Synthesis and application of flavin based oxidation catalysts

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CHAPTER 5

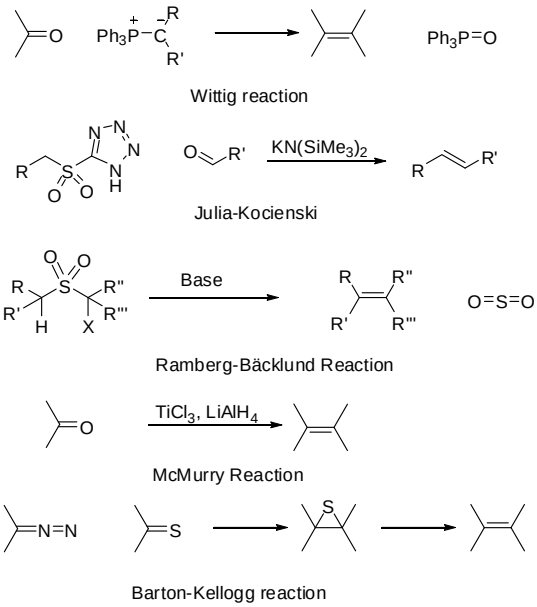
Reduction of Carbon-Carbon Double Bonds using Organocatalytically Generated Diimide

In this chapter a system for the reduction of carbon-carbon double bonds with diimide, catalytically generated in situ from hydrazine hydrate, is described. The employed flavin catalyst was prepared in one step from riboflavin (vitamin B2) as is described in chapter 2. Reactions are carried out in air and are a valuable alternative for metal catalyzed hydrogenations.

Part of this chapter has been published:
Smit, C.; Fraaije, M.W.; Minnaard, A.J. *J. Org. Chem.*, **2008**, *73*, 9482.

5.1 Introduction

The reduction of carbon-carbon double bonds is a central reaction in organic synthesis,[1] and is often used in the synthesis of natural products and pharmaceutical compounds either to introduce chirality via asymmetric hydrogenation or as a consequence of the strategy applied to connect molecular fragments. Established methods to form carbon-carbon double bonds are the Wittig- and related reactions, the Julia-Kocienski, Ramberg-Bäcklund, aldol, Knoevenagel, McMurry and Barton-Kellogg reactions and, more recently, olefin metathesis and allylic substitution reactions (Scheme 5.1).

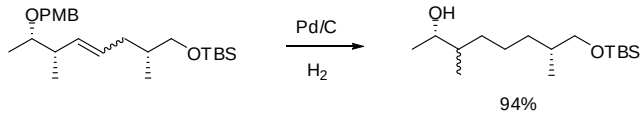


Scheme 5.1: Selected examples of synthetic methods for connecting fragments together, thereby forming a double bond.

5.1.1 Transition metal catalysts

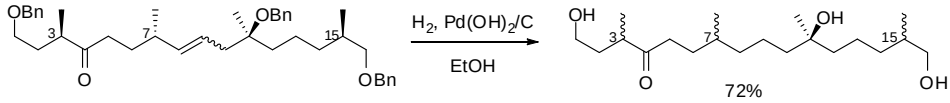
Reduction of non-polarized carbon-carbon double bonds is normally accomplished using hydrogen and heterogeneous transition metal catalysts, e.g. Rh/C, Pd/C, Raney Nickel (Ra-Ni) or Adam's catalyst (PtO_2). Alternatively, homogeneous transition metal complexes such as Wilkinson's catalyst are applied, whereas enantioselective hydrogenation is mostly based on homogeneous catalysis as well.[2] Although these hydrogenations using transition metal catalysts often proceed efficiently, there are important limitations. Using heterogeneous catalysts, hydrogenolysis[3] of benzylic, allylic and propargylic alcohols and amines is often inevitable, and an important drawback when the corresponding benzyl, Cbz and Alloc protecting groups are present.[4] In addition, several functional groups such as nitro groups, benzylic ketones and aryl halides are rapidly reduced as well.

A less recognized feature of transition metals is their tendency to isomerize double bonds.[5] This holds for all commonly used transition metals both in heterogeneous and in homogeneous catalysis. Although often overlooked in cases in which the isomerized product is subsequently reduced without consequence, this process can lead to epimerization, ring opening of cyclopropanes and, most difficult to detect, racemization. Several studies in natural product synthesis have explicitly reported epimerization or racemization in the course of the synthetic route.[6] Mori *et al.* observed partial racemization in the synthesis of 6-acetoxy-19-methylnonacosane.[7] Curran *et al.* observed, upon careful analysis during the synthesis of the pinesaw fly sex pheromones, epimerization due to hydrogenation with Pd/C and Ra Ni (Scheme 5.2).[8]



Scheme 5.2: Example of epimerization taking place in the synthesis of the pinesaw fly sex pheromone.

Very recent examples include the synthesis of the mating hormone of *Phythophthera infestans* which was hampered by the same problem, showing epimerization at the C^7 (Scheme 5.3).[9]

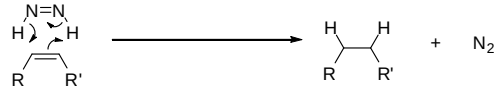


Scheme 5.3: Example of epimerization taking place in the synthesis of the mating hormone of *Phythophthera infestans*.

Hayashi *et al.* observed, during an absolute configuration determination, a small amount of racemization of a terminal alkyne upon hydrogenation.[10]

5.1.2 Diimide reductions

One of the few alternatives to transition metal catalyzed hydrogenation for the reduction of non-polarized carbon-carbon double bonds is the use of cis-diimide (diazene, HN=NH). It hydrogenates alkenes, alkynes and polyenes, with selective delivery of hydrogen to one face of the substrate. This gives the same stereoselectivity as metal-catalyzed syn addition of H_2. The advantages of using diazene are that there is no need for high pressure or potentially explosive dihydrogen gas (the only gas released is dinitrogen) and no need for expensive metal catalysts. With diimide, double bonds are reduced via a cycloaddition mechanism as depicted in Scheme 5.4 and therefore hydrogenolysis or isomerization do not take place.[11] Diimide exists in a distinct cis and trans stereoisomer because each nitrogen atom bears one hydrogen and one lone pair and double bonds cannot rotate. Only with cis-diimide the cycloaddition can take place. Isomerization of the *trans*- to the *cis*-isomer occurs, most probably involving a rapid protonation-deprotonation sequence.

