270;

(f) threo- and erythro-2h: T. Maruyama, Proc. Imp. Acad. 10 (1934) 467–469, Chem. Zentralbl. 106 (1935) 2358; Chem. Abstr. 29 (1935) 1062;

(g) 2i: C.E. Bishop, G.W. Morrow, J. Org. Chem. 48 (1983) 657–660;

(h) 2k: J.K. Espenson, Z. Zhu, T.H. Zauche, J .Org. Chem. 64 (1999) 1191–1196;

(i) 2l: B.P. Das, D.W. Boykin, J. Med. Chem. 14 (1971) 56–58;

(j) 2n: F. Foubelo, F. Lloret, M. Yus, Tetrahedron 50 (1994) 5131–5138.

[29] G. Bellucci, C. Chiappe, F. Marioni, F. Marchetti, J. Chem. Soc., Perkin Trans. 2 (1992) 637–642, and references therein.

[30] (a) Literature references to reaction products: 3d: S.D. Higgins, B.C. Thomas, J. Chem. Soc., Perkin Trans. 1 (1982) 235–242;

(b) 3e: G. Foulard, T. Brigaud, C. Portella, Tetrahedron 52 (1996) 6187–6200;

(c) (E)-3g: G. Rankoff, Chem. Ber. 63 (1930) 2139–2142;

(d) (E)-3i: J.R. Vyvyan, C.L. Hoist, A.J. Johnson, C.M. Schwenk, J. Org. Chem. 67 (2002) 2263–2265;

(e) 3k: T. Ohta, N. Miyata, M. Hirobe, Chem. Pharm. Bull. 29 (1981) 1221–1230;

(f) 3l: C.S. Marvel, W.E. Garrison, J. Am. Chem. Soc. 81 (1959) 4737–4744;

(g) 4: C.D. Hurd, W.H. Saunders, J. Am. Chem. Soc. 74 (1952) 5324–5329.

[31] P. Lombardi, Chem. Ind. London (1990) 708.