Tetrahedron 65 (2009) 10495–10505

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Endo-selective Diels–Alder reaction of methacrylonitrile: application to the synthesis of Georgywood

Andras Borosy, Georg Frater, Urs Müller, Fridtjof Schröder *

Research Chemistry Department, Givaudan Schweiz AG, CH-8600 Dübendorf, Switzerland

ARTICLE INFO

Article history:
Received 14 August 2009
Received in revised form
21 September 2009
Accepted 23 September 2009
Available online 25 September 2009

ABSTRACT

Diels–Alder reactions of alkyl-substituted dienes with acrylonitriles give good yields and *endo*-selectivities if catalyzed by (organo)aluminum, (organo)boron or gallium halides. The activity of these group IIIa Lewis acids in this reaction correlates with the coordination strength of their nitrile complexes, which deactivate Lewis acids sufficiently, so that the subsequently added diene partner undergoes the Diels–Alder reaction without serious side-reactions. Boron trichloride is the most effective catalyst for this purpose. This method gives the best *endo*/*exo*-ratios reported so far for these components and was applied in the selective synthesis of the olfactory vector of Georgywood®.

1. Introduction

Isomer **1a** is the powerful olfactory vector of Georgywood® (Fig. 1),[1] an isomer mixture (**1a**/**1c**) produced at Givaudan and used as a woody, ambery fragrance ingredient in perfumery applications.[2] Since its first synthesis[3] various routes have been realized, which give the desired **1a** with higher selectivity.[4]

As part of the search for new fragrance molecules, *cis*-configured nitrile **4a** has been recently prepared from aldehyde **3a**[1b] in our laboratories. Upon treatment with H_3PO_4, diene **4a** underwent carbocationic 1,5-cyclization giving bicyclic nitrile **5a** with excellent selectivity (Scheme 1).

The exclusive formation of **5a** from **4a** raised our attention because the corresponding Brønsted acid promoted cyclization of ketone **6a** gives mixtures of ketones **1a** and **1c**, which have their origin in a pre-isomerization of the endocyclic double bond of cyclization precursor **6a**.[4b] Instead of preparing cyclization precursor **4a** from aldehyde **3a** (Scheme 1) we envisioned that **4a** could be more efficiently accessed from homomyrcene **2a**[3,4a] by an *endo*-selective Diels–Alder (DA) reaction with methacrylonitrile (MAN) (Scheme 2).

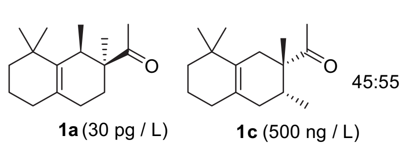


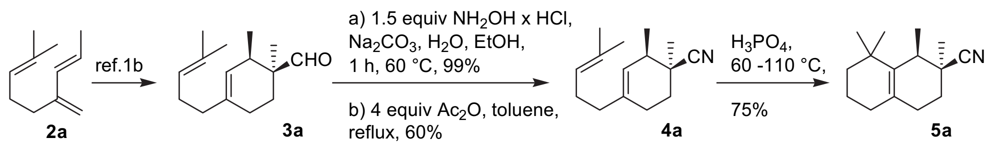
Figure 1. Main isomers of Georgywood® (olfactory thresholds in brackets). Isomer ratio **1a**/**1b**=45:55.

Endo/*exo*-selectivities for DA reactions of acrylonitriles with alkyl-substituted dienes,[5] however, have been only reported from endocyclic[6] dienes so far, and in case of methacrylonitrile only for the DA reaction with cyclopentadiene, where none- or *exo*-selectivities have been obtained, either thermally[7] or in the presence of zeolites.[8] In DA reactions with other dienes such as butadiene or furan, MAN has been reported as being much less reactive or even unreactive.[9] In his fundamental study on the thermal DA reaction of alkyl-substituted endocyclic dienes with α-alkyl-acrylonitriles, Mellor has found that *endo*/*exo* ratios and reaction rates decrease with the bulk of the α-alkyl-substituent R (Fig. 2).[7c,d] Mellor has attributed this effect to the centrosymmetric nature of the nitrile group, which has less freedom for secondary orbital overlap. Hence, with increasing bulk of R and R′ in *endo*-transition state **8a** nonbonding repulsive steric interactions between the bridging alkylidene group R′ of the endocyclic diene and the α-alkyl-substituent R of the acrylonitrile become predominant. From this we expected that methacrylonitrile and acyclic dienes such as homomyrcene **2a** would preferentially react via *endo*-transition state **9a**, due to the lack of the bridging alkylidene group R′ of the diene.

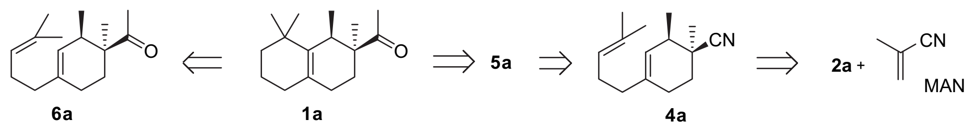
Other authors have reported slightly increased reaction rates and *endo*/*exo*-ratios for the DA reaction of cyclopentadiene with acrylonitrile in the presence of Lewis acids.[10] Similar effects were observed in Lewis acid/ionic liquid systems.[11] Although *endo*/*exo* ratios obtained from this transformation did not exceed 71:29,[10d,11a] this hinted at the possibility that Lewis acids could also increase the *endo*-ratios in methacrylonitrile Diels–Alder (MANDA) reactions of homomyrcene **2a**, via transition state **10a**, to access *cis*-product **4a** and to exploit such a product for a selective synthesis of **1a**.

* Corresponding author.
E-mail address: fridtjof.schroeder@givaudan.com (F. Schröder).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.089



Scheme 1. Synthesis of nitrile **5a** from aldehyde **3a**.



Scheme 2. Retrosynthesis of Georgywood vector **1a**.

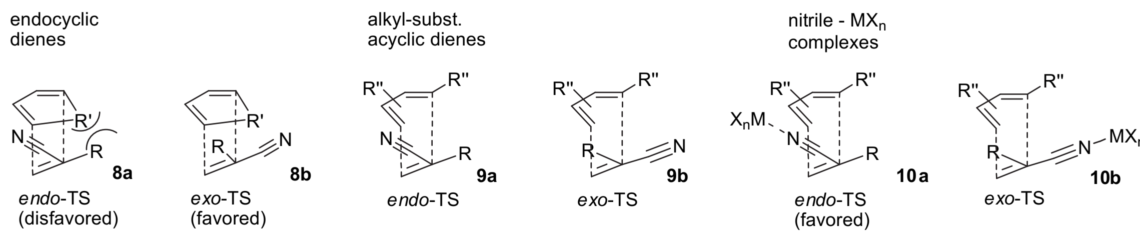
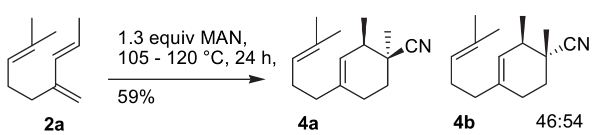


Figure 2. Transitions states (TS) of endocyclic (R′=alkylidene) and acyclic dienes, depending on nonbonding repulsive interactions of the bridging group R′ or the absence of this group with acrylonitriles. R′=methylidene, 1,1-cyclopropylidene, and ethylidene according to Ref. [7d] R″=methyl, alkyl. M=metal, X=halide.

2. Results and discussion

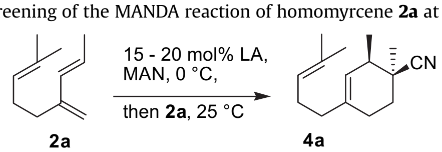
Solvent-free DA reaction of homomyrcene **2a** and methacrylonitrile at reflux gave the diastereomer mixture **4a**/**4b** with slight *exo*-preference (Scheme 3). NMR-data of *cis*-diastereomer **4a** were superimposible with the ones obtained already for this compound via the oxime route (Scheme 1). The structure of *trans*-isomer **4b** was determined after preparative GC separation from the **4a**/**4b** mixture and NMR-analysis.



Scheme 3. Thermal DA reaction of homomyrcene **2a** with methacrylonitrile (MAN).

A Lewis acid screening[12] of this reaction at 60 °C showed that especially metal halides MX_3 of the IIIa group (BX_3, AlX_3, and GaX_3 with X=Cl, Br) gave good reaction rates and *endo*/*exo*-ratios (Table 1, entries 1–7). $GaCl_3$, however, gave a much lower yield (run 7) and $InCl_3$ was inactive. $EtAlCl_2$ and especially $MeAlCl_2$ were similarly effective (runs 4–5) but organoaluminum reagents of weaker Lewis acidity such as AlF_3, $AlEt_3$, $Al(iBu)_3$ or Me_2AlCl gave very poor conversions. Methylaluminoxane (MAO) or $Al(OTf)_3$ gave only traces of DA adduct. The corresponding ZnX_2 salts (X=Cl, Br) were also reactive but needed longer reaction times and gave inferior *endo*/*exo*-ratios (runs 8–9).

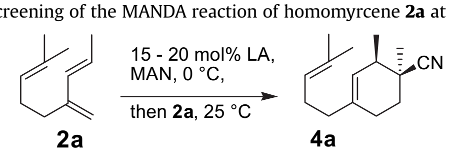
Table 1
Lewis acid screening of the MANDA reaction of homomyrcene **2a** at 60 °C



Entry	Lewis acid (LA)	mol % LA[c]	Solvent	Time [h]	Yield[a]	*cis*/*trans*	Other dienes[b]
1	$AlCl_3$	20%	Toluene	4 h	51%	81:19	20%
2	$AlCl_3$/*n*-$PrNO_2$ 1:2[d]	15%	None	4 h	63%	77:23	29%
3	$AlBr_3$	20%	Toluene	4 h	62%	78:22	20%
4	$EtAlCl_2$	20%	Toluene	4 h	73%	64:36	10%
5	$MeAlCl_2$	20%	Tol, hex	1 h	73%	81:19	5%
6	BCl_3	10%	Xylene	1 h	64%	84:16	9%
7	$GaCl_3$	20%	Toluene	3 h	43%	79:21	26%
8	$ZnCl_2$	20%	Toluene	21 h	58%	66:34	33%
9	$ZnBr_2$	20%	Toluene	48 h	54%	70:30	27%

Conditions: Homomyrcene **2a** added to 10–25 mol % Lewis acid and 1.2 equiv methacrolynitrile under cooling, stirring and nitrogen, then heated to 60 °C until complete conversion of the diene.
[a] Yields (*exo*+*endo*) after distillation and corrected by purity of substrate **2a** and product **4**.
[b] Mainly unconverted terminal dienes **2b** and **2d** and methyllimonene **2c** before distillation.
[c] Molar ratio relative to substrate in %.
[d] Molar ratio.

