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Selective ethenolysis and oestrogenicity of compounds from cashew nut shell liquid†

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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-non-8-enylphenol (**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 CO_2-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 are 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 per annum 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**) (Fig. 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]

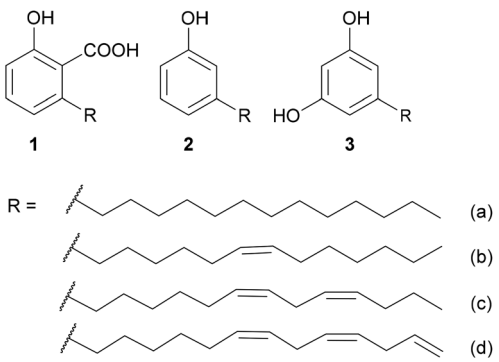

Fig. 1 Components of CNSL.

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*-posi-

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tion, it can be easily modified to valuable chemicals by introducing novel functionalities.

Several applications of cardanol (**2**) or CNSL are known. For example, the synthesis of biscardanol derivatives as monomers, additives in surface coatings and resins[6] and the synthesis of sodium cardanol sulfate as detergents[7] have all been reported. **2** can also be functionalised to its corresponding ethers, which have been used as polymer additives[8] 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 sidechain, 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 kairomone 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 billion[11] 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 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 ^{1}H-NMR analysis showed almost pure cardanol (**2**), which contained 38% monoene **2b**, 20% diene **2c**, 38% triene **2d** and 5% 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 methylidene 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 methylidene 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 (Fig. 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 (Fig. 3).

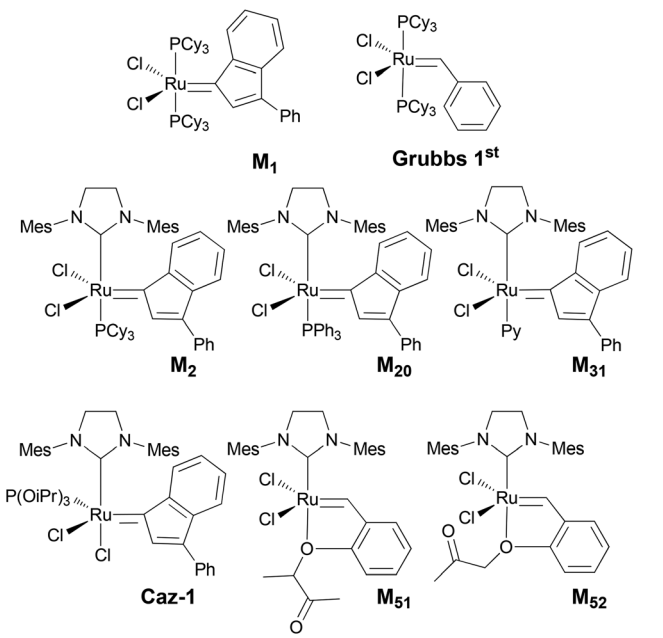

Fig. 2 Homogeneous metathesis catalysts tested for the ethenolysis of cardanol (**2**).

