

Green Chemistry

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/greenchem

Green Chemistry – Guidelines for Referees

***Green Chemistry* publishes high quality research and reviews demonstrating a significant advance in green and sustainable chemistry.**

To warrant publication in *Green Chemistry*, manuscripts must demonstrate:

1. Innovative, high quality research with high scientific integrity.
2. Significant novelty and advance with respect to green and sustainable chemistry.

Please ensure that your report comments on both of these aspects



***Green Chemistry* has a 2012 impact factor of 6.83 and publishes only the highest quality research, therefore, routine and incremental work – however competently researched and reported – should not be recommended for publication.**

If you believe that a paper would be better suited to a more specialised journal, please state so in your report. Please note that the rejection rate for *Green Chemistry* is currently about 75% of submitted manuscripts.

Thank you for your assistance in evaluating this manuscript – your help and guidance is greatly appreciated.

General Guidance

Journal Scope: Details regarding the journal scope of *Green Chemistry* can be found [here](#). All manuscripts must be written so as to be widely accessible (conceptually) to chemists and technologists. *Green Chemistry* does not publish research associated with 'end-of-pipe' or remediation issues.

Please note that the same quality standards which apply for the Royal Society of Chemistry's specialised journals must apply to papers submitted to *Green Chemistry*. This includes characterisation of new compounds or materials. It is the responsibility of authors to provide fully convincing evidence for the homogeneity, purity and identity of all compounds they claim as new. Please consult the relevant specialised journal documentation for further guidance.

- Organic Chemistry, please see [Organic & Biomolecular Chemistry](#) guidelines
- Materials Chemistry, please see [Materials Horizons](#) guidelines
- Physical Chemistry, please see [PCCP](#) guidelines
- Inorganic Chemistry, please see [Dalton Transactions](#) guidelines.

Referees have the responsibility to treat the manuscript as confidential. Please be aware of our [Refereeing Procedure and Policy](#), which contains full information on the responsibilities of referees and authors, and our [Ethical Guidelines](#).

When preparing your report, please:

- Comment on the originality, significance, impact and scientific reliability of the work;
- State clearly whether you would like to see the article accepted or rejected and give detailed comments (with references, as appropriate) that will both help the Editor to make a decision on the article and the authors to improve it.

Please inform the Editor if:

- There is a conflict of interest;
- There is a significant part of the work which you are not able to referee with confidence;
- The work, or a significant part of the work, has previously been published;
- You believe the work, or a significant part of the work, is currently submitted elsewhere;
- The work represents part of an unduly fragmented investigation.

When submitting your report, please:

- Provide your report rapidly and within the specified deadline, or inform the Editor immediately if you cannot do so. We welcome suggestions of alternative referees.

If you have any questions about reviewing this manuscript, please contact the Editorial Office at green@rsc.org

ARTICLE

Selective Ethenolysis and Oestrogenicity of Compounds from Cashew Nut Shell Liquid

Cite this: DOI: 10.1039/x0xx00000x

Jennifer Julis,^a Stuart A. Bartlett^a, Sabrina Baader,^b Nicola Beresford,^c Edwin J. Routledge,^c Catherine S. J. Cazin^a and David J. Cole-Hamilton^{a*}

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The ethenolysis of cardanol (**2**), a waste product from cashew kernel production, was carried out using a variety of metathesis catalysts. Surprisingly, the best activities and selectivities could be observed with ruthenium based-1st generation type catalysts converting cardanol (**2**) almost completely to the corresponding 1-octene (**6**) and 3-nonylphenol (**4**), a potential detergent precursor. Detailed investigation of the reaction system showed that the high activity and selectivity were due to a combination of ethenolysis and internal self-metathesis of the unsaturated cardanol mixture, **2**. Self-metathesis of cardanol (**2**) containing three double bonds led to the formation of 3-non-8-enylphenol (**4**) and 1,4-cyclohexadiene (**7**). The latter was crucial for a high selectivity and activity in the ethenolysis, not only of cardanol (**2**), but also of other substrates like methyl oleate (**10**) when using ruthenium based-1st generation catalysts. The endocrine disrupting properties of 3-nonylphenol and related compounds are compared.

Introduction

In the last decade the up-grading of renewable resources has received increasing attention. Not only the diminishing fossil resources and the increasing anthropogenic CO₂-emission, but also the rising conscience of society regarding global warming have intensified the efforts to establish new supply chains based on sustainable resources. To avoid competition between food and chemicals for land use, it is especially attractive to use waste products, like agricultural waste, as sustainable resources rather than renewable feedstocks which is also part of the food supply chain.

In this context, cashew nut shell liquid (CNSL) is a very interesting biodegradable and renewable natural resource, which is obtained as a by-product during processing of cashew nuts. Although 300 000 t/a of CNSL are currently available, only few applications exist and most of this raw material is considered as a waste stream.¹

CNSL is a phenolic mixture, which consists of three major compounds, namely anacardic acid (**1**), cardanol (**2**) and cardol (**3**) (Figure 1). Their proportion depends on the processing method of the cashew nuts. Solvent extraction of the nuts gives predominately anacardic acid whilst roasting of the nuts gives mainly cardanol (**2**) due to the decarboxylation of anacardic acid on heating. All three components have a fifteen carbon linear chain in the *meta*-position to the phenolic group with a varying degree of saturation, dependant on the origin of the cashew nuts.²⁻⁴

Anacardic acid (**1**) can be isolated from CNSL by precipitation with calcium hydroxide. Separation and acidification of the calcium anacardate gives the pure acid **1**, which can be

transformed to cardanol (**2**) by heating to 200 °C.⁵ Further purification by vacuum distillation gives pure cardanol (**2**) without alteration of the side-chain. Its versatility as a renewable starting material arises from its structure. Due to the phenol group and the unsaturated side-chain in the *meta*-position, it can be easily modified to valuable chemicals by introducing novel functionalities.

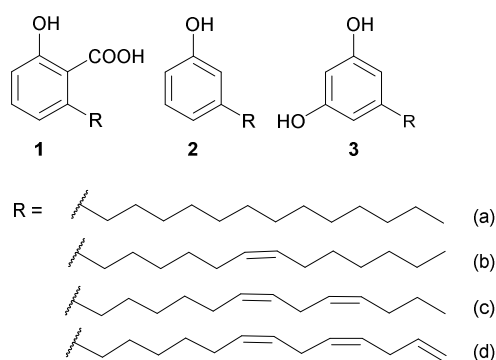


Figure 1 Components of CNSL.

Several applications of cardanol (**2**) or CNSL are known. For example, the synthesis of biscardanol derivatives as monomers, additives in surface coatings and resins⁶ and the synthesis of sodium cardanol sulfate as detergents⁷ have all been reported. **2** can also be functionalised to its corresponding ethers, which have been used as polymer additives⁸ or in nanofibers.⁹ However, the selective homogeneous catalysed transformation

of cardanol (**2**) to valuable intermediates is only rarely described and just a few examples like the double bond metathesis of cardanol (**2**) exist.^{6,9} Due to its unsaturated side-chain, metathesis is an attractive tool for functionalising **2** to intermediates of higher added-value. Vasapollo *et al.* reviewed the transformation of cardanol (**2**) to new fine chemicals as well as new hybrid functional materials, such as cardanol porphyrins, cardanol phthalocyanines and cardanol fullerenes *via* alkene-metathesis.⁹ However, no applications of the newly synthesised materials have been reported. Therefore, it is of particular interest to convert cardanol (**2**) selectively to intermediates which can be used directly as substitutes in the value-added chain. We have recently reported the selective synthesis of kairumone and other chemicals from **2**.¹⁰ Amongst other reactions, we reported that ethenolysis of cardanol (**2**), in that case with a high monoene (**2b**) content, could lead to 3-non-8-enylphenol (**4**) and 1-octene (**6**), which are both potentially important products. 1-Octene **6**, is mainly used as a comonomer for polyethylene with annual sales of 600,000 worth \$1.2 billion¹¹ and 3-nonylphenol has the potential for replacement of 4-nonylphenol, which makes an excellent detergent *via* ethoxylation, but has been banned in Europe because of its endocrine disrupting properties.^{12, 13} Using a Grubbs-Hoveyda type catalyst for the ethenolysis of cardanol (**2**), the selectivity towards the desired products was moderate.¹⁰ In a recent study, Grubbs-Hoveyda catalysts containing unsymmetrical *N*-heterocyclic carbenes where one *N* substituent is alkyl and the other aryl have been shown to be highly selective catalysts for the ethenolysis of methyl oleate, the best having di(2-propyl)phenyl and norbornyl substituents at loadings as low as 50 ppm, although conversions and reaction rates are moderate (conversion 47 %, selectivity to ethenolysis products 98 % at 500 ppm catalyst loading).¹⁴

We now report a detailed study of the selective ethenolysis of cardanol (**2**). Unexpectedly, first generation catalysts give very high selectivity to the desired products and very high conversions. We also report oestrogenicity studies on 3-nonyl phenol which show that it is 2 orders of magnitude less oestrogenic than commercial 4-nonylphenol.