Table 2
Lewis acid screening of the MANDA reaction of homomyrcene **2a** at 25 °C



Entry	Lewis acid (LA)	mol % LA	Solvent	Time [h]	Yield[a]	*cis* /*trans*	Other dienes[b]
1	$AlCl_3$	20%	CH_2Cl_2	72 h	39%	79:21	3%
2	$AlCl_3$	15%	None	44 h	60%	73:27	20%
3	$MeAlCl_2$	15%	Toluene	22 h	51%	82:18	24%
4	BCl_3	20%	Xylene	3 h	65%	85:15	10%
5	BBr_3	20%	Toluene	3 h	63%	85:15	12%
6	*n*-Bu-BCl_2	20%	Hexane	24 h	43%	85:15	7%
7	Ph-BCl_2	20%	Toluene	18 h	54%	85:15	8%

Conditions: Homomyrcene **2a** added to 0.15–0.2 equiv Lewis acid and 1.2 equiv methacrolynitrile under cooling, stirring and nitrogen, then stirred at 25 °C until complete conversion of the diene.
CH_2Cl_2 instead of toluene gave similar results.
[a] Yields (*exo*+*endo*) after distillation and corrected by purity of substrate **2a** and product **4**.
[b] Mainly unconverted terminal dienes **2b** and **2d** and methyllimonene **2c** before distillation.

The most reactive of these Lewis acids (Table 1) could be efficiently employed at 25 °C (Table 2). $AlCl_3$ (runs 1–2)[13] and $MeAlCl_2$ (run 3), however, gave the DA adduct **4** only after prolonged reaction times and with decreased yields and *endo*/*exo*-ratios, whereas BCl_3 and BBr_3 (runs 4–5) catalyzed this reaction with best efficiency at this temperature. *n*-$BuBCl_2$ and $PhBCl_2$ were less reactive but also gave an *endo*/*exo* ratio of 85:15 (runs 6–7). Reactivity was drastically reduced with BEt_3· $B(C_6F_5)_3$[14] catalyzed this reaction with good *endo*/*exo* selectivity but much slower. Corey's o-Tolyl-CBS-oxazaborolidine triflimide catalyst[4c] was inactive as was gaseous BF_3 or $BF_3(MeCN)$. Similar reaction rates were obtained in xylene, toluene, and CH_2Cl_2. Ether solvents are inhibiting.[15]

Attempts to decrease the catalyst load of $MeAlCl_2$ and BCl_3 below 15% were not successful, higher temperatures are then necessary for complete conversion, which come close to the temperature of the unselective thermal reaction (run 6).

Homomyrcene **2a**, produced as described,[3] contains the isomers **2b** and **2d** as main impurities,[16] which are eluted closely to **2a** in the GC (Fig. 3). Selective DA reaction of **2a** with methacrylonitrile (under the conditions of Tables 1 and 2) leave the less reactive **2b** and unreactive methyllimonene **2c** (at GC-retention times close to **2a**) untouched. No defined byproducts are formed. With some less efficient catalysts such as $Cu(OTf)_2$/BINAP, MAO, and $TiCl_4$ slow isomerization of **2a** to **2b**, **2c**, and **2e** was observed by GC. With $Bi(OTf)_3$ in CH_2Cl_2 competitive cyclization/isomerization to **2e** became predominant.

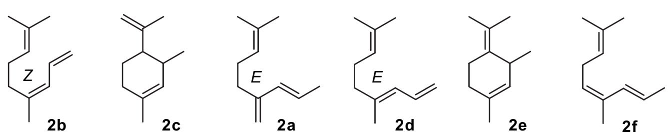
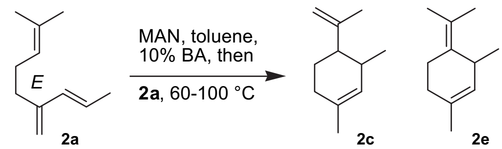


Figure 3. Homomyrcene **2a** and $C_{11}H_{18}$ isomers **2b–f** (order of elution on a DB5 column). Preparation of reference compounds: **2a** (Ref. [3]), **2b** (Ref. [16]), **2c** (from *Citral*, MeMgCl, THF, 0 °C, then $FeCl_3$, tetraethyleneglycol dimethylether, 80 °C), **2d** (Ref. [16]), **2e** (from homomyrcene **2a**, methacrylonitrile, 10% $Bi(OTf)_3$, CH_2Cl_2, 64%, dist), **2f** (Refs. [4a–b]).

Silver salts slightly increased *endo*/*exo*-ratios under the conditions of Table 1, e.g., up to 62:38 with $AgBF_4$, but the reaction run very sluggishly.[17] Copper[18] and zinc[19] complexes were less effective and other Lewis acids were found to be inactive,[20] i.e., lanthanide triflates.[21]

It should also be mentioned that Brønsted acids did not promote a Diels–Alder reaction of homomyrcene and **MAN** but gave mainly mixtures of methyllimonenes **2c** and **2e** with moderate yields (Scheme 4).[22] Replacing homomyrcene **2a** by cyclopentadiene gave no DA product at all under these conditions, whereas in the presence of BCl_3 the desired **13** was obtained readily (vide infra).



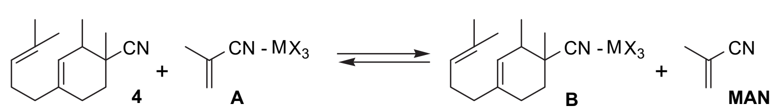
Scheme 4. Cyclization of homomyrcene **2a** in the presence of Brønsted acids. BA=H_2SO_4, pTSA, TFA (all with 0.1 equiv) or formic acid (5 equiv).

2.1. Discussion

The observed catalytic activity of the boron and aluminum halides (Tables 1 and 2) correlates with the strength of the methacrylonitrile σ-orbital coordination to the boron and aluminum center as known from the literature. The order $BBr_3 \geq BCl_3 >> BF_3$ has been reported from coordination studies with acetonitrile,[23] formation constants for complexes with *p*-fluorobenzonitrile have been reported to follow the order $BBr_3 \sim BCl_3 >> BF3 > pFC_6H_4BCl_2$, BMe_3.[24] In a more recent study of methacrylonitrile coordination with a series of strong Lewis acids MCl_n ($M = Ti^{(IV)}$, $Sn^{(IV)}$, $B^{(III)}$, $Sb^{(V)}$) by far the most stable complex of methacrylonitrile was formed with BCl_3.[25] The order of activity $AlCl_3 \sim MeAlCl_2 > EtAlCl_2 >> AlEt_3$, $Al(iBu)_3$, $Me_2AlCl > MAO$ was observed in reactions promoted by ketone Lewis acid complexation.[4a] From another study it has been reported that especially group III metal chlorides MX_3 undergo strong coordination with saturated nitriles and the order Al>Ga>Zn>Fe>Sn>Ti was observed.[26]

A reliable quantitative structure–activity relationship (QSAR) was established between the *log t* values ($\log_{10}$ of Time [h] in Tables 1 and 2) and the molecular structures of 22 catalysts, including the ones employed and some others. The root mean square error (RMSE) of prediction of the best model is 1.15 in log units.[27] This QSAR explains, for example, why Brønsted acids don't promote MANDA reactions: the coordination of MAN with a proton is as weak as coordination with boron trifluoride, for example, therefore Brønsted acids simply don't activate MAN for DA reaction.[28]

The calculation of coordination complexes of **4** with $AlCl_3$ and BCl_3 shows, that these complexes (**B**) are only 2–3 kcal lower in Gibbs free energy than the corresponding complexes of methacrylonitrile (**A**).[29] This can be explained by an increased electron



Scheme 5.

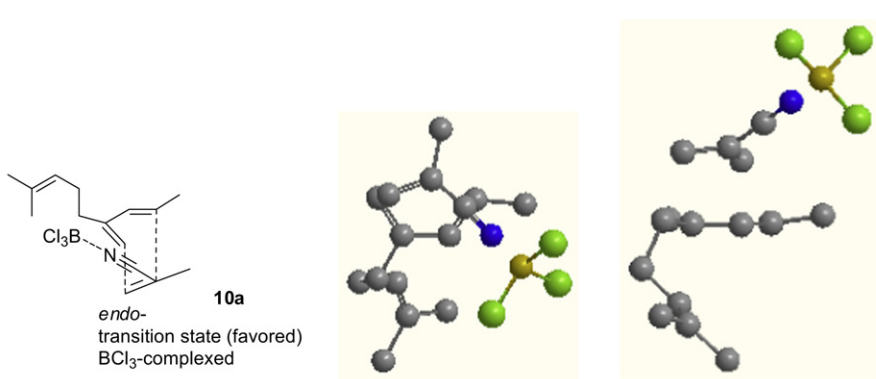
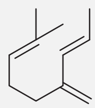
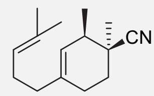
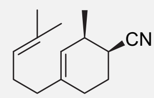
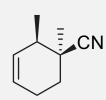
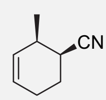
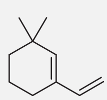
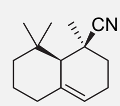
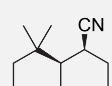
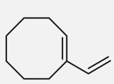
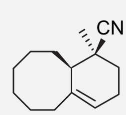
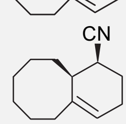
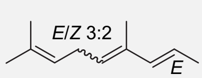
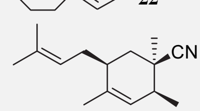
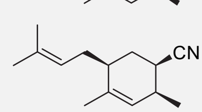


Figure 4. *Ab initio* calculation of Diels–Alder transition **10a** (*endo*): top view (left) and side view (right).

density at the nitrile lone pair orbital of **4** versus the more delocalized electron density in methacrylonitrile. The relatively low energy difference allows equilibration and a catalytic activity of these Lewis acids on methacrylonitrile (Scheme 5). The *endo*/*exo* ratios are independent from the progress of the reaction and the amount of catalyst used.

The enhanced *endo*-selectivities can be explained by the decreased LUMO of the methacrylonitrile–MX_3 complex, thus

Table 3
DA reactions of various dienes with acrylonitrile (AN) and methacrylonitrile (MAN)

Entry	Dienes[a]	Dienophile	*T* [°C]	*t* [h]	DA adduct (main isomers)	Yield[b]	*endo* /*exo*[c]
1	 **2a**	MAN	25 °C	3 h	 **4a**	89%[d]	85:15
2	**2a**	AN	25 °C	1 h	 **12**	66%	87:13
3	Cyclopentadiene	MAN	25 °C	18 h	 **13**	68%	86:14
4	Cyclopentadiene	AN	25 °C	1 h	 **14**	69%	69:31
5	*E*-1,3-Pentadiene	MAN	70 °C	1 h	 **15**	58%	78:22
6	*E*-1,3-Pentadiene	AN	25 °C	1 h	 **16**	71%	92:8[c]
7	 **17**	MAN	60 °C	72 h	 **19**	50%	76:24
8	**17**	AN	25 °C	72 h	 **20**	91%	85:15
9	 **18**	MAN	60 °C	1 h	 **21**	47%	57:22:14:7[e]
10	**18**	AN	25 °C	1 h	 **22**	84%	64:12:12:12[e]
11	 **2f**	MAN	25 °C	5 h	 **23**	59%	78:19:3
12	**2f**	AN	25 °C	5 h	 **24**	82%[f]	88:4:4:4[e]

Conditions: Diene added to 0.15–0.2 equiv BCl_3 in xylene and 1.2 equiv acrylonitrile or methacrolynitrile under cooling, stirring and nitrogen, then stirred at indicated temperature until complete conversion of the diene.