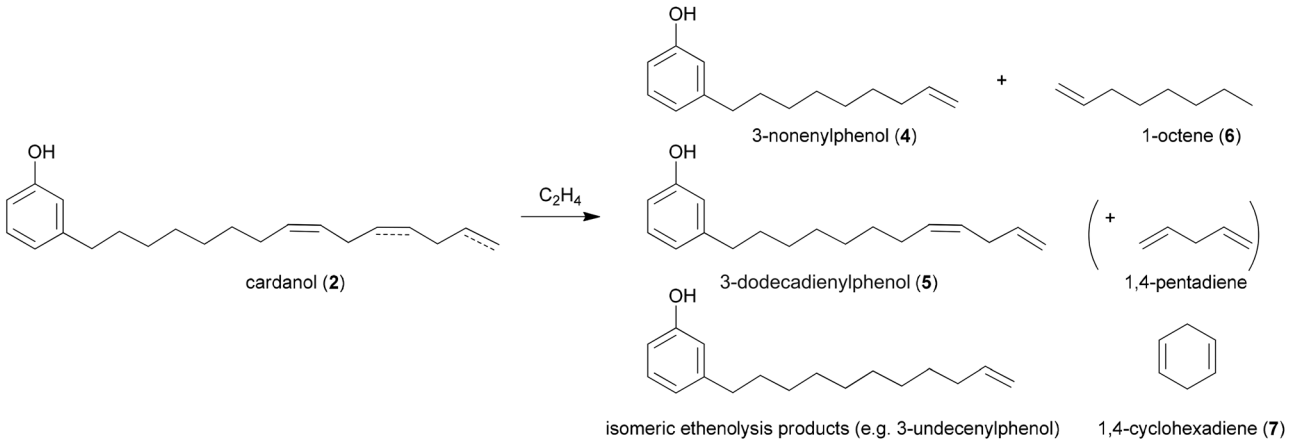

Fig. 3 Cross-metathesis of cardanol (2) with ethene.

The isomeric ethenolysis products are mainly formed *via* isomerisation of the mono-unsaturated cardanol (**2b**), followed by cross-metathesis with ethene. Ethenolysis at the unsaturated C_{11}-position of the diene (**2c**) and triene (**2d**) leads 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 $\mathbf{M_1}$ 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*/*z* 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-non-8-enylphenol (**4**) and 1,4,7-octatriene, followed by the internal self-metathesis of the 1,4,7-triene to ethene and **7** (see ESI, Fig. 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, Fig. S1.†

As some of the side-products such as the diene (**7**) and the linear alkenes with an alkyl chain < C7 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 $\mathbf{M_1}$ 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

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	$\mathbf{M_1}$	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 1st**	20	90	91	5	4
6		40	91	90	5	5
7	$\mathbf{M_2}$	20	57	19	14	67
8		40	61	34	12	54
9		70	84	68	12	20
10	$\mathbf{M_{20}}$	20	26	43	25	32
11		40	83	54	20	27
12		70	87	49	15	37
13	$\mathbf{M_{31}}$	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	$\mathbf{M_{51}}$	20	82	50	12	38
20		40	93	16	4	80
21		70	90	22	6	72
22	$\mathbf{M_{52}}$	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.

(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 $\mathbf{M_1}$, but with no ethene present, showed that **2** can undergo self-metathesis to form 1,4-cyclohexadiene (**7**) and the desired 3-non-8-enylphenol (**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 (38%;

the slight difference is within the experimental error of the GC measurements). This result indicates that metathesis of **2** with $\mathbf{M_1}$ 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 type[16–19] catalysts $\mathbf{M_2}$, $\mathbf{M_{20}}$, $\mathbf{M_{31}}$ 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 $\mathbf{M_1}$, 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 $\mathbf{M_2}$ (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.

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 $\mathbf{M_1}$ 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 $\mathbf{M_{51}}$ 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 $\mathbf{M_{51}}$ and $\mathbf{M_{52}}$ 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 $\mathbf{M_{51}}$ and $\mathbf{M_{52}}$ 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 catalysts 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 $\mathbf{M_1}$ catalysts in the ethenolysis reaction. However, adding phenol to the ethenolysis reaction of **2** with $\mathbf{M_1}$ 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 (Fig. 4).[24] The methyl cardanol (**8**) was tested in the ethenolysis with $\mathbf{M_1}$ under standard reaction conditions. In comparison to the unprotected cardanol (**2**) the conversion (62%) and selectivity towards the desired 3-non-8-enylphenolmethylether (**9**) (84%) were both lower than when using cardanol (**2**) itself as substrate, but higher than when using any of the other metathesis catalysts shown in Fig. 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 $\mathbf{M_1}$ 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 mono-unsaturated 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 $RuCl_3 \cdot xH_2O$ 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 $\mathbf{M_1}$, **Caz-1** and $\mathbf{M_{51}}$ under the standard reaction conditions (Table 2).

The reaction was somewhat dependent upon the batch of starting material, but surprisingly, we only observed zero or very low conversion of the mono-unsaturated cardanol with $\mathbf{M_1}$ (entry 1, Table 2 and footnote *b*, Table 2). The catalytic system **Caz-1** (entry 2, Table 1) and $\mathbf{M_{51}}$ (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

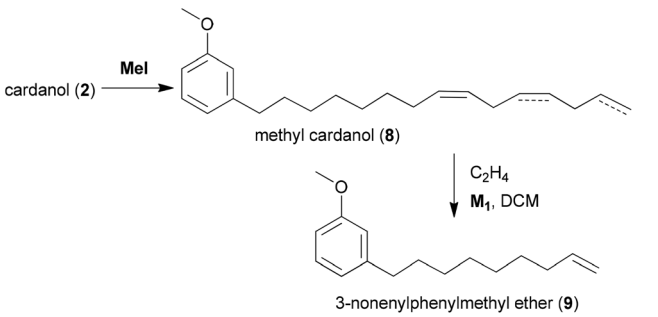

Fig. 4 Synthesis of methyl cardanol (**8**) and ethenolysis to 3-nonenylphenylmethyl ether (**9**).