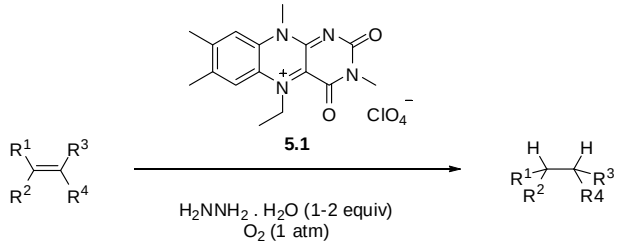


Scheme 5.4: Diimide reductions take place via a concerted six membered mechanism.

5.1.3 Diimide Generation

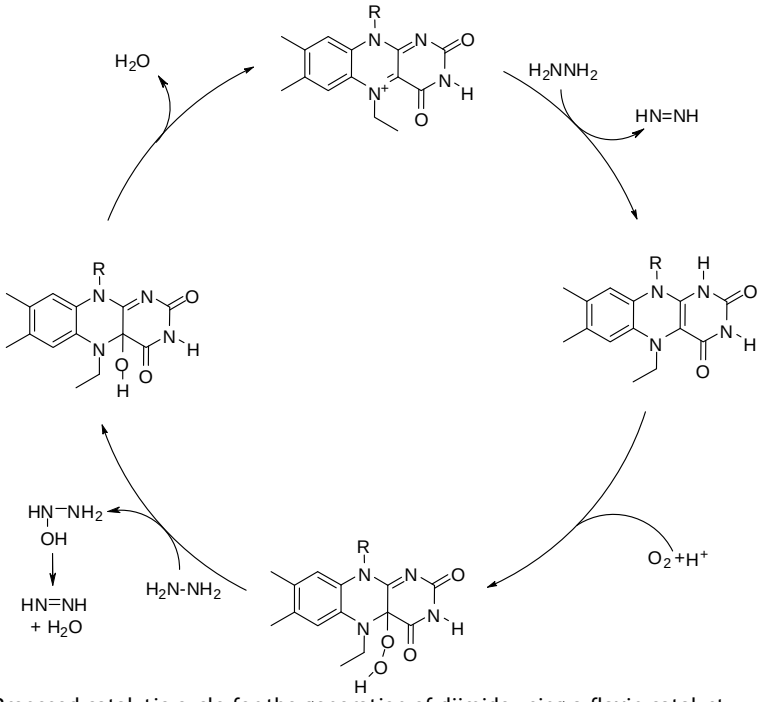
Diimide itself is unstable due to the fact that it disproportionates into dihydrogen and dinitrogen and therefore a large number of methods for its in situ generation have been reported. The most well known among these methods are the generation of diimide from a large excess of hydrazine hydrate using oxygen, generally in the presence of Cu(II) and/or a carboxylic acid, the oxidation of hydrazine hydrate with periodate and the protolytic decarboxylation of azodicarboxylate. More modern approaches use the base induced elimination of substituted hydrazines[12] and the copper-catalyzed oxidation of anhydrous hydrazine. Anhydrous hydrazine is not easily prepared, however, and generally not commercially available. For all these approaches holds that in general a (large) excess of the reagent is needed and although excellent yields are occasionally reported, disappointing yields are commonly observed together with the recovery of starting material.

Recently, Imada *et al.* reported the generation of diimide from hydrazine hydrate and dioxygen using the flavin-type compound **5.1**, depicted in scheme 5.5, as catalyst.[13] Remarkably, a large excess of hydrazine hydrate was not necessary. Because the synthesis of the reported catalyst required several steps and the reactions were carried out under an oxygen atmosphere instead of air, we aimed in our studies to develop a easily prepared flavin catalyst that would efficiently generate diimide from hydrazine hydrate and air. The advantage of using air instead of pure oxygen is that the reaction conditions are less dangerous.[14] This catalyst system should efficiently reduce carbon-carbon double bonds in high yields and should also be applicable in solid phase organic synthesis, an area in which double bond reduction is particularly difficult.



Scheme 5.5: First reported flavin catalyst applied for diimide formation

An important feature in these reactions is the fact that hydrazine not only acts as substrate for the flavin, but also as a reductant, as is depicted in Scheme 5.6. In the proposed catalytic cycle, 2 equiv. of diimide is formed for one equivalent of dioxygen consumed. A remaining disadvantage of the use of hydrazine, however, is its toxicity and carcinogenicity.

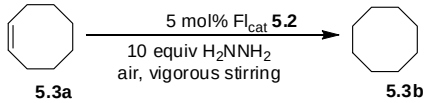


Scheme 5.6: Proposed catalytic cycle for the generation of diimide using a flavin catalyst.

5.2 Optimization of the reaction conditions

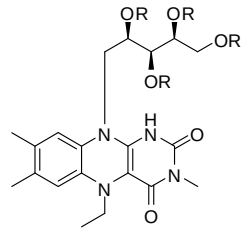
From the catalysts described in chapter 2, 5-ethyl-riboflavin (**5.2**) is the most easily accessible and can be prepared in one step. Therefore, generation of diimide from low-cost hydrazine hydrate with this catalyst would be a convenient alternative to other diimide generating methods. First, we had to investigate if we could utilize the riboflavin based catalyst for diimide reductions and make sure that no side reactions would take place. The activity of **5.2** as a catalyst in the conversion of hydrazine hydrate to diimide with O_2 (air) was investigated by following the reduction of cyclooctene. First, the effect the solvents was investigated(Table 5.1).

Table 5.1: Solvent dependency of cyclooctene reduction using **5.2** and hydrazine hydrate in air.



5.3a **5.3b**

Solvent	Conversion
DMSO	100
THF	24
2-Propanol	95
2,2,2-Trifluoroethanol	100
n-Heptane	4
Methanol	49
Ethanol	100
Toluene	12
Hydrazine hydrate	100



5.2

Reaction conditions: 0.5 mmol of substrate, 3.5 ml of solvent, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst **5.2**, vigorous stirring in air for 4 h. Conversion was determined using GC.

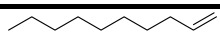
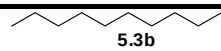
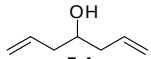
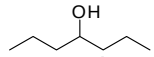
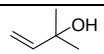
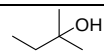
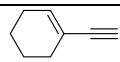
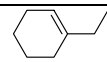
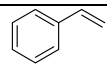
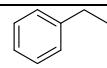
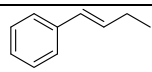
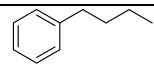
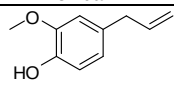
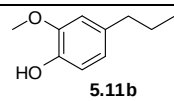
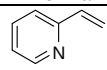
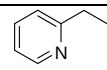
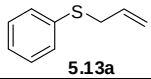
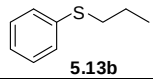
Cyclooctene is reduced most efficiently in polar solvents. The low reactivity in apolar solvents is probably due to low solubility of the catalyst whereas the lower conversion in methanol remained unexplained. Ethanol was chosen as the optimal and most practical solvent. Vigorous stirring proved to be necessary, probably to facilitate the uptake of O_2 in the solvent. No side products were observed in the course of these reactions.