[a] Diene substrates: cyclopentadiene was obtained by distillative cracking of commercial dicyclopentadiene, *E*-1,3-Pentadiene is commercially available, **17** was prepared from Artemol[39] by Pd-cat. elimination. **18**[33] and **2f**[4a-b] were prepared according to the literature.

[b] Yields not optimized, after distillation or flash chromatography.

[c] *Endo*/*exo* ratio of the crude before distillation or FC.

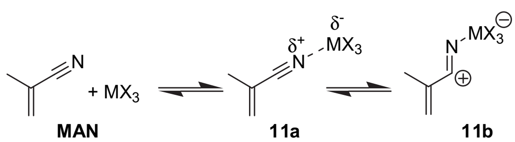
[d] Yield optimized.

[e] Isomer ratio by NMR analysis.

[f] Yield based on the *E*-isomer (62%) of methylocimene **2f**.

allowing tighter secondary orbital interaction with the HOMO of the diene in *endo*-transition state **10a**. Primary and secondary orbital interaction were visualized by *ab initio* calculation (Fig. 4), with activation energies of 80.5 and 82.5 kJ/mol for the uncomplexed *endo* and *exo* transition states **9a** and **9b** (Fig. 2) and 26.9 and 34.6 kJ/mol for the BCl_3-complexed transition states **10a** and **10b**, respectively. This is in accordance with increased reaction rates and *endo*/*exo* selectivities in the BCl_3 promoted DA reaction of homomyrcene **2a** with MAN.

The *ab initio* calculation of transition state **10a** shows also that the C–CN group maintains its centrosymmetric geometry with only minimal distortion in coordination complex **10a**. The more ionic coordination complex **11b** would have higher freedom for secondary orbital interaction (Scheme 6).



Scheme 6. Formation of methacrylonitrile/MX_3 complexes. M=Al, B, Zn. X=Cl, Br.

2.2. Scope of the *endo*-selective MANDA reaction

The *cis*-configured DA adducts **4a**, **12**–**19**, **21**, and **23**–**24** were obtained with moderate to good yields and *cis*/*trans*-ratios by BCl_3-catalyzed reaction of dienes **2a**, cyclopentadiene, *E*-1,3-pentadiene, **17**–**18**, and **2f** with acrylonitrile or methacrylonitrile (Table 3). The *cis*-selectivities were comparable to the one already obtained for DA adduct **4a** (run 1). Furan did not undergo DA reaction with **MAN** under these conditions.

Endo/*exo*-selectivities have been reported from DA reactions of cyclopentadiene or *E*-1,3-pentadiene with acrylonitrile or methacrylonitrile. Whilst the moderate *cis*/*trans* ratio of **14** was comparable to the ratios obtained for this compound from DA reactions in the literature,[10,11] **13** and **16** were obtained with much better *endo*-selectivities. As expected, **MAN** is less reactive than acrylonitrile in these reactions. 1,2-Dialkylsubstituted dienes such as **17** and **18** underwent the (meth)acrylonitrile DA reaction with the same regioselectivity, as reported by Nazarov for the thermal DA reaction of 1,2-dimethylbutadiene or 1-vinylcyclohexene with acrylonitrile,[30] giving cyclohex-3-ene-1-carbonitriles substituted in their 1,2,3- or 2,3-positions (**19**–**22**). The high temperatures ($\geq$200 °C) required for the thermal DA reactions,[30] are decreased to 20–60 °C under BCl_3 catalysis. DA reactions of acrylonitriles with 1,2,4-trialkylsubstituted butadienes such as **2f** have not been reported so far.[31] Here the *E*,*E*-isomer of **2f** selectively underwent the DA reaction, in contrast to the less reactive 2*E*,4*Z*-isomer,[32] giving mainly the all-*cis* cyclohex-3-enecarbonitriles **23** and **24**.

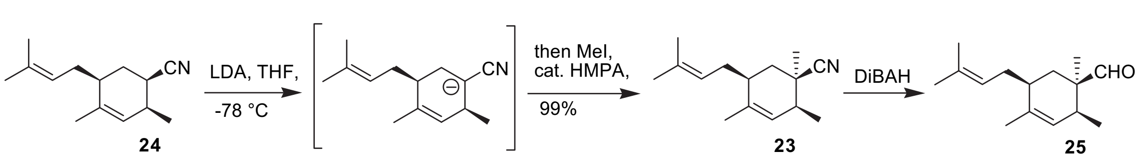
The relative configuration of the main isomers of the DA reaction (Table 3) was confirmed by NMR-analysis or by comparison with literature data (**13**, **14**, **16**). To obtain more reliable NMR-data on **23** this nitrile was further converted to aldehyde **25**, whose relative configuration was analyzed by NMR. The relative configuration of **23** was also confirmed by methylation of secondary nitrile **24**, which occurs preferentially at the less hindered side of the corresponding carbanion (Scheme 7).[7b]

The *cis*- and *trans* isomers have generally superimposable MS spectra, with the *cis*-isomers having lower GC-retention times in the case of the **MAN**-derived α-trisubstituted DA adducts **4a**, **13**, **15**, **19**, **21**, and **23**, whereas in the case of acrylonitrile-derived α-disubstituted DA adducts **12**, **14**, **16**, and **24** this order is reversed. The main diastereomers of the secondary nitriles **20** and **22**, which could not be analyzed by NMR, are also eluted at higher r_T and are therefore likely to be *cis*-configurated. Minor amounts of regioisomers were only detected in the case of the DA adducts (**21**–**24**) derived from dienes **18** and **2f**.

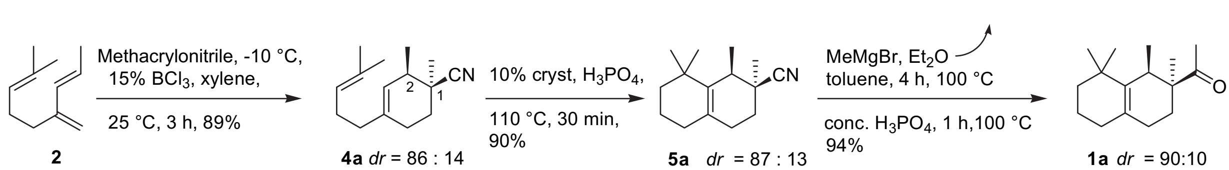
2.3. Application to the synthesis of Georgywood

Further conversion of the above obtained *cis*-diene **4a** to *cis*-β-Georgywood **1a** was carried out as depicted in Scheme 8. The yield of **4a** was improved by using freshly distilled homomyrcene **2a** in the MANDA step (a). Cyclization of **4a** upon exposure to cryst. H_3PO_4 at 110 °C readily gives **5a**. Grignard-addition to this relatively hindered nitrile (**5a**) went smoothly after distillative removal of diethyl ether from the Grignard reagent and running the Grignard-addition at 100 °C in toluene.[34] Hydrolysis of the intermediate imine with concd H_3PO_4 gave Georgywood **1a** with very good chemical and good olfactory yield (77%) after distillation.

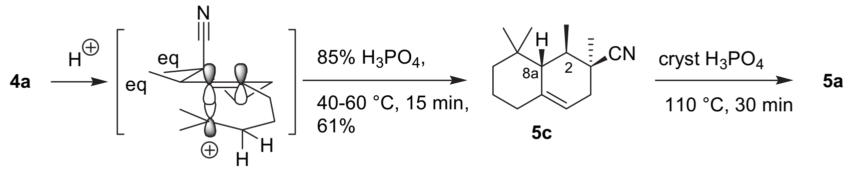
The H_3PO_4-catalyzed cyclization to **5a** proceeds via γ-isomer **5c**, which was isolated after cyclization of **4a** with less concentrated H_3PO_4 (85%) at lower temperatures and, which can be further converted to **5a** under more drastic conditions (Scheme 9). Cyclization of **4a** occurs from the less hindered α-face, thus avoiding steric interaction with the C(2)-methyl group shielding the β-face, giving **5c** with *r*-1,*c*-2,*t*-8a-configuration.[35] This is in agreement with studies on the cyclization of the corresponding acetyl-precursor **6a** to **1a**.[4b] The nitrile group of **4a**, however, cannot interact intramolecularly with the endocyclic double bond of the molecule (as **6a** does, thus facilitating pre-isomerization by intramolecular enolization),[4b] which results in a highly selective cyclization of **4a** to **5a**.



Scheme 7. Relative stereochemistry of **23**.



Scheme 8. Synthesis of Georgywood **1a** via nitrile **4a**. The (slightly) higher yield and diastereomer ratio (dr) of **4a** (compared to the one of Table 3, entry 1) is probably due to a better quality of homomyrcene **2a**, which was freshly distilled before use. The dr's were found to be gradually improved through the sequence, due to enrichment of the *cis*-isomers by distillation.



Scheme 9. H_3PO_4 promoted cyclization of **4a** to **5a** via γ-isomer **5c**.

3. Conclusion

Diels–Alder reactions of alkyl-substituted dienes and acrylonitriles give good yields and *endo*/*exo*-ratios if catalyzed by (organo)boron or aluminum halides with borontrichloride being the most effective Lewis acid for this purpose. The activity of these group IIIa Lewis acids in this reaction correlates with the coordination strength of their complexes with nitriles, as this is well known in the literature. Therefore, it is surprising that their use in Diels–Alder reactions with acrylonitriles has not yet been reported. This method gives the best *endo*/*exo*-ratios reported so far for these dienophiles and was applied in the selective synthesis of the olfactory vector **1a** of Georgywood®. After Diels–Alder reaction a highly selective 1,5-diene cyclization gave the bicyclic tertiary nitrile **5a**, which was efficiently transformed to the corresponding *tert*-alkyl methyl ketone **1a**.

4. Experimental

4.1. General

Reagents and solvents were purchased from commercial suppliers and used without further purification. Solvents for moisture-sensitive reactions contained <0.1% water. Moisture-sensitive reactions were conducted in oven-dried (130 °C) glassware under nitrogen and stirring. The given temperatures refer to reaction thermometers. All reactions were carried out under stirring. The silica gel used for flash chromatography was Sorbsil, 0.04–0.063 mm (Merck). Standard work-up includes phase separation, extraction of the aqueous phase with *tert*-butyl methyl ether (pentane, hexane), washing of the combined organic phase to pH 7, drying over $MgSO_4$, filtration, and evaporation of the solvent under reduced pressure.

^1H- and ^{13}C NMR: Bruker-DPX-400 MHz spectrometer; all spectra were recorded at 400 MHz and in $CDCl_3$; δ in ppm rel to $SiMe_4$; coupling constants *J* in Hertz. GC/MS: Agilent 5973 MSD with 6890 GC; relative intensities in % of the base peak. High Resolution GC/MS: Finnigan MAT95 with HP 5890 series II GC. IR: Bruker FT-IR Vector 22 spectrometer, ν∼ in cm^{-1}. Peak intensities assigned as strong (s), middle (m), and weak (w).