Table 2 Ethenolysis with mono-unsaturated cardanol (**2b**)[a]

Entry	Catalyst	*T*/°C	Conversion/%	**4**/%	Isomeric products/%
1	$\mathbf{M_1}$[b]	0	0	0	60
2	**Caz-1**	70	28	13	87
3	$\mathbf{M_{51}}$	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 ethenolysis of cardanol. Especially in the case of $\mathbf{M_1}$ their presence seems to be essential.

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 mono-unsaturated 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%) underwent metathesis and 3-non-8-enylphenol (**4**) was formed (55% 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 $\mathbf{M_1}$ 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 $\mathbf{M_1}$ catalyst in the ethenolysis of **2b**. The effect of 1,5-cyclooctadiene on the catalytic activity was less pronounced, giving a lower conversion (31%, 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 $\mathbf{M_1}$ and its activity in the metathesis reaction of cardanol (**2**) with ethene.

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.

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.

Caz-1 and $\mathbf{M_{51}}$ 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 $\mathbf{M_{51}}$ 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 $\mathbf{M_1}$, we also analysed the influence of 1,4-cyclohexadiene (**7**) on the ethenolysis of **2b** protected *via* etherification with methyl iodide (see Table 5).

In contrast to the results of Tables 3 and 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.

Ethenolysis of oleate 10 and linoleate esters 12. The highly beneficial combination of $\mathbf{M_1}$ + 1,4-cyclohexadiene (**7**) was also tested in the ethenolysis of oleate and linolenate based substrates (Fig. 5).

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, $\mathbf{M_1}$ is inactive for the metathesis of methyl linolenate (**12**) in the presence or absence of the diene **7** (entries 5 and 6, Table 6).

To confirm that it was not the phenol in cardanol (**2**) that was allowing the excellent results obtained in ethenolysis reac-

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]	$\mathbf{M_1}$	53	50	50
2[b]	$\mathbf{M_1}$ + 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]	$\mathbf{M_{51}}$	77	2	98
6[d]	$\mathbf{M_{51}}$ + 1,4-CHD	86	3	97

[a] Conditions as in Table 1. [b] rt. [c] 70 °C. [d] 40 °C.

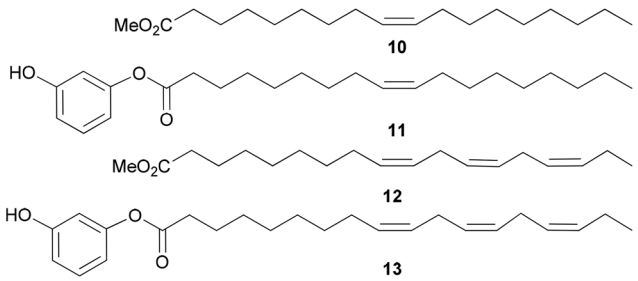

Fig. 5 Oleate (**10**) and linoleate ester (**11**).

Table 6 Ethenolysis of different olefinic substrates (**10–13**, Fig. 5) with $\mathbf{M_1}$[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.

tions using $\mathbf{M_1}$, we synthesised the resorcinol esters of oleic (**11**) and linolenic (**13**) acids (Fig. 5). 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 $\mathbf{M_1}$ 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 $\mathbf{M_1}$ in the ethenolysis of methyl cardanol (**8**, see above), we directly investigated a range of Grubbs–Hoveyda type catalysts shown in Fig. 1 and 6 which showed high efficiency in our previously investigated isomerising ethenolysis of methyl oleate[26] 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, $\mathbf{HG_1}$, shows high activity and selectivity at 25 °C and a