Results

As homogeneous metathesis catalysts are very sensitive towards impurities, cardanol (**2**) was purified prior to use. Following a known literature procedure anacardic acid (**1**) was isolated from CNSL and heated to 200 °C for 3 h.³ After decarboxylation a brown viscous liquid remained, which was further purified by distillation at 230 °C under vacuum. **2** could be isolated as a pale yellow, slightly viscous liquid, which was stored under nitrogen atmosphere. GC-MS and ¹H-NMR analysis showed almost pure cardanol (**2**), which contained 37.9 % monoene **2b**, 19.9 % diene **2c**, 37.5 % triene **2d** and 4.7 % saturated cardanol **2a**. Separation of these various unsaturated compounds *via* column chromatography proved difficult, so the cardanol mixture **2** was used without further purification.

Cardanol ethenolysis

In a first set of experiments various homogeneous metathesis catalysts were tested in the ethenolysis of cardanol **2**. During ethenolysis, a propagating methylenidene species is formed, which reacts with cardanol (**2**) to release a terminal alkene 3-non-8-enyl phenol (**4**) in the case of mono-unsaturated cardanol **2b**.¹⁵ Most alkene metathesis catalysts are unstable as methylenidene complexes and undergo rapid decomposition,

which affects the selectivity and productivity of the ethenolysis reaction.¹⁴ Therefore, 1st generation type, 2nd generation type and Grubbs-Hoveyda type catalysts were screened in order to identify a suitable catalyst system for the selective ethenolysis of cardanol (Figure 2).

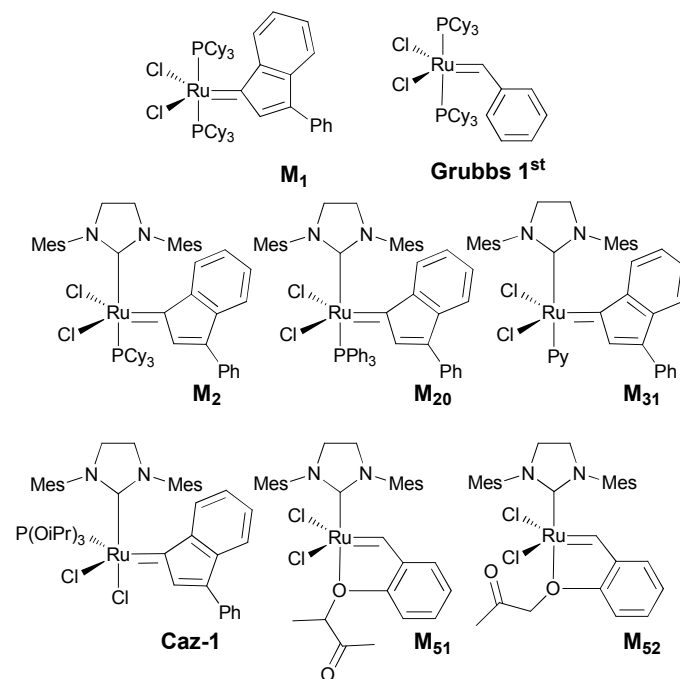


Figure 2 Homogeneous metathesis catalysts tested for the ethenolysis of cardanol (**2**).

Due to their varying stability and activity the performance of the metathesis catalyst was investigated at various temperatures. Beside the expected ethenolysis products, 3-non-8-enylphenol (**4**) and 1-octene (**6**), which are formed by cross-metathesis of ethene with **2** containing only 1 double bond, 1,4-cyclohexadiene (**7**), 3-dodecadienylphenol (**5**) and various isomeric ethenolysis products were also observed in the reaction mixture (Figure 1). The isomeric ethenolysis products are mainly formed *via* isomerisation of the monounsaturated cardanol (**2b**), followed by cross-metathesis with ethene. Ethenolysis at the unsaturated C₁₁-position of the diene (**2c**) and triene (**2d**) lead to the side-product 3-dodeca-8,11-dienylphenol (**5**). However, due to their volatility the corresponding side-products 1,4-pentadiene and 1-pentene were not observed.

Reacting **2** with **M1** at room temperature in the absence of ethene gives almost exclusive conversion (43 %) to 3-non-8-enylphenol (**4**, 81 % selectivity) and its isomers together with 1,4-cyclohexadiene (**7**), the remaining unreacted cardanol (**2**) contains no **2d** (absence of peaks with *m/e* 298, [M]⁺; Entry 2, Table 1). This reaction shows that **7** can be formed by direct internal self-metathesis of the triene (**2d**) to **7** and **4**. However, in the presence of ethene, **7** might also be formed from the ethenolysis of the triene (**2d**) at the unsaturated C_{8,9}-position, giving 3-nonylphenol (**4**) and 1,4,7-octatriene, followed by the internal self-metathesis of the 1,4,7-triene to ethene and **7** (see ESI, Figure S1).

Because of the high percentage of triene (**2d**) in the starting material, the amount of 1,4-cyclohexadiene (**7**) is significant and almost in the same range as 1-octene (**6**). The reactions that

are believed to occur during ethenolysis of cardanol (**2**) are summarised in the ESI, Figure S1.

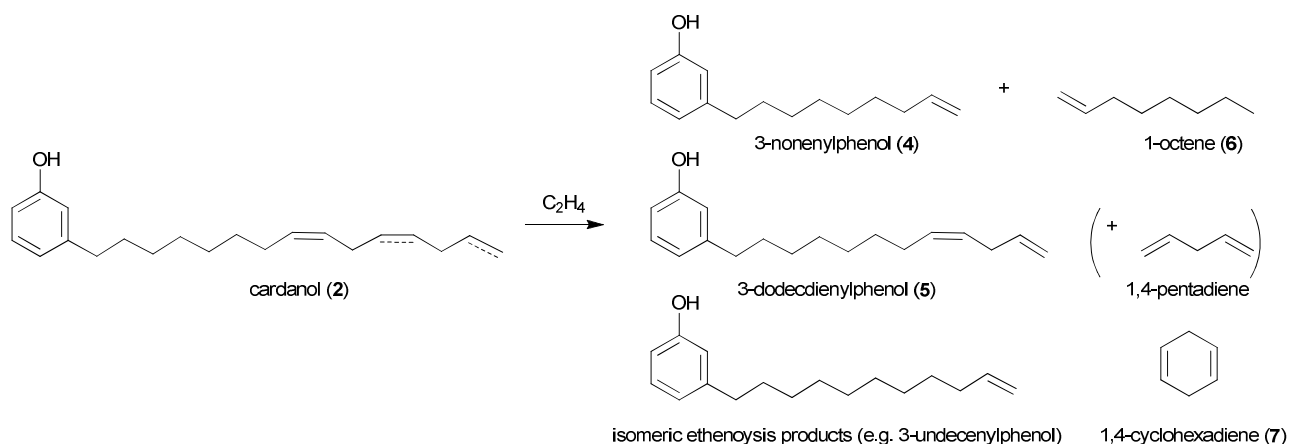


Figure 3 Cross-metathesis of cardanol (**2**) with ethene.

As some of the side-products such as the diene (**7**) and the linear alkenes with an alkyl chain $< C_7$ are volatile, it was not possible reliably to determine their exact amounts *via* GC analysis. Therefore, we analysed the distribution of the corresponding alkenylphenols.

The results in Table 1 show that the conversion and the selectivity in the ethenolysis of cardanol (**2**) strongly depend on the metathesis catalyst and the reaction temperature. Quite unexpectedly the best results were obtained with the M_1 and the Grubbs 1st generation catalysts (Entries 1-6, Table 1). Both catalytic systems exhibited an excellent performance in the ethenolysis with yields and selectivities $> 90\%$ towards the desired product, **4**, (catalyst loading, 0.05 mol %). Only a minor influence of the temperature on the activity was observed (Entries 1 and 3, 5 and 6, Table 1) and changing to the more environmentally acceptable solvent, toluene from CH_2Cl_2 was only slightly detrimental. (Entry 4, Table 1.) Furthermore, the metathesis reaction of cardanol (**2**) with M_1 , but with no ethene present showed that **2** can undergo self-metathesis to form 1,4-cyclohexadiene (**7**) and the desired 3-nonenylphenol (**4**) (Entry 2, Table 1). Only the tri-unsaturated cardanol (**2d**) is able to react to give **4** and **7** *via* self-metathesis, hence the conversion of the reaction (43 %) is similar to the amount of tri-unsaturated cardanol (**2d**) in the substrate mixture (37.5 %; the slight difference is within the experimental error of the GC measurements). This result indicates that metathesis of **2** with M_1 and ethene probably proceeds by a combination of self-metathesis (for **2d**) and ethenolysis (for **2b** and **2c**).