The Georgywood isomers **1a**,[1b] **1b**,[36] and **1c**[1b] are known from the literature.

4.2. Procedures for the preparation of compounds 2

Homomyrcene **2a** was prepared as described.[3] The terminal dienes **2b** and **2d** were prepared for reference purposes.[16] *E*/*Z*-Methylocimene **2f**[4a–b] was prepared as described.

4.2.1. 1,3-Dimethyl-4-(prop-1-en-2-yl)cyclohex-1-ene ***2c***. Citral (11.4 g, 75 mmol) in tetraethyleneglycol dimethylether (13 ml) was added dropwise over 1 h to methylmagnesium chloride 3 M in THF (26 ml, 80 mol) and tetraethyleneglycol dimethylether (27 ml) at 5 °C. The mixture was stirred for 1 h at 25 °C, then $FeCl_3$ (12.2 g, 75 mmol) was added portion wise under cooling (0–20 °C). The reaction was heated at 80 °C for 2 h, cooled to 5 °C and poured onto H_2O/pentane. Extraction with *tert*-butyl methyl ether and standard work-up gave a yellow liquid (12 g), which was distilled at 45 °C/0.15 Torr giving 7.2 g (64%) of a yellow liquid, which consisted of 65% **2c** (*cis*/*trans* 14:86) and 27% **2e**. Analytical data of *trans*-**2c**: ^1H NMR ($CDCl_3$): δ 0.7 (d, 3H), 1.67 (s, 3H), 1.73 (s, 3H), 1.55–1.65 (2H), 1.9–2.05 (2H), 2.2 (1H), 2.35 (1H), 4.6 (m, 1H), 4.8 (m, 1H), 5.4 (d, 1H) ppm. ^{13}C NMR: δ 15.3 (q), 21.7 (t), 22.5 (q), 23.4 (q), 31.0 (d), 31.1 (t), 43.65 (d), 109.1 (t), 127.6 (d), 132.7 (s), 148.2 (s). MS (EI): *m*/*z* (%) 150 (M^+, 12), 135 (11), 121 (10), 107 (27), 82 (100), 67 (82). IR (film): ν=2964 (m), 2928 (m), 1646 (w), 1449 (m), 1374 (m), 1179 (w), 1157 (w), 1037 (w), 963 (w), 887 (s), 842 (m), 808 (w) cm^{-1}. HRMS calcd for $C_{11}H_{18}$: 150.1408; found 150.1404.

4.2.2. 1,3-Dimethyl-4-(propan-2-ylidene)cyclohex-1-ene ***2e***. Homomyrcene (**2a**) of 76% purity (5 g, 25 mmol)[3] was added dropwise to $Bi(OTf)_3$ (0.5 g, 2.5 mmol) and methacrylonitrile (1.7 g, 25 mmol) in dichloromethane (20 ml) at 5 °C. After 5 h at 25 °C water was added. Extraction with pentane and standard work-up gave 4.6 g of a residue, which was bulb-to-bulb distilled at 45 °C/0.15 Torr giving 3.3 g (55%, corr) of a liquid, which contains 62% **2e** and 17% **2c** (*cis/trans* 43:57). Analytical data of **2e**: ^1H NMR ($CDCl_3$): δ 1.0 (d, 3H), 1.67 (10H), 1.95 (s, 3H), 2.6 (m, 1H), 3.05 (m, 1H), 5.3 (m, 1H) ppm. ^{13}C NMR: δ 19.7 (q), 19.8 (q), 20.6 (q), 23.0 (t), 23.4 (q), 31.7 (t), 33.3 (d), 121.4 (s), 127.3 (d), 132.7 (s), 133.4 (s). MS (EI): *m*/*z* (%) 150 (M^+, 50), 135 (100), 119 (10), 107 (79), 93 (40), 91 (44), 79 (20), 77 (21). IR (film): ν=2962 (s), 2911 (s), 2964 (m), 1449 (s), 1373 (s), 1180 (m), 1085 (m), 1053 (m), 967 (m), 838 (s) cm^{-1}. HRMS calcd for $C_{11}H_{18}$: 150.14085; found 150.1408.

4.2.3. Preparation of ***2e*** *by Brønsted-acid promoted cyclization.* Homomyrcene (**2a**) of 76% purity (5 g, 24 mmol)[3] was added dropwise to methacrylonitrile (1.9 g, 28 mmol) in formic acid (5 ml) at 25 °C. After 2 h at 60 °C the reaction mixture was poured onto satd $NaHCO_3$ (100 ml). Extraction with *tert*-butyl methyl ether and standard work-up gave 5.1 g of a residue, which was bulb-to-bulb distilled at 45 °C/0.15 Torr giving 3 g (68%) of a liquid, which contains 59% **2e** and 23% **2c**. Analytical data: see above.

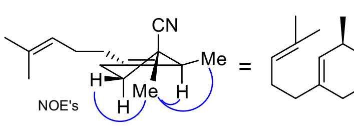
4.3. Procedure A

4.3.1. Preparation of ***4a*** *by BCl_3-catalyzed MANDA reaction.* Methacrylonitrile (111 g, 1.65 mol) was added dropwise at 10–20 °C to boron trichloride 1 M in xylene (225 ml, 0.22 mol). Freshly distilled homomyrcene (**2a**) of 76% purity (225 g, 1.1 mol)[3] was added at 10–20 °C over 40 min. The reaction was kept for another 40 min at 10–20 °C, then for 3 h at 25 °C. After complete conversion the reaction mass was poured onto ice-cold $NaHCO_3$ and extracted with *tert*-butyl methyl ether. Standard work-up gave 306 g of a red oil. After addition of 65 g paraffin oil, 15 g Na_2CO_3 and 0.2 g hydroquinone the residue was short-path-distilled giving pre-fractions at 69 °C/0.05 Torr and 214 g of **4a** at 105 °C/0.05 Torr. Yield: 89% (dist, corr, based on purity of the homomyrcene and the *cis*-isomer). R_T=8.4 (86%, *cis*-isomer **4a**), 8.6 (14%, *trans*-isomer **4b**) min (GC). MS of *trans*-isomer **4b** identical to the one of *cis*-isomer **4a.** The analytical data of the *cis*-isomer were identical with the ones obtained for **4a** synthesized below from *cis*-aldehyde **3a**.

4.4. Methods and data

*4.4.1. cis-1,2-Dimethyl-4-(4-methylpent-3-enyl)cyclohex-3-ene-carbonitrile **4a** from aldehyde **3a**.* *Cis*-1,2-Dimethyl-4-(4-methylpent-3-enyl)cyclohex-3-enecarbaldehyde **3a** (50 g, 0.23 mol)[1b] in ethanol (250 ml) was added slowly to $NH_2OH \times HCl$ (24 g, 0.35 mol) and Na_2CO_3 (24 g, 0.23 mol) in water (60 ml). The mixture was heated to 60–70 °C for 1 h, then poured onto water (0.5 l). Extraction with *tert*-butyl methyl ether and standard work-up gave the crude oxime (62 g). For analytical measurements 2 g of the crude were purified by bulb-to-bulb distillation giving 1.75 g (99%) of pure oxime. Analytical data of the oxime: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.9 (d, 3H), 1.1 (s, 3H), 1.6 (s, 3H), 1.6 (m, 1H), 1.7 (s, 3H), 1.75 (m, 1H), 2.9 (4H), 2.1 (3H), 5.1 (m, 1H), 5.2 (s, 1H), 8.8 (br, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): 17.1 (q), 17.7 (q), 23.3 (q), 25.7 (q), 25.7 (t), 26.4 (t), 32.8 (t), 37.2 (t), 38.2 (s), 39.3 (d), 124.15 (d), 125.6 (d), 131.5 (s), 136.3 (s), 137.1 (s), 156.5 (d) ppm. GC/MS: 218 (2%, $[M-OH]^+$), 217 (1%, $[M-H_2O]^+$), 202 (3%, $[M-H_2O-CH_3]^+$, 174 (8%), 161 (4%), 149 (5%), 134 (6%), 121 (5%), 107 (20%), 69 (100%), 53 (12%), 41 (70%). IR (film): 3318 (br), 2965 (m), 2916 (m), 1449 (m), 1374 (m), 1305 (w), 1102 (w), 943 (s), 836 (w), 748 (w).

The crude oxime (60 g, 0.22 mol) in toluene (20 ml) was added dropwise over 20 min to acetanhydride (102 g, 1 mol) and toluene (130 ml) at reflux. Then water (20 ml) was added at 70–80 °C. Extraction with hexane and standard work-up gave a residue, which was purified by flash chromatography over 1.2 kg silica gel using hexane/*tert*-butyl methyl ether 4:1 as eluent. After evaporation of the solvents the residue was purified by distillation giving 31 g (65%) of **4a** as an oil. Odor: anisic, earthy, calamus, agrestic.



4a

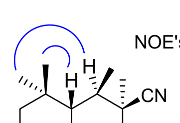
*4.4.1.1. Analytical data of **4a**.* ^{1}H NMR ($CDCl_3$, 400 MHz): 1.2 (d, 3H), 1.4 (s, 3H), 1.6 (s, 3H), 1.7 (s, 3H), 2.0 (5H), 2.1 (3H), 2.3 (1H), 5.1 (2H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 17.4 (q), 17.7 (q), 24.7 (q), 25.65 (q), 26.1 (t), 26.3 (t), 33.7 (t), 37.05 (t), 37.1 (s), 38.95 (d), 122.8 (s), 123.9 (d), 124.0 (d), 131.6 (s), 137.1 (s) ppm. Relative configuration determined by NMR-analysis (HSQC, HMBC, COSY, and NOESY) in C_6D_6. It was also deduced from the relative configuration of precursor **3a** and proven by conversion to **1a**. GC/MS: 217 (5%, M^+), 202 (6%, $[M-15]^+$), 174 (13%), 149 (7%), 134 (7%), 107 (13%), 69 (100%), 41 (28%). IR (film): 2969 (s), 2926 (s), 2857 (w), 2233 (w, CN), 1669 (w), 1453 (s), 1376 (m), 1343 (w), 1287 (w), 1173 (w), 1145 (w), 1105 (w), 984 (w), 885 (w), 829 (m), 635 (w), 611 (w), 603 (w). HRMS calcd for $C_{15}H_{23}N$: 217.1830; found 217.1829.

*4.4.2. Preparation of **4a**/**4b** by thermal DA reaction.* Methacrylonitrile (44 g, 0.66 mol), freshly distilled homomyrcene (**2a**) of 76% purity (100 g, 0.51 mol), and hydroquinone monomethyl ether (0.1 g) are heated at reflux (130 °C) for 36 h. After cooling to rt the reaction mass is distilled at 0.05 mbar giving 22 g pre-fractions at 25–75 °C and 71 g (65% d. Th.) of **4a**/**4b** at 130 °C. R_T=8.4 (53% **4a**), 8.6 (47% **4b**) min (GC). MS of *trans*-isomer **4b** identical to the one of *cis*-isomer **4a.** The analytical data of the *cis*-isomer were identical with the ones obtained for **4a** synthesized from aldehyde **3a**.