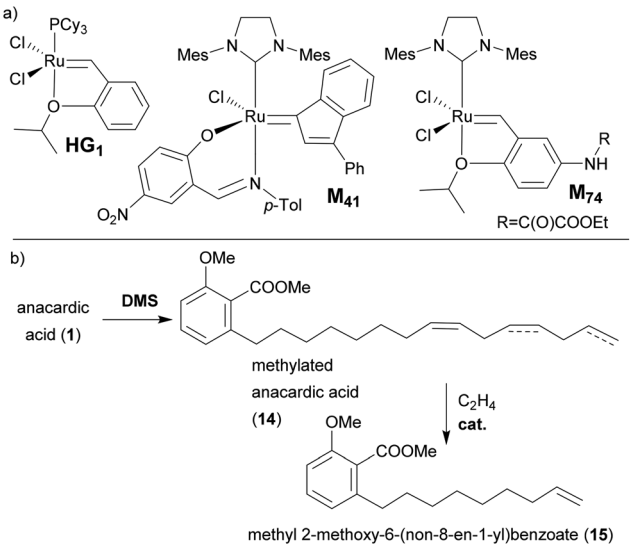

Fig. 6 (a) Catalysts used for the ethenolysis of methylated anacardic acid (**14**); (b) synthesis and ethenolysis of **14**. DMS = dimethylsulfate.

Table 7 Ethenolysis of dimethylated anacardic acid **14**[a]

Entry	Metathesis catalyst	T/°C	Conversion/%	Selectivity/%
1	$\mathbf{HG_1}$	25	93	93
2	$\mathbf{M_{31}}$	25	17	13
3	$\mathbf{M_{41}}$	25	30	18
4	$\mathbf{M_{51}}$	25	96	36
5	$\mathbf{M_{74}}$	25	90	37
6[b]	$\mathbf{HG_1}$	60	74	57
7[b]	$\mathbf{M_{51}}$	60	88	16
8[b]	$\mathbf{M_{31}}$	60	56	11
9[b]	$\mathbf{M_{41}}$	60	44	19
10[b]	$\mathbf{M_{74}}$	60	93	7
11[c,d]	$\mathbf{HG_1}$	25	98	92
12[c,e]	$\mathbf{HG_1}$	25	92	93
13[c,f]	$\mathbf{HG_1}$	25	78	93

[a] Conditions: **14** (0.25 mmol), cat. (1 mol%), CH_2Cl_2 (1 mL), 16 h; 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%).

catalyst loading of 1 mol% over 16 h (entry 1, Table 7). Amongst the other catalysts (entries 2–5, Table 7), only $\mathbf{M_{51}}$ and $\mathbf{M_{74}}$ show good activity (entries 4 and 5, Table 7), but their selectivity towards the desired product **15** bearing an 8-nonenyl substituent is low. There is little or no improvement for any of the catalysts at higher temperature (entries 6–10, Table 7) but $\mathbf{HG_1}$ is adversely affected. At 25 °C $\mathbf{HG_1}$ performs well even at lower catalysts loadings (entries 11–13, Table 7) with a slight drop in activity but with the high selectivity being retained.

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 impor-

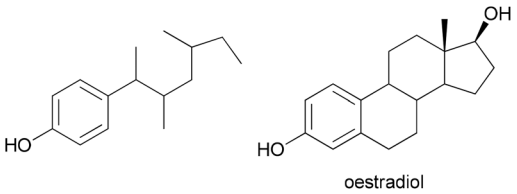

Fig. 7 One isomer of 4-nonylphenol showing how it can adopt a structure related to that of oestradiol.

tant 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 C_9 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 (Fig. 7).

We reasoned that 3-nonylphenol might be less endocrine disrupting than 4-nonylphenol since it has a linear C_9 chain in the 3-position and should not so readily mimic oestradiol. Some of us have shown[13] 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 before[13] and is known to show lower oestrogenicity than the commercial 4-nonylphenol with mixed alkyl chains, but 3-nonyl phenol has not been examined.

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 C_9 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.