5.3 Substrate Scope

To study the scope of the reaction, the reduction of a variety of substrates was investigated using the flavin/hydrazine hydrate system in ethanol (Table 5.2).

5.3.1 Reactive alkenes as substrates

Table 5.2: Reduction of terminal and strained carbon-carbon double bonds[a]

Entry	Substrate	Product	Conversion	isolated yield
1	 **5.3a**	 **5.3b**	quant.	
2	 **5.4a**	 **5.4b**	quant.	
3	 **5.5a**	 **5.5b**	quant.	
4	 **5.6a**	 **5.6b**	quant.	
5	 **5.7a**	 **5.7b**	quant.	
6	 **5.8a**	 **5.8b**	quant.	
7	 **5.9a**	 **5.9b**	quant.	
8	 **5.10a**	 **5.10b**	quant	99[b]
9	 **5.11a**	 **5.11b**	quant.	78 [b]
10	 **5.12a**	 **5.12b**	quant.	73 [b]
11	 **5.13a**	 **5.13b**	quant.	99 [b]

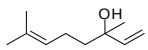
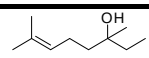
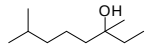
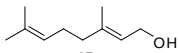
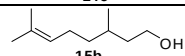
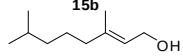
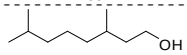
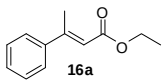
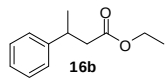
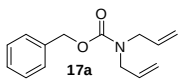
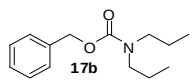
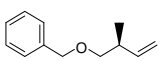
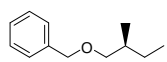
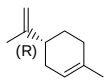
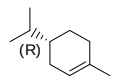
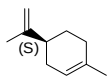
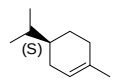
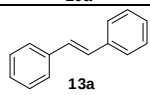
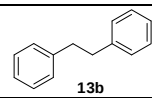
[a]Reaction conditions: 0.5 mmol of substrate, 3.5 ml of EtOH, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst **5.2**, vigorous stirring in air for 4 h. [b]Reactions performed with 5 mmol of substrate, 20 ml EtOH, 5 ml hydrazine hydrate, 100 mg of catalyst. The lower yield of **5.11b** and **5.12b** is due to loss of product during isolation.

As expected, the reduction of terminal and strained alkenes is fast with full conversion reached within 4 h. With additional substituents on the double bond, the reduction proceeded slower. Entry 6 showed fast reduction of the alkyne to the exocyclic alkane. The intermediate alkene was not observed whereas the internal tri-substituted double bond is not reduced. In entry 9-11 a number of functional groups are present which did not affect the reduction. In the presence of a ketone or imine however, as expected, hydrazone formation was detected by GC-MS.

5.3.2 Challenging substrates

A number of more challenging alkenes was studied to investigate the general applicability of our system (Table 5.3).

Table 5.3: Reduction of carbon-carbon bonds in selected substrates[a]

Entry	Substrate	Product	Conversion (isolated yield, %)	
			4h	20h
1	 14a	 14b	90	70
		 14c	5	30
2	 15a	 15b	11	42
		 15c		
		 15d	0	11
3	 16a	 16b	5	23
4	 17a	 17b	quant. (99)[b]	n.d.
5	 18a	 18b	quant. (99)	n.d
6	 19a	 19b	quant. (72) [b]	n.d
7	 20a	 20b	quant. (89)[b]	n.d
8	 13a	 13b	no conversion	

[a]0.5 mmol of substrate, 3.5 ml EtOH, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst **5.2**, vigorous stirring for 4 h. [b]Reactions performed with 5 mmol of substrate, 20 ml EtOH, 5 ml hydrazine hydrate, 100 mg of catalyst

Entry 1, 2 and 3 clearly show that the reduction of terminal double bonds proceeds considerably faster than the reduction of triple substituted double bonds. To illustrate the versatility of the present catalyst system in cases where transition metal-catalyzed reduction is problematic due to hydrogenolysis or racemization, we selected a number of challenging substrates in this respect. Entry 4 and 5 show compounds with hydrogenolysis sensitive CBz and benzyl groups, respectively. Using **5.2** and hydrazine hydrate, quantitative conversion into the desired products took place without hydrogenolysis. In entry 5-7, the double bond is situated next to a stereogenic center. **5.2**/Hydrazine reduction afforded the desired products in quantitative conversions and, as expected, without racemization as determined by chiral GC. Stilbene (entry 8) turned out to be unreactive, most likely due to decreased solubility of the subtrate..

5.3.3 Selectivity of the reaction

In the case of compounds with multiple sites that can be reduced, such as substrate **5.8a**, **5.14a**, **5.15a** and **5.19a** it is important to determine which site is reduced first. If there is a considerable preference for the reduction of one of the carbon carbon double bonds over the other, a reaction can be stopped at the point at which most of the desired product is formed. Therefore, we investigated the selectivity in the reduction of these substrates.

During the reduction of **5.8a**, multiple products can be formed due to successive reductions taking placing. Since it is known that the reduction of internal carbon-carbon double bonds is more difficult than the reduction of terminal carbon-carbon double bonds we hoped to be able to selectively reduce only the terminal double bond. The compounds that were expected to be formed during the reaction are shown in Figure 5.1.

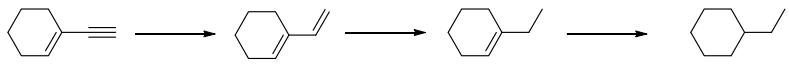
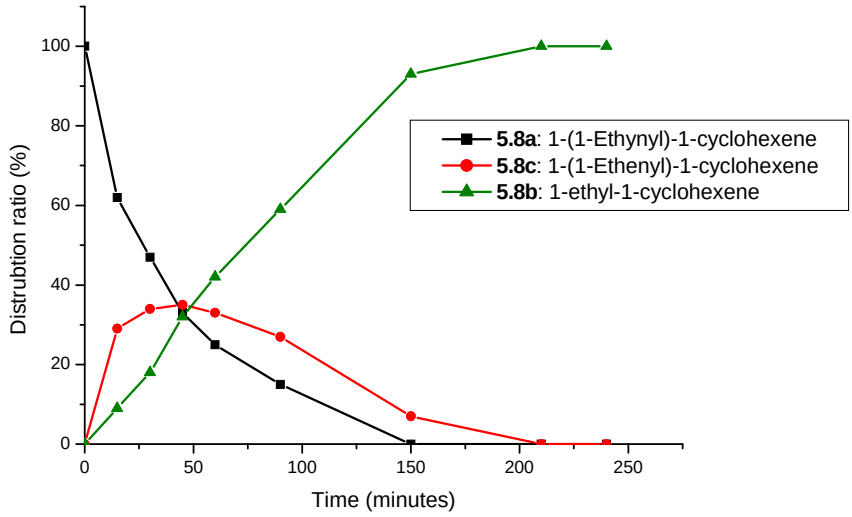


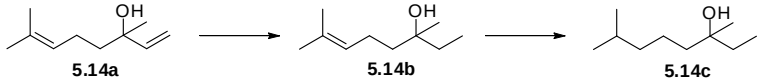
Figure 5.1: Expected products in the reduction of 1-(1-ethynyl)-1-cyclohexene (**5.8a**).