The N-heterocyclic carbene (NHC) bearing 2nd generation type¹⁶⁻¹⁹ catalysts M_2 , M_{20} , M_{31} and **Caz-1** (Entries 7-18, Table 1) were generally less active and selective in the ethenolysis of cardanol (**2**) compared to the Grubbs 1st generation catalyst and M_1 , especially at 20 °C where the conversion and the selectivity were much lower in comparison to the 1st generation type catalysts. With increasing temperature the activity and selectivity improved with M_2 (Entries 8 and 9, Table 1) and **Caz-1** (Entries 17 and 18, Table 1) catalysts giving good performances at 70 °C and 90 °C respectively.

Table 1 Conversion and selectivity in the ethenolysis of cardanol (**2**) using a variety of ruthenium based catalysts.^a

Entry	Catalyst	T / °C	Conv. / %	4 / %	5 / %	Isomeric products / %
1	M_1	20	95	94	2	4
2 ^b		20	43	81	0	19
3		40	96	93	3	4
4 ^c		20	84	87	8	5
5	Grubbs 1 st	20	90	91	5	4
6		40	91	90	5	5
7	M_2	20	57	19	14	67
8		40	61	34	12	54
9		70	84	68	12	20
10	M_{20}	20	26	43	25	32
11		40	83	54	20	27
12		70	87	49	15	37
13	M_{31}	20	67	46	24	30
14		40	83	53	19	28
15		70	87	59	22	20
16	Caz-1	40	61	9	12	79
17		70	58	22	14	65
18		90	92	75	12	13
19	M_{51}	20	82	50	12	38
20		40	93	16	4	80
21		70	90	22	6	72
22	M_{52}	20	88	23	7	70
23		40	95	24	10	66
24		70	89	22	7	72

^a **2** (0.54 mmol), C_2H_4 (8 bar), CH_2Cl_2 (1.35 mL), catalyst (0.05 mol%), Analysis *via* GC using *n*-tetradecane as internal standard.6 h; ^b no ethene; ^c toluene (1.35 mL) as solvent.

This increased activity with higher reaction temperature could be related to the activation energy of the catalyst since it is known that the latent **Caz-1** must isomerise from *cis* to *trans* before it becomes active.^{20, 21} For the metathesis reaction the catalyst must provide a free coordination site, which is generated *via* dissociation of a ligand. In contrast to the tricyclohexylphosphine ligands, which readily dissociate at

room temperature, phosphite ligands are much less labile and need higher temperature to leave the metal center.^{20, 21} Nevertheless, even at elevated temperature the activities of the 2nd generation type catalysts are lower than those of the 1st generation and **M**₁ catalysts. The reduced activity in the ethenolysis is not only visible in the lower conversion, but is also seen in the lower selectivities to product **4**.

The Grubbs-Hoveyda type catalysts show even less selectivity in the ethenolysis of cardanol (**2**). Only in the case of **M**₅₁ is significant selectivity towards the desired 3-non-8-enylphenol (**4**) observed at 20 °C (Entry 19, Table 1). Furthermore, the activity and selectivity of **M**₅₁ and **M**₅₂ show only minor dependencies on the reaction temperature (Entries 19-24, Table 1). Both catalytic systems are active at 20 °C and 40 °C respectively, but catalyse mainly the self-metathesis reactions of **2**. In comparison to the 2nd generation type catalysts, the boomerang-type ligand in **M**₅₁ and **M**₅₂ can easily dissociate to generate a free coordination site. It has been proposed that the ligand remains close to the metal centre and re-coordinates after the catalytic cycle to stabilise the complex,¹⁵ but this recoordination has been disputed.²² In any case, they are much more active in the conversion of **2** than the 2nd generation type catalysts. In general, NHC-based ruthenium catalyst are known to be more active and stable than the first-generation catalyst but are significantly less selective in ethenolysis, as they tend to promote self-metathesis.¹⁴

Forman *et al.* showed that the performance of certain alkene metathesis reactions by 1st generation catalysts could be enhanced by the addition of phenols.²³ In the presence of phenol only small quantities of undesired by-products were detected and the activity of the catalytic system was significantly increased. We reasoned, therefore, that the phenol present in cardanol (**2**) might be responsible for the excellent activity and selectivity provided by 1st generation and **M**₁ catalysts in the ethenolysis reaction. However, adding phenol to the ethenolysis reaction of **2** with **M**₁ did not improve the catalytic performance. In contrast, we observed no conversion of **2** indicating that, in our case, the addition of phenol inhibits the cross-metathesis of ethene and cardanol (**2**).

Metathesis of methyl protected cardanol **8**

The effect of the phenolic group in cardanol (**2**) was further tested by etherification of the phenolic –OH with methyl iodide (Figure 4).²⁴ The methyl cardanol (**8**) was tested in the ethenolysis with **M**₁ under standard reaction conditions. In comparison to the unprotected cardanol (**2**) the conversion (62.4 %) and selectivity towards the desired 3-non-8-enylphenol methylether (**9**) (84.0 %) were both lower than when using cardanol (**2**) itself as substrate, but higher than when using any of the other metathesis catalysts shown in Figure 2. The result shows that, although the phenolic structure of **2** may have some beneficial effect on the ethenolysis reaction, there must also be some other reason for the excellent results obtained when using **M**₁ or Grubbs 1st generation catalysts.

Ethenolysis of mono-unsaturated cardanol (**2b**)

Further information as to the important influences involved in the ethenolysis reactions came from a study of monounsaturated cardanol (**2b**), which was originally initiated to avoid the formation of 1,4-cyclohexadiene (**7**) and to maximise the production of 1-octene (**6**).

Recently, Perdriau *et al.* reported the selective transfer hydrogenation of a cardanol mixture **2** to mono-unsaturated compound **2b** with RuCl₃·xH₂O in 2-propanol.²⁵ The transfer-hydrogenation gives access to almost pure **2b**, although some double bond isomerisation occurs during the transfer hydrogenation reaction. The mono-unsaturated cardanol **2b** was tested in the ethenolysis with **M**₁, **Caz-1** and **M**₅₁ under the standard reaction conditions (Table 2).

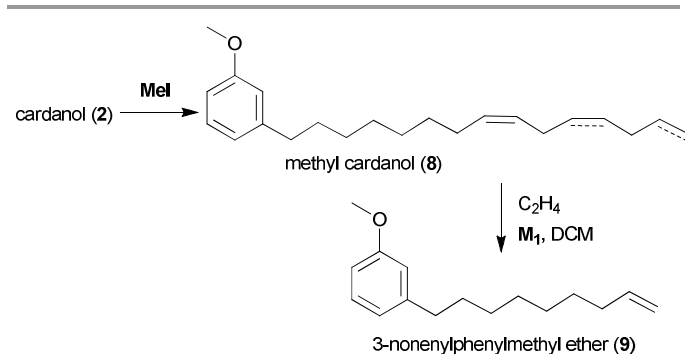


Figure 4 Synthesis of methyl cardanol (**8**) and ethenolysis to 3-nonenylphenylmethyl ether (**9**).

Table 2 Ethenolysis with mono-unsaturated cardanol (**2b**).^a

Entry	Catalyst	T / °C	Conversion / %	4 / %	Isomeric products / %
1	M ₁ ^b	0	0	0	60
2	Caz-1	70	28	13	87
3	M ₅₁	70	72	9	93

^a Conditions as in Table 1. ^b Using a different batch of **2b**, the conversion was 12 % and **4** made up 40 % of the alkyl phenols

The reaction was somewhat dependent upon the batch of starting material, but surprisingly, we only observed no or very low conversion of the mono-unsaturated cardanol with **M**₁ (Entry 1, Table 2 and footnote *b*, Table 2). The catalytic system **Caz-1** (Entry 2, Table 1) and **M**₅₁ (Entry 3, Table 2) showed some conversion in the ethenolysis, but in comparison to the unsaturated cardanol mixture **2** the activity and selectivity were also much lower. This observation indicates that the di- and tri-unsaturated cardanol (**2c** and **2d**) are highly beneficial for the ethenolysis of cardanol. Especially in the case of **M**₁ their presence seems to be essential.

Table 3 Ethenolysis of mono-unsaturated cardanol (**2b**) with additives.^a

Entry	Additive	Conversion / %	4 / %	Isomeric products / %
1	None ^b	0-	0	0
2	1,4-cyclohexadiene (7) ^c	64	55	46
3	1,4-hexadiene	63	46	55
4	1,5-cyclooctadiene	31	47	53
5	1,7-octadiene	69	46	54

^a Conditions as in Table 1; additive (0.1 equiv). ^b Using a different batch of **2b**, the conversion was 12 % and **4** made up 40 % of the alkyl phenols; ^c Using the batch of **2b** used for the reaction described in footnote *b*, the conversion was 49 % and **4** made up 38 % of the alkyl phenols

A major difference between the mono-unsaturated compound **2b** and the natural cardanol mixture (**2**) is the formation of 1,4-cyclohexadiene (**7**) during the metathesis reaction of **2d** in the

latter. To analyse the role of 1,4-cyclohexadiene (**7**) in the ethenolysis reaction, we added 0.1 equivalent of 1,4-cyclohexadiene (**7**) to **2b** and repeated the metathesis reaction under the standard reaction conditions (Table 3).