*4.4.3. trans-1,2-Dimethyl-4-(4-methylpent-3-enyl)cyclohex-3-ene-carbonitrile **4b**.* For configurational analysis the *trans*-isomer **4b** was separated from the **4a**/**4b** mixture (prepared above) by preparative GC. Its structure was proven by NMR-analysis (HSQC, HMBC, COSY, NOESY comparison with **4a**) in C_6D_6. Analytical data of **4b**: ^{1}H NMR (C_6D_6, 500 MHz): δ 0.72 (d, J=7.05 Hz, 3H), 0.82 (s, 3H), 1.36 (m, 1H), 1.48 (m, 3H), 1.5 (s, 3H), 1.55 (m, 1H), 1.65 (d, J=1.07 Hz, 3H), 1.78 (m, 1H), 1.84 (t, J=7.48 Hz, 2H), 2.03 (m, 2H), 2.28 (dd, J=7.05, 1.71 Hz, 1H), 4.94 (m, 1H), 5.11 (m, 1H) ppm. ^{13}C NMR (C_6D_6, 500 MHz): δ 16.2 (q), 17.7 (q), 18.5 (q), 25.0 (t), 25.8 (q), 26.6 (t), 31.5 (t), 34.4 (s), 37.4 (d), 37.4 (t), 123.9 (d), 124.4 (d), 125.2 (s), 131.5 (s), 136.2 (s) ppm. GC/MS: 217 (4%, M^+), 202 (5%, $[M-15]^+$), 174 (15%), 149 (5%), 134 (7%), 121 (5%), 107 (14%), 69 (100%), 41 (29%). HRMS calcd for $C_{15}H_{23}N$: 217.1830; found 217.1829.

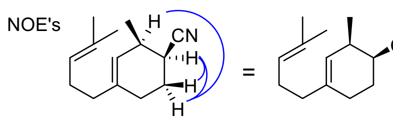
*4.4.4. cis-1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carbonitrile **5a**.* *Cis*-1,2-dimethyl-4-(4-methylpent-3-enyl)cyclohex-3-enecarbonitrile **4a** (*cis/trans* 86:14, 55 g, 0.25 mol) was added over 10 min to molten crystalline H_3PO_4 (22 g, 0.22 mol) at 105°–120 °C under stirring and nitrogen. After another 15 min at this temperature the mixture was cooled and water (150 ml) added at 80 °C. Extraction with hexane and standard work-up gave 55 g of an orange oil, which was short-path-distilled giving 51.5 g of **5a** at 84 °C/0.04 Torr. Yield: 90% (dist, corr). Odor: woody, cedarwood with a sweet floral touch, earthy. Analytical data of **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): 0.96 (s, 3H), 1.07 (s, 3H), 1.28 (s, 3H), 1.3 (s, 3H), 1.47 (m, 2H), 1.66 (m. 2H), 1.65–1.95 (4H), 2.01 (m, 1H), 2.15 (ddd, 1H), 2.27 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 19.05 (t), 20.62 (q), 22.65 (q), 26.25 (t), 26.30 (t), 28.31 (q), 29.47 (q), 30.82 (t), 34.04 (s), 36.13 (d), 36.44 (s), 40.05 (t), 125.44 (s), 125.67 (s), 135.93 (s) ppm. Relative configuration proven by conversion to **1a**. GC/MS: 217 (11%, M^+), 202 (100%, $[M-15]^+$), 175 (21%), 135 (28%), 121 (10%), 107 (12%), 105 (10%), 91 (14%), 79 (7%), 77 (11%), 75 (10%). R_T=8.74 (12%, *trans*-isomer **5b**), 8.9 (6%, **5c**), 9.0 (81%, *cis*-isomer **5a**) min (GC). IR (film): 2930 (s), 2836 (m), 2231 (w), 1459 (s), 1379 (s), 1361 (w), 1281 (w), 1261 (w), 1235 (w), 1204 (w), 1180 (w), 1166 (w), 1114 (w), 1068 (w), 1029 (w), 995 (w), 945 (w), 874 (w), 843 (w), 645 (w). HRMS calcd for $C_{15}H_{23}N$: 217.1830; found 217.1828.

*4.4.5. cis-1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carbonitrile **5c**.* Diels–Alder adduct **4a** (3.5 g, 11 mmol, *cis/trans* 86:14) and 85% H_3PO_4 (1.4 g, 14 mmol) were stirred for 5 days at 25 °C, then the reaction mass was poured onto satd $NaHCO_3$. Extraction with *tert*-butyl methyl ether and standard work-up gave 3.3 g of a yellow oil, which was purified by flash-chromatography over silica gel using hexane/*tert*-butyl methyl ether 98:2 as eluent giving after evaporation of the solvents 2.8 g (80%) of **5c**. Analytical data of **5c**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.76 (s, 3H), 1.03 (s, 3H), 1.27 (d, 3H), 1.4 (s, 3H), 1.4–2.1 (10H), 5.55 (d, 1H) ppm. ^{13}H NMR ($CDCl_3$, 400 MHz): δ 19.70 (q), 19.90 (q), 24.09 (t), 25.40 (q), 31.20 (q), 36.21 (t), 36.43 (t), 37.63 (s), 38.75 (d), 39.01 (s), 42.76 (t), 53.64 (d), 117.14 (d), 123.94 (s), 142.08 (s) ppm. Relative configuration proven by NMR-analysis (HSQC, HMBC, COSY, and NOESY) in C_6D_6. GC/MS: 217 (12%, M^+), 202 (42%, $[M-15]^+$), 174 (32%), 161 (14%), 149 (14%), 134 (11%), 107 (19%), 91 (20%), 69 (100%), 55 (12%). R_T=8.7 (8%, **5b**), 8.9 (70%, **5c**), 9.0 (19%, *trans*-isomer of **5c**) min. IR (film): 2926 (s), 2869 (m), 2843 (m), 2231 (w), 1455 (m), 1385 (m), 1364 (m), 1338 (w), 1263 (w), 1221 (w), 1188 (w), 1146 (w), 1115 (w), 1060 (w), 1046 (w), 970 (w), 932 (w), 841 (m), 799 (w), 608 (w). HRMS calcd for $C_{15}H_{23}N$: 217.1830; found 217.1829.



5c

4.4.6. cis-2-Methyl-4-(4-methylpent-3-enyl)cyclohex-3-enecarbonitrile ***12***. Prepared according to Procedure A from Homomyrcene (**2a**) of 76% purity (3 g, 15 mmol),[3] acrylonitrile (1.3 g, 24 mmol), and boron trichloride 1 M in xylene (3 ml, 3 mmol) at 25 °C in 1 h. Standard work-up and flash-chromatography (silica gel, hexane/*tert*-butyl methyl ether 95:5) gave 2 g (66%) of **12** as colorless oil. Analytical data of the *cis*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.18 (d, 3H), 1.6 (s, 3H), 1.7 (s, 3H), 1.85 (m, 1H), 1.95–2.1 (6H), 2.2 (m, 1H), 2.45 (m, 1H), 2.9 (m, 1H), 5.08 (m, 1H), 5.2 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 17.7 (q), 18.8 (q), 24.3 (t), 25.57 (t), 25.65 (q), 26.2 (t), 31.2 (d), 31.5 (d), 37.3 (t), 120.75 (s), 123.77 (d), 123.82 (d), 131.7 (s), 137.2 (s) ppm. Relative configuration determined by NMR-analysis: NOESY, HSQC, COSY, HMBC. GC/MS: 203 (3%, M^+), 188 (4%, $[M-15]^+$), 160 (12%), 135 (4%), 107 (5%), 91 (6%), 69 (100%). R_T=8.6 (13%, *trans*-isomer), 8.7 (87%, *cis*-isomer) min (GC). MS of *trans*-isomer identical to the one of the *cis*-isomer. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.41; H, 10.51; N, 6.68.



12

4.4.7. endo-2-Methylbicyclo[2.2.1]hept-5-ene-2-carbonitrile ***13***. Prepared according to Procedure A from freshly distilled cyclopentadiene (1.3 g, 20 mmol), methacrylonitrile (1.6 g, 24 mmol), and boron trichloride 1 M in xylene (3 ml, 3 mmol) at 25 °C in 18 h. Standard work-up and bulb-to-bulb distillation gave 1.8 g (68%) of **13** as a solid. R_T=5.0 (86%, *cis*-isomer), 5.2 (14%, *trans*-isomer) min (GC). Analytical data for these isomers have been reported.[7c]

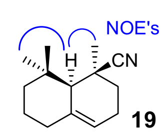
4.4.8. endo-Bicyclo[2.2.1]hept-5-ene-2-carbonitrile ***14***. Prepared according to Procedure A from freshly distilled cyclopentadiene (1 g, 15 mmol), acrylonitrile (0.9 g, 18 mmol), and boron trichloride 1 M in xylene (3 ml, 3 mmol) at 25 °C in 1 h. Standard work-up and bulb-to-bulb distillation gave 1.2 g (58%) of **14**. R_T=4.4 (31%, *trans*-isomer), 4.7 (69%, *cis*-isomer) min (GC). Analytical data for these isomers have been reported.[37]

4.4.9. cis-1,2-Dimethylcyclohex-3-enecarbonitrile ***15***. Prepared according to Procedure A from freshly distilled *E*-1,3-pentadiene (1.4 g, 20 mmol), methacrylonitrile (2 ml, 24 mmol), and boron trichloride 1 M in xylene (3 ml, 3 mmol) at 60 °C in 1 h. Standard work-up and flash chromatography (silica gel, hexane) gave 1.4 g (50%) of **15**. Analytical data of **15**: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.2 (d, 3H), 1.4 (s, 3H), 1.6 (m, 1H), 2.0 (m, 1H), 2.1–2.2 (2H), 2.35 (m, 1H), 5.4 (m, 1H), 5.75 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 17.1 (q), 22.9 (t), 24.8 (q), 33.2 (t), 37.0 (s), 38.8 (d), 122.7 (s), 126.1 (d), 129.9 (d) ppm. Relative configuration determined by NMR-correlation with **4a**. GC/MS: 135 (11%, M^+), 120 (3%, $[M-15]^+$), 108 (3%), 93 (10%), 68 (100%), 67 (34%), 53 (12%). R_T=5.1 (78%, *cis*-isomer), 5.2 (22%, *trans*-isomer) min (GC). The mass spectra of the *cis*- and *trans*-isomers are identical. IR (film): 3025 (w), 2971 (m), 2935 (m), 2879 (w), 2232 (w, CN), 1455 (s), 1434 (m), 1378 (m), 1164 (w), 1115 (w), 954 (w), 758 (m), 697 (s), 656 (m), 634 (m). Anal. Calcd for $C_{19}H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.10; H, 9.94; N, 10.07.