As can be deduced from the results presented in graph 5.1 the reduction of the terminal alkyne, and the successive reduction of the terminal alkene take place before reduction of the internal carbon carbon double bond. Even after running the reaction for an additional 18 hours, only a trace amount of the product **5.8d** was observed.



Graph 5.1: Distribution of compounds **5.8a-c** during the course of the reduction with 0.5 mmol of substrate, 3.5 ml EtOH, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst, vigorous stirring for 4 h.

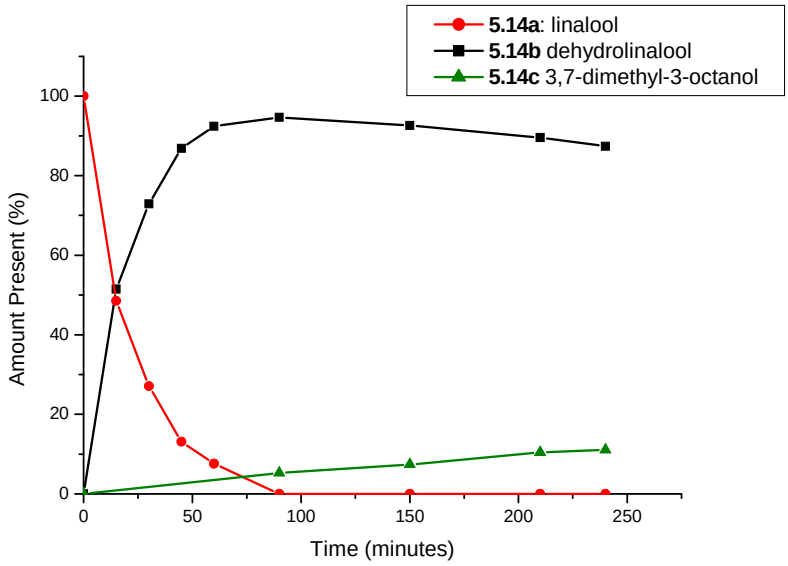
A related case is the reduction of linalool (**5.14a**), to first dehydrolinalool (**5.14b**) and subsequently after a second reduction to 3,7-dimethyl-3-octanol (**5.14c**) as depicted in Figure 5.2.



5.14a **5.14b** **5.14c**

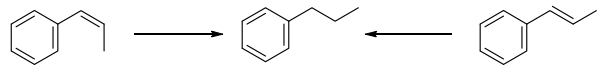
Figure 5.2: Expected products in the reduction of linalool

As depicted in Graph 5.2 we observed very rapid reduction of the terminal double bond, followed by a much slower reduction of the internal trisubstituted double bond. We followed the reduction using GC-MS and could therefore only afterwards determine at which time the concentration of **5.14b** was highest. With spectroscopic methods, it should be possible to follow the reaction online and determine concentrations of the products. The data show that if the reaction is quenched at the moment that the concentration of **5.14b** is at the maximum, it is possible to obtain a good yield of this product.



Graph 5.2: Concentration of compounds **5.14a-c** during the course of reduction with 0.5 mmol of substrate, 3.5 ml EtOH, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst, vigorous stirring for 4 h.

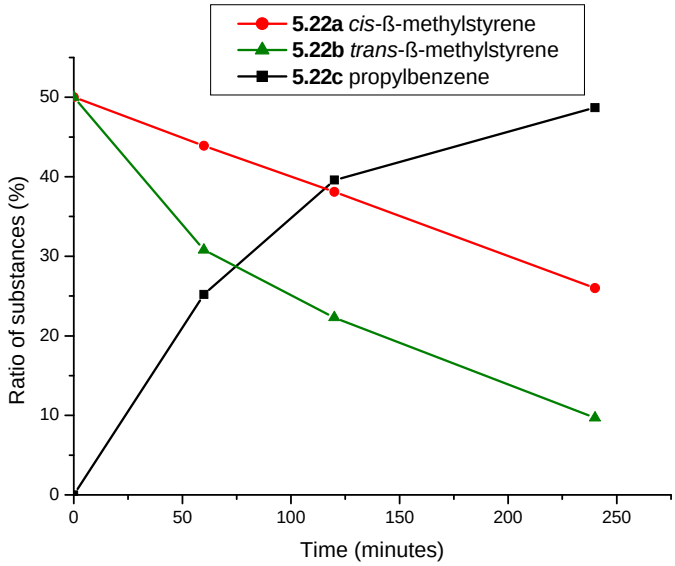
Next to the difference in reactivity between terminal and internal carbon-carbon double bonds, diimide reduction can also have a preference for the stereochemistry of the double bond. We investigated this selectivity of our system in the reduction of cis- and trans-β-styrene to propylbenzene (Figure 5.3).



5.22a **5.22c** **5.22b**

Figure 5.3: Reduction of cis- and trans-beta-styrene (resp. **5.22a** and **5.22b**) to yield propylbenzene (**5.22c**).

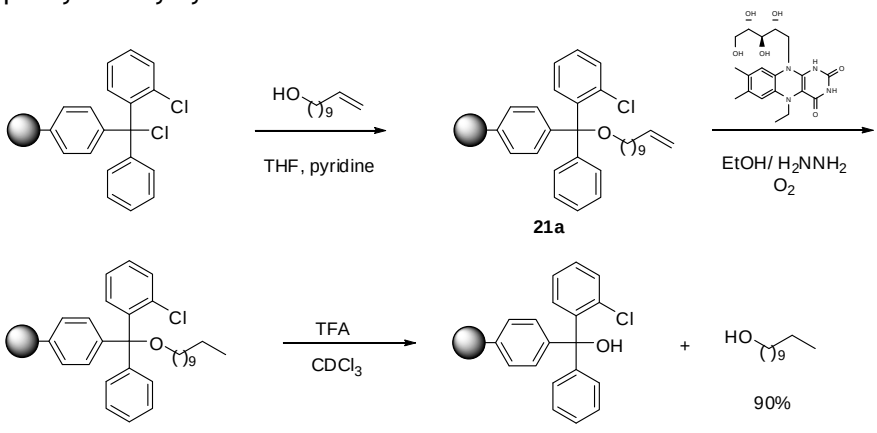
As Graph 5.3 clearly shows, the reduction with diimide has a preference for reducing the trans-β-styrene over cis-β-styrene. After some time the rates of both reductions seem to be the same, probably due to a difference in concentration.