The addition of 1,4-cyclohexadiene (**7**) had a major impact on the ethenolysis of monounsaturated cardanol (**2b**) (compare Entries 1 and 2 in Table 3 and footnotes *b* and *c* in Table 3). In the presence of 1,4-cyclohexadiene **2b** (64.4 %) underwent metathesis and 3-nonenylphenol (**4**) was formed (54.5 % selectivity). The other products were mainly different chain length metathesis products, which arose from double bond positional isomers of the monoene (**2b**) that were formed during the transfer hydrogenation reaction.²⁵ Since without diene **7** we observed no or very little reaction, these results indicate that **7** has a positive effect on the **M₁** catalyst during the ethenolysis reaction. We also tested other dienes as additives in the metathesis of mono-unsaturated cardanol **2b** (Entries 3-5, Table 3.). With all three additives we could see an improved activity of the **M₁** catalyst in the ethenolysis of **2b**. The effect of 1,5-cyclooctadiene on the catalytic activity was less pronounced, giving a lower conversion (31.2 %, Entry 4, Table 1). This is possibly because 1,5-cyclooctadiene can coordinate through both double bonds to the metal centre and hence may block coordination of the double bond in **2b**. However, it still gives better catalysis than is obtained in its absence. These results suggest that the formation of 1,4-cyclohexadiene (**7**) in the ethenolysis of the natural cardanol mixture **2** is very important for the stabilisation of **M₁** and its activity in the metathesis reaction of cardanol (**2**) with ethene.

Caz-1 and **M₅₁** were also tested in the ethenolysis of mono-unsaturated cardanol (**2b**) with and without 1,4-cyclohexadiene (**7**) as additive, see Table 4.

In the case of **Caz-1** the addition of **7** leads to an increase in conversion of **2b** up to 80 %. However, mainly isomeric products of cardanol (**2**) were formed and only 10.5 % of the desired 3-non-8-enylphenol (**4**) was detected. With **M₅₁** no enhancement of the catalytic performance was observed. These results indicate that the effect of the diene (**7**) strongly depends on the ethenolysis catalyst employed.

Due to its positive effect in the ethenolysis of mono-unsaturated cardanol **2b** with **M₁**, we also analysed the influence of 1,4-cyclohexadiene (**7**) on the ethenolysis of **2b** protected *via* etherification with methyl iodide (see Table 5).

Table 4 Ethenolysis of mono-unsaturated cardanol **2b** with different catalysts with or without 1,4-cyclohexadiene (**7**).^a

Entry	Catalyst	Conversion / %	4 / %	Isomeric products / %
1 ^b	Caz-1	28	13	87
2 ^b	Caz-1 + 1,4-CHD	78	11	90
3 ^c	M₅₁	72	7	93
4 ^c	M₅₁ + 1,4-CHD	64	2	98

^a Conditions as in Table 1; ^b 70 °C; ^c 40 °C.

Table 5 Ethenolysis of methyl-protected mono-unsaturated cardanol **8b** with different catalysts and **7** as additive.^a

Entry	Catalyst	Conversion / %	4 / %	Isomeric products / %
1 ^b	M₁	53	50	50
2 ^b	M₁ + 1,4-CHD	56	53	37
3 ^c	Caz-1	71	6	94
4 ^c	Caz-1 + 1,4-CHD	80	8	92
5 ^d	M₅₁	77	2	98-5
6 ^d	M₅₁ + 1,4-CHD	86	3	97

^a Conditions as in Table 1; ^b rt; ^c 70 °C; ^d 40 °C.

Ethenolysis of oleate **10** and linoleate esters **12**

In contrast to the results of Table 3 and Table 4, the addition of 1,4-cyclohexadiene (**7**) to the reaction mixture only led to a minor improvements of the catalytic activity when using methyl protected monounsaturated cardanol **8b** as the substrate.

The highly beneficial combination of **M₁** + 1,4-cyclohexadiene (**7**) was also tested in the ethenolysis of oleate and linoleate based substrates.

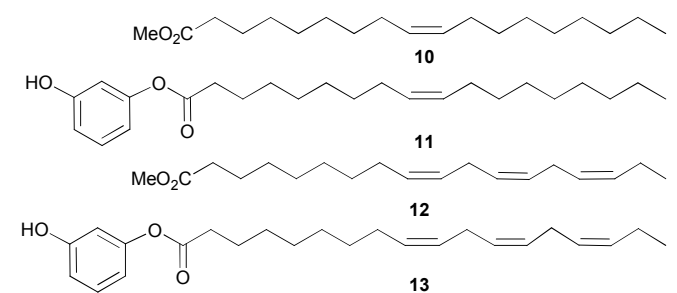


Figure 5 Oleate (**10**) and linoleate ester (**11**).

The results in Table 6 show that **7** also has a positive effect in the ethenolysis of methyl oleate (**10**) (Entries 1 and 2, Table 6), increasing the conversion of **10** to the ethenolysis product methyl 9-decenoate by more than 25 %. However, **M₁** is inactive for the metathesis of methyl linolenate (**12**) in the presence or absence of the diene **7** (Entries 5 and 6, Table 6).

Table 6 Ethenolysis of different olefinic substrates (**10-13**) with **M₁**.^a

Entry	Substrate	Conversion / %	Selectivity / %
1	10	47	89
2	10 + 1,4-CHD	76	94
3	11	7	62
4	11 + 1,4-CHD	13	57
5	12	-	-
6	12 + 1,4-CHD	-	-
7	13	36	75
8	13 + 1,4-CHD	5	-

^a Conditions as in Table 1.

To confirm that it was not the phenol in cardanol (**2**) that was allowing the excellent results obtained in ethenolysis reactions using **M₁**, we synthesised the resorcinol esters of oleic (**11**) and linolenic (**13**) acids. Introducing the phenol moiety into the oleic ester dramatically reduced the conversion and the

selectivity towards the desired dec-9-enoic acid ester (Entry 3, Table 6), a result that was hardly improved by adding **7** (Entry 4, Table 6). In the case of linolenate, there was some small improvement as a result of using the resorcinol ester **13** (Entry 7, Table 6), but this was nullified by adding the diene (**7**) (Entry 8, Table 6). Overall, the results of these ethenolysis reactions with oleate and linoleate esters **10-13** confirm that the phenol moiety is at best neutral or inhibiting to the reactions, but that 1,4-cyclohexadiene (**7**) can provide a positive effect.

Ethenolysis of anacardic acid (**1**) and its derivatives

Anacardic acid (**1**) can also be obtained directly from CSNL, but using fewer steps than are required for the isolation of cardanol (**2**). It can potentially give the desired 3-non-8-enylphenol (**4**) by ethenolysis followed by decarboxylation. Preliminary studies on the ethenolysis of anacardic acid itself using **M**₁ catalyst (conditions reported in Entry 1, Table 1) showed no evidence for reaction. We therefore methylated anacardic acid at both the phenolic and acidic positions. The ester **14** could then be purified by distillation without decarboxylation of the carboxyl group. Because of the lower activity of **M**₁ in the ethenolysis of methyl cardanol (**8**, see above) we directly investigated a range of Grubbs-Hoveyda type catalysts shown in Figure 6 which showed high efficiency in our previously investigated isomerising ethenolysis of methyl oleate²⁶ and of alkenyl benzenes.²⁷

The results of these studies, collected in Table 7, show that of all the catalysts tested only the phosphine containing catalyst, **HG**₁ shows high activity and selectivity at 25 °C and a catalyst loading of 1 mol % over 16 h (Entry 1, Table 7). Amongst the other catalysts (Entries 2-5, Table 7), only **M**₅₁ and **M**₇₄ show good activity (Entries 4 and 5, Table 7), but their selectivity towards the desired product **15** bearing an 8-nonyl substituent is low. There is little or no improvement for any of the catalysts at higher temperature (Entries 6-10, Table 7) but **HG**₁ is adversely affected. At 25 °C **HG**₁ performs well even at lower catalysts loading (Entries 11-13, Table 7) with a slight drop in activity but with the high selectivity being retained.