4.4.10. cis-2-Methylcyclohex-3-enecarbonitrile ***16***. Prepared according to Procedure A from freshly distilled *E*-1,3-pentadiene (1 g, 14 mmol), acrylonitrile (0.83 g, 17 mmol), and boron trichloride 1 M in xylene (2.8 ml, 2.8 mmol) at 25 °C in 1 h. Standard work-up and bulb-to-bulb distillation gave 1.35 g (71%) of **15**. R_T=4.4 (8%, *trans*-isomer), 4.6 (92%, *cis*-isomer) min (GC). The mass spectra of the *cis*- and *trans*-isomers are identical. Analytical data for these isomers have been reported.[38]

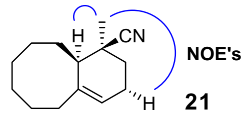
4.4.11. 3,3-Dimethyl-1-vinylcyclohex-1-ene ***17***. Ethyl chloroformate (4.2 g, 39 mmol) was added dropwise to 1-(3,3-dimethylcyclohex-1-enyl)ethanol (Artemol)[39] (5 g, 32 mmol) in toluene (20 ml) and pyridine (3.3 g, 42 mmol) under cooling. The mixture was stirred at 25 °C until complete conversion was detected by GC or TLC. Standard work-up, filtration over silica gel, and evaporation of the solvent gave 7 g (97%) of the mixed carbonate as yellow oil. Under solvent-free conditions and stirring 1,5-bis(diphenylphosphino)-pentane (dpppe) (0.15 g, 0.35 mmol) was added at 60 °C, followed by $Pd(OAc)_2$ (31 mg, 0.14 mmol). After further heating distillation/elimination set in at 90°–105 °C, methanol was distilled off, until complete conversion to **17** was detected by TLC or GC. Further distillation gave 5 g (95%) of **17** as colorless oil (92% purity). Analytical data of **17**: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.0 (s, 6H), 1.4 (m, 2H), 1.7 (m, 2H), 2.05 (m, 2H), 4.9 (d, 1H), 5.1 (d, 2H), 5.45 (1H), 6.3 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 19.35 (t), 23.8 (t), 29.7 (q, 2C), 32.1 (s), 37.2 (t), 110.2 (t), 133.7 (s), 140.0 (d), 140.4 (d) ppm. GC/MS: 136 (40%, M^+), 121 (100%, $[M-15]^+$), 107 (27%), 93 (78%), 91 (36%), 79 (48%), 77 (30%). IR (film): 2954 (m), 2929 (s), 2864 (m), 1747 (m), 1639 (w), 1604 (w), 1453 (m), 1359 (w), 1267 (s), 1208 (w), 1182 (w), 1036 (w), 988 (m), 940 (w), 893 (s), 869 (s). HRMS calcd for $C_{10}H_{16}$: 136.1252; found 136.1252.

4.4.12. cis-1,8,8-Trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile ***19***. Prepared according to Procedure A from diene **17** (1 g, 7 mmol), methacrylonitrile (0.6 g, 8.4 mmol), and boron trichloride 1 M in xylene (1 ml, 1 mmol) at 60 °C in 72 h. Standard work-up with *tert*-butyl methyl ether and bulb-to-bulb distillation gave 0.7 g (50%) of **19** as colorless oil. Analytical data of the *cis*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.05 (s, 3H), 1.4 (s, 3H), 1.45 (s, 3H), 0.8–2.3 (10H), 5.5 (m, 1H) ppm. ^{13}C NMR (C_6D_6, 400 MHz): δ 20.8 (t), 21.4 (q), 24.0 (t), 28.0 (q), 31.3 (q), 32.8 (s), 32.9 (t), 37.4 (s), 37.7 (t), 45.6 (t), 54.9 (d), 120.0 (d), 126.5 (s), 136.2 (s) ppm. Relative configuration tentatively assigned by NMR-analysis: NOESY, HSQC, COSY, HMBC. GC/MS: 203 (11%, M^+), 188 (11%, $[M-15]^+$), 160 (21%), 147 (5%), 133 (21%), 108 (36%), 93 (16%), 91 (19%), 69 (100%). R_T=8.2 (76%, *cis*-isomer), 8.5 (24%, *trans*-isomer) min (GC). The mass spectra of the *cis*- and *trans*-isomers are identical. IR (film): 2954 (m), 2929 (s), 2864 (m), 1747 (m), 1639 (w), 1604 (w), 1453 (m), 1359 (w), 1267 (s), 1208 (w), 1182 (w), 1036 (w), 988 (m), 940 (w), 893 (s), 869 (s). HRMS calcd for $C_{14}H_{21}N$: 203.1674; found 203.1665.



19

4.4.13. (1SR,8aRS)-8,8-Dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile ***20***. Prepared according to Procedure A from diene **17** (1 g, 7 mmol), acrylonitrile (0.4 g, 8 mmol), and boron trichloride 1 M in xylene (1.4 ml, 1.4 mmol) at 25 °C in 72 h. Standard work-up and bulb-to-bulb distillation gave 1.2 g (91%) of **20** as colorless oil. Analytical data of the main-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.1 (s, 3H), 1.15 (s, 3H), 0.9–2.4 (11H), 3.1 (m, 1H), 5.5 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 21.6 (t), 21.7 (q), 22.4 (t), 26.75 (t), 27.0 (d), 29.9 (q), 34.8 (t), 35.3 (s), 44.0 (t), 48.5 (d), 121.2 (d), 122.9 (s), 135.9 (s) ppm. GC/MS: 189 (7%, M^+), 174 (5%, $[M-15]^+$), 146 (20%), 133 (4%), 121 (4%), 119 (5%), 91 (10%), 79 (7%), 77 (6%), 69



21

(100%), 41 (24%). R_T=8.1 (15%, *trans*-isomer), 8.2 (85%, *cis*-isomer) min (GC). Relative configurations of these isomers deduced from their retention times (comparison with **12**, **14**, **16**, and **24**). The mass spectra of the *cis*- and *trans*-isomers are identical. IR (film): 2929 (s), 2867 (m), 2846 (m), 2234 (w), 1454 (m), 1440 (m), 1367 (m), 868 (m), 809 (m). HRMS calcd for $C_{14}H_{21}N$: 189.1517; found 189.1525. HRMS calcd for $C_{13}H_{18}N$: 174.1283; found 174.1295.

*4.4.14. cis-1-Methyl-1,2,3,5,6,7,8,9,10,10a-decahydrobenzo[8]annulene-1-carbonitrile **21**.* Prepared according to Procedure A from diene **18** (5 g, 32 mmol),[33] methacrylonitrile (2.55 g, 38 mmol), and boron trichloride 1 M in xylene (4.7 ml, 4.7 mmol) at 60 °C in 1 h. Standard work-up with *tert*-butyl methyl ether and bulb-to-bulb distillation gave 2.7 g (42%) of **21** as colorless oil, which slowly crystallized upon standing. Analytical data of the *cis*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.3 (s, 3H), 1.4–1.5 (3H), 1.5–1.7 (6H), 1.85 (m, 1H), 1.95–2.1 (4H), 2.25 (m, 1H), 2.4 (m, 1H), 5.4 (m, 1H) ppm. ^{13}C NMR ($CHCl_3$, 400 MHz): δ 21.9 (t), 24.1 (q), 26.3 (t), 26.5 (t), 26.8 (t), 27.5 (t), 30.2 (t), 30.8 (t), 35.8 (t), 37.0 (s), 46.1 (d), 121.2 (d), 124.7 (s), 138.7 (s) ppm. Relative configuration of the isomers determined by NMR-analysis (NOESY, HSQC, COSY, HMBC): 57% (*cis*-isomer), 22% (*trans*-isomer), 14% and 7% (2 regioisomers). GC/MS: 203 (32%, M^+), 188 (19%, $[M-15]^+$), 175 (19%), 174 (14%), 161 (16%), 160 (17%), 148 (16%), 136 (53%), 121 (62%), 108 (100%), 107 (56%), 95 (46%), 94 (67%), 93 (68%), 91 (58%), 81 (39%), 80 (44%), 79 (79%), 77 (44%), 68 (62%), 67% (50%). R_T=8.88 (63%, *cis*-isomer), 8.93 (37%) min (GC). IR (film): 2921 (s), 2850 (m), 2230 (w), 1445 (m), 1379 (w), 1019 (w), 851 (w), 812 (w), 746 (w). HRMS calcd for $C_{14}H_{21}N$: 203.1647; found 203.1657.

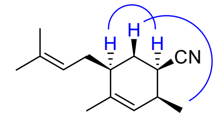
*4.4.15. 1,2,3,5,6,7,8,9,10,10a-decahydrobenzo[8]annulene-1-carbonitrile **22**.* Prepared according to Procedure A from diene **18** (1 g, 6.3 mmol),[33] acrylonitrile (0.36 g, 7.6 mmol), and boron trichloride 1 M in xylene (1.3 ml, 1.26 mmol) at 25 °C in 1 h. Standard work-up with *tert*-butyl methyl ether and bulb-to-bulb distillation at 135 °C/0.1 mbar gave 1 g (81%) of **22** as colorless oil. Analytical data of the main isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.6 (s, 3H), 1.25–2.5 (17H), 1.5–1.7 (6H), 2.8 (m, 1H), 5.45 (m, 1H) ppm. ^{13}C NMR ($CHCl_3$, 400 MHz): δ 22.5 (t), 23.6 (t), 25.8 (t), 26.2 (t), 26.8 (t), 27.3 (t), 30.7 (t), 32.5 (d), 35.7 (t), 39.3 (d), 121.9 (d), 139.95 (s) ppm. Isomer ratio according to NMR: 64:12:12:12. GC/MS: 189 (61%, M^+), 174 (18%, $[M-15]^+$), 160 (51%), 146 (52%), 133 (47%), 121 (36%), 119 (58%), 106 (51%), 93 (70%), 91 (92%), 81 (52%), 77 (64%). R_T=8.8 (5%, *trans*-isomer), 8.9 (68%, *cis*-isomer), 9.0 (25%, regioisomers) min. The mass spectra of the *cis*- and *trans*-isomers are identical. IR (film): 3365 (br), 2921 (s), 2853 (m), 2237 (w), 1666 (w), 1446 (m), 1025 (w), 885 (w), 742 (w). HRMS calcd for $C_{13}H_{19}N$: 189.1518; found 189.1523.

*4.3.16. (1RS,2SR,5SR)-1,2,4-Trimethyl-5-(3-methylbut-2-enyl)cyclohex-3-enecarbonitrile **23**.* Prepared according to Procedure A from methylocimene **2f** (*E*/*Z* 3:2, 10 g, 63 mmol),[4a–b] methacrylonitrile (5.1 g, 76 mmol), and boron trichloride 1 M in xylene (12.6 ml, 13 mmol) at 25 °C in 5 h. Standard work-up with *tert*-butyl methyl ether and bulb-to-bulb distillation at 140 °C/0.07 mbar gave 5.2 g (59%, based on the *E*,*E*-isomer of **2f**) of **23** as colorless oil. R_T=8.1 (78%, *cis*-isomer), 8.2 (19%, diastereomer) min (GC).