Fig. 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 $[RhCl(PPh_3)_3]$ 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

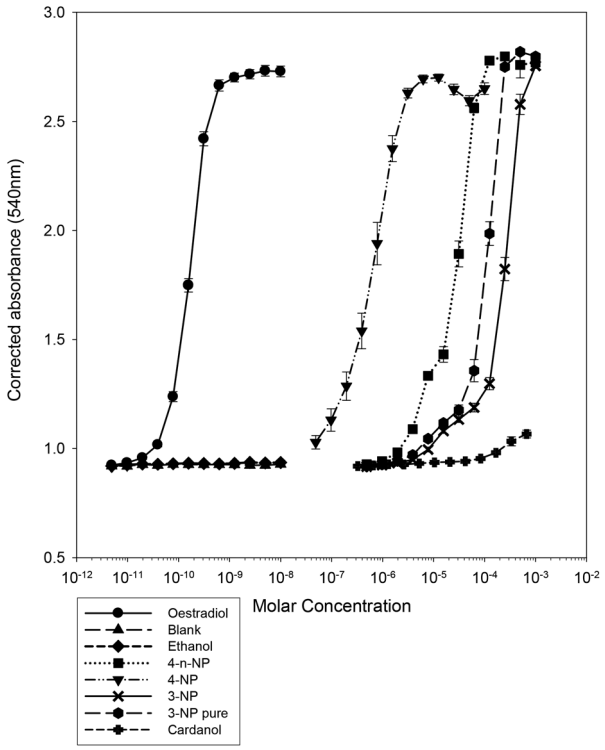

Fig. 8 Oestrogenic response curves for a variety of substrates obtained using a YES assay.

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.

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 (Fig. 9).

Experimental

All reagents were purchased from Sigma-Aldrich and used as received unless otherwise stated. 17 β-Oestradiol (≥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 N_2 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 method[3] 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 glovebox of model type

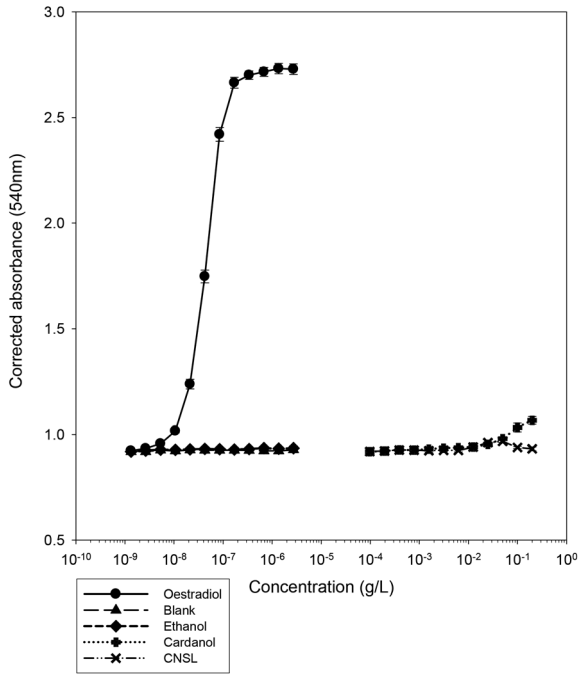

Fig. 9 YES assay for cardanol and CNSL compared with oestradiol.

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^{-1}. The ^1H NMR and ^{13}C 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 δ = 0 ppm. Chemical shifts, δ, are reported in ppm relative to TMS. All ^{13}C NMR spectra were proton-decoupled.

Analysis of cardanol (2). Cardanol was analysed *via* GC and NMR. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93–1.00 (m, 1.9 H, CH_3/CH_2), 1.33–1.45 (m, 12.4 H, CH_2), 2.05–2.14 (m, 2.1 H, CH_2), 2.57–2.62 (m, 3.1 H, CH_2), 2.83–2.92 (m, 1.9 H, CH_2), 5.03–5.16 (m, 0.8 H, C*H*), 5.33–5.56 (m, 4.0 H, C*H*), 5.82–5.95 (m, 0.4 H, C*H*), 6.70–7.22 (m, 4H, Ar-*H*) ppm. ^{13}C (75 MHz, $CDCl_3$): 14.3, 14.6 (CH_3), 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 (CH_2). 127.3, 128.0, 128.4, 128.6 129.7, 129.8 (*C*H), 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] $RuCl_3{\cdot}xH_2O$ (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 N_2 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 CH_2Cl_2 (20 ml) and filtered over a 5 cm^3 plug of silica to give a yellow oil. Yield: 0.43 g, 1.4 mmol (86%). ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_3); 1.3 (m, 16 H, CH_2); 2.0 (m, 4H, CH_2–C=C); 2.6 (m, 2H, Ar–CH_2–); 5.4 (m, 2H, *H*C=C*H*); 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 × 20 ml), dried over $MgSO_4$, 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 ($CDCl_3$): δ 0.9 (t, 3H, CH_3); 1.3 (m, 16 H, CH_2); 2.0 (m, 4H, CH_2–C=C); 2.6 (m, 2H, Ar–CH_2–); 3.8 (s, 3H, OCH_3); 5.4 (m, 2H, *H*C=C*H*); 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 CH_2Cl_2 (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 CH_2Cl_2 washings of the aqueous phase (2 × 5 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness. The product was separated on a silica column using hexane–EtOAc (4 : 1). GCMS analysis if 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($CDCl_3$): δ 0.91 (t, ^3J = 6.9 Hz, 3 H, CH_3), 1.27–1.45 (m, 20 H, CH_2), 1.75–1.79 (m, 2 H, CH_2), 2.01–2. 07 (m, 4 H, CH_2), 2.57 (t, ^3J = 7.8 Hz, CH_2), 5.36–5.42 (m, 2 H,