Graph 5.3: Ratio of compounds **5.22a-c** during the course of reduction with 0.5 mmol of substrate, 3.5 ml EtOH, 0.5 ml of hydrazine hydrate, 10 mg (5 mol%) of catalyst, vigorous stirring for 4 h.

5.3.4 Reductions with diimide applied in solid phase organic synthesis (SPOS)

In SPOS, reduction of double bonds is especially challenging as heterogeneous catalysts are ineffective due to phase transfer limitations whereas homogeneous catalysts appear to be slow and are quickly deactivated. Building on earlier work,[15] it has been shown recently by Buszec and Brown that the reduction of carbon-carbon double bonds in solid phase synthesis can be performed using diimide generated from *o*-nitrophenylsulfonylhydrazide.[12,16]



Scheme 5.7: Reduction of a carbon-carbon double bond in a substrate coupled to 2-chlorotrityl polymer resin.

We investigated the reduction of 1-undecenol coupled to a solid phase (Scheme 5.7). First 1-undecenol was coupled to commercially available Merrifield polymer resin. Since the reaction mixture cannot be stirred vigorously without grinding the resin, a shaking plate was used and the reaction was performed under an oxygen atmosphere. We found that reduction with **5.2** and hydrazine takes place readily, although slower compared to reductions in solution. We did not observe any cleavage of the substrate from the resin. Apparently, even in ethanol as the solvent, in which the polystyrene resin swells badly, the reaction still takes place due to the ease with which diimide penetrates the resin and reaches the double bond. This phenomenon has also been observed in the hydrogenation of polybutadiene-based rubbers in latex form with diimide by Wideman.[17]

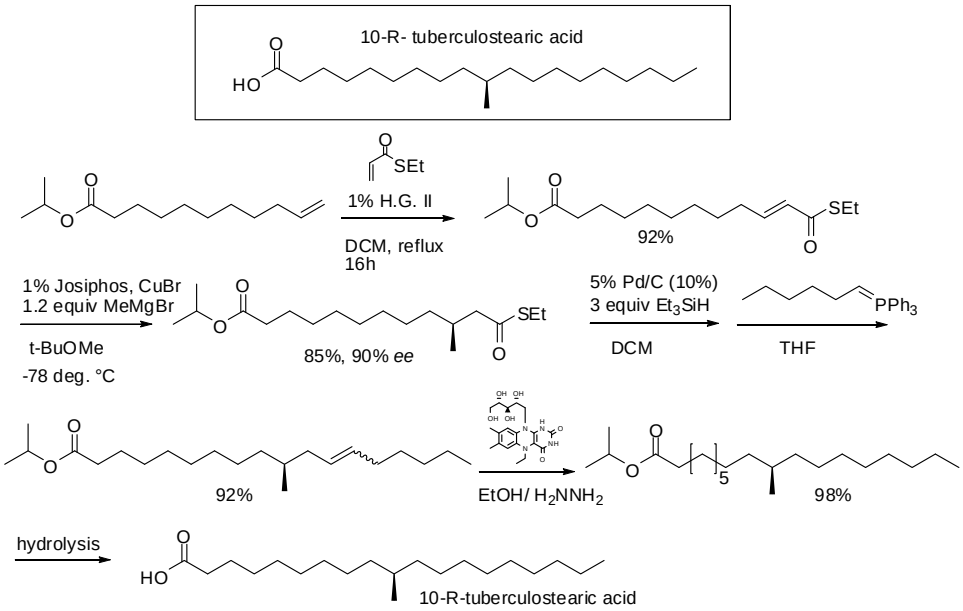
5.4 Applications in synthesis projects

The methodology for diimide generation as described in this chapter has already been successfully applied in several synthesis projects in the institute as illustrated below.

5.4.1 Total synthesis of 10-R-tuberculostearic acid

10-R-Methyloctadecanoic acid, or tuberculostearic acid (TBSA) is a major component of the lipids of the tubercle bacillus and related bacterial species (Scheme 5.8). Its presence in bacterial cultures and sputum from patients is used in the diagnosis of tuberculosis.[18] TBSA can be readily detected using GC-MS. A limitation, however, is that TBSA is universally distributed throughout mycobacterial species and related *nocardial* pathogens.[19]

TBSA was already reported in 1927,[20] after isolation from the phosphatide fraction of the H.37 strain of *Mycobacterium tuberculosis.* In 1934, Spielman *et al.* confirmed the molecular formula to be $C_{19}H_{38}O_2$ and it was suggested that TBSA possesses a chiral centre.[21] In the following decades, a number of routes to the single enantiomers and routes to the racemic mixture were published. However, most methods either contained steps in which nucleophilic substitution led to partial loss of enantiopurity or had relatively complex purification steps. In 2006, a straightforward synthesis was devised by Baird *et al.*[22] in which S and R citronellyl bromide were used as starting material to obtain the desired 10-R- and 10-S-TBSA in 53% overall yield. An alternative route for the synthesis of TBSA, developed in our group by ter Horst uses asymmetric catalysis to introduce the stereogenic centre.[23] In this route chain elongation takes place using a Wittig reagent, resulting in a carbon carbon double bond located ß to the chiral centre. Reduction of the carbon carbon double bond utilizing our flavin-diimide system gave excellent yield.[24] By performing the reduction with this method no loss of *ee* will occur and there is no need to check the *ee* of the product.



Scheme 5.8: Total synthesis of 10-R-tuberculostearic acid

5.4.2 Total synthesis of a Palaeo-indicator

Another interesting group of lipids are the membrane-spanning glycerol-based tetraether lipids. These lipids are typically found in Archaea. Their membrane consists of lipids composed of alkyl chains linked by ether bonds to a glycerol backbone to form a glycerol dialkyl diether (figure 5.4a) and glycerol dialkyl glycerol tetraether (GDGT) (figure 4b). A cell membrane predominantly composed of GDGTs forms a mono-layer which is thought to be more rigid than a bi-layered membrane composed of diethers or diesters as are generally present in Bacteria.