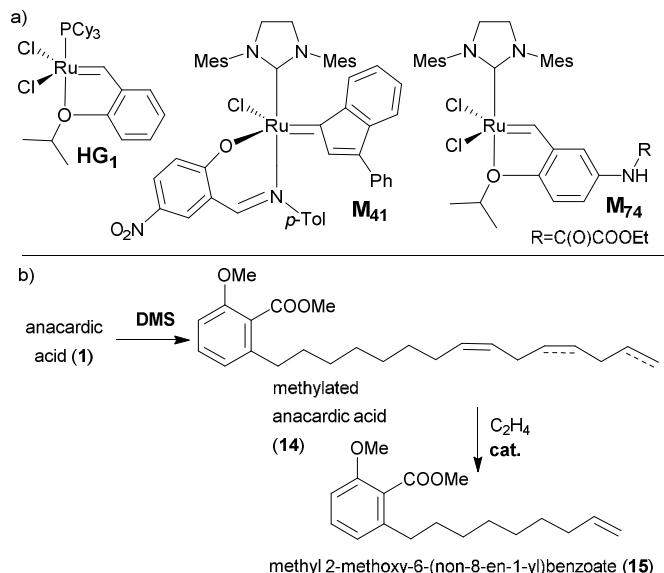


Figure 6 a) Catalysts used for the ethenolysis of methylated anacardic acid (**14**); b) synthesis and ethenolysis of **14**. DMS = dimethylsulfate.

Table 7 Ethenolysis of dimethylated anacardic acid **14**.^a

Entry	Metathesis catalyst	T / °C	Conversion / %	Selectivity / %
1	HG ₁	25	93	93
2	M ₃₁	"	17	13
3	M ₄₁	"	30	18
4	M ₅₁	"	96	36
5	M ₇₄	"	90	37
6 ^b	HG ₁	60	74	57
7 ^b	M ₅₁	"	88	16
8 ^b	M ₃₁	"	56	11
9 ^b	M ₄₁	"	44	19
10 ^b	M ₇₄	"	93	7
11 ^{c, d}	HG ₁	25	98	92
12 ^{c, e}	"	"	92	93
13 ^{c, f}	"	"	78	93

^a Conditions: **14** (0.25 mmol), cat. (1 mol %), CH₂Cl₂ (1 mL), 16 h; ^a yields were determined using *n*-dodecane as internal standard; ^b THF (1 mL); ^c reaction time 6 h; d cat. (0.5 mol %); ^e cat. (0.1 mol %); ^f cat. (0.05 mol %).

Test for oestrogenicity

Due to their excellent properties, ethoxylated alkylphenols (APE) are widely used in various applications, for example as emulsifiers, detergents or surfactants in household products. Nevertheless, they are being replaced by ethoxylated alcohols because of environmental concerns. One of the most important APEs has been banned in Europe because its precursor, 4-nonylphenol is an endocrine disrupter.^{12, 13} For example, it has been shown to induce testes-ova, and intersex condition, in the post-hatching stages of development of male Japanese Medaka fish.²⁸ The form of 4-nonylphenol used has a variety of differently branched C₉ chains in the 4 position of the phenol and its endocrine disrupting properties have been attributed to its ability to mimic the structure of oestradiol (Figure 7).

We reasoned that 3-nonylphenol might be less endocrine disrupting than 4-nonylphenol since it has a linear C₉ chain in the 3 position and should not so readily mimic oestradiol. Some of us have shown¹³ that the oestrogenicity of alkyl phenols increases in the order 2<3<4 alkyl substitution on the ring and primary~secondary<tertiary. Linear 4-nonyl phenol has been studied before¹³ and is known to show lower oestrogenicity than the commercial 4-nonylphenol with mixed alkyl chains, but 3-nonyl phenol has not been examined.

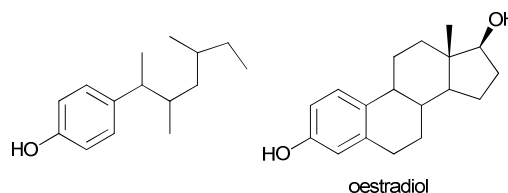


Figure 7 One isomer of 4-nonylphenol showing how it can adopt a structure related to that of oestradiol.

In order to test our hypothesis that 3-nonylphenol might show less oestrogenicity than either the linear or the branched 4-nonylphenol, we have carried out a yeast oestrogen screen (YES) assay which is specific for oestradiol mimics. For comparison, we also tested oestradiol, 4-nonylphenol with mixed C₉ chains (4-NP), 4-nonylphenol with a linear chain (4-n-NP), 3-nonylphenol (3-NP) prepared in this study by hydrogenation of 3-non-8-enylphenol, cardanol and crude cashew nut shell liquid. We appreciate that oestrogenicity is only one environmental hazard and further testing of any compounds that show promise for reducing oestrogenicity

would be required. This aspect is discussed in more detail in the concluding section of the paper.

Figure 8 shows the oestrogenic response of 3-NP and 4-n-NP tested over a concentration range of 1×10^{-3} mol dm⁻³ to 5×10^{-7} mol dm⁻³. Consistent with previous reports,¹³ moving the linear alky group from the 4- to the 3- position resulted in a 10-fold reduction in oestrogenic activity to produce a full dose response curve with a potency approximately 1.5×10^6 and 300-fold less than 17 β -oestradiol and 4-NP (mixed isomers), respectively. The initial sample of 3-NP, which had been obtained using Pd/C as the hydrogenation catalyst contained small amounts of ring hydrogenated product as a result of over hydrogenation. A second sample was prepared using [RhCl(PPh₃)₃] as the hydrogenation catalyst. This sample which did not contain any ring hydrogenation products, exhibited a 2-fold increase in oestrogenicity, which was still 150 times lower than that of 4-NP mixed isomers. The reason for the difference between the pure and contaminated samples is unknown, but may suggest that impurities containing saturated rings in the sample may have contributed to the loss of oestrogenicity, and/or that the ring hydrogenated products are less oestrogenic.

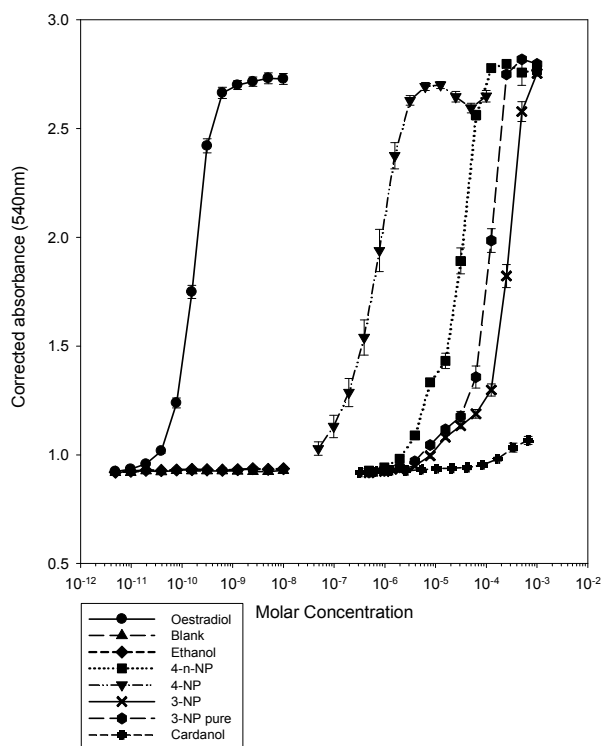


Figure 8 Oestrogenic response curves for a variety of substrates obtained using a YES assay.

Cardanol produced a very weak oestrogenic response at the highest concentrations tested whereas the cashew nut shell liquid was not oestrogenic in the YES assay when tested over the same concentration range (Figure 9).

Experimental

All reagents were purchased from Sigma–Aldrich and used as received unless otherwise stated. 17 β -oestradiol ($\geq 98\%$ pure) was purchased from Sigma Chemical Company Ltd. (Dorset, UK) and ethanol ($>99.7\%$) was purchased from Hayman

Speciality Products (Essex, UK). All other solvents were purchased from Sigma–Aldrich and were distilled under N₂ using the appropriate drying reagent.²⁹ CNSL was extracted from shells collected from Naliendele in Mtwara, Tanzania. Anacardic acid was obtained from the oil by a literature method³ and cardanol (**2**) from the anacardic acid (**1**) as previously published.¹⁰ The cardanol (**2**) was vacuum dried before it was subjected to ethenolysis reactions.

Instrumentation All weighing manipulations of air- and moisture-sensitive chemicals were carried out in the glove box of model type FF100 Recirc 13649 series, where the port was evacuated for 30 minutes and flooded with nitrogen gas for 3 cycles. All reactions which used air sensitive chemicals were carried out under nitrogen atmosphere using standard Schlenk line and catheter techniques.

GC–MS analyses were carried out using a Hewlett-Packard 6890 series gas chromatograph instrument equipped with a flame ionization detector for quantitative analysis and a Hewlett-Packard 5973 series mass selective detector fitted with hp1 film for mass spectral identification of products. Helium was used as the carrier gas with initial flow of 1 mL/min. The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AM 400 NMR spectrometer at 400 and 100 MHz or a Bruker AM 300 spectrometer at 300 and 75 MHz, respectively. Samples were dissolved in deuterated solvents which were referenced internally relative to tetramethylsilane (TMS) at $\delta = 0$ ppm. Chemical shifts, δ , are reported in ppm relative to TMS. All ¹³C NMR spectra were proton-decoupled.