Alternatively, **23** was prepared from secondary nitrile **24**: *n*-butyllithium 1.6 M in hexane (3.5 ml, 5.6 mmol) was added dropwise to diisopropylamine (0.56 g, 5.6 mmol) in tetrahydrofuran (5 ml) at −78 °C. After 30 min **24** (1 g, 4.6 mmol) was added at this temperature. After another 40 min methyl iodide (1.3 g, 9.3 mmol) and hexamethylphosphoramide (0.3 ml, 1.7 mmol) were added at −78 °C. The reaction was allowed to warm up to 25 °C overnight and poured onto a 2 M HCl/ice mixture. Extraction with *tert*-butyl methyl ether, washing of the combined organic phases with concd $NaHCO_3$ and water, drying over $MgSO_4$, filtration, and evaporation of the solvents gave 1 g of crude **23** (99%) as an oil (isomer ratio 78:19:3).

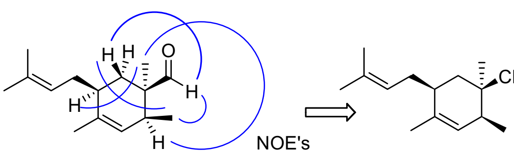
4.4.16.1. Analytical data of the main isomer. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.2 (d, 3H), 1.35 (s, 3H), 1.65 (s, 3H), 1.7 (s, 3H), 1.73 (s, 3H), 1.9 (m, 1H), 2.0–2.1 (3H), 2.2 (m, 1H), 2.3 (m, 1H), 5.0 (m, 1H), 5.3 (1H) ppm. ^{13}C NMR ($CHCl_3$, 400 MHz): δ 17.95 (q), 18.0 (q), 21.3 (q), 24.4 (q), 25.8 (q), 30.2 (t), 34.4 (t), 34.9 (s), 36.4 (d), 38.0 (d), 121.8 (d), 124.8 (s), 125.3 (d), 133.5 (s), 134.8 (s) ppm. The minor isomer (19%) is a diastereomer (NMR-analysis). GC/MS: 217 (8%, M^+), 202 (2%, $[M-15]^+$), 149 (12%), 148 (7%), 134 (7%), 122 (6%), 121 (7%), 107 (13%), 94 (18%), 91 (10%), 69 (100%). Analytical data of the minor isomer: ^{13}C NMR ($CHCl_3$, 400 MHz): δ 15.6 (q), 18.0 (q), 18.7 (q), 21.0 (q), 28.8 (q), 30.1 (t), 33.6 (t), 35.0 (s), 37.5 (d), 37.65 (d), 121.1 (d), 125.7 (s), 126.9 (d), 133.35 (s), 135.65 (s) ppm. GC/MS: 217 (2%, M^+), 202 (2%, $[M-15]^+$), 151 (13%), 148 (10%), 134 (5%), 121 (12%), 107 (11%), 106 (9%), 94 (13%), 91 (11%), 69 (100%). The relative configuration of **23** was proven by α-methylation of nitrile **24**, and by conversion of **23** to aldehyde **25** and NMR-analysis of the latter. IR (film): 2968 (s), 2932 (s), 2917 (s), 2875 (m), 2858 (m), 2232 (w), 1668 (w), 1451 (s), 1377 (s), 1297 (w), 1167 (w), 1108 (w), 1093 (w), 1070 (w), 985 (w), 840 (m), 779 (w). HRMS calcd for $C_{15}H_{23}N$: 217.1831; found 217.1833.

*4.4.17. (1RS,2SR,5SR)-2,4-Dimethyl-5-(3-methylbut-2-enyl)cyclohex-3-enecarbonitrile **24**.* Prepared according to Procedure A from methylocimene **2f** (*E*/*Z* 3:2, 10 g, 63 mmol),[4a–b] acrylonitrile (3.7 g, 76 mmol), and boron trichloride 1 M in xylene (12.6 ml, 13 mmol) at 25 °C in 5 h. Standard work-up with *tert*-butyl methyl ether and bulb-to-bulb distillation at 110 °C/0.1 mbar gave 5.9 g (82%, based on the *E*,*E*-isomer of **2f**) of **24** as colorless oil. Analytical data of the main isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.15 (d, 3H), 1.55–1.7 (1H), 1.65 (s, 3H), 1.7 (s, 3H), 1.72 (s, 3H), 1.9 (m, 1H), 2.0–2.2 (2H), 2.3 (m, 1H), 2.45 (m, 1H), 2.8 (m, 1H), 5.0 (m, 1H), 5.4 (1H) ppm. ^{13}C NMR ($CHCl_3$, 400 MHz): δ 17.4 (q), 18.0 (q), 21.3 (q), 25.8 (q), 27.3 (t), 30.1 (d), 30.5 (t), 30.7 (d), 38.6 (d), 121.2 (d), 122.0 (s), 126.4 (d), 133.7 (s), 135.8 (s) ppm. Relative configuration determined by NMR-analysis in C_6D_6: NOESY, HSQC, COSY, HMBC. GC/MS: 203 (5%, M^+), 188 (1%, $[M-15]^+$), 135 (6%), 107 (5%), 81 (10%), 69 (100%), 41 (25%). R_T=7.8 (4%), 8.0 (4%), 8.1 (88%, *cis*-isomer), 8.2 (4%) min (GC). IR (film): 2965 (s), 2916 (m), 2873 (m), 2237 (m), 1447 (s), 1378 (s), 1325 (w), 1311 (w), 1285 (w), 1185 (w), 1132 (w), 1110 (w), 1061 (w), 1041 (w), 1018 (w), 986 (w), 920 (w), 839 (m), 805 (w), 776 (w). HRMS calcd for $C_{15}H_{23}N$: 203.1674; found 203.1669.



24

*4.4.18. (1RS,2SR,5SR)-1,2,4-Trimethyl-5-(3-methylbut-2-enyl)cyclohex-3-enecarbaldehyde **25**.* DiBAH 1.2 M in toluene (25 ml, 31 mmol) was added dropwise to nitrile **23** (4 g, 18 mmol) in CH_2Cl_2 (160 ml) at −78 °C. After 5 h at −78 °C and 15 h at 25 °C the reaction was quenched with 2 M HCl. Extraction with *tert*-butyl methyl ether, washing of the organic phase with satd NaCl, drying over $MgSO_4$, filtration, and evaporation of the filtrate gave 3.8 g of an oil, which was purified by bulb-to-bulb-distillation (110 °C, 0.2 mbar) to give 3 g (78%) of a colorless oil with 98% purity. Analytical data of the main isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 0.9 (d, 3H), 1.1 (s, 3H), 1.5 (1H), 1.65 (s, 3H), 1.7 (s, 3H), 1.72 (s, 3H), 2.0–2.2 (3H), 2.3 (m, 1H), 5.05 (t, 1H), 5.4 (d, 1H), 9.55 (s, 1H) ppm. ^{13}C NMR ($CHCl_3$, 400 MHz): δ 17.9 (q), 18.0 (q), 19.65 (q), 21.1 (q), 25.8 (q), 28.9 (t), 30.8 (t), 36.0 (d), 36.15 (d), 47.7 (s), 121.7 (d), 126.6 (d), 133.0 (s), 134.9 (s), 1207.0 (s) ppm. Relative configuration determined by NMR-analysis in C_6D_6: NOESY, HSQC, COSY, HMBC. GC/MS: 220 (5%, M^+), 202 (2%), 151 (12%), 133 (14%), 123 (45%), 121 (50%), 107 (100%), 91 (20%), 81 (29%), 69 (82%), 55 (15%), 41 (70%). R_T (GC)=7.85 (15%, diastereomer), 7.9 (79%, *all-cis*-isomer), 8.25 (3%). The mass spectra of the diastereomers are identical. IR (film): 2963 (m), 2928 (m), 2970 (m), 2687 (w), 1725 (s), 1450 (m), 1375 (m), 912 (w), 840 (m), 718 (w), 696 (w). HRMS calcd for $C_{15}H_{23}N$: 220.1827; found 220.1829.



25

*4.4.19. 1-((cis)-1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanone **1a**.* Water-free toluene (100 ml) was added to methylmagnesium bromide 3 M in diethylether (73.4 ml, 0.22 mol) under nitrogen and stirring. At 60 °C the diethyl ether was distilled off in the nitrogen stream leaving a clear solution to which nitrile **5a** (*cis*/*trans* 87:13, 43.5 g, 0.2 mol) in toluene (150 ml) was added. The solution was heated to reflux (120 °C) for 4 h. Water (20 ml) was added at 90°–70 °C, followed by 85% H_3PO_4 (29 g, 0.3 mol) and the mixture was heated for 1 h at reflux (100 °C). The phases were separated at 80 °C and the water phase extracted with toluene at this temperature. The combined organic phase was washed with water and satd $NaHCO_3$ to pH 8. Concentration under reduced pressure gave 105 g of an oily residue to which paraffin oil (30 g) and hydroquinone (0.5 g) were added. Distillation gave 47 g of **1a** at 90 °C/0.05 Torr. Yield 91% (dist, corr, based on *cis*-isomer **5a**). Olfactory yield: 77% (corr). R_T=8.9 (8.6%, *trans*-isomer **1b**), 9.06 (78.4%, *cis*-isomer **5a**) min (GC). The analytical data of **1a** were identical with the ones reported for this compound.[1b]

Acknowledgements

For skillful experiments we thank S. Elmer, C. Luzi, J. Oetiker and T. Reinmann, for GC/MS-, HRMS- and NMR measurements we thank J. Schmid and G. Brunner and for preparative GC-separations H. Koch (all Givaudan Dübendorf). For olfactory evaluation we thank J.-J. Rouge (Givaudan Vernier), A. Alchenberger and R. Kaiser (both Givaudan Dübendorf). For advice on transition state calculations we thank Prof. A.-C. Corminboeuf (Federal Institute of Technology, Lausanne). For discussions we thank Prof. P. Chen (ETH Zürich), Prof. A. Hoveyda (Boston College) and Prof. A. Vasella (ETH Zürich). For proofreading we thank C. Furniss and S. Derrer (both Givaudan Dübendorf).