C*H*), 6.23 (b, 1 H, O*H*), 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%. ^{1}H NMR ($CDCl_3$): δ 1.01 (t, ^3J = 7.5 Hz, 3 H, CH_3), 1.29–1.46 (m, 8 H, CH_2), 1.73–1.82 (m, 2 H, CH_2), 2.06–2.16 (m, 4 H, CH_2), 2.58 (t, ^3J = 7.5 Hz, 2 H, CH_2), 2.81–2.86 (m, 4 H, CH_2), 5.31–5.48 (m, 6 H, C*H*), 6.03 (b, 1 H, O*H*), 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 $[RhCl(PPh_3)_3]$[30] (30 mg, 46 μmol) dissolved in degassed toluene (5 ml) and transferred to a Fischer–Porter bottle which was charged with H_2 (6 bar) and left to stir overnight at 60 °C. The solution was filtered over a plug of silica (5 cm^3) using CH_2Cl_2 (100 mL). The solvent was removed to give a colourless oil. Yield: 0.96 g, 4.4 mmol (96%). ^{1}H NMR (CDCl3): δ 0.91 (t, 3 H, CH_3); 1.3 (m, 12 H, CH_2); 1.6 (m, 2H, CH_2CH_2Ar); 2.6 (m, 2H, CH_2Ar); 4.7 (s, 1H, O*H*); 6.7–7.2 (m, 4H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ 14.1 (*C*H_3); 22.7 (*C*H_2); 29.2 (*C*H_2); 29.3 (*C*H_2); 29.6 (*C*H_2); 29.8 (*C*H_2); 31.2 (*C*H_2); 31.9 (*C*H_2); 36.0 (Ar-*C*H_2); 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%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, ^3J = 6.9 Hz, 3 H, CH_3), 1.19–1.40 (m, 12 H, CH_2), 1.54–1.67 (m, 2 H, CH_2), 5.57 (t, ^3J = 8.1 Hz, 2 H, CH_2), 4.94 (b, 1 H, O*H*), 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. ^{13}C (75 MHz, $CDCl_3$): 14.6 (*C*H_3), 23.2 (*C*H_2), 29.8 (*C*H_2), 30.0 (*C*H_2), 30.1 (*C*H_2), 30.2 (*C*H_2), 31.8 (*C*H_2), 32.4 (*C*H_2), 36.3 (*C*H_2), 112.9 (Ar-*C*H), 115.9 (Ar-*C*H), 121.5 (Ar-*C*H), 129.8 (Ar-*C*H), 145.4 (Ar-*C*), 155.8 (Ar-*C*) ppm.

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

Anacardic acid methyl 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 × 30 mL). The organic layer was washed with distilled water (1 × 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}H NMR ($CDCl_3$): δ = 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, CH_2–C=C); 2.5 (m, 1.89 H, C=C–CH_2–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, *H*C=C*H*); 5.8 (m, 0.72 H, *H*C=CH_2); 6.7–7.2 (m, 4H, Ar) ppm. MS (*m*/*z*): 374.

Typical catalytic experiments

The catalyst (M_1; 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 CPGR 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^{-1}) 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

M_1 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 **M_1** 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 **M_1**, 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 $[RhCl(PPh_3)_3]$ 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-NP[33] and following the outcomes of internationally agreed and validated OECD test methods developed for the identification of endocrine disrupters, 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) approach.[34]

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