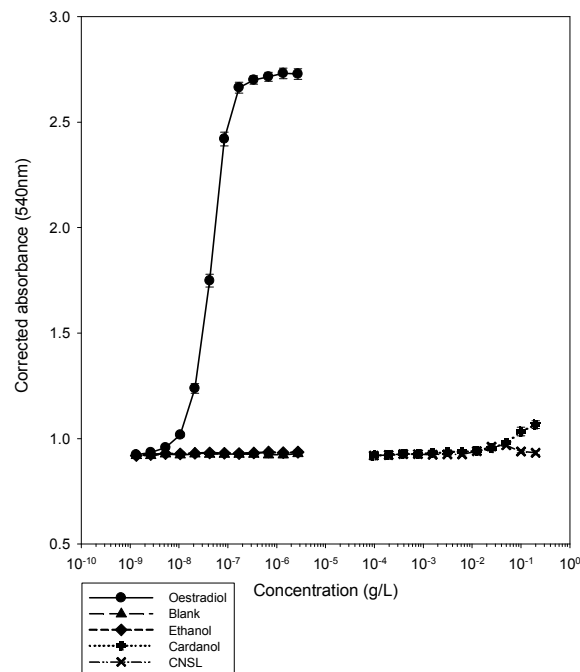


Figure 9 YES assay for cardanol and CNSL compared with oestradiol

Analysis of Cardanol (2). Cardanol was analysed via GC and NMR. ¹H NMR(300 MHz, CDCl₃): δ 0.93 – 1.00 (m, 1.9 H, CH₃/CH₂), 1.33 – 1.45 (m, 12.4 H, CH₂), 2.05 – 2.14 (m, 2.1 H, CH₂), 2.57 – 2.62 (m, 3.1 H, CH₂), 2.83 – 2.92 (m, 1.9 H, CH₂), 5.03 – 5.16 (m, 0.8 H, CH), 5.33 – 5.56 (m, 4.0 H, CH), 5.82 – 5.95 (m, 0.4 H, CH), 6.70 – 7.22 (m, 4H, Ar-H) ppm. ¹³C (75

MHz, CDCl₃): 14.3, 14.6 (CH₃), 32.1, 23.3, 26.0, 26.1, 27.6, 27.7, 29.4, 29.7, 29.8, 29.9, 30.1, 30.1, 30.2, 31.7, 32.0, 32.2, 36.3 (CH₂). 127.3, 128.0, 128.4, 128.6, 129.7, 129.8 (CH), 130.4, 130.6, 130.8, 137.3, 145.3, 155.8 (Ar-C) ppm. The integration of the ¹H NMR-signals did not result in even numbers, as cardanol is a mixture of compounds of different saturation. Furthermore, more than 21 C-signals can be observed due to the different degrees of saturation. The composition of saturated, mono-, di- and tri-unsaturated cardanol was calculated from integration of the olefinic proton signals the protons adjacent to the double binds and the aromatic protons.

Monounsaturated cardanol (2d)²⁵ RuCl₃·xH₂O (17 mg, 1.1 mmol) was dissolved in 2-propanol (5 mL) and cardanol (0.5 g, 1.66 mmol) was added. The reaction was refluxed for 18 h under an N₂ atmosphere. The resulting brown solution was cooled to room temperature and the solvent removed to give a viscous brown oil. The oil was dissolved in CH₂Cl₂ (20 ml) and filtered over a 5 cm³ plug of silica to give a yellow oil. Yield: 0.43 g, 1.4 mmol (86 %). ¹H NMR (CDCl₃): δ 0.9 (t, 3H, CH₃); 1.3 (m, 16 H, CH₂); 2.0 (m, 4H, CH₂-C=C); 2.6 (m, 2H, Ar-CH₂); 5.4 (m, 2H, HC=CH); 6.7-7.2 (m, 4H, Ar) ppm. MS (m/z): 302, 304 (saturated cardanol).

Methyl protected monounsaturated cardanol (8b)²⁴ Monounsaturated cardanol (1 g, 3.3 mmol) and potassium carbonate (0.9 g, 6.6 mmol) were suspended in dry acetone (15 mL). Methyl iodide (0.4 mL, 6.6 mmol) was added dropwise and the mixture allowed to reflux for 6 h. The reaction was then allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml). The organic layer was washed with water (3 x 20 ml), dried over MgSO₄, filtered and evaporated to give a yellow oil. The oil was then purified over a silica column using hexane:EtOAc (5:1). Yield: 55 %. ¹H NMR (CDCl₃): δ 0.9 (t, 3H, CH₃); 1.3 (m, 16 H, CH₂); 2.0 (m, 4H, CH₂-C=C); 2.6 (m, 2H, Ar-CH₂); 3.8 (s, 3H, OCH₃); 5.4 (m, 2H, HC=CH); 6.7-7.2 (m, 4H, Ar) ppm. MS (m/z): 316.

Methyl linolenate (12). Oleic acid (0.92 g, 3.5 mmol) and polyethyleneglycol-750 (1.24 g) were dissolved in CH₂Cl₂ (5 mL). KOH (0.37 g) was added and, after stirring for 1 h, MeI (0.5 g, 0.22 mL, 3.4 mmol). After stirring for 5 h, during which time a white precipitate formed, water was added followed by NaCl to break the emulsion. The organic phase was collected combined with CH₂Cl₂ washings of the aqueous phase (2 x 5 mL), dried over anhydrous MgSO₄ and evaporated to dryness. The product was separated on a silica column using hexane:EtOAc (4:1). GCMS analysis of the product showed it to be contaminated with up to 50 % methyl linoleate and traces of methyl oleate. NMR integration also suggests that significant amounts of methyl linoleate are present.

3-hydroxyphenyl oleate (11) Oleic acid (1.6 g, 4.21 mmol) and resorcinol (1.6 g, 14.82 mmol) were dissolved in THF (10 mL). The reaction mixture was cooled to 0 °C and slowly N,N-dicyclohexylcarbodiimide (991 mg, 4.81 mmol) and DMAP (22 mg, 0.18 mmol) were added. The reaction mixture turned turbulent and a white precipitate was formed. The suspension was allowed to warm and was stirred for 85 h at room temperature. Ethyl acetate (25 mL) was added to the mixture and the precipitate was collected by filtration. The filtrate was evaporated and the remaining residue was purified via column chromatography with hexane/EtOAc (4:1) as eluent. Yield: 62 %. ¹H NMR(CDCl₃): δ 0.91 (t, ³J = 6.9 Hz, 3 H, CH₃), 1.27 – 1.45 (m, 20 H, CH₂), 1.75 – 1.79 (m, 2 H, CH₂), 2.01 – 2.07 (m, 4 H, CH₂), 2.57 (t, ³J = 7.8 Hz, CH₂), 5.36-5.42 (m, 2 H,

CH), 6.23 (b, 1 H, OH), 6.57 – 6.70 (m, 3 H, Ar-H), 7.21 (t, ³J = 9.0 Hz, 1 H, Ar-H) ppm. ESMS (m/z): 373 [M-H]⁻

The product was contaminated with a product of slightly lower GC retention time (see ESI)

3-hydroxyphenyl linolenate (13) was similarly prepared from linolenic acid (1.2 g, 4.43 mmol), resorcinol (1.6 g, 14.82 mmol), N,N-dicyclohexylcarbodiimide (998 mg, 4.84 mmol) and DMAP (18.3 mg, 0.15 mmol). Yield: 58 %. ¹H NMR(CDCl₃): δ 1.01 (t, ³J = 7.5 Hz, 3 H, CH₃), 1.29 – 1.46 (m, 8 H, CH₂), 1.73 – 1.82 (m, 2 H, CH₂), 2.06 – 2.16 (m, 4 H, CH₂), 2.58 (t, ³J = 7.5 Hz, 2 H, CH₂), 2.81 – 2.86 (m, 4 H, CH₂), 5.31 – 5.48 (m, 6 H, CH), 6.03 (b, 1 H, OH), 7.56 (b, 1 H, Ar-H), 6.66 (t, ³J = 8.4 Hz, 2 H, Ar-H), 7.21 (t, ³J = 8.4 Hz, 1 H, Ar-H) ppm.