A number of branched GDGTs were detected in coastal and lake sediments. However, due to a mixture of archaeal and bacterial characteristics it was first uncertain whether these compounds were from archaeal or bacterial origins. Since non-isoprenoid lipids have not been encountered in Archea, but dialkyl glycerol diethers have been encountered in some thermophilic bacteria, a bacterial origin has been suggested.[25]

Via detection of the various lipids, it is possible to investigate past continental climate and soil organic fluxes to the ocean.[26] Lipids can be extracted from marine sediments after which intact diether or diester membrane lipids can be measured using GC/MS techniques, because the molecules are relatively volatile. Intact GDGT membrane lipids are less volatile and are determined using HPLC/MS.[27]

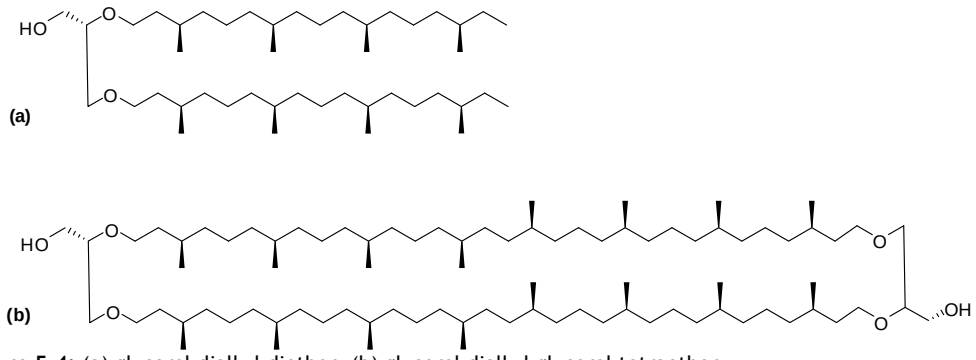


figure 5.4: (a) glycerol dialkyl diether, (b) glycerol dialkyl glycerol tetraether.

Not only the detection of these so called palaeo-indicators is important, they can also be used for determining the amount of terrestrial organic matter in sea sediment. Since synthetically produced lipids could be used as reference compounds it is very important to obtain them in pure form. A total synthesis project of a GDGT with only four methyl substituents (figure 5.5) was started in our group by Hernandez-Olmos to elucidate the stereochemistry of the natural product.

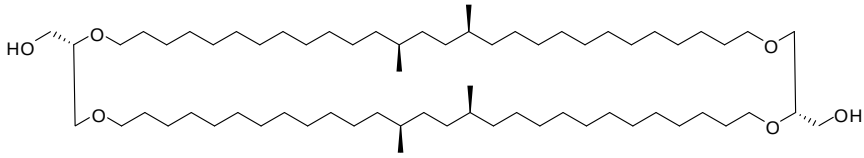
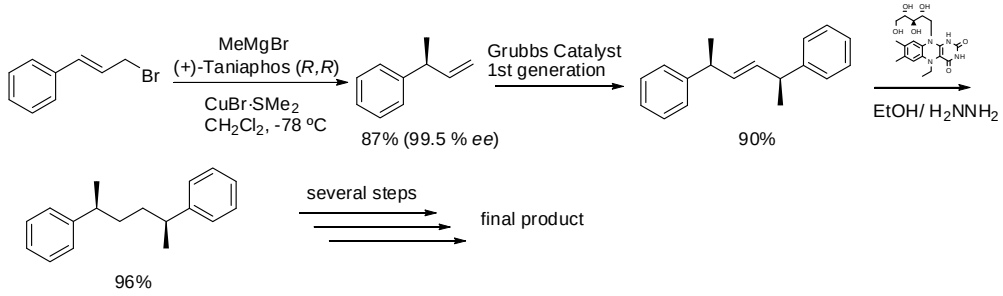


Figure 5.5: Target compound: A membrane spanning glycerol-based tetraether lipid.

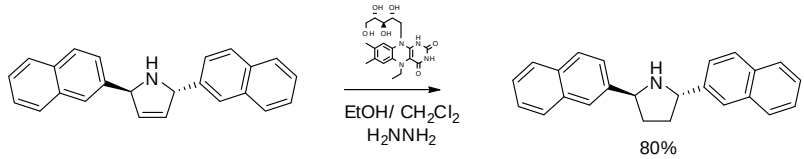
Already early in the synthesis, two molecules of (S)-but-3-en-2-ylbenzene were coupled using 1st generation Grubbs catalyst. The double bond in the resulting (2S,5S,E)-hex-3-ene-2,5-diyldibenzene which is located next to two chiral centra had to be reduced. Due to the importance of keeping the stereogenic centra intact, diimide based reduction is the appropriate choice. The reduction of (2S,5S,E)-hex-3-ene-2,5-diyldibenzene was performed using our methodology and the desired product was obtained in high yield although an additional amount of catalyst was needed to drive the reaction to completion.[28]



Scheme 5.9: First steps in the synthesis of membrane spanning glycerol-based tetraether lipid.

5.4.3 Reduction of a double bond in (2S,5S)-2,5-di(naphthalen-2-yl)pyrroline

The final step in the synthesis of (2S,5S)-2,5-di(naphthalen-2-yl)pyrrolidine (scheme 5.10) is, as in the synthesis of the tetraether lipid, the reduction of a carbon-carbon double bond next to two stereogenic centra. This substrate turned out to be resistant to reduction using the standard flavin/hydrazine hydrate conditions. Only trace amount of product was obtained. Reduction of the substrate could be accomplished in low yield, however, with diimide generated from o-nitrophenylsulfonylhydrazide, provided that the reaction was carried out at considerable elevated temperature.[12] Further investigations into the reaction showed that the solubility of the substrate limited the reaction. It turned out that if the **5.2**/hydrazine reaction was carried out using a 1:1 solvent mixture of ethanol and dichloromethane instead of pure ethanol the desired product could be obtained in 80% yield.



Scheme 5.10: Reduction of the carbon-carbon double bond in (2S,5S)-2,5-di(naphthalen-2-yl)pyrroline.

5.5 Limitations of the method

There are some limitations in the reduction of carbon carbon double bonds with in situ generated diimide from hydrazine hydrate. As expected, the reduction of carbon-carbon double bonds in the presence of a keton or an aldehyde did not work due to nucleophilic attack of the hydrazine on the ketone/aldehyde. We did however observe reduction of the double bond in the resulting compounds. The reduction of polarized double bonds using diimide was also observed to proceed much slower.[11]

5.6 Conclusions

Concluding, 5-ethyl riboflavin **5.2** is an efficient catalyst for the formation of diimide for the reduction of carbon-carbon double bonds. The catalyst can be prepared in one step on multigram scale from readily available riboflavin (vitamin B2) in excellent yield. Reductions are carried out in air and at room temperature. As this catalyst system affords high yields for terminal and disubstituted alkenes and does not give double bond isomerization, it is a valuable alternative for metal catalyzed hydrogenations.