References and notes

1. (a) Fráter, G.; Müller, U.; Nussbaumer, C. Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13–17, 1997, Publisher: American Chemical Society, Washington, DC; (b) Frater, G.; Müller, U.; Schröder, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3967–3972.
2. Georgywood® as ingredient in iconic fine fragrances 2008: (a) Gucci pour Homme (Gucci). (b) John Galliano (John Galliano). (c) Secret Obsession (Calvin Klein). Other prominent perfums containing Georgywood®: (d) Higher (Eau de Cologne) from Christian Dior. (e) Attraction (Eau de Parfum) from L'Oréal /Lancôme. (f) Brit (Eau de Cologne) from Burberrys. (g) Golden Moments (Eau) from Priscilla Presley. (h) Pour Femme (Eau de Parfum) from Yohji Yamamoto. (i) Love Fills L'Air Du Temps (Eau) from Nina Ricci. (j) Egeo Man (Desodorante Colônia) from O Boticário. (k) Quasar Feminino (Desodorante Colônia) from O Boticario. (l) Men's moon sparkle (shower gel) from Escada. (m) Hinoki (Eau) from Commes des Garçons.
3. Bajgrowicz, J. A.; Bringhen, A.; Fráter, G. EP 0743297, priority 16.5. 1995 to Givaudan; *Chem. Abstr. 126*, 103856 h.
4. (a) Barras, J.-P.; Bourdin, B.; Schröder, F. *Chimia* **2006**, *60*, 574–579; (b) Frater, G.; Schröder, F. *J. Org. Chem.* **2007**, *72*, 1112–1120; (c) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346–1352; (d) Bella, M.; Cianflone, M.; Montemuro, G.; Passacanilli, G.; Piancatelli, G. *Tetrahedron* **2004**, *60*, 4821–4827.
5. Tetracyclone (a), methyl coumalate (b) and furan (c) were not considered for comparison with Homomyrcene **2** due to additional carbonyl, phenyl or oxygen substituents in conjugation with the diene. Endo-selective DA reactions from these dienes and (meth)acrylonitrile have been reported: (a) Khazaei, A.; Zolfigol, M. A.; Manesh, A. A. *J. Chin. Chem. Soc. (Taiwan)* **2005**, *52*, 515–518; (b) Shimo, T.; Yamasaki, S.; Date, K.; Uemura, H.; Somekawa, K. *J. Heterocycl. Chem.* **1993**, *30*, 419–423; (c) Fraile, J. M.; García, J. I.; Massam, J.; Mayoral, J. A.; Pires, E. *J. Mol. Catal. A: Chem.* **1997**, *123* 43–37.
6. All four carbon atoms of an endocyclic conjugated diene are part of a cyclic structure, not to be confused with the *endo*/*exo* descriptors of the Diels–Alder transition states. The *endo*/*exo* description of the obtained Diels–Alder adducts is identical with the *cis*/*trans* description of the diastereomers **a** and **b**, respectively.
7. (a) Kas'yan, A. O.; Zlenko, E. T.; Okovityi, S. I.; Golodaeva, E. A.; Kas'yan, L. I. *Russ. J. Org. Chem.* **2001**, *37*, 1564–1569; (b) Fermann, M.; Herpers, E.; Kirmse, W.; Neubauer, R.; Renneke, F.-J.; Siegfried, R.; Wonner, A.; Zellmer, U. *Chem. Ber.* **1989**, *122*, 975–984; (c) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17–22; (d) Cantello, B. C. C.; Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 22–25; (e) Mekhtiev, S. D.; Musaev, M. R.; Sakhnovskaya, E. B.; Sultanov, V. T. *Zh. Org. Khim.* **1969**, *5*, 1364–1366; (f) Sauers, R. R. *J. Am. Chem. Soc.* **1958**, *81*, 4873–4876.
8. (a) Imachi, S.; Onaka, M. *Tetrahedron Lett.* **2004**, *45*, 4943–4946; (b) Najafi-Mahmoudi, H.; Ghandi, M.; Farzaneh, F. *Chem. Lett.* **2000**, 358–359.
9. (a) MAN+Butadiene: Doucet, J.; Rumpf, P. *Bull. Soc. Chim. Fr.* **1954**, 610–613; (b) Moore, J. A.; Partain, E. M., III. *J. Org. Chem.* **1983**, *48*, 1105–1106.
10. (a) Neodymium complex [(THF)2Nd(MBMP)2Na(THF)2]: Xu, X.; Ma, M.; Yao, Y.; Zhang, Y.; Shen, Q. *Eur. J. Inorg. Chem.* **2005**, 676–684; (b) Pt(II)-NCN-Pincer complex: Fossey, J. S.; Richards, C. J. *Organometallics* **2002**, *21*, 5259–5264; (c) $AlClEt_2$ or $ZnCl_2$ on SiO_2: García, J. I.; Mayoral, J. A.; Pires, E.; Brown, D. R.; Massam. *J. Catal.* **1996**, *37*, 261–266; (d) $AlMe_3$: Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115–12116.
11. (a) $Sc(OTf)_3$: Vidis, A.; Kusters, E.; Sedelmeier, G.; Dyson, P. J. *J. Phys. Org. Chem.* **2008**, *21*, 264–270; (b) [HMI][BF_4]: López, I.; Silvero, G.; Arélavo, M. J.; Babiano, R.; Palacios, J.-C.; Bravo, J.-L. *Tetrahedron* **2007**, *63*, 2901–2906; (c) $Sc(OTf)_3$: Silvero, G.; Arélavo, M. J.; Bravo, J. L.; Ávalos, M.; Jiménez, J. L.; López, I. *Tetrahedron* **2005**, *61*, 7105–7111; (d) $ZnCl_2$: Sun, I.-W.; Wu, S.-Y.; Su, C.-H.; Shu, Y.-L.; Wu, P.-L. *J. Chin. Chem. Soc. (Taiwan)* **2004**, *51*, 367–370.
12. Ion resins or acid clays gave no conversion. See Ref. 8 for the use of Zeolites in the DA reaction of cyclopentadiene and methacrylonitrile.
13. $AlCl_3$ has been reported to catalyze DA reactions of butadiene or isoprene with (meth)acrylonitriles, but no data about *endo*/*exo* selectivities were given: Efendiev, E. Kh.; Rasulbekova, T. I.; Akhmedov, R. M. *Azerbaidzhanskii Khimicheskii Zhurnal* **1979**, 43–46.
14. For coordination chemistry of $B(C_6F_5)_3$ with nitriles, see: Focante, F.; Mercandelli, P.; Sironi, A.; Resconi, L. *Coord. Chem. Rev.* **2006**, *250*, 170–188.
15. Probably due to competing complexation/inactivation of the Lewis acid as experienced in other LA-promoted reactions, see for example Ref. 4b.
16. (a) Maurer, B.; Hauser, A.; Froidevaux, J.-C. *Tetrahedron Lett.* **1986**, *27*, 2111–2112; (b) Leopold, E. *J. Org. Synth.* **1986**, *64*, 164–174.
17. Silver salts AgX were less- or ineffective: X=CF_3CO_2, Cl, OAc, BF_4, OTf, SbF_6, BARF.
18. Copper complexes were less- or ineffective: CuBr, $Cu(OTf)_2$ with or without BOX or BINAP, $Cu(MeCN)_4PF_6$ with or without BINAP, $Cu(NO_3)_2$ with or without dimethyl-bispyridine.
19. Zinc salts ZnX_2 were less or ineffective: X=Br, I, OTf.
20. Other ineffective Lewis acids: LiBr, $TiCl_4$ (decomposition), TiF_3, $CpTiCl_3$, $FeCl_3$, $CpFe(CO)_2BF_4$, $CoCl_2$, $H_2Ru(PPh_3)_4$, $PdCl_2$, $SnCl_2$, $SnBr_4$, SbF_6, $AuCl_3$, $BiCl_3$, SmI_2.
21. Lanthanide and related triflates in CH_2Cl_2 were inactive: $Yb(OTf)_3$, $Sc(OTf)_3$ with or without BINOL or in H_2O, $Y(OTf)_3$, $Lu(OTf)_3$.
22. Acidic ion resins or clays gave no conversion up to 80 °C. MANDA reaction of **2a** in ethanol showed no effect.
23. Shriver, D. F.; Swanson, B. *Inorg. Chem.* **1971**, *10*, 1354–1365.
24. Taft, R. W.; Carten, J. W. *J. Am. Chem. Soc.* **1964**, *86* 4199–4120.
25. El-Erian, M. A. I.; Huggett, P. G.; Wade, K. *Polyhedron* **1991**, *18*, 2131–2136.
26. Oikawa, Eizo; Kambara, Shu *J. Polym. Sci.* **1964**, *2*, 649–653.
27. Equations have been generated by using all the available molecular descriptors and genetic function approximation of Molecular Operating Environment (MOE), version 2007.09, Chemical Computing Group Inc. Montreal, Canada, 2007. The root mean square error of prediction could be probably improved with more accurate experimental data.
28. Bini, R.; Chiappe, C.; Mestre, V. L.; Pomelli, C. S.; Welton, T. *Org. Biomol. Chem.* **2008**, *6*, 2522–2529.
29. Geometry optimizations and Gibbs free energy values in toluene have been computed by applying the COSMO-RS solvent modeling approach (*From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design*, Andreas Klamt, Elsevier Science Ltd., Amsterdam, The Netherlands **2005**, ISBN: 0-444-51994-7) based on *ab inito* wavefunctions (HF:svp_ahlrichs/DFT: B97-2//

tzvp_alrichs/MP2-SCS) by using Parallel Quantum Solutions (2013 Green Acres Road Suite A, Fayetteville, Arkansas, 72703, U.S.A.) software (version 3. 3) at our Quantum Cube parallel computer (8 AMD 2.4 GHz CPUs). For transition state search, TS option was used with a subsequent frequency analysis.
30. Nazarov, I. N.; Kuznetsova, A. I.; Kuznetsov, N. V. *Zh. Obshch. Khim.* **1955**, *25*, 88–108.
31. For the thermal DA reaction of an 1,1,2-trialkylsubstituted diene see: Nazarov, I. N.; Mavrov, M. V. *Zh. Obshch. Khim.* **1959**, *29*, 1169–1176.
32. The *cisoid* conformer of *E*,*E*-**2f** is sterically less hindered than the one of the *E*,*Z*-isomer. See for example: Sauer, J. *Angew. Chem.* **1967**, *79*; Chapter B376–94.
33. Herz, W.; Juo, R. R. *J. Org. Chem.* **1985**, *50*, 618–627 and references therein.
34. Ether-free Grignard-addition to sterically hindered nitriles followed by hydrolysis with strong acids, see for example: (a) Prashad, M.; Seth, M.; Bhaduri, A. P. *J. Indian Chem. Soc.* **1980**, *57*, 1115–1117; (b) Bruzau, Mme. *Ann. Chim.* **1934**, 257–358.
35. *Cis/trans* designation of cyclic compounds: see March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, NY, Chichester, UK, Brisbane, Toronto, Singapore, 1992.
36. Erman, M. B.; Hoffmann, H. M.; Cardenas, C. G. EP 0985651, priority 19.8. 1998 to Millennium Specialty Chemicals, Inc., *Chem. Abstr. 132*, 207981.
37. (a) Sera, A.; Takagi, K.; Nakamura, M.; Seguchi, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1271–1272; (b) Alder, K.; Heimbach, K.; Reubke, R. *Chem. Ber.* **1958**, *91*, 1516–1524; (c) Alder, K.; Krieger, H.; Weiss, H. *Chem. Ber.* **1955**, *88*, 144–155.
38. (a) Von Doering, W.; Cheng, X.; Lee, K.; Lin, Z. *J. Am. Chem. Soc.* **2002**, *124*, 11642–11652; (b) Guner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1988**, *53*, 5348–5351.
39. Kraft, P.; Eichenberger, W. *Eur. J. Org. Chem.* **2004**, 354–365.