The product was contaminated with a product of slightly lower GC retention time (see ESI)

3-nonylphenol 3-non-8-enylphenol (1 g, 4.6 mmol), in degassed toluene (10 ml), was added to a solution of [RhCl(PPh₃)₃]³⁰ (30 mg, 46 μmol) dissolved in degassed toluene (5 ml) and transferred to a Fischer-Porter bottle which was charged with H₂ (6 bar) and left to stir overnight at 60 °C. The solution was filtered over a plug of silica (5 cm³) using CH₂Cl₂ (100 mL). The solvent was removed to give a colourless oil. Yield: 0.96 g, 4.4 mmol (96 %). ¹H NMR (CDCl₃): δ 0.91 (t, 3 H, CH₃); 1.3 (m, 12 H, CH₂); 1.6 (m, 2H, CH₂CH₂Ar); 2.6 (m, 2H, CH₂Ar); 4.7 (s, 1H, OH); 6.7 – 7.2 (m, 4H, Ar-H) ppm. ¹³C NMR (CDCl₃): δ 14.1 (CH₃); 22.7 (CH₂); 29.2 (CH₂); 29.3 (CH₂); 29.6 (CH₂); 29.8 (CH₂); 31.2 (CH₂); 31.9 (CH₂); 36.0 (Ar-CH₂); 113.1 (Ar); 115.6 (Ar); 120.7 (Ar); 129.9 (Ar); 144.8 (qAr); 156.1 (qAr) ppm. MS (m/z): 220.

Hydrogenation of 3-non-8-enylphenol (4) with Pd/C 3-non-8-enylphenol (4) (800 mg, 3.6 mmol) and Pd/C (5 wt%, 39 mg) were placed in an autoclave and dichloromethane (5 mL) was added. The autoclave was pressurized with hydrogen to 10 bar and the suspension was stirred at 40 °C for 6 h. The reaction was then allowed to cool to room temperature and the autoclave was slowly depressurized. The solvent was removed under reduced pressure and the residue was purified *via* column chromatography with hexane, ethylacetate and diethylether as eluent (7:1:1). Yield 78 %. ¹H NMR(300 MHz, CDCl₃): δ 0.91 (t, ³J = 6.9 Hz, 3 H, CH₃), 1.19 – 1.40 (m, 12 H, CH₂), 1.54 – 1.67 (m, 2 H, CH₂), 5.57 (t, ³J = 8.1 Hz, 2 H, CH₂), 4.94 (b, 1 H, OH), 6.64 – 6.71 (m, 2 H, Ar-H), 6.78 (bd, ³J = 8.4 Hz, 1 H, Ar-H), 7.16 (t, ³J = 8.4 Hz, 1 H, Ar-H) ppm. ¹³C (75 MHz, CDCl₃): 14.6 (CH₃), 23.2 (CH₂), 29.8 (CH₂), 30.0 (CH₂), 30.1 (CH₂), 30.2 (CH₂), 31.8 (CH₂), 32.4 (CH₂), 36.3 (CH₂), 112.9 (Ar-CH), 115.9 (Ar-CH), 121.5 (Ar-CH), 129.8 (Ar-CH), 145.4 (Ar-C), 155.8 (Ar-C) ppm.

Some completely hydrogenated 3-non-8-enylphenol to 3-nonylcyclohexanol can be observed in the ¹H NMR spectrum.

Anacardic acid ester (14)³¹ To a stirred solution of anacardic acid (1) (5.00 g, 14.6 mmol) in acetone (30 mL) was added potassium carbonate (8.07 g, 58.4 mmol). Dimethylsulfate (3.72 g, 29.2 mmol) was added in portions over about 10 min at room temperature. After the addition was complete, the solution was heated to reflux for 4 h. The solution was cooled to room temperature and quenched with ammonium chloride (10 mL). Distilled water (30 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with distilled water (1 x 10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was further purified by Kugelrohr

distillation (270 °C, 1×10^{-3} mbar) to yield 4.31 g (11.6 mmol, 80 %) of a bright yellow oil. $^1\text{H NMR}$ (CDCl_3): $\delta = 0.9$ (m, 1.77 H, CH_3); 1.3 (m, 12.07 H, CH_2); 1.6 (m, 2.23 H, CH_2); 2.0 (m, 3.02 H, $\text{CH}_2\text{-C=C}$); 2.5 (m, 1.89 H, $\text{C=C-CH}_2\text{-C=C}$); 2.8 (m, 2 H, Ar-CH_2); 3.8 (s, 3 H, OCH_3); 3.9 (s, 3 H, COOCH_3); 5.0 (m, 0.72 H, C=CH_2); 5.4 (m, 2H, HC=CH); 5.8 (m, 0.72 H, HC=CH_2); 6.7-7.2 (m, 4H, Ar) ppm. MS (m/z): 374.

Typical catalytic experiments

The catalyst (M1; 2 mg, 2.2 μmol) was weighed in the glove box and made up to a standard solution in CH_2Cl_2 (2 mL), in a Schlenk tube under dinitrogen atmosphere. When required, the additive was added to the standard solution in the correct molar amounts (1,4-cyclohexadiene; 27 μl , 55 μmol). The substrate (0.18 ml, 0.55 mmol) was degassed and added to a previously dried and inert Fischer-Porter bottle with magnetic stirrer bar under dinitrogen atmosphere, in CH_2Cl_2 (1.3 mL). The appropriate amount of catalyst was syringed from the standard solution (0.26 mL) and added to the Fischer-Porter bottle to give the correct substrate concentration (typically 0.35 mol dm^{-3} , 1:2000 [catalyst: substrate]). The glass bottle was sealed, flushed with ethene five times and pressurised to 8 bar. The solution was allowed to stir for 6 h at the predetermined temperature in the sealed vessel. The reaction was quenched with ethylvinyl ether (0.05 ml) and analysed by GC and GCMS.

Recombinant yeast oestrogen screen

The recombinant hER yeast strain was developed by Glaxo Wellcome and details of the yeast oestrogen screen have been described previously.³²

In brief, yeast cells were transfected with the human oestrogen receptor gene together with expression plasmids; the oestrogen response element and the *lac-Z* gene encoding the enzyme β -galactosidase. The yeast cells were incubated in a medium containing the test chemical and the chromogenic substrate, chlorophenol red- β -D-galactosidase (CPRG). Active ligands induced β -gal expression. The β -galactosidase secreted into the medium causes the yellow CPRG to change into a red product, and this is measurable by absorbance.

Assay procedure The medium components were prepared and the standard assay procedure was followed.³² Chemicals were serially diluted in ethanol and 10 μL volumes were transferred to 96-well flat-bottom plates where the ethanol was allowed to evaporate to dryness. Then, 200 μL medium containing CPRG and yeast (final cell number of 5×10^5 cells/mL) was added to each well. Included with every assay was a negative control, ethanol, and a positive control, 17 β -oestradiol (stock solution of 17 β -oestradiol (2×10^{-7} mol dm^{-3}) serially diluted in ethanol to achieve final concentrations of 1×10^{-8} mol dm^{-3} to 4.88×10^{-12} mol dm^{-3} in the wells).

The plates were incubated at 32 °C for 3 days, after which absorbance readings were taken at 540 and 620 nm (the second absorbance being a measure of cell density and hence yeast growth). The absorbance values were corrected for cell density using the following equation:

$$\text{Corrected value} = \text{chemical}_{540\text{nm}} - (\text{chemical}_{620\text{nm}} - \text{ethanol blank}_{620\text{nm}}).$$

All chemicals were tested in duplicate and each YES was carried out at least three times.

Conclusion

M₁ and **Grubbs'** 1st generation catalysts are very active and selective for the ethenolysis of cardanol (**2**) to 3-non-8-enylphenol (**4**), an intermediate for potential surfactants. The unexpectedly high catalytic performance of **M₁** is due to the side-product 1,4-cyclohexadiene (**7**), which is formed during the ethenolysis from the tri-unsaturated component of cardanol (**2d**). 1,4-cyclohexadiene (**7**) stabilises the catalytically active species and prevents inhibition by the phenolic group. Absence of **7** leads to a complete deactivation of **M₁**, as the results of the ethenolysis of mono-unsaturated cardanol showed. The positive impact of **7** on the catalytic performance was also observed with other substrates such as methyl oleate. It also enables the use of less expensive homogeneous metathesis catalysts in the ethenolysis reaction, one of the most challenging reactions in metathesis.

One application of 3-non-8-enylphenol (**4**) is for it to be hydrogenated to 3-nonylphenol for use as a possible replacement for 4-nonylphenol which has been banned in many countries on the basis of its endocrine disrupting properties. A YES assay shows that 3-nonylphenol prepared by ethenolysis of cardanol followed by hydrogenation using $[\text{RhCl}(\text{PPh}_3)_3]$ is at least 150 times less potent in oestrogenicity than the banned substance and some 10^{-6} times as oestrogenic as 17 β -oestradiol. Cardanol and cashew nut shell liquid are even less potent showing very little oestrogenicity in the YES assay. We recognise that the >150-fold reduction in oestrogenic activity between 4-NP and 3-NP, although desirable, is not enough to secure the long-term use of 3-NP as a replacement for use in alkylphenol ethoxylate surfactants where non-estrogenic alternatives (including alcohol ethoxylates) already exist. However, in countries lacking restrictions on the use and release of 4-NP into the environment, or in industrial applications where alternatives are not readily available, the reduction in oestrogenicity of 3-NP over 4-NP may be seen a useful stop-gap measure in the transition away from 4-NP use. The significance of the loss of oestrogenicity of 3-NP in terms of its safety in use can only be determined following robust investigations on its fate and persistence in the environment, further knowledge of the wider biological/toxicological hazard of 3-NP³³ and following the outcomes of internationally agreed and validated OECD test methods developed for the identification of endocrine disruptors, including oestrogenicity, (anti)androgenicity and thyroid disruption. Finally, this work is an example of how green chemistry can be used to design endocrine disruption out of the next generation of chemicals as proposed in the Tiered Protocol for Endocrine Disruption (TiPED) approach³⁴.