5.7 Experimental section

General: ^{1}H-NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent. Progress and conversion of the reactions was determined by GC-MS equipped with an HP-1 column.

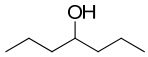
Materials: Riboflavin, acetaldehyde, palladium (10%) on activated carbon, $H_2NNH_2 \cdot H_2O$, methyl-p-tolylsulfide, 1-decene, 1,6-heptadien-4-ol, norbornylene, cis-cyclooctene, 1-(1-ethynyl)-1-cyclohexene, styrene, 4-allyl-2-methoxyphenol (eugenol), 2-vinylpyridine, allyl phenyl sulfide, trans-stilbene, 3,7-dimethyl-6-octadien-3-ol (linalool), geraniol, (+)- and (-)-limonene, 10-undecen-1-ol and chlorotrityl chloride polymer resin were commercially available and used without further purification. (−)-(((S)-2-methylbut-3-enyloxy)methyl)benzene (**18a**) was donated by A.W. van Zijl,[29] benzyl diallylcarbamate was prepared according to a literature procedure.[30] V. Hernandez-Olmos, B. ter Horst and J. Teichert investigated, respectively, the reductions in the synthesis of glycerol dialkyl diether, 10-R-tuberculostearic acid and (2S,5S)-2,5-di(naphthalen-2-yl)pyrroline.

The products decane, propyl phenyl sulfide and dihydrolinalool have been previously described (see appropriate references in the following pages) following a similar reaction procedure. The hydrogenation of the olefins was followed by GC-MS, conversion was calculated based on disappearance of the signal of the substrate and appearance of a signal corresponding to the product(s). Both the GC-MS library and observed mass were used to confirm the identity of the products. The volatile products 4-heptanol, norbornane, and cyclooctene were not isolated. The products 1-ethyl cyclohexene, 2-methoxy-4-propylphenol, 2-ethylpyridine, citronellol, 3,7-dimethyl-1-hydroxy-2-octene, 3,7-dimethyl-1-octanol, N-(benzyloxycarbonyl)dipropyl amine, (+) and (-)-1-ethyl-4-isopropylcyclohexene and 1-undecanol afforded ^{1}H NMR spectra identical to the literature.

Typical Procedure for the hydrogenation of an olefin with 20 equivalent of hydrazine monohydrate and 5 mol% of flavin catalyst 5.2.
A mixture of olefin (0.5 mmol), flavin catalyst *2* (10.0 mg, 0.025 mmol), and $NH_2NH_2 \cdot H_2O$ (0.5 g, 11 mmol) in ethanol (4.0 mL) was stirred vigorously at 25 °C under air. Samples of 200 µL were eluted with ethanol over a short $MgSO_4$ column and subjected to GC-MS analysis. Note: GC-MS analysis was carried out on samples passed through a short plug of $MgSO_4$ to remove hydrazine, diimide and water.

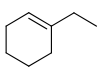
CAUTION: hydrazine is a cancer suspect agent.

The following compounds were synthesized from according the starting materials described in tables 5.2 and 5.3.



4-heptanol (5b): conversion and purity (>95%) based on GC-MS analysis after 4 h. No side products were observed.

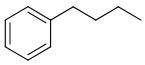
cyclooctane (3b): conversion and purity (>95%) based on GC-MS analysis after 4 h. No side products were observed.



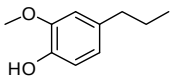
1-ethylcyclohexene(7b)[31]: conversion and purity (>95%) based on GC-MS

analysis after 4 h. No side products were observed.

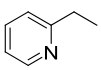
Ethylbenzene (8b)[32]: conversion and purity (>95%) based on GC-MS analysis after 4 h. No side products were observed.



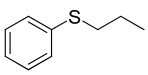
n-Butylbenzene (9b)[33]: Purification by extraction with 4x 5 ml pentane followed by washing of the organic layer with brine and evaporation of the solvent afforded a yellow oil. (99% yield) 1H-NMR δ 7.05-7.35 (m, 5H), 5.5 (t, 2H), 1.05-1.80 (m, 4H), 0.9 (t, 3H). >95% (GC-MS).



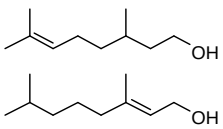
2-methoxy-4-propylphenol (10b)[34]: Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. [78% yield] 1H-NMR δ 6.83 (m, 1H), 6.67 (m, 2H), 5.52 (s, 1H), 3.86 (s, 3H), 2.57 (t, J = 7.61 Hz, 2H), 1,61 (m, 2H), 0.92 (m, 3H); 13C-NMR δ 146.5 (C), 143.8 (C), 134.9 (C), 121.2 (CH), 114.3 (CH), 111.3 (C), 56.1 (CH_3), 38.0 (CH_2), 25.1 (CH_2), 14.0 (CH_3). >95% (GC-MS). HRMS calcd for $C_{10}H_{15}O_2$ 167.1066, found 167.1069



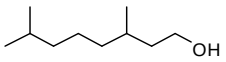
2-ethylpyridine(11b)[35]: Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. [73% yield] 1H-NMR δ 8.52 (d, J = 4.8 Hz, 1H), 7.59 (m, 1H), 7.16 (d, J = 4.8 hz, 1H), 7.09 (m, 1H), 2.83 (q, J = 7.6 Hz, 2H), 1.31 (m, 3H); 13C-NMR δ 165.3 (C), 149.4 (CH), 136.6 (CH), 122.2 (CH), 121.1 (CH), 31.6 (CH_2), 14.1 (CH_3). >95% (GC-MS). HRMS calcd for $C_7H_{10}N$ 108.0807, found 108.0817



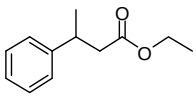
propyl phenyl sulfide(12b) Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil (99 % yield, >95% determined by GC-MS).



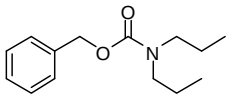
Citronellol (15b) [36] **/3,7-dimethyl-1-hydroxy-2-octene (15c)**: Conversion based on GC-MS data. Except for the expected 3,7-dimethyl-1-hydroxy-2-octene, no other products were observed.



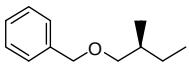
3,7-dimethyl-1-octanol (15d)[37]: Conversion based on GC-MS data. Except for the expected 3,7-dimethyl-1-octanol, no other products were observed.



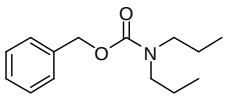
Benzenepropanoic acid, ß-methyl-, ethyl ester (16b) [38] : Conversion based on GC-MS data.



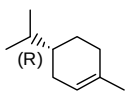
N-(Benzyloxycarbonyl)dipropylamine (17b) [39]: Purification by extraction with 4x 5 ml ethyl acetate followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. (90% yield) 1H-NMR δ 7.30 (m, 5H), 5.11 (s, 2H), 3.18 (br s, 4H), 1.54 (br s, 4H), 0.85 (br, 6H); 13C-NMR δ 137.6 (C), 128.9 (CH), 128.2 (CH), 128.1 (CH), 110.3 (CO), 67.2 (CH_2), 49.7 (CH_2), 49.1 (CH_2), 22.3 (CH_2), 21.8 (CH_2), 11.7 (CH_3). HRMS calcd for $C_{14}H_{22}NO_2$ 236.1666, found 236.1645.



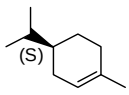
(-)-(((S)-2-methylbutoxy)methyl)benzene (18b): Starting from (−)-(((S)-2-methylbut-3-enyloxy)methyl)benzene (**18a**) with an *ee* of 92%. Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. (99% yield): 1H-NMR δ 7.34 (d, J = 4.5 Hz, 4H), 7.32-7.23 (m, 1H), 4.53 (s, 2H), 3.36 (m, 1H), 3.28 (m, 1H), 1.72 (m, 1H), 1.51 (m, 1H), 1.18 (m, 1H), 0.94 (m, 6H); 13C-NMR δ 139.1 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 76.0 (CH_2), 73.2 (CH_2), 35.3 (CH), 26.5 (CH_2), 16.9 (CH_3) , 11.6 (CH_3); HRMS [M+ NH_4+] calcd for $C_{12}H_{18}O$ 196.1701, found 196.1695. Enantioselectivity was determined by chiral HPLC analysis, Chiralcel OD-H (99.75% heptane/ 0.25% i-PrOH), 40 ºC, retention times (min): 9.7 (major) and 9.9 (minor).



Racemic ((2-methylbutoxy)methyl)benzene(17c): was obtained by reduction of racemic ((2-methylbut-3-enyloxy)methyl)benzene following the same procedure as for **17b**. Purification by extraction with 4x 5 ml pentane followed by washing of the organic layer with brine and evaporation of the solvent afforded a yellow oil. (99% yield).

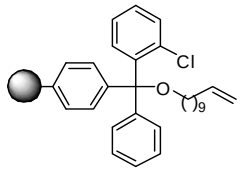


(+)-1-ethyl-4-isopropylcyclohexene (19b) [40] : starting from (+)-limonene with an ee of 87%. Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. (72% yield, 90% *ee*) 1H-NMR δ 5.32 (s, 1H), 4.79-1.08 (m, 8H), 1.64 (s, 3H), 0.99-0.72 (m, 6H); 13C-NMR δ 133.6 (C), 120.7 (CH), 39.7 (CH), 32.0 (CH), 30.5 (CH_2), 28.6 (CH_2), 26.2 (CH), 23.1 (CH_3), 19.7 (CH_3), 19.4 (CH_3); The *ee* was determined using GC with a Chiraldex B-PM column, 50 ºC for 5 min followed by heating to 150 ºC in 10 min. After 15 min at 150 ºC cooling to 50 ºC in 15 min.



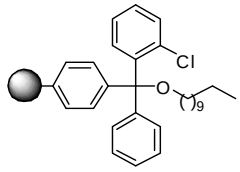
(-)-1-ethyl-4-isopropylcyclohexene (20b)[40]: starting from (-)-limonene with an ee of 99+%. Purification by extraction with 4x 5 ml pentane followed by washing the organic layer with brine and evaporation of the solvent afforded a yellow oil. (89% yield, 99+% *ee*). 1H-NMR δ 5.32 (s,

1H), 4.79-1.08 (m, 8H), 1.64 (s, 3H), 0.99-0.72 (m, 6H); 13C-NMR δ 133.6 (C), 120.7 (CH), 39.7 (CH), 32.0 (CH), 30.5 (CH_2), 28.6 (CH_2), 26.2 (CH), 23.1 (CH_3), 19.7 (CH_3), 19.4 (CH_3). The *ee* was determined using GC with a Chiraldex B-PM column, 50 ºC for 5 min followed by heating to 150 ºC in 10 min. After 15 min at 150 ºC cooling to 50ºC in 15 min.



10-undecen-1-ol coupled to 2-chlorotrityl chloride polymer resin. To 0.5 gram of 2-chlorotrityl chloride polymer resin (0.5-0.7 mmol Cl per gram, 1% crosslinked with DVB, 200-400 mesh) in 5 ml dry THF was added 119 mg undecenol (0.7 mmol) and 110 mg pyridine (1.4 mmol). The mixture was shaken for 6 hours at 60 °C after which the resin was filtered and washed 3 times with DCM/MeOH/DIEA (17/2/1), 3 times with DCM, 3 times with DMF and 3 times with methanol. After drying in vacuum over KOH, 450 mg of product was obtained.

Cleavage of 10-undecen-1-ol from 2-chlorotrityl polymer resin
To 150 mg of the resin loaded with 10-undecen-1-ol was added 3 ml $CDCl_3$, and 0.01 ml TFA. The mixture was shaken for two hours. The resin was filtered and the amount of undecanol was determined by ^{1}H NMR to be 0.26 mmol per gram, by applying TMS as an internal standard.



Reduction of 10-undecen-1-ol coupled to 2-chlorotrityl chloride polymer resin. To 500 mg of resin was added 3.5 ml EtOH, 0.5 ml hydrazine hydrate, and 10 mg catalyst **5.2**. The reaction vessel was shaken for 24 hours under an O_2 atmosphere (balloon). Afterwards, the resin was filtered and washed 3 times with dichloromethane and three times with MeOH.

Cleavage of 10-undecanol from 2-chlorotrityl chloride polymer resin
To 150 mg of resin was added 3 ml $CDCl_3$ and 0.01 ml TFA. The mixture was shaken for two hours. The resin was filtered and the yield of the product was determined by ^{1}H-NMR by addition of 10 µL TMS (72.5 µmol) as internal standard. 90% yield, >95% (GC-MS), no remaining undecenol was observed.

Acknowledgements
T.D. Tiemersma-Wegman is acknowledged for assistance with GC, HPLC and LC-MS. A.W. van Zijl is acknowledged for the generous donation of substrates. Victor Hernandez-Olmos, Bjorn ter Horst and Johannes Teichert are gratuitously thanked for showing practical applications and limitations of our system.

5.8 References and notes

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