Acknowledgments

We thank the EPSRC for Postdoctoral and other funding (J. J. and S. A. B) and Deutsche Bundesstiftung Umwelt (Fellowship to S. B.). We also thank Umicore AG for the donation of chemicals. C. S. J. C. thanks the Royal Society for a University Research Fellowship.

Notes and references

^a EaStCHEM, School of Chemistry, University of St. Andrews, St. Andrews, KY16 9ST; Tel: +44-1334-463805; Fax: +44-1334-463808; e-mail: djc@st-and.ac.uk

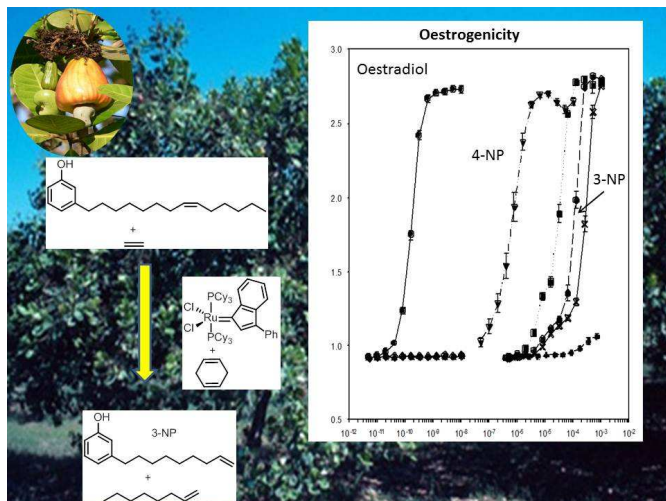
^b Fachbereich Chemie, Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße 54, 67663 Kaiserslautern, Germany

^c Institute for the Environment, Brunel University, Cleveland Road, Uxbridge, Middlesex, UB8 3PH

Electronic Supplementary Information (ESI) available: [Origin of the products of metathesis of cardanol, ¹H and ¹³C NMR spectra and GC analysis of selected reactions]. See DOI: 10.1039/b000000x/

1. S. H. Azam-Ali and E. C. Judge, *Small scale cashew nut processing* Food and Agriculture Organisation, Rome, 2004.
2. J. H. P. Tyman, *Chem. Soc. Rev.*, 1979, 8, 499.
3. R. Paramashivappa, P. P. Kumar, P. J. Vithayathil and A. S. Rao, *J. Agric. Food Chem.*, 2001, 49, 2548.
4. P. P. Kumar, R. Paramashivappa, P. J. Vithayathil, P. V. S. Rao and A. S. Rao, *J. Agric. Food Chem.*, 2002, 50, 4705.
5. L. P. L. Logrado, C. O. Santos, L. A. S. Romeiro, A. M. Costa, J. R. O. Ferreira, B. C. Cavalcanti, O. Manoel de Moraes, L. V. Costa-Lotufo, C. Pessoa and M. L. dos Santos, *Eur. J. Med. Chem.*, 2010, 45, 3480.
6. Y.-C. Guo, G. Mele, F. Martina, E. Margapoti, G. Vasapollo and W.-J. Xiao, *J. Organomet. Chem.*, 2006, 691, 5383.
7. P. Peungjitton, P. Sangvanich, S. Pornpakakul, A. Petsom and S. Roengsumran, *J. Surfactants, Detergents*, 2009, 12, 85.
8. R. K. Paul and C. K. S. Pillai, *Synthetic Metals*, 2000, 114, 27.
9. G. Vasapollo, G. Mele and R. Del Sole, *Molecules*, 2011, 16, 6871.
10. J. A. Mmongoyo, Q. A. Mgani, S. J. M. Mdachi, P. J. Pogorzelec and D. J. Cole-Hamilton, *Eur. J. Lipid. Sci. Technol.*, 2012, 114, 1183.
11. <http://www.icis.com/Articles/2007/08/06/9050162/chemical-profile-1-octene.html>.
12. F. L. P. Gabriel, E. J. Routledge, A. Heidlberger, D. Rentsch, K. Guenther, W. Giger, J. P. Sumpter and H.-P. E. Kohler, *Env. Sci. Technol.*, 2008, 42, 6399.
13. E. J. Routledge and J. P. Sumpter, *J. Biol. Chem.*, 1997, 272, 3280.
14. R. M. Thomas, B. K. Keitz, T. M. Champagne and R. H. Grubbs, *J. Am. Chem. Soc.*, 2011, 133, 7490.
15. D. Astruc, *New J. Chem.*, 2005, 29, 42.
16. L. Ackermann, A. Furstner, T. Weskamp, F. J. Kohl and W. A. Herrmann, *Tetrahedron. Lett.*, 1999, 40, 4787.
17. J. K. Huang, E. D. Stevens, S. P. Nolan and J. L. Petersen, *J. Am. Chem. Soc.*, 1999, 121, 2674.
18. M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, 1, 953.
19. M. Scholl, T. M. Trnka, J. P. Morgan and R. H. Grubbs, *Tetrahedron. Lett.*, 1999, 40, 2247.
20. X. Bantreil, A. Poater, C. A. Urbina-Blanco, Y. D. Bidal, L. Falivene, R. A. M. Randall, L. Cavallo, A. M. Z. Slawin and C. S. J. Cazin, *Organometallics*, 2012, 31, 7415.
21. X. Bantreil, T. E. Schmid, R. A. M. Randall, A. M. Z. Slawin and C. S. J. Cazin, *Chem. Commun.*, 2010, 46, 7115.
22. T. Vorfalt, K. J. Wannowius, V. Thiel and H. Plenio, *Chem. Eur. J.*, 16, 12312.
23. G. S. Forman, A. E. McConnell, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, M. M. Kirk, C. L. Dwyer and D. W. Serfontein, *Organometallics*, 2005, 24, 4528.
24. R. Holzwarth, R. Bartsch, Z. Cherkaoui and G. Solladie, *Chem. Eur. J.*, 2004, 10, 3931.
25. S. Perdriau, S. Harder, H. J. Heeres and J. G. de Vries, *ChemSusChem*, 2012, 5, 2427.
26. D. M. Ohlmann, N. Tschauder, J. P. Stockis, P. Goossen, M. Dierker and L. J. Goossen, *J. Am. Chem. Soc.*, 2012, 134, 13716.
27. S. Baader, D. M. Ohlmann and L. J. Goossen, *Chem. Eur. J.*, 2013, 19, 9807.
28. M. A. Gray and C. D. Metcalfe, *Env. Tox. Chem.*, 1997, 16, 1082.
29. C. L. L. C. Wilfred and L. F. Armarego, *Purification of Laboratory Chemicals*, Elsevier, North Holland, 2003.
30. J. A. Osborn, F. H. Jardine, J. F. Young and Wilkinso.G, *J. Chem. Soc. A*, 1966, 1711.
31. R. Paramashivappa, P. P. Kumar, P. V. S. Rao and A. S. Rao, *J. Agric. Food Chem.*, 2002, 50, 7709.
32. E. J. Routledge and J. P. Sumpter, *Env. Tox. Chem.*, 1996, 15, 241.
33. R. R. Tice, C. P. Austin, R. J. Kavlock and J. R. Bucher. *Environ Health Perspect* 2013, 121, 756
34. T. T. Schug, R. Abagyan, B. Blumberg, T. J. Collins, D. Crews, P. L. DeFur, S. M. Dickerson, T. M. Edwards, A. C. Gore, L. J. Guillette, T. Hayes, J. J. Heindel, A. Moores, H. B. Patisaul, T. L. Tal, K. A. Thayer, L. N. Vandenberg, J. C. Warner, C. S. Watson, F. S. vom Saal, R. T. Zoeller, K. P. O'Brien and J. P. Myers. *Green Chem.*, 2013, 15, 181

Graphical Abstract



Title Amplification

First generation ruthenium metathesis catalysts are the best for ethenolysis of cardanol from cashew nut shell liquid to 3-nonylphenol, a precursor to 3-nonylphenyl (3-NP) a potential replacement for the banned 4-nonylphenol (4-NP). The oestrogenicity of 3-NP is reduced by a factor of 150 compared with 4-